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Using Artificial Intelligence and Magnetic Resonance Imaging to Address Limitations in Response Assessment in Glioma

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ABSTRACT

Gliomas are rapidly progressive, neurologically devastating, nearly uniformly fatal brain tumors. In WHO grade IV tumors like glioblastoma, the standard of care involves maximal surgical resection followed by concurrent radiation therapy (RT) and temozolomide (TMZ) chemotherapy followed by adjuvant TMZ. This results in overall survival (OS) of less than 30% at two years. Currently, tumor progression assessment is based on clinician assessment and MRI interpretation using Response Assessment in Neuro-Oncology (RANO) criteria. These criteria classify response as complete, partial, stable, or progression. This approach, however, suffers from significant limitations due to the difficulty in interpreting MRI findings on T1 gad and T2 FLAIR sequences, lack of concurrent correlation with radiation therapy fields, inconsistent follow-up imaging, concurrent administration of steroids, and systemic management, including immunotherapy. The neuro-oncology field struggles with classifying true progression vs. pseudoprogression vs. pseudoresponse with progression guidelines actively evolving. The lack of consensus on the definition of progression impairs the ability to initiate earlier management upon progression, judge the impact of therapies, and optimize and personalize management. Due to the pivotal role of imaging, radiology is at the center of the question of optimizing and advancing response criteria [1-5]. The hypothesis is that MRI images of patients with glioma, when subjected to change over time analysis (at diagnosis, prior to and post-radiation therapy), can identify features predictive of treatment failure helping guide patient management in the clinic. Likely a combination of imaging and biospecimen-driven biomarkers is needed. Given the large amount of data generated by both approaches, success in this space hinges on leveraging computational approaches and artificial intelligence algorithms validated using large-scale publicly available data sets to disentangle the complexity and heterogeneity inherent in glioma progression.

Keywords: Artificial Intelligence, Glioma, Response, Assessment.

INTRODUCTION

Despite numerous advances in molecular characterization [6-9] and imaging [10], the reality of the clinical interaction with patients in the neuro-oncology clinic remains focused on the ever-present challenge embedded in the question: "Did the patient progress or not? Was the treatment effective? When should a different treatment be initiated?" Arguably most, if not all, provider-patient interactions, whether at first consult or upon follow-up, center on these questions. There is widespread recognition of the limitations in interpreting imaging in the context of glioma progression, which directly affects patient care, personalization of patient management, and outcomes and further limits how we interpret ongoing evidence as it develops [11-13]. The understanding and interpretation of progression have a significant impact on patient management and outcomes [14], and there is increasing awareness that response criteria, primarily when predicated on human assessments of morphologic change in tumor size, do not capture the complexity of tumor heterogeneity or management, particularly in the context of molecular-targeted therapies [15]. Most imaging findings are also challenging to distinguish from the radiation therapy effect [13]. The lack of consensus on the definition of progression impairs the ability to judge the impact of therapies and,

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therefore, the management optimization. Since imaging is likely to remain the cornerstone of response assessment for the foreseeable future, radiology is at the center of the question of optimizing and advancing response criteria [1-5,11-13]. This review will summarize the ongoing barriers to response criteria in glioma and how they may be addressed by harnessing data embedded in imaging already collected as the standard of care in brain tumor patients. We will also review how advancement will include novel imaging, the augmentation of imaging-driven response criteria using biospecimen data, and the additive benefit of artificial intelligence.

THE EVOLUTION AND LIMITATIONS OF APPROACHES TO GLIOMA RESPONSE CRITERIA

The Macdonald criteria initially modeled on the RECIST criteria [16] were published in 1990 [17] initially developed for CT and extrapolated to MRI. These initial criteria grouped classified tumor response into four categories: complete response (CR) or partial response (PR) with options to classify ongoing findings as stable disease (SD) or progressive disease (PD). Complete response was defined as meant disappearance of all enhancing tumors, with the patient no longer on steroids and neurologically stable or improved. Partial response was employed as AIF, a 50% reduction in the size of the enhancing tumor was identified, steroids were stable or reduced, and the patient was neurologically stable or improved. Progressive disease was defined as a greater than 25% increase in the size of the enhancing tumor, identification for any new tumor or neurologic worsening, and steroids stable or increased (Table 1).

Progression criteria	Parameter					Barriers to ETL data for ML				Capture in publicly avail data base repository
	Clinical	Imaging	Steroids	Radiation field evaluation	Potential solutions Guideline revision	Clinical data	Imaging	Steroids	Solutions towards ETL	
RECIST[16]	no	One dimensional contrast enhancement	no	no	Optimise to reflect MRI imaging	N	D	N	Imaging data sets platform	no
Macdonald (1990)[17]	clinical deterioration	Two dimensional of contrast enhancement assessment of tumor size ≥25% increase in the enhancing disease, new lesions	Increasing steroid use	no	Capture T2 FLAIR changes Avoid treatment discontinuation base don't pseudoprogression	N, B, S	D, M, Q	N, B, S	Imaging data sets platform NLP for clinical and pharmacy records AI /radiomics for imaging	no
RANO (2010)[18]	clinical deterioration	≥25% increase in the enhancing and/or significant increase in the non-enhancing disease, new lesions, clear progression in non-measurable disease	Increasing doses of steroids represents progression	New lesion outside 80% isodose line	Separate criteria for LGG and HGG and immunotherapy	M, B, S	D, M, Q	M, B, S	Imaging data sets platform NLP for clinical and pharmacy records AI /radiomics for imaging	Yes* [74-77]
RANO-HGG[5]	clinical deterioration	Exclude progression in first 3 months following completion of chemoradiation; Confirmatory scan at 3 months	Increasing doses of steroids represents progression	New lesion outside 80% isodose line	Objectively capture clinical deterioration	M, D, B, S, Q	D, M, Q, O	M, D, B, Q, S, O	Clinical and Imaging data sets platform NLP for clinical and pharmacy records AI /radiomics for imaging Clinical trial endpoints	Yes*[74-77]
RANO-LGG[5]	clinical deterioration	T2 FLAIR based (>=25% or new lesion) = progression Category of minor response (25%-49% decrease in size of T2/FLAIR lesion)	Increasing doses of steroids alone does not represent progression if clinically stable	New lesion outside 80% isodose line	Objectively capture clinical deterioration	M, D, B, S, Q	D, M, Q, O	M,D, B, Q, S, O		Yes*[74-77]
iRANO[31]	Per RANO	Abnormal enhancement within 6 months of starting agent defined as unconfirmed progressive disease; new lesion allowed to continue study; histopathology progression only if viable tumor	Increasing dose =not achieved response. Decreased dose prior to MRI= not evaluable	New lesion outside 80% isodose line	Optimise to avoid delay in diagnosis of progressive disease Therapy specific biomarkers and radiomic analysis	M, D, B, S, Q	D, M, Q, O	M, D, B, Q, S, O		no
NANO[33]	NANO scale	Not included	If neuro change possibly related to steroid management, neuro progression "non-evaluable"	Not included	Aggregate with criteria that also capture imaging	M, D, Q, O	N	M, D, O	Data sets platform NLP ML	no

Table 1. The evolution of progression criteria in glioma over time based on clinical data, imaging interpretation, steroid, and RT administration. N – manual input, minimal to no capture; M – manual, limited capture; D-digital capture; B-binary capture; S-subjective; Q-quantitative information may be captured; O – attempt at objective data capture. *variable inputs, may not include imaging and may only include limited clinical information.

For a patient to have responded, a sustained (defined as persisting > 1 month) and significant (defined as > 50% reduction in the size of the enhancing tumor on CT or MRI scans) was required [17]. These criteria were revised to the RANO criteria in 2010 [18] themselves since revised [5,18,19] (Figure 1).

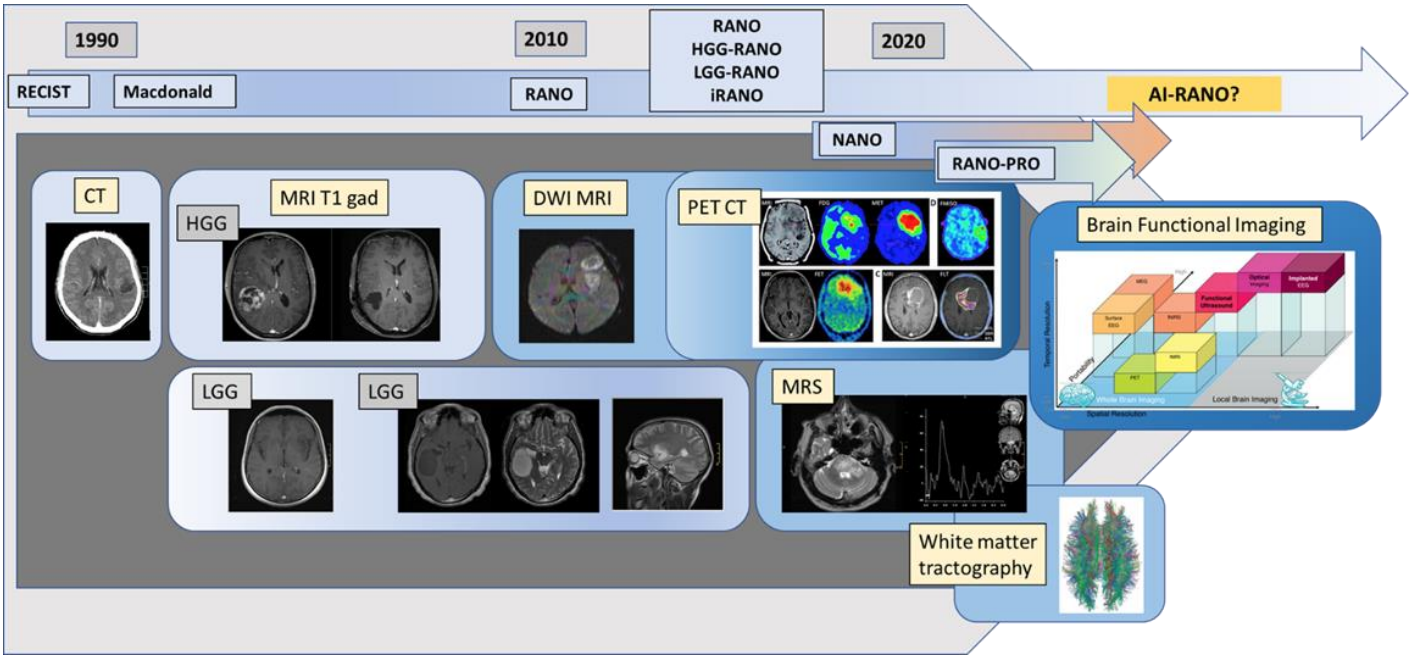

Figure 1. The evolution of response criteria in glioma. Left: Macdonald criteria modeled on the RECIST criteria, implemented for CT and extrapolated to MRI (1990`s). Middle: Revision of Macdonald criteria to RANO criteria (2010`s) with inclusion of the non-enhancing tumor component in low-grade glioma (LGG) on T2-weighted and fluid-attenuated inversion recovery (FLAIR) image sequences (lower panel). Evolution of DWI and RANO criteria with working groups assigned to different facets of the progression problem: (LGG) (RANO-LGG), high-grade glioma (HGG) (RANO-HGG), administration of immunotherapy (iRANO), neurological progression (NANO) and patient reported outcomes (RANO-PRO). Right: novel imaging modalities (PET-CT, MRS, white matter tractography and brain functional imaging) [86-90] [91-94].

The initial revision occurred in response to the limitations difficulties of the MacDonald criteria, in capturing specifically the recognition of pseudo progression in patients receiving radiotherapy and temozolomide and due to the introduction of antiangiogenic agents that rendered previous approaches to classifying progression more challenging [18]. The revision included assessing the non-enhancing component of the tumor originating in T2-weighted and fluid-attenuated inversion recovery (FLAIR) image sequences, an ongoing challenge since this sequence defines both peritumoral edema and delayed radiation white matter changes with similar radiographic appearances. At the time of publication, the authors commented on the difficulty in both precise quantifications of the increase in T2/FLAIR signal and the ongoing challenges in different abnormal T2/FLAIR representative of tumor progression from other causes of increased T2 or FLAIR signal (radiation field related changes, decreased corticosteroids, postoperative changes, systemic management) [18] (Figure 1). The parameter of quantifying progression for patients being considered for enrollment in clinical trials based on enhancing lesions (>25% increase in the product of perpendicular diameters compared to baseline or best response and estimated volumetric change of >=40%) is problematic since bidirectional measurements are operator dependent and correlate poorly to tumor volume [4,20,21]. While all the above factors are currently needed to interpret progression in glioma (tumor dimensions, corticosteroid dosing, presence of comorbidities, neurological exam), they remain inconsistently captured in most retrospective data sets with quantification of the T2/FLAIR signal in relationship to radiation therapy fields rarely examined in a systemic therapy context in the clinic and equally ignored in registries. However, RANO criteria continue to be used, and several working groups have now been assigned to different facets of the progression problem, including the interpretation of response in low-grade glioma (LGG) (RANO-LGG), high-grade glioma (HGG) (RANO-HGG), in the context of the administration of immunotherapy (iRANO) and the definition of neurological progression (NANO) [4,5,19,22] (Figure 1).

GLIOMA PROGRESSION AND MRI – DOCTOR, DID THE TREATMENT WORK? – THE "NEEDLE OF TRUTH," THE "TEST OF TIME."

Standard of care guidelines support MRI of the brain prior to tumor resection, following tumor resection, then 2 to 8 weeks following radiation and subsequently every 2-4 months for three years, and then every 3-6 months indefinitely [31]. The current guidelines acknowledge that MRI of the brain may not be available at all institutions. Additional imaging modalities such as MR spectroscopy, MR perfusion imaging, and PET may have even less availability than MRI [23]. Nonetheless, MRI of the brain currently represents the most extensive available data set that can be studied to advance analysis that may improve the response criteria. The first MRI of the brain following completion of standard of care management is performed 2 to 8 weeks following radiation therapy. This first post-treatment scan is marked by a significant increase in contrast enhancement, often indistinguishable from treatment effect, and is fraught with the risk of mistaking pseudo progression for true progression [24]. As a result, In an attempt to account for this phenomenon, the RANO criteria recommended that within the first 312 weeks months after irradiation, patients not be labeled as having recurred to prevent early or inadequate patient enrollment on being excluded from clinical trials for recurrent disease unless progression is a new lesion was noted outside the radiation field or there is clear histologic tumor tissue documentation of progression was available [18]. Therefore, existing guidelines allow for increased enhancement to be considered tumor progression only if the enhancement is located "outside the radiation field" or there is tissue confirmation of progression if tissue diagnosis of tumor presence after chemoradiation is available. However, both aspects remain theoretical in that, most often, the radiologist interpreting and reporting the imaging does not know where the radiation field is in relation to the contrast enhancement. The intricacies of the radiation field itself with respect to the dose delivered and its relationship to the tumor volume prior and following radiation are not often viewed. In tertiary neuro-oncology centers, the isodose RT map may be shown, illustrating how "a picture is worth a thousand words" with all the affiliated specialties including neurosurgery, neuro-oncology, and radiology as a team able to interpret the findings on the scan while comparing and referencing the radiation therapy dose. Such a scenario is less likely outside of expertise centers and particularly challenging in resource strained settings with more limited or delayed MRI availability and clinician time. It is also unlikely a realistic prospect in settings where patient volume is exceptionally high due to resource limitations.

The second parameter of possible early progression is histologic documentation of progression. The question of obtaining tissue in this vulnerable patient cohort with existing, resolving, or progressing neurological symptoms considering the poor prognosis is equally challenging when recurrence may be radiologically suspected. Surgical intervention may be associated with considerable risks for the patient. Hence, fewer than 10% of patients may have repeat tissue obtained at this point in the treatment course [25]. Further, histopathologic findings may not correlate with clinical outcomes [25]. When tissue is obtained, barriers to consistent pathological interpretation remain due to both sampling heterogeneity and difficulties in interpreting tumor progression vs. treatment effect [2,13,24,26,27]. Therefore, when faced with uncertainty regarding progression at 2-8 weeks following completion of chemoradiation (CRT), the management de facto is the continuation of standard of care or trial management and repeating imaging at the 3-month mark [28]. Per RANO, equivocal at this time, if it is unclear whether the patient has progressed on imaging, they may continue changes allow patients to stay on a study with a repeat scan in >= four weeks, and if at that time the suspected progression is confirmed deemed real, the time of progression is backdated to the time point at which progression was suspected [18]. At 12 weeks following completion of treatment, RANO criteria describe progression (Table 1). However, questions remain since biological tumor behavior is heterogenous (low grade vs. high-grade tumor) and treatment has been ongoing (temozolomide or study drug), thus making it very difficult to connect cause and effect or examine biological relationships that underpin response vs. progression. The lack of clarity leads to challenges when studying novel agents. The inconsistent assessment of progression-free survival (PFS) combined with the limitations above is augmented by the ongoing evolution of response criteria, causing data collection, analysis, and interpretation variability. As evidenced in a recent study of Vorasidenib (AG-881), a first-in-class, dual inhibitor of mIDH1/2, response assessment is a serious challenge. The response here was defined as complete or partial, as determined by the investigator based on RANO criteria [18] or RECIST version 1.1[16], respectively[29]. However, in the context of patients with non-enhancing tumors, the response was defined as CR, PR, and minor response (MR) as determined by the investigator based on RANO-LGG [30]. In this study, the authors acknowledge that due to the challenges of assessing tumor response on MRI in

low-grade glioma, the RANO working group considers a 25–50% reduction in tumor size compared to baseline clinically meaningful, with several classifications now including MR as a measure of treatment effect [18,31]. Notably, in the context of immunotherapy, these aspects are still more complicated, hence the iRANO effort [31] allowing patients to continue management. The iRANO criteria allow the patient to continue immunotherapy within the first six months of initiating it since pseudoprogression is most likely to be observed. If MRI scans show radiologic progression (a 25% increase in area or appearance of new lesions), if provided, the patient is clinically stable, and patients may be observed closely with advising close observation with repeat MRI [4,31].

Another issue is what constitutes clinical neurological progression in a patient population where experienced clinicians can often pick up on very subtle changes that may be difficult to quantify and capture, the use of steroids complicating the picture further [32]. This difficulty led to the need to standardize clinical progression assessment with the Neurologic Assessment in Neuro-Oncology (NANO) scale, a standardized objective metric designed as an objective framework to measure neurological function in neuro-oncology [33]. NANO, a means to render the clinical findings more objective, reproducible, and quantifiable, became a necessity of robust classification. Incidentally, the capture of steroids initiation, discontinuation, and dose changes, particularly considering the need to taper and adjust based on clinical improvement or deterioration combined with the complexity of doing so in patients with varying levels of neurological detriment, is a challenge in and of itself. Pharmacy records are often available, but the data is nearly impossible to interpret in isolation, and capture is generally complex to achieve robustly outside of clinical trials (Table 1). Per It should be noted that NANO, the neurologic response would be classified as allows for response to be non-evaluable if it changes are potentially attributable to AIS more likely than not that factors other than underlying tumor presence or progression activity contributed to an observed change in neurologic function [33]. These Examples include changes in concurrent medications, especially corticosteroids, sedatives, narcotics [33]. The realization that steroids management needs to be robustly captured for this feature to be used as an endpoint led to the Response Assessment in Neuro-Oncology (RANO) Working Group effort to better define corticosteroid use endpoints in neuro-oncology brain tumor clinical trials [32]. This effort is ongoing. In the context of radiation therapy, despite increased emphasis on imaging, genomics, and computational approaches, the role of radiation therapy fields and correlation of imaging changes to isodose lines does not feature significantly [2,34-38]. Both pseudoprogression and tumor necrosis occur in the radiation therapy field [32]. The timing (pseudoprogression defined as appearance <5 months after radiotherapy vs. tumor necrosis > five months after RT) and imaging features, however, appear to be distinct and poorly understood as recent evidence examining clinical, radiographic, and histopathological data show [39]. Complexity is further added since it also appears that proton vs. photon RT may be exhibiting different contrast enhancement patterns following radiation therapy with a different timing and pseudoprogression pattern [27,40]. There is also increasing evidence that tumors "pseudo progress" differently based on their biology and management [2,24,27,40,41]. The sum of the above limitations is a universal clinical challenge with added patient anxiety, psychological uncertainty, and frustration on patients, families, and clinicians. Consults and follow-ups predicated on delivering the best care and sustaining hope struggle without clarity surrounding progression to offer the best management. These limitations raise several questions: if the MRI at 2-8 weeks' time point rarely if ever alters management, then patients want to understand why it is being performed. If MRI is the best option for determining when tumor progression has occurred, is the neuro-oncology field harnessing all the information MRI provides to the best ability? Are there potentially other means that may augment MRI findings to directly address these persistent clinical questions, e.g., biospecimen-driven biomarkers? Furthermore, is evolution possible without robust computational analysis endpoints embedded in clinical trials and real-world data collection? (Figure 1).

IS THE MRI THE BEST IMAGING MODALITY TO EXAMINE PROGRESSION VS. STABILITY, AND IS THE NEURO-ONCOLOGY FIELD HARNESSING ALL THE INFORMATION MRI PROVIDES TO OUR BEST ABILITY?

While current guidelines support the ongoing use of MRI for response assessment in glioma, they acknowledge both the lack of across-the-board accessibility and the concurrent use of other imaging modalities [28]. Standardized imaging protocols are proposed and generally implemented in Europe and North America [5]. MRI is the most likely imaging method available to patients in most North American and European clinical settings. Insignificant resource strained settings CT is still significantly in use. Novel imaging methods such as

MR, including spectroscopy, perfusion- imaging weighted MRI, Positron Emission Tomography/Computed Tomography (PET/CT), or Single-photon Emission Computerized Tomography (SPECT/CT) based on functional or molecular aspects are promising but not accessible to most patients [23,42]. With MRI, there are, however, limitations even in less resource strained settings which include lack of consistent imaging following surgical resection and variable timing depending on access to the scanner, the lack of further imaging in patients with early progression, significant comorbidities, or poor neurological function causing scan delays or making scans impossible. More imaging scans are being performed in younger patients with superior performance status upon suspicion of progression. These aspects can add significant bias to currently available data sets. The ability to fully harness the staggering amount of information embedded in MRI data sets is the subject of ongoing analyses. It is increasingly clear that enhanced T1-weighted MRI in isolation is unreliable [43]. As previously noted, T2 FLAIR changes initially not included in the Macdonald criteria were subsequently added in RANO; however, this was largely binary without a quantitative component (due to difficulty in measuring the extent of FLAIR signal and attributing its cause) and hence subjective[18] (Table 1). Novel advanced MRI techniques have been studied receive ongoing attention, but their accuracy is not well known. Recent evidence suggests that tumor volume may be superior for determining response assessment in LGGs due to more stable measures of tumor growth rates allowing for assessment of tumor growth over time with less variability, highest and possibly superior inter-reader agreement, and lowest reader discordance rates[44].The extent and alteration overtime of the T2 FLAIR signal remains a significant challenge in LGG since these tumors are non-enhancing upfront but is also pivotal in HGG since the T2 FLAIR signal is altered by radiation therapy as well other factors [18,22]. Recent evidence when analyzing longitudinal normalized FLAIR images using voxel-wise Parametric Response Mapping (PRM) to monitor volume fractions of increased, decreased, or unchanged altered FLAIR intensity, showed that PRMrFLAIR+ exceeding 10%, stratified patients for at risk of failure after 5.6 months ($p<0.0001$), while RANO criteria did not stratify these patients until 15.4 months ($p <0.0001$)[45]. Similarly, Gatson et al. used the T2 FLAIR signal to show that 75% of patients in their cohort developed progression on average 3.4 months before RANO-assessed progression with 84% sensitivity. T2 FLAIR signal intensity predicted for the neurological decline, significantly poorer outcomes for PFS (median, 10 vs. 15 months) and OS (median, 20 vs. 29 months) compared to SI-negative [46]. More complex MRI sequences derived quantitative parameters such as might be obtained from IVIM-DWI and 3D-ASL, including apparent diffusion coefficient (ADC), slow diffusion coefficient (D), fast diffusion coefficient (D*), perfusion fraction (f), and cerebral blood flow (CBF), remain the subject of ongoing investigations[47]. A recent meta-analysis defining the role of diffusion MRI-derived quantitative ADC identified six studies on this subject. It showed that ADC represents an effective approach that may be an exciting avenue for differentiation of glioma recurrence from progression and pseudo progression [48]. A recent publication showed that perfusion imaging with ASL-MRI can predict malignant progression within 12 months in patients with grade II glioma[33]. Another study showed that IVIM modeling of diffusion MRI during chemoradiation could predict therapeutic outcomes response in IDH wild type glioblastoma [49]. While all perfusion parameters measurements appear to be higher in patients with true disease progression, 3D pseudo-continuous arterial spin labeling (3D PCASL) and dynamic susceptibility contrast-enhanced (DSC). Perfusion MRI has revealed nearly equivalent performance for the differentiation of separating progressive disease and from pseudo progression. It appears that although 3D PCASL may be less sensitive to susceptibility susceptible to artifact [34].Existing guidelines do incorporate the use of MRI with additional sequences, including DWI and PWI, both supported by evidence in the context of progression vs. pseudo-progression[50]. These sequences, however, are not standardized between institutions, and reporting of findings based on these additional sequences is inconsistently performed. In a recent metanalysis, both DWI and PWIdiffusion and perfusion imaging provided optimal reasonable diagnostic performance in differentiating separating pseudo progression from true tumor progression in cerebral glioblastoma, but neither technique proved, although neither was superior[50]. Regarding functional imaging, there are challenges foremost with access and the interpretation of PET signal in the brain. A recent metanalysis identified that [18F]FET, [11C]MET, and [18F]FDOPA PET in combination with MRI showed promising results for improving accuracy in diagnosing tumor recurrence and was able to detect, detecting early treatment failure sooner, while and distinguishing between tumor progression and treatment-induced changes in patients with HGG treated effect in patients treated with bevacizumab[51]. Recent data shows that changes of 18F-FET PET parameters may be helpful to identify responders to adjuvant TMZ early after treatment initiation [52]. Although

these novel approaches are promising, they are less likely available to most patients and clinicians with data sets yet small and evolving. Future analysis as data is growing will likely allow for progress.

ARE THERE POTENTIALLY OTHER DATA SOURCES THAT MAY HELP ANSWER THE PROGRESSION QUESTION, E.G., BIOSPECIMEN DRIVEN BIOMARKERS?

The existing shortcomings of current response criteria have fostered ongoing efforts in researching biomarker avenues for progression [53]. Given the above discussion of the limitations of interpreting imaging concerning tumor progression, increasing emphasis is being placed on circulating biomarkers that may theoretically augment response criteria (Figure 2). A recent systematic review evaluated circulating biomarkers' differential expression and diagnostic accuracy for several outcomes. Including pseudoprogression, tumor progression, and radionecrosis, pseudoresponse in patients undergoing treatment for World Health Organization grades II-IV diffuse astrocytic and oligodendroglial tumors [54]. They identified 58 studies and 133 distinct biomarkers based on 1,853 patients across various treatment modalities. Fifteen markers for the response, progression, or stable disease and five markers for pseudoprogression or radionecrosis reached level IB. No biomarkers reached level IA, and only five studies contained data related to diagnostic accuracy measures. The authors noted that the overall methodological quality of included studies was low, with no biomarkers ready for clinical application identified [54]. A systematic review looking at combinations of MR imaging biomarkers including T1, T2, FLAIR, T1c, and perfusion-weighted and diffusion-weighted imaging (449 abstracts) showed that multi-parametric biomarkers could predict clinical outcomes in gliomas, particularly when linked to specific subcompartments of the tumors [55]. Promising evolving options involve liquid biopsy [56] in the form of blood draw, saliva, urine predicated on CSF based on tumor contents shed into the circulation, enabled by a leaky blood-brain barrier in glioma [57]. Examples of analyses based on liquid biopsy include research into: extracellular vesicles (EVs) (eg. serum exosomes)[54,58,59]; cellular markers (eg. circulating tumor cells (CTCs), platelets)[56,60]; circulating nucleic acids (eg. cell-free DNA (CfDNAs) [61], circulating tumor DNA (ctDNA) [62], and protein markers (e.g., hypermethylation)[8,63], all of which can allow for real-time monitoring and have been analyzed concerning response in glioma [54]. Hypermethylation, treatment, and survival are intertwined entities complicating imaging and biomarker analysis [64]. Recent data suggest that miR-21, -222, and -124-3p in serum exosomes may be useful to represent exciting new molecular biomarkers that can augment clinical evaluation of early tumor progression during post-surgical therapy in patients with HGGin glioma[58]. Multiple modality data aggregations with imaging can help identify cause/effect relationships between tumor biology and management and make these more analyzable to allow for earlier identification of progression.

In summary, several evolving avenues aim to identify biomarkers for progression at earlier time points, which may augment MRI interpretation. The clinical applicability of this evolving research area is undermined by a lack of sufficient tissue and the need for multiple testing of the same tissue, which further limits the available testing material. The use of heterogeneous and non-CLIA (Clinical Laboratory Improvement Amendments) approved analyses combined with the lack of tissue available upon recurrence and the transformation of tumors over time renders biospecimen-related conclusions static as the disease evolves in response to management. Thus, shortcomings persist, and although data sets in this space are growing, they remain small and heterogeneous. There is, however, increasing understanding that biomarkers that may be validated for one therapy may not carry over to other therapies and may be particularly challenging to interpret when patients undergo multiple treatments with a different mechanism of action, e.g., chemotherapy, and radiation, and potentially other agents including immunotherapy concurrently or separated in space and time. Concerning RT, a tumor volume target-based treatment modality, neither imaging changes nor molecular targeting have been implemented to address progression and adapt or optimize management. This raises whether every intervention should carry a robust biomarker to ensure management optimization and to what extent this is realistic. RT-related biomarkers are lacking[65,66], and efforts need to be made to grow from data mining to data farming despite data sharing and the complex interplay between management and specimen collection [60,67,68].

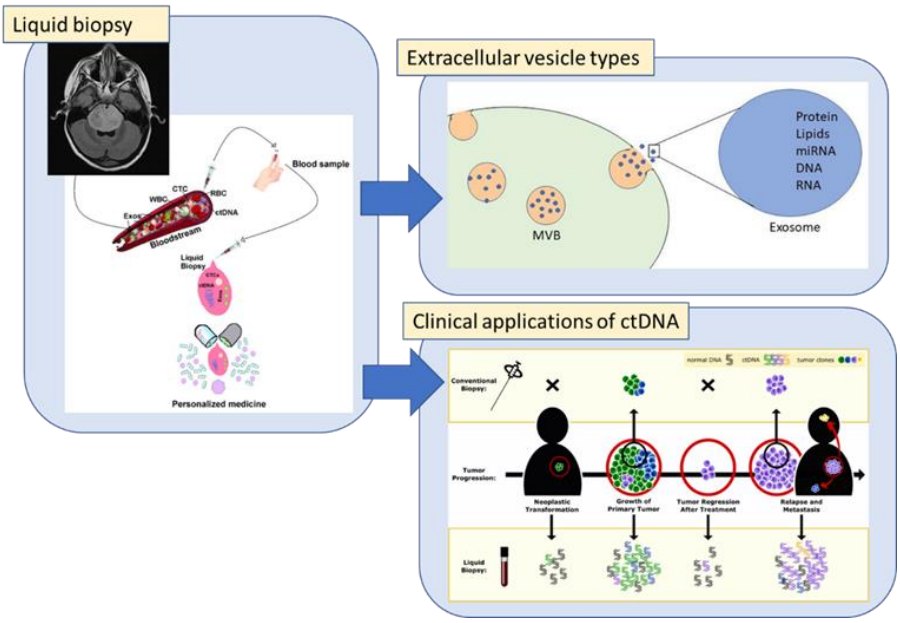

Figure 2. Circulating biomarkers in glioma with applicability to real-time response assessment[95-98]. Left panel: Liquid biopsy in blood draw with tumor contents shed into the circulation enabled by a leaky blood-brain barrier in glioma. Right upper panel: Example of analyses based on liquid biopsy, including research into extracellular vesicle types. Right lower panel: Clinical applications of circulating tumor DNA (ctDNA) in general oncology comparing conventional biopsy (upper) with liquid biopsy (lower) with sample collection (normal DNA, ctDNA, tumor clones) across the natural history of the malignancy from neoplastic transformation to growth of the primary tumor to tumor progression following treatment, to eventual metastasis.

IS ADVANCEMENT IN DEFINING GLIOMA PROGRESSION POSSIBLE WITHOUT COMPUTATIONAL ANALYSIS AND ROBUST ENDPOINTS EMBEDDED IN CLINICAL TRIALS AND REAL-WORLD DATA COLLECTION?

We would argue that based on the growth of available data, clinical imaging largely MRI based, specimen related data paralleled by the significant development of novel agents, defining glioma progression in terms of tumor dimensions or clinical deterioration is no longer realistic or likely to provide the much-needed clinical answers. Exact numbers for data growth in this space are lacking; however, evidence is mounting rapidly [6,12,55,69-72]. The how of data analysis has become the cornerstone of obtaining clinically meaningful results. Data is abundant and complex and often not consistently interpretable by humans (e.g., MRI ADC map or CBV). Machine learning has been widely applied to the processing of MRI data in glioma research and continues to reveal significant potential for clinical applicability. A recent systematic review analyzed the current state of machine learning applications to glioma MRI data by using machine learning for systematic review automation analysis [73]. Various data points were extracted from 153 studies wherein natural language processing (NLP) analysis was employed for keyword extraction, topic modeling, and document classification. The authors founds that machine learning has been applied to tumor grading and diagnosis, tumor segmentation, non-invasive genomic biomarker identification, detection of progression and patient survival prediction with model performance generally strong (AUC = 0.87 ± 0.09; sensitivity = 0.87 ± 0.10; specificity = 0.0.86 ± 0.10; precision = 0.88 ± 0.11)[73]. Top performers were convolutional neural networks, support vector machines, and random forest algorithms. They also notably pointed out that NLP and transfer learning resources enabled the successful development of a replicable method for automating the systematic review article screening process with the potential to increase the efficiency of data evaluation and clinical implementation. Liu et al. described a clinical study aimed at evaluating quantitative parameters from a number of novel imaging approaches for diagnostic performance of quantitative parameters obtained from IVIM-DWI and 3D-ASL, including apparent diffusion coefficient (ADC), slow diffusion coefficient (D), fast diffusion coefficient (D*), perfusion fraction (f), and cerebral blood flow (CBF)[47]. However, institutional results will not be generalizable without standardization of imaging acquisition.

Consistent data processing to allow for a "lowest common denominator" is needed when standardization is lacking. Large-scale data sets for training and testing are growing. This includes TCGA-GBM (617 GBM cases)[74], TCGA – LGG (199 cases)[75], Rembrandt/ open access Georgetown Database of Cancer (G-DOC) (671 cases)[76], GliomaDB[77] (amalgamates 21,086 samples from 4303 patients integrating multi-channel data from glioblastoma multiforme (GBM) and low-grade glioma (LGG) originating in The Cancer Genome Atlas (TCGA), Gene Expression Omnibus (GEO), the Chinese Glioma Genome Atlas (CGGA), the Memorial Sloan Kettering Cancer Center Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT), the US Food and Drug Administration (FDA), and PharmGKB). There is wide-ranging variability in the origin and period patients were treated how and what data is captured [74,75,77], which can significantly impact feature selection and results[12,26,71,78-80]. TCGA, for example, collects gender, ethnicity, methylation status, age at diagnosis, and vital status but has limited resection status information or information on the administration of therapeutic agents, the treatment intent, or the details of radiation therapy administration). We are now seeing very promising CI for many analyses but whether these can be replicated in large data sets or with different institutional data remains unclear, with some approaches proving unstable [81]. Since there are many avenues of feature selection, deep learning, and approaches that combine with limited validation, there is an ongoing lack of clinical confidence as the field progresses. Superior confidence indexes are often reported on [82], but validation is often not published, or results are difficult to replicate for many approaches. This reflects the use of smaller institutionally curated data sets and may be mitigated using federated learning [83]. When examining the multifaceted challenges embedded in glioma progression criteria, data would need consistent acquisition, processing, and analysis with successful approaches that can be cross-validated to achieve success. Federated approaches are growing [10, 83-85], but problems persist with data heterogeneity, a notable lack of RT data use to allow for progression analysis, and a lack of publicly available RT data sets. Radiology reporting is inconsistent, and although NLP may allow for more in-depth data mining, it could also add further bias as we work towards biomarker development.

CONCLUSION

In conclusion, our data suggest that CIP is an independent and strong prognostic factor in MM that should be included in the baseline workup and monitoring of both NDMM and SMM. When IP is measured by conventional methods (CIP), it is present in most patients at the moment of diagnosis, and it is associated with a higher tumor burden. Despite this, we recommend that more specific alternatives such as the HLC assay should be used instead. The immune profiling may play a crucial role in the outcome of MM [19], but probably only a complete immune evaluation will successfully predict survival in MM patients [20].

REFERENCES

[1] Bera K, Braman N, Gupta A, Velcheti V, Madabhushi A. Predicting cancer outcomes with radiomics and artificial intelligence in radiology. Nat Rev Clin Oncol. 2021;19:132–46. https://doi.org/10.1038/s41571-021-00560-7

[2] Abdalla G, Hammam A, Anjari M, D'Arco DrF, Bisdas DrS. Glioma surveillance imaging: current strategies, shortcomings, challenges and outlook. BJR Open. 2020;2(1):20200009. https://doi.org/10.1259/bjro.20200009

[3] 3Leao DJ, Craig PG, Godoy LF, Leite CC, Policeni B. Response Assessment in Neuro-Oncology Criteria for Gliomas: Practical Approach Using Conventional and Advanced Techniques. Am J Neuroradiol. 2019;41(1):10–20. https://doi.org/10.3174/ajnr.a6358

[4] Ellingson BM, Sampson J, Achrol AS, Aghi MK, Bankiewicz K, Wang C, et al. Modified RANO, Immunotherapy RANO, and Standard RANO Response to Convection-Enhanced Delivery of IL4R-Targeted Immunotoxin MDNA55 in Recurrent Glioblastoma. Clin Cancer Res. 2021;27(14):3916–25. https://doi.org/10.1158/1078-0432.ccr-21-0446

[5] Ellingson BM, Wen PY, Cloughesy TF. Modified Criteria for Radiographic Response Assessment in Glioblastoma Clinical Trials. Neurotherapeutics. 2017;14(2):307–20. https://doi.org/10.1007/s13311-016-0507-6

[6] 6Brennan Cameron W, Verhaak Roel GW, McKenna A, Campos B, Noushmehr H, Salama Sofie R, et al. The Somatic Genomic Landscape of Glioblastoma. Cell. 2013;155(2):462–77. https://doi.org/10.1016/j.cell.2013.09.034

[7] Echle A, Rindtorff NT, Brinker TJ, Luedde T, Pearson AT, Kather JN. Deep learning in cancer pathology: a new generation of clinical biomarkers. Br J Cancer. 2020;124(4):686–96. https://doi.org/10.1038/s41416-020-01122-x

[8] Klughammer J, Kiesel B, Roetzer T, Fortelny N, Nemc A, Nenning K-H, et al. The DNA methylation landscape of glioblastoma disease progression shows extensive heterogeneity in time and space. Nat Med. 2018;24(10):1611–24. https://doi.org/10.1038/s41591-018-0156-x

[9] Lombardi G, Barresi V, Castellano A, Tabouret E, Pasqualetti F, Salvalaggio A, et al. Clinical Management of Diffuse Low-Grade Gliomas. Cancers. 2020;12(10):3008. https://doi.org/10.3390/cancers12103008

[10] Zwanenburg A, Vallières M, Abdalah MA, Aerts HJWL, Andrearczyk V, Apte A, et al. The Image Biomarker Standardization Initiative: Standardized Quantitative Radiomics for High-Throughput Image-based Phenotyping. Radiology. 2020;295(2):328–38. https://doi.org/10.1148/radiol.2020191145

[11] Booth CM, Goodman AM. Practicing on the edge of oncology: when standard of care feels uncomfortable. Nat Rev Clin Oncol. 2021;18(11):673–4. https://doi.org/10.1038/s41571-021-00550-9

[12] Booth TC, Williams M, Luis A, Cardoso J, Ashkan K, Shuaib H. Machine learning and glioma imaging biomarkers. Clin Radiol. 2020;75(1):20–32. https://doi.org/10.1016/j.crad.2019.07.001

[13] Johnson DR, Guerin JB, Ruff MW, Fang S, Hunt CH, Morris JM, et al. Glioma response assessment: Classic pitfalls, novel confounders, and emerging imaging tools. Br J Radiol. 2019;92(1094):20180730. https://doi.org/10.1259/bjr.20180730

[14] Harrison RA, Ou A, Naqvi SMAA, Naqvi SM, Weathers SS, O'Brien BJ, et al. Aggressiveness of care at end of life in patients with high-grade glioma. Cancer Med. 2021;10(23):8387–94. https://doi.org/10.1002/cam4.4344

[15] Ko C-C, Yeh L-R, Kuo Y-T, Chen J-H. Imaging biomarkers for evaluating tumor response: RECIST and beyond. Biomark Res. 2021;9(1). https://doi.org/10.1186/s40364-021-00306-8

[16] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228–47. https://doi.org/10.1016/j.ejca.2008.10.026

[17] Macdonald DR, Cascino TL, Schold SC, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol. 1990;8(7):1277–80. https://doi.org/10.1200/jco.1990.8.7.1277

[18] Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, et al. Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group. J Clin Oncol. 2010;28(11):1963–72. https://doi.org/10.1200/jco.2009.26.3541

[19] Eisele SC, Wen PY, Lee EQ. Assessment of Brain Tumor Response: RANO and Its Offspring. Curr Treat Options Oncol. 2016;17(7). https://doi.org/10.1007/s11864-016-0413-5

[20] Galanis E, Wu W, Cloughesy T, Lamborn K, Mann B, Wen PY, et al. Phase 2 trial design in neuro-oncology revisited: a report from the RANO group. Lancet Oncol. 2012;13(5):e196–204. https://doi.org/10.1016/s1470-2045(11)70406-5

[21] Huang RY, Rahman R, Ballman KV, Felten SJ, Anderson SK, Ellingson BM, et al. The Impact of T2/FLAIR Evaluation per RANO Criteria on Response Assessment of Recurrent Glioblastoma Patients Treated with Bevacizumab. Clin Cancer Res. 2015;22(3):575–81. https://doi.org/10.1158/1078-0432.ccr-14-3040

[22] Chukwueke UN, Wen PY. Use of the Response Assessment in Neuro-Oncology (RANO) criteria in clinical trials and clinical practice. CNS Oncol. 2019;8(1):CNS28. https://doi.org/10.2217/cns-2018-0007

[23] Bolcaen J, Kleynhans J, Nair S, Verhoeven J, Goethals I, Sathekge M, et al. A perspective on the radiopharmaceutical requirements for imaging and therapy of glioblastoma. Theranostics. 2021;11(16):7911–47. https://doi.org/10.7150/thno.56639

[24] Le Fèvre C, Lhermitte B, Ahle G, Chambrelant I, Cebula H, Antoni D, et al. Pseudoprogression versus true progression in glioblastoma patients: A multiapproach literature review. Crit Rev Oncol Hematol. 2021;157:103188. https://doi.org/10.1016/j.critrevonc.2020.103188

[25] Patrizz A, Dono A, Zhu P, Tandon N, Ballester LY, Esquenazi Y. Tumor recurrence or treatment-related changes following chemoradiation in patients with glioblastoma: does pathology predict outcomes? J Neurooncol. 2021;152(1):163–72. https://doi.org/10.1007/s11060-020-03690-7

[26] Akbari H, Rathore S, Bakas S, Nasrallah MP, Shukla G, Mamourian E, et al. Histopathology-validated machine learning radiographic biomarker for noninvasive discrimination between true progression and pseudo-progression in glioblastoma. Cancer. 2020;126(11):2625–36. https://doi.org/10.1002/cncr.32790

[27] Bronk JK, Guha-Thakurta N, Allen PK, Mahajan A, Grosshans DR, McGovern SL. Analysis of pseudoprogression after proton or photon therapy of 99 patients with low grade and anaplastic glioma. Clin Transl Radiat Oncol. 2018;9:30–4. https://doi.org/10.1016/j.ctro.2018.01.002

[28] Nabors LB, Portnow J, Ahluwalia M, Baehring J, Brem H, Brem S, et al. Central Nervous System Cancers, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2020;18(11):1537–70. https://doi.org/10.6004/jnccn.2020.0052

[29] Mellinghoff IK, Penas-Prado M, Peters KB, Burris HA, Maher EA, Janku F, et al. Vorasidenib, a dual inhibitor of mutant IDH1/2, in recurrent or progressive glioma; Results of a first-in-human Phase I trial. Clin Cancer Res. 2021;27(16):4491–9. https://doi.org/10.1158/1078-0432.CCR-21-0611

[30] van den Bent M, Wefel J, Schiff D, Taphoorn M, Jaeckle K, Junck L, et al. Response assessment in neuro-oncology (a report of the RANO group): assessment of outcome in trials of diffuse low-grade gliomas. Lancet Oncol. 2011;12(6):583–93. https://doi.org/10.1016/s1470-2045(11)70057-2

[31] Okada H, Weller M, Huang R, Finocchiaro G, Gilbert MR, Wick W, et al. Immunotherapy response assessment in neuro-oncology: a report of the RANO working group. Lancet Oncol. 2015;16(15):e534–42. https://doi.org/10.1016/s1470-2045(15)00088-1

[32] Arvold ND, Armstrong TS, Warren KE, Chang SM, DeAngelis LM, Blakeley J, et al. Corticosteroid use endpoints in neuro-oncology: Response Assessment in Neuro-Oncology Working Group. Neuro Oncol. 2018;20(7):897–906. https://doi.org/10.1093/neuonc/noy056

[33] Nayak L, DeAngelis LM, Brandes AA, Peereboom DM, Galanis E, Lin NU, et al. The Neurologic Assessment in Neuro-Oncology (NANO) scale: a tool to assess neurologic function for integration into the Response Assessment in Neuro-Oncology (RANO) criteria. Neuro Oncol. 2017;19(5):625–35. https://doi.org/10.1093/neuonc/nox029

[34] Brothwell MRS, West CM, Dunning AM, Burnet NG, Barnett GC. Radiogenomics in the Era of Advanced Radiotherapy. Clin Oncol. 2019;31(5):319–25. https://doi.org/10.1016/j.clon.2019.02.006

[35] El Naqa I, Kerns SL, Coates J, Luo Y, Speers C, West CML, et al. Radiogenomics and radiotherapy response modeling. Phys Med Biol. 2017;62(16):R179–206. https://doi.org/10.1088/1361-6560/aa7c55

[36] El Naqa I, Pandey G, Aerts H, Chien J-T, Andreassen CN, Niemierko A, et al. Radiation Therapy Outcomes Models in the Era of Radiomics and Radiogenomics: Uncertainties and Validation Int J Radiat Oncol Biol Phys. 2018;102(4):1070–3. https://doi.org/10.1016/j.ijrobp.2018.08.022

[37] Kerns SL, Chuang K-H, Hall W, Werner Z, Chen Y, Ostrer H, et al. Radiation biology and oncology in the genomic era. Br J Radiol. 2018;91(1091):20170949. https://doi.org/10.1259/bjr.20170949

[38] Kocher M, Ruge MI, Galldiks N, Lohmann P. Applications of radiomics and machine learning for radiotherapy of malignant brain tumors. Strahlenther Onkol. 2020;196(10):856–67. https://doi.org/10.1007/s00066-020-01626-8

[39] Winter SF, Vaios EJ, Muzikansky A, Martinez-Lage M, Bussière MR, Shih HA, et al. Defining Treatment-Related Adverse Effects in Patients with Glioma: Distinctive Features of Pseudoprogression and Treatment-Induced Necrosis. Oncologist. 2020;25(8):e1221–32. https://doi.org/10.1634/theoncologist.2020-0085

[40] Ritterbusch R, Halasz LM, Graber JJ. Distinct imaging patterns of pseudoprogression in glioma patients following proton versus photon radiation therapy. J Neurooncol. 2021;152(3):583–90. https://doi.org/10.1007/s11060-021-03734-6

[41] Kebir S, Khurshid Z, Gaertner FC, Essler M, Hattingen E, Fimmers R, et al. Unsupervised consensus cluster analysis of [18F]-fluoroethyl-L-tyrosine positron emission tomography identified textural features for the diagnosis of pseudoprogression in high-grade glioma. Oncotarget. 2016;8(5):8294–304. https://doi.org/10.18632/oncotarget.14166

[42] Galldiks N, Lohmann P, Albert NL, Tonn JC, Langen K-J. Current status of PET imaging in neuro-oncology. Neurooncol Adv. 2019;1(1). https://doi.org/10.1093/noajnl/vdz010

[43] van Dijken BRJ, van Laar PJ, Holtman GA, van der Hoorn A. Diagnostic accuracy of magnetic resonance imaging techniques for treatment response evaluation in patients with high-grade glioma, a systematic review and meta-analysis. Eur Radiol. 2017;27(10):4129–44. https://doi.org/10.1007/s00330-017-4789-9

[44] Huang RY, Young RJ, Ellingson BM, Veeraraghavan H, Wang W, Tixier F, et al. Volumetric analysis of IDH-mutant lower-grade glioma: a natural history study of tumor growth rates before and after treatment. Neuro Oncol. 2020;22(12):1822–30. https://doi.org/10.1093/neuonc/noaa105

[45] Hoff BA, Lemasson B, Chenevert TL, Luker GD, Tsien CI, Amouzandeh G, et al. Parametric Response Mapping of FLAIR MRI Provides an Early Indication of Progression Risk in Glioblastoma. Acad Radiol. 2021;28(12):1711–20. https://doi.org/10.1016/j.acra.2020.08.015

[46] Gatson NTN, Bross SP, Odia Y, Mongelluzzo GJ, Hu Y, Lockard L, et al. Early imaging marker of progressing glioblastoma: a window of opportunity. J Neurooncol. 2020;148(3):629–40. https://doi.org/10.1007/s11060-020-03565-x

[47] Liu Z-C, Yan L-F, Hu Y-C, Sun Y-Z, Tian Q, Nan H-Y, et al. Combination of IVIM-DWI and 3D-ASL for differentiating true progression from pseudoprogression of Glioblastoma multiforme after concurrent chemoradiotherapy: study protocol of a prospective diagnostic trial. BMC Med Imaging. 2017;17(1). https://doi.org/10.1186/s12880-017-0183-y

[48] Yu Y, Ma Y, Sun M, Jiang W, Yuan T, Tong D. Meta-analysis of the diagnostic performance of diffusion magnetic resonance imaging with apparent diffusion coefficient measurements for

differentiating glioma recurrence from pseudoprogression. Medicine. 2020;99(23):e20270. https://doi.org/10.1097/md.0000000000020270

[49] Jabehdar Maralani P, Myrehaug S, Mehrabian H, Chan AKM, Wintermark M, Heyn C, et al. Intravoxel incoherent motion (IVIM) modeling of diffusion MRI during chemoradiation predicts therapeutic response in IDH wildtype glioblastoma. Radiother Oncol. 2021;156:258–65. https://doi.org/10.1016/j.radonc.2020.12.037

[50] Tsakiris C, Siempis T, Alexiou GA, Zikou A, Sioka C, Voulgaris S, et al. Differentiation Between True Tumor Progression of Glioblastoma and Pseudoprogression Using Diffusion-Weighted Imaging and Perfusion-Weighted Imaging: Systematic Review and Meta-analysis. World Neurosurg. 2020;144:e100–9. https://doi.org/10.1016/j.wneu.2020.07.218

[51] Hughes KL, O'Neal CM, Andrews BJ, Westrup AM, Battiste JD, Glenn CA. A systematic review of the utility of amino acid PET in assessing treatment response to bevacizumab in recurrent high-grade glioma. Neurooncol Adv. 2021;3(1). https://doi.org/10.1093/noajnl/vdab003

[52] Ceccon G, Lohmann P, Werner J-M, Tscherpel C, Dunkl V, Stoffels G, et al. Early treatment response assessment using 18F-FET PET compared to contrast-enhanced MRI in glioma patients following adjuvant temozolomide chemotherapy. J Nucl Med. 2020;62(7):918–25. https://doi.org/10.2967/jnumed.120.254243

[53] Kan LK, Drummond K, Hunn M, Williams D, O'Brien TJ, Monif M. Potential biomarkers and challenges in glioma diagnosis, therapy and prognosis. BMJ Neurol Open. 2020;2(2):e000069. https://doi.org/10.1136/bmjno-2020-000069

[54] Raza IJ, Tingate CA, Gkolia P, Romero L, Tee JW, Hunn MK. Blood Biomarkers of Glioma in Response Assessment Including Pseudoprogression and Other Treatment Effects: A Systematic Review. Front Oncol. 2020;10:1191. https://doi.org/10.3389/fonc.2020.01191

[55] Oltra-Sastre M, Fuster-Garcia E, Juan-Albarracin J, Sáez C, Perez-Girbes A, Sanz-Requena R, et al. Multi-parametric MR Imaging Biomarkers Associated to Clinical Outcomes in Gliomas: A Systematic Review. Curr Med Imaging Rev. 2019;15(10):933–47. https://doi.org/10.2174/1573405615666190109100503

[56] Dianat-Moghadam H, Azizi M, Eslami-S Z, Cortés-Hernández LE, Heidarifard M, Nouri M, et al. The Role of Circulating Tumor Cells in the Metastatic Cascade: Biology, Technical Challenges, and Clinical Relevance. Cancers. 2020;12(4):867. https://doi.org/10.3390/cancers12040867

[57] Almutairi MMA, Gong C, Xu YG, Chang Y, Shi H. Factors controlling permeability of the blood–brain barrier. Cell Mol Life Sci. 2015;73(1):57–77. https://doi.org/10.1007/s00018-015-2050-8

[58] Olioso D, Caccese M, Santangelo A, Lippi G, Zagonel V, Cabrini G, et al. Serum Exosomal microRNA-21, 222 and 124-3p as Noninvasive Predictive Biomarkers in Newly Diagnosed High-Grade Gliomas: A Prospective Study. Cancers. 2021;13(12):3006. https://doi.org/10.3390/cancers13123006

[59] Tankov S, Walker PR. Glioma-Derived Extracellular Vesicles – Far More Than Local Mediators. Front Immunol. 2021;12:679954. https://doi.org/10.3389/fimmu.2021.679954

[60] Jelski W, Mroczko B. Molecular and Circulating Biomarkers of Brain Tumors. Int J Mol Sci. 2021;22(13):7039. https://doi.org/10.3390/ijms22137039

[61] Mouliere F, Smith CG, Heider K, Su J, Pol Y, Thompson M, et al. Fragmentation patterns and personalized sequencing of cell-free DNA in urine and plasma of glioma patients. EMBO Mol Med. 2021;13(8):e12881. https://doi.org/10.15252/emmm.202012881

[62] Yu J, Sheng Z, Wu S, Gao Y, Yan Z, Bu C, et al. Tumor DNA From Tumor In Situ Fluid Reveals Mutation Landscape of Minimal Residual Disease After Glioma Surgery and Risk of Early Recurrence. Front Oncol. 2021 Oct 11;11:742037. https://doi.org/10.3389/fonc.2021.742037

[63] Maros ME, Capper D, Jones DTW, Hovestadt V, von Deimling A, Pfister SM, et al. Machine learning workflows to estimate class probabilities for precision cancer diagnostics on DNA methylation microarray data. Nat Protoc. 2020;15(2):479–512. https://doi.org/10.1038/s41596-019-0251-6

[64] Seidlitz A, Beuthien-Baumann B, Löck S, Jentsch C, Platzek I, Zöphel K, et al. Final Results of the Prospective Biomarker Trial PETra: [11C]-MET-Accumulation in Postoperative PET/MRI Predicts Outcome after Radiochemotherapy in Glioblastoma. Clin Cancer Res. 2020;27(5):1351–60. https://doi.org/10.1158/1078-0432.ccr-20-1775

[65] McGee KP, Hwang K, Sullivan DC, Kurhanewicz J, Hu Y, Wang J, et al. Magnetic resonance biomarkers in radiation oncology: The report of AAPM Task Group 294. Med Phys. 2021;48(7):e697–732. https://doi.org/10.1002/mp.14884

[66] McGee KP, Tyagi N, Bayouth JE, Cao M, Fallone BG, Glide-Hurst CK, et al. Findings of the AAPM Ad Hoc committee on magnetic resonance imaging in radiation therapy: Unmet needs, opportunities, and recommendations. Med Phys. 2021;48(8):4523–31. https://doi.org/10.1002/mp.14996

[67] Mathios D, Phallen J. Circulating Biomarkers in Glioblastoma. Cancer J. 2021;27(5):404–9. https://doi.org/10.1097/ppo.0000000000000541

[68] Eibl RH, Schneemann M. Liquid Biopsy and Primary Brain Tumors. Cancers. 2021;13(21):5429. https://doi.org/10.3390/cancers13215429

[69] Sobhani F, Robinson R, Hamidinekoo A, Roxanis I, Somaiah N, Yuan Y. Artificial intelligence and digital pathology: Opportunities and implications for immuno-oncology. Biochim Biophys Acta Rev Cancer. 2021;1875(2):188520. https://doi.org/10.1016/j.bbcan.2021.188520

[70] Willems SM, Abeln S, Feenstra KA, de Bree R, van der Poel EF, Baatenburg de Jong RJ, et al. The potential use of big data in oncology. Oral Oncol. 2019;98:8–12. https://doi.org/10.1016/j.oraloncology.2019.09.003

[71] Beig N, Bera K, Tiwari P. Introduction to radiomics and radiogenomics in neuro-oncology: implications and challenges. Neurooncol Adv. 2020;2(Supplement_4):iv3–14. https://doi.org/10.1093/noajnl/vdaa148

[72] Shui L, Ren H, Yang X, Li J, Chen Z, Yi C, et al. The Era of Radiogenomics in Precision Medicine: An Emerging Approach to Support Diagnosis, Treatment Decisions, and Prognostication in Oncology. Front Oncol. 2021;10:570465. https://doi.org/10.3389/fonc.2020.570465

[73] Buchlak QD, Esmaili N, Leveque J-C, Bennett C, Farrokhi F, Piccardi M. Machine learning applications to neuroimaging for glioma detection and classification: An artificial intelligence augmented systematic review. J Clin Neurosci. 2021;89:177–98. https://doi.org/10.1016/j.jocn.2021.04.043

[74] TCGA-GBM - The Cancer Imaging Archive (TCIA) Public Access - Cancer Imaging Archive Wiki. [Accessed 2021 Nov 23]. Available from: https://wiki.cancerimagingarchive.net/display/Public/TCGA-GBM

[75] TCGA-LGG - The Cancer Imaging Archive (TCIA) Public Access - Cancer Imaging Archive Wiki. [Accessed 2021 Nov 23]. Available from: https://wiki.cancerimagingarchive.net/display/Public/TCGA-LGG

[76] Gusev Y, Bhuvaneshwar K, Song L, Zenklusen J-C, Fine H, Madhavan S. The REMBRANDT study, a large collection of genomic data from brain cancer patients. Sci Data. 2018;5:180158. https://doi.org/10.1038/sdata.2018.158

[77] Yang Y, Sui Y, Xie B, Qu H, Fang X. GliomaDB: A Web Server for Integrating Glioma Omics Data and Interactive Analysis. Genomics Proteomics Bioinformatics. 2019;17(4):465–71. https://doi.org/10.1016/j.gpb.2018.03.008

[78] Ismail M, Hill V, Statsevych V, Huang R, Prasanna P, Correa R, et al. Shape Features of the Lesion Habitat to Differentiate Brain Tumor Progression from Pseudoprogression on Routine Multiparametric MRI: A Multisite Study. Am J Neuroradiol. 2018;39(12):2187–93. https://doi.org/10.3174/ajnr.a5858

[79] Kim JY, Park JE, Jo Y, Shim WH, Nam SJ, Kim JH, et al. Incorporating diffusion- and perfusion-weighted MRI into a radiomics model improves diagnostic performance for pseudoprogression in glioblastoma patients. Neuro Oncol. 2018;21(3):404–14. https://doi.org/10.1093/neuonc/noy133

[80] Lao J, Chen Y, Li Z-C, Li Q, Zhang J, Liu J, et al. A Deep Learning-Based Radiomics Model for Prediction of Survival in Glioblastoma Multiforme. Scientific Reports. 2017;7(1):10353.

[81] Loureiro H, Becker T, Bauer-Mehren A, Ahmidi N, Weberpals J. Artificial Intelligence for Prognostic Scores in Oncology: a Benchmarking Study. Front Artif Intell. 2021;4:625573. https://doi.org/10.3389/frai.2021.625573

[82] Jiang H, Yu K, Li M, Cui Y, Ren X, Yang C, et al. Classification of Progression Patterns in Glioblastoma: Analysis of Predictive Factors and Clinical Implications. Front Oncol. 2020;10:590648. https://doi.org/10.3389/fonc.2020.590648

[83] Sheller MJ, Edwards B, Reina GA, Martin J, Pati S, Kotrotsou A, et al. Federated learning in medicine: facilitating multi-institutional collaborations without sharing patient data. Sci Rep. 2020;10(1):12598. https://doi.org/10.1038/s41598-020-69250-1

[84] Davatzikos C, Barnholtz-Sloan JS, Bakas S, Colen R, Mahajan A, Quintero CB, et al. AI-based prognostic imaging biomarkers for precision neuro-oncology: the ReSPOND consortium. Neuro Oncol. 2020;22(6):886–8. https://doi.org/10.1093/neuonc/noaa045

[85] Rathore S, Mohan S, Bakas S, Sako C, Badve C, Pati S, et al. Multi-institutional noninvasive in vivo characterization of *IDH*, 1p/19q, and EGFRvIII in glioma using neuro-Cancer Imaging Phenomics Toolkit (neuro-CaPTk). Neurooncol Adv. 2020;2:iv22–34. https://doi.org/10.1093/noajnl/vdaa128

[86] Kalinin M. Glioma of the left parietal lobe. CT scan with contrast enhancement. 2009 [Accessed 2021 Nov 29]. Available from: https://commons.wikimedia.org/wiki/File:Glioma.gif

[87] Neurochirurgica A. MRI Image of a Glioblastoma before and after surgery. [Accessed 2021 Nov 29]. Available from: https://commons.wikimedia.org/wiki/File:Glioblastom_(WHO_Grad_IV)_im_MRI_praeoperativ_und_postoperativ.png

[88] Dilmen N. Low Grade brain glioma. [Accessed 2021 Nov 29]. Available from: https://commons.wikimedia.org/wiki/File:Brain_MRI_glioma_112.jpg

[89] RadsWiki. Oligodendroglioma, MRI T1 (left), MRI T2 (right) with gadolinium contrast. [Accessed 2021 Nov 29]. Available from: https://commons.wikimedia.org/wiki/File:Oligodendroglioma_009_006.jpg

[90] Dilmen N. Diffusion MRI images. Colored by direction of diffusion.. [Accessed 2021 Nov 29]. Available from: https://commons.wikimedia.org/wiki/File:Diffusion_MRI_22-37-52_nevit.jpg

[91] TattwamasiB. Brain PET CT with various agents – Tumor. [Accessed 2021 Nov 29]. Available from: https://commons.wikimedia.org/wiki/File:PET_CT_in_Management_of_Patients.jpg

[92] Mschocke. MRS Brainstem Glioma. [Accessed 2021 Nov 29]. Available from: https://commons.wikimedia.org/wiki/File:Mrs_brainstem_glioma.png

[93] Gigandet X , H.P., Kurant M,Cammoun L, Meuli R, Thiran JP. Estimating the Confidence Level of White Matter Connections Obtained with MRI Tractography. [Accessed 2021 Nov 29]. Available from: https://commons.wikimedia.org/wiki/File:White_Matter_Connections_Obtained_with_MRI_Tractography.png

[94] Tanter TD Charlie Demene, Mathieu Pernot, Mickael. Main brain functional imaging techniques on a three-axis chart (temporal resolution, spatial resolution, portability). [Accessed 2021 Nov 29]. Available from: https://commons.wikimedia.org/wiki/File:Main_brain_functional_imaging_technique_resolutions.svg

[95] Tdvorak. Brain stem glioma. MRI axial, with contrast. [Accessed 2021 Nov 29]. Available from: https://commons.wikimedia.org/wiki/File:Tumor_BrainstemGlioma1.JPG

[96] D'Agnano I, B.A.C. Extracellular Vesicles, A Possible Theranostic Platform Strategy for Hepatocellular Carcinoma—An Overview. [Accessed 2021 Nov 29]. Available from: https://commons.wikimedia.org/wiki/File:Graphical_scheme_of_the_possible_therapeutic_platform_that_translates_EVs_for_liquid_biopsy_and_drug_delivery_in_the_scenario_of_personalized_medicine.png

[97] Kalamedits. Eexosomes are 30-150 nm extracellular vesicle containing various cargoes like RNA and proteins. [Accessed 2021 Nov 29]. Available from: https://commons.wikimedia.org/wiki/File:Exosome_kalamedits.jpg

[98] Anmery. Clinical applications of ctDNA. [Accessed 2021 Nov 29]. Available from: https://commons.wikimedia.org/wiki/File:Clinical_applications_of_ctDNA.png