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Integrating multi-modal imaging in radiation treatments for glioblastoma

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Abstract

Advances in diagnostic and treatment technology along with rapid developments in translational research may now allow the realization of precision radiotherapy. Integration of biologically informed multimodality imaging to address the spatial and temporal heterogeneity underlying treatment resistance in glioblastoma is now possible for patient care, with evidence of safety and potential benefit. Beyond their diagnostic utility, several candidate imaging biomarkers have emerged in recent early-phase clinical trials of biologically based radiotherapy, and their definitive assessment in multicenter prospective trials is already in development. In this review, the rationale for clinical implementation of candidate advanced magnetic resonance imaging and positron emission tomography imaging biomarkers to guide personalized radiotherapy, the current landscape, and future directions for integrating imaging biomarkers into radiotherapy for glioblastoma are summarized. Moving forward, response-adaptive radiotherapy using biologically informed imaging biomarkers to address emerging treatment resistance in rational combination with novel systemic therapies may ultimately permit improvements in glioblastoma outcomes and true individualization of patient care.

Keywords

glioblastoma | MRI | PET | radiomics | radiotherapy

Radiation therapy remains a backbone of treatment for glioblastoma (GBM), and is one of very few therapies to improve survival in this lethal disease.[1] With increasing knowledge regarding the biologic factors underlying treatment resistance, incorporation of advanced imaging modalities capable of interrogating tumor biology and associated imaging phenotypes remains an area of unmet need. While advances in molecular and genomic analysis of GBM through pathologic and cerebrospinal fluid studies will continue to elucidate the biologic underpinnings and help advance therapies in this disease, these methods lack the ability to spatially and anatomically assess tumor heterogeneity and to differentially direct local therapies. Until recently, various multimodal imaging techniques assessing aspects of tumor metabolism, microenvironment, and factors associated with tumor growth/proliferation have been primarily investigated for their prognostic utility in patients with GBM. Tumor characteristics identified with advanced magnetic resonance imaging (MRI) and positron emission tomography (PET) incorporated into the diagnostic assessment of patients with suspected malignant gliomas have been associated with survival, and response in biologic tumor volumes has been associated with improved outcomes in several studies.[2–7] More recently, advanced MRI has been incorporated into prospective glioma clinical trials to guide patient-specific radiotherapy. Combined with recent evidence for the integration of advanced PET into the radiation treatment of glioblastoma, this review outlines the history, current status, and future landscape of biologically informed precision radiotherapy in the treatment of GBM.

Rationale for Multi-Modal Imaging in Radiation Treatments

For at least the past 4 decades, radiation therapy for GBM has focused on treatment of gadolinium-enhancing tumor

volumes identified by standard anatomic MRI consisting of T1-weighted gadolinium enhanced, and T2-weighted fluid-attenuated inversion recovery (FLAIR) images. Enhancing tumor regions have been presumed to represent the most aggressive and biologically relevant regions of disease.[8–10] Standard surgical approaches aim for maximal safe resection primarily of enhancing areas of tumor, and efforts to intensify radiation therapy have similarly been focused on dose-escalation to regions of contrast enhancement.[11,12] In a single institution phase I/II dose-escalation trial utilizing anatomic MRI to define the enhancing tumor target, an alteration in patterns of failure was observed, with evidence for decreased central (in-field) failures with increasing radiation dose, suggesting the potential to alter the natural history of GBM, in which the vast majority of recurrences occur in-field following standard therapy.[12]

Still, the presence of non-contrast-enhancing tumors is well-established and underscores the need for improved imaging to optimize tumor target delineation and treatment.[13] Numerous studies demonstrate that incomplete resection or inadequate radiation coverage of biologically relevant non-enhancing disease is associated with worse outcomes.[14] Tumor unrecognized by anatomic MRI and identified using diffusion-weighted (DW) MRI, elevated cerebral blood volume (CBV) maps derived from perfusion MRI, and 11C-Methionine PET imaging are associated with tumor recurrence, and worse progression-free (PFS) and overall survival (OS).[15–17]

Radiotherapy dose-escalation for GBM is an area of controversy due to mixed results in the literature, but incorporation of advanced imaging to specifically guide treatment has not been explored with this therapeutic approach. While smaller previous studies appeared to show promise for dose-escalation for GBM, initial reporting of outcomes from the randomized phase 3 NRG BN-001 trial did not show improvements in either progression-free or overall survival with photon-based radiation dose-escalation for GBM.[11,12,18] However, this study only utilized anatomic MR imaging, and recent phase II studies incorporating advanced imaging to guide radiation therapy demonstrate a potential avenue to improve the therapeutic ratio of this treatment approach.[19,20] To date, the utility of advanced imaging to guide patient-specific radiotherapy has not been assessed in the cooperative group setting, and whether targeting biologically relevant, and especially non-enhancing diseases using advanced technologies will improve outcomes in patients with GBM remains an unanswered question. Results from recent clinical trials may now challenge the dogma of "one-size-fits-all" and allow for implementation of advanced imaging biomarkers to guide precision radiotherapy in the context of multicenter prospective trials.[21] Implementation of clinically feasible and reproducible advanced imaging biomarkers will be a key component to success, and will depend on multidisciplinary and multi-institutional coordination.[22]

Rationale for Multiparametric Perfusion and High *b*-value DW-MRI

As a step towards implementing advanced MR imaging for precision radiation treatment, several centers have investigated the utility of perfusion MRI. Dynamic contrast-enhanced (DCE) and dynamic susceptibility contrast MRI provide estimates of CBV, which is elevated in the process of growth and neovascularization in GBM.[23] CBV quantification provides prognostic information regarding recurrence and survival beyond anatomic MRI in patients with GBM. Elevated mean relative CBV in gliomas is significantly associated with shorter time to progression for both low- and high-grade tumors. Elevated tumor CBV prior to radiation therapy (TV_{CBV}) is associated with shorter time to progression and OS in patients with GBM, independent of enhancing tumor volume, FLAIR volume, age, extent of resection, and chemotherapy.[24] Even when incorporating molecularly classified GBM subtypes, OS is better predicted by incorporating maximum tumor CBV.[25,26]

Conventional DW-MRI (b = 0–1000 s/mm2) is routinely acquired in brain tumor imaging protocols for the assessment of the mobility of water molecules in the tissue microenvironment, and has been used as a surrogate for tumor cellularity.[27,28] While conventional DW-MRI and apparent diffusion coefficient maps may be nonspecific and limited in distinguishing peritumoral edema from cellular tumor, increasing diffusion weighting to high b-values (ie, b = 3000 s/mm2) may permit more specific delineation of cellular tumor. Hypercellular tumor volume regions (TV_{HCV}) remaining after maximal resection quantitated directly from high b-value DW-MR images prior to radiation therapy correlate with worse PFS and earlier tumor recurrence in patients with GBM. Despite its aggressive behavior, this biologically relevant extent of disease may be missed by therapeutic doses of radiation since approximately 40% of these hypercellular TV_{HCV} regions are non-enhancing.[17] Prior studies demonstrate that a significant amount of hypercellular tumor volume TV_{HCV} identified using high b-value DW-MRI extends beyond the contrast-enhanced or elevated CBV tumor regions.[17,29] Combining both DCE and high b-value DW-MRI has been demonstrated to identify high-risk tumor regions with only approximately 20% overlap, but with clinically relevant extension beyond standard-of-care radiotherapy target volumes that may be missed using anatomically defined, conventional radiotherapy fields.[17,29]The combination of DCE and high b-value DW-MRI is better than either in isolation in predicting the pattern of failure, and the overlap between the 2 has a nearly 80% likelihood of spatially predicting subsequent progression, indicating that the combination of advanced imaging techniques detecting tumor hyperperfusion and hypercellularity may potentially identify treatment-resistant tumor prior to therapy that is likely to recur after standard radiation treatment based on anatomic imaging alone.[29]

Rationale for Magnetic Resonance Spectroscopic Imaging

Proton magnetic resonance spectroscopic imaging (MRSI) can analyze the chemistry of tissues, including metabolic abnormalities reflective of tumor cell proliferation, which predicts PFS and OS in GBM.[30–32] Specifically, the ratio of choline to N-acetylaspartate (C/N) is increased in areas of increased cellular proliferation and reduced normal neural tissue, as would be found in areas of high-grade glioma.[33]

In a pilot study of 20 patients with malignant glioma, MRSI was performed and integrated into a surgical

neuronavigation system to allow for pathologic sampling of areas of abnormal C/N ratio. In both gadolinium-enhancing and non-enhancing samples, there were histologic and molecular findings (ie, Sox2 density) consistent with tumor infiltration. This study provides histologic and molecular evidence that MRSI is able to detect infiltrative tumors beyond contrast enhancement in a quantitative fashion.[34,35]

Identification of anatomic volumes with an increased C/N ratio can be used to predict areas of relapse after standard treatment, and define radiation targets.[36–38] Specifically, a C/N ratio of >2 appeared to be predictive of site of relapse, and potentially represents a threshold to use when integrating MRSI with radiation.[34,35,39]

Rationale for ^{18}F-DOPA and 18F-FET PET

There is increasing data and support for the use of PET imaging to guide treatment and monitoring of glioma patients.[40] The amino acid PET radiotracer 3,4-dihydroxy-6-[18F]-fluoro-L-phenylalanine (^{18}F-DOPA) has been demonstrated to show high uptake in tumor tissue and lower uptake in normal brain, with higher SUV values correlating with higher-grade tumor.[41] ^{18}F-DOPA is transported into cells independent of breakdown of the blood-brain barrier, allowing for uptake beyond gadolinium contrast-enhancing tumor. In a prospective study of 10 patients with suspected malignant brain tumors, biopsies were stereotactically performed on areas of concordant and discordant contrast enhancement and ^{18}F-DOPA PET avidity.[41] This study demonstrated high ^{18}F-DOPA uptake in tumors up to 3.5 cm beyond contrast enhancement, and established tumor-to-normal ratios of SUV values for high- and low-grade tumors, to be utilized in future studies incorporating ^{18}F-DOPA PET for radiation and surgical planning.[20,42,43] ^{18}F-DOPA also represents a logistical improvement over other commonly used radiotracers such as ^{11}C-methionine PET because it has a longer half-life potentially allowing for transport between centers, and may therefore potentially be implemented in a multi-institutional study where not all institutions have on-site cyclotron access.

Another PET radiotracer used in recent studies of glioblastoma is fluorine-18-fluoroethyltyrosine (^{18}F-FET).[44] ^{18}F-FET provides benefits of efficient radiosynthesis and potentially decreased physiologic uptake in the striatum, which is a useful property for assessing the extent of tumors approaching or involving the caudate nucleus. However, early data hinted towards decreased tumor to normal tissue contrast with ^{18}F-FET compared to ^{18}F-DOPA.[45]

These candidate imaging biomarkers are highlighted as having crossed the threshold of clinical implementation to guide patient-specific radiotherapy, and continued development of novel tracers may allow the combination of advanced PET with more widely used MRI-based imaging strategies.

Translation of Candidate Imaging Biomarkers to Clinical Care

The potential translation of these candidate advanced imaging biomarkers to patient-specific radiotherapy has been investigated in several recent prospective clinical trials in patients with newly diagnosed glioblastoma. Collectively, these studies have demonstrated the feasibility and safety of this novel approach, with early evidence for potentially improved tumor outcomes (Table 1).

Implementation of Multiparametric MRI

In a prior study, commissioning and quality assurance of MRI scanner hardware and image processing software was conducted, and image acquisition and processing were optimized for clinical usability. Quality assurance to warrant accuracy and reproducibility of multiparametric MRI for clinical use on trial was established.[46] A single institution phase II trial was conducted enrolling 26 patients with newly diagnosed GBM.[19] Patients with >1 cc hyperperfused/hypercellular (TV_{HCV}/TV_{CBV}) tumor volume remaining after surgery, identified using high b-value DW-MRI and DCE perfusion MRI, were treated with 75 Gy in 30 fractions of chemoradiation with a primary objective of estimating improvement in 12-month OS. Approximately 20% of patients had O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, and 87% underwent subtotal or gross total resection. With follow-up of 26 months (95% CI: 19-not reached), 12-month OS rate was 92% (95% CI: 78%–100%, $P = .03$) among patients boosted by the combination of TV_{HCV}/TV_{CBV}. Median OS was 20 months (95% CI: 14–29 months) among the whole study cohort, and more favorable among patients with early 3-month response of TV_{HCV}/TV_{CBV} (29 vs. 12 months, $P = .02$). Interestingly, central- or in-field tumor progression was observed in just 31% of patients, representing a marked reduction from typical patterns of failure analyses, with the majority (69%) occurring outside the high-dose region, and 20% of patients experiencing a distant pattern of failure.[19] Among non-progressing patients, 1- and 7-month deterioration in quality of life, symptoms, and neurocognitive function were similar in incidence to standard therapy, and late grade 3 neurologic toxicity occurred in 2 patients.[19]

Implementation of 3D Proton MR Spectroscopy

Two recent prospective trials have utilized MRSI to guide radiation. A recently published multicenter prospective phase III randomized trial from France randomized 180 patients with GBM to standard dose chemoradiation versus standard treatment with a simultaneous integrated boost to 72 Gy in 30 fractions to the MRSI identified volume. Treatment volumes were modified by MRSI in approximately two-thirds of patients. There was no difference in progression-free survival, overall survival, or toxicity between the groups. Of note, the survival for MGMT-methylated patients was 38 months for patients receiving MRSI-guided dose-escalation, versus 28 months for patients on the standard arm.[37] There did not appear to be excess toxicity. Given the lack of improvement in outcomes on this randomized trial, careful thought towards patient selection and implementation is needed to identify patient subsets who may potentially benefit from this treatment approach.

In another multi-institutional pilot trial including 30 patients treated with spectroscopic MRI with dose-escalation

Table 1. Prospective Clinical Trials Utilizing Advanced Imaging to Guide Radiation Treatment Volumes for Newly Diagnosed Glioblastoma

Clinical Trial	Imaging Modality	Phase	Number of Patients	Radiation Dose	Primary Endpoint	Outcomes	High-grade Neurotoxicity
University of Michigan	Multiparametric perfusion and high b-value diffusion-weighted MRI	2 (non-randomized)	26	75 Gy in 30 fractions	12-month OS compared to historical control	OS improved compared to historical controls	Early grade 3+: 15%, Late grade 3+: 8%. No grade 5 toxicity.
French Multicenter study	Magnetic resonance spectroscopic imaging assessing Choline/N-acetylaspartate ratio	3 (randomized between standard dose RT and MRSI-guided dose-escalation to 72 Gy in 30 fractions	180	72 Gy in 30 fractions	Overall survival	No difference in OS (22.6 vs. 22.2 months) or PFS (8.6 vs. 7.8 months) between arms	Not specifically reported, G3+ any toxicity was 34% in experimental arm versus 36% in standard arm (no difference). No radiation necrosis was described.
Emory University, University of Miami, Johns Hopkins University	Magnetic resonance spectroscopic imaging assessing Choline/N-acetylaspartate ratio	1 (pilot)	30	75 Gy in 30 fractions	Pilot study	Median OS 23 months, median PFS 16.6 months	4/30 patients (13%) appeared to have RT-related grade 3+ neurotoxicity
Mayo Clinic	^{18}F-DOPA PET/CT	2 (non-randomized)	75	76 Gy in 30 fractions	6-month PFS in MGMT-unmethylated patients compared to historical control	PFS improved for MGMT-unmethylated patients, improved OS for MGMT-methylated patients	13% (improved with bevacizumab in all cases). No grade 5 toxicity.
Aachen University Hospital, Germany	^{18}FET PET/CT	2 (non-randomized)	22	72 Gy in 30 fractions	Pilot study	Median OS 14.8 months, median PFS 7.8 months	No radiation-related toxicity beyond alopecia was reported, including no radiation necrosis.
Prof. Franciszek Lukaszczyk Memorial Oncology Center, Poland	^{18}FET PET/CT, dual timepoint	1 (pilot)	17	78 Gy in 30 fractions	Pilot study, OS at 1 and 2 years	Median OS 24 months, median PFS 12 months	Two patients (11%) did not complete RT due to seizures. Six patients (40%) had grade 3+ necrosis, which was positively associated with OS

to 75 Gy in 30 fractions, median overall survival was promising at 23 months without excess toxicities.[38] In contrast to the SPECTRO GLIO study, this group describes using 3D echo-planar spectroscopic imaging and full field-of-view including cortical surface regions on 3T scanners, thereby improving imaging resolution and signal-to-noise ratio. They have also developed software tools to facilitate adoption of the technique at other institutions, a critical step in implementation of advanced imaging technologies.[38]

Implementation of Amino Acid PET/CT

After establishing optimal ^{18}F-DOPA PET tumor/normal ratios for high- and low-grade tumors, a single-arm prospective phase II study was conducted utilizing ^{18}F-DOPA PET/CT and standard MRI-based dose-escalation for 76 patients with glioblastoma, with no limitations based on tumor size or multifocality.[20,41] The primary study endpoint to improve PFS at 6 months in patients with MGMT-unmethylated glioblastoma compared to historical controls was met (median PFS 8.7 vs. 6.6 months, $P = .017$). MGMT-methylated patients were also included, and had improved OS compared to historical controls (35.5 vs. 23.3 months, $P = .049$). Of note, there was no improvement in PFS in MGMT-methylated patients, likely owing to dose-escalation causing increased radiation treatment effect and determinations of progression by RANO criteria when in fact there was not yet true progression, which may remain a diagnostic challenge for glioblastoma trials utilizing dose-escalation with a PFS endpoint.[20,47] Central failure was noted in the high-dose 76 Gy volume in just 46% of patients, indicating this approach altered the typical pattern of failure.[2] Grade 3+ CNS necrosis was noted in 13% of patients; patients with ^{18}F-DOPA PET-defined tumor volumes over 50 cc's had significantly higher rates of grade 3+ necrosis ($P < .0001$). All improved symptomatically with bevacizumab, but these non-trivial rates of serious CNS toxicity support the need for precise radiation targeting using advanced imaging.[2]

Two additional single-arm phase II prospective trials utilizing ^{18}F-DOPA PET/CT-guided radiotherapy for glioblastoma have been recently reported. In a study of adult patients with recurrent or progressive high-grade glioma undergoing re-irradiation, ^{18}F-DOPA PET/CT-guided radiotherapy expanded tumor volumes by a median of 43%, and significantly improved PFS compared to historical controls without excessive toxicities.[42] In a population of 43 glioblastoma patients age 65 years and older utilizing ^{18}F-DOPA PET/CT-guided hypofractionated proton radiation over 1–2 weeks with a reduced anatomic margin, the primary endpoint of improving OS at 12 months was met, including a promising OS of 29.8 months in MGMT-methylated patients.[43] Advanced imaging may facilitate reduction in empiric anatomic radiation target volume expansions and overall treatment volumes, thereby allowing for safer hypofractionation.

^{18}FET-PET has also been implemented in early prospective clinical trials to guide radiation volumes. A phase II single-arm study from Germany integrated ^{18}FET-PET with standard MRI volumes in 22 patients, resulting in a median OS of 14.8 months and no significant radiation-related toxicities.[48] More recently, a single-arm study from Poland used dual timepoint ^{18}FET-PET with standard MRI in 17 patients, and demonstrated a promising OS of 24 months.[49] Grade 3+ radiation necrosis was noted in 40% of patients and anatomically associated with the high-dose PET-defined volume, though necrosis was associated with improved OS. These high rates of grade 3+ necrosis underscore the need for careful patient selection, precise dose-escalation, thoughtful consideration of anatomy and eloquence of treatment region, and aggressive supportive care. Given the observed improvement in outcome with necrosis, the selective use of steroids and bevacizumab may be warranted in select cases to mitigate symptoms associated with treatment effect.

While each of the advanced imaging modalities described above may identify biologically relevant non-contrast-enhancing GBM, it is unclear how much they overlap with one another, and whether if used in combination they would be additive or redundant. With a hypothesis that advanced PET imaging could be synergistic with high *b*-value diffusion- and perfusion-based multiparametric MRI for tumor delineation, an ongoing clinical trial is incorporating multiparametric MRI with ^{18}F-DOPA PET/CT for target delineation, and randomizing patients between a standard length course versus a hypofractionated course of radiation (NCT05781321). This study will provide data on the concordance and discordance of these 2 advanced imaging modalities, and indicate whether they are complementary in identifying biologically distinct non-enhancing tumors (Figure 1A-J).

Future Directions

Translation to Prospective, Multicenter Clinical Trials

With the emergence of evidence supporting the clinical feasibility, safety, and potential benefit of implementing advancing imaging biomarkers to guide patient-specific radiotherapy, a systematic approach is recommended for the assessment of these imaging biomarkers in the context of prospective, multicenter clinical trials. FDA approval of imaging techniques and radiotracers would allow for use outside of centers completing Investigational New Drug applications. Although outside the scope of this particular review and the subject of other ongoing collaborative initiatives, a multi-step approach to establish quality and feasibility outside of highly specialized centers with technical expertise is a critical next step. Generalizing precision radiotherapy processes across the spectrum of image acquisition, quantification, tumor volume processing, and radiation planning and delivery will be necessary to ensure the requisite harmonization and standardization for a definitive multicenter clinical trial.[22] A "pick-the-winner" trial design comparing standard-of-care radiation therapy based on anatomic imaging with precision radiotherapy approaches incorporating candidate imaging biomarkers may optimally allow an unbiased approach to evaluating the feasibility and benefit of this novel therapy. A study of this type is currently under development.

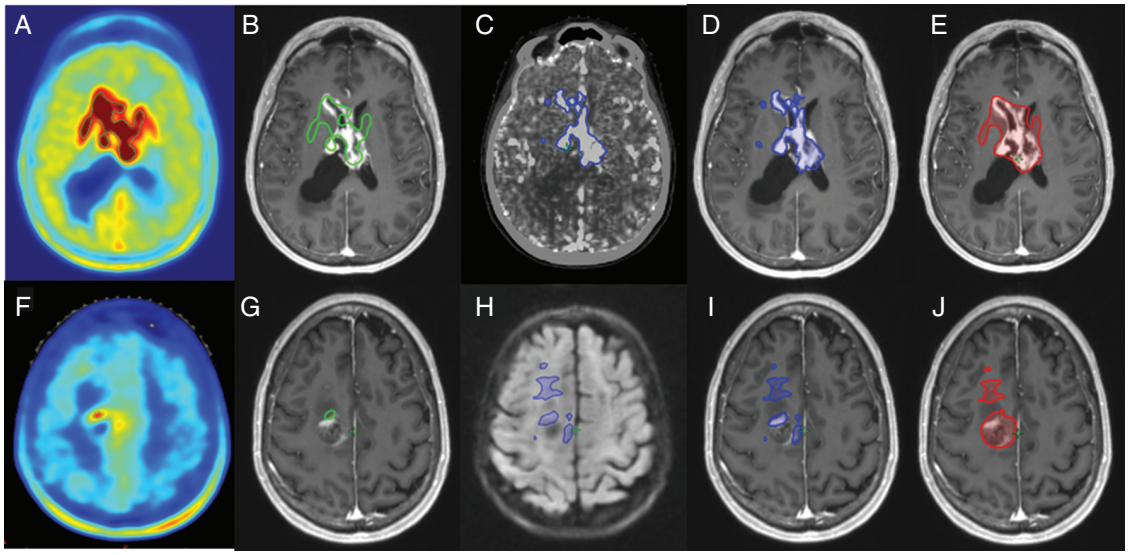

Figure 1. Multimodality imaging for a patient with newly diagnosed glioblastoma. 1A: ^{18}F-DOPA/PET defined gross tumor volume (GTV). 1B: ^{18}F-DOPA/PET defined GTV overlayed on T1 post-gadolinium series to demonstrate avidity beyond volume of contrast enhancement. 1C: Cerebral blood volume maps derived from perfusion magnetic resonance imaging (MRI) demonstrating tumor at the same axial level (diffusion images not shown). 1D: Multiparametric MRI-defined GTV overlayed on T1 post-gadolinium series. 1E: Combined GTV defined by ^{18}F-DOPA/PET and multiparametric MRI. 1F-J: Analogous images to 1A-E but further superior in the brain of the same patient, with diffusion image shown rather than perfusion image. While on the anatomic level demonstrated in Figure 1A-E the ^{18}F-DOPA/PET identified more non-enhancing tumors, on the slice demonstrated by Figures 1F-J multiparametric MRI demonstrated more non-enhancing tumors. In the same patient, there appears to be biologic heterogeneity reflected in the differential imaging findings, and these complementary imaging modalities may be needed to optimally image the infiltrative tumor.

Improving the Therapeutic Ratio: Response-Adaptive Radiation Therapy

Assessing temporal heterogeneity through identification of a treatment-resistance phenotype and its dynamics during the treatment course may permit further optimization of the therapeutic ratio of radiation therapy, and safe, selective treatment intensification in a patient-specific manner. Early response assessment using multiparametric MRI including high b-value DW-MRI and perfusion MRI has been associated with survival, and persistent or emerging areas of putative treatment resistance during the course of radiotherapy identified using this imaging signature have been independently associated with worse OS (adjusted hazard ratio 1.2, 95% CI: 1.0–1.4, $P = .02$).[3] A novel approach of response-adaptive radiotherapy is under investigation to assess not just the anatomic changes accompanying standard treatment, but biologic changes identified using imaging biomarkers during radiation that are associated with tumor progression and survival. In an ongoing phase II clinical trial enrolling patients with newly diagnosed GBM (NCT04574856), persistent and developing regions of treatment resistance identified using this multiparametric MR signature are adaptively targeted with high-dose radiotherapy mid-way during the course of radiation (Figure 2). A pre-specified interim analysis after enrolling 16 of a planned 30 patients has demonstrated successful individualized, offline response-adaptive replanning using an advanced imaging biomarker for boost without treatment break in any patient, and an acceptable rate of neurologic toxicity with safety to continue to target enrollment.[50] Future studies may further elucidate optimal timing for acquisition of biologically based imaging that will identify meaningful tumor and microenvironmental changes with adequate delivered dose, while permitting real-time modification of radiation therapy and potentially informing rational combinations with novel systemic agents in the concurrent and adjuvant setting.

Towards Tailored Radiotherapy and Integration With Systemic Therapy

Currently, radiation doses and volumes for patients with glioblastoma are determined primarily by their tumor histology and grade, a limited number of molecular markers, and the patient's age and performance status. Current efforts are underway in the field of radiation oncology to further personalize treatment by determining the specific radiation dose needed for a specific tumor.[51] While genomic and serum markers are likely to play a critical role in these advancements, issues related to tumor heterogeneity and incomplete pathologic sampling require anatomic assessment by imaging. Along these lines, artificial intelligence is likely to play a major role in analyzing imaging data, predicting areas at highest risk for local failure that may benefit from dose-escalation, and identifying patients at highest risk for distant brain failure who may benefit less from intensified local therapy.[52–54]

Beyond the potential for improving tumor control, accurate tumor visualization using advanced imaging may allow radiation oncologists to confidently reduce treatment volumes based on nonspecific anatomic imaging,

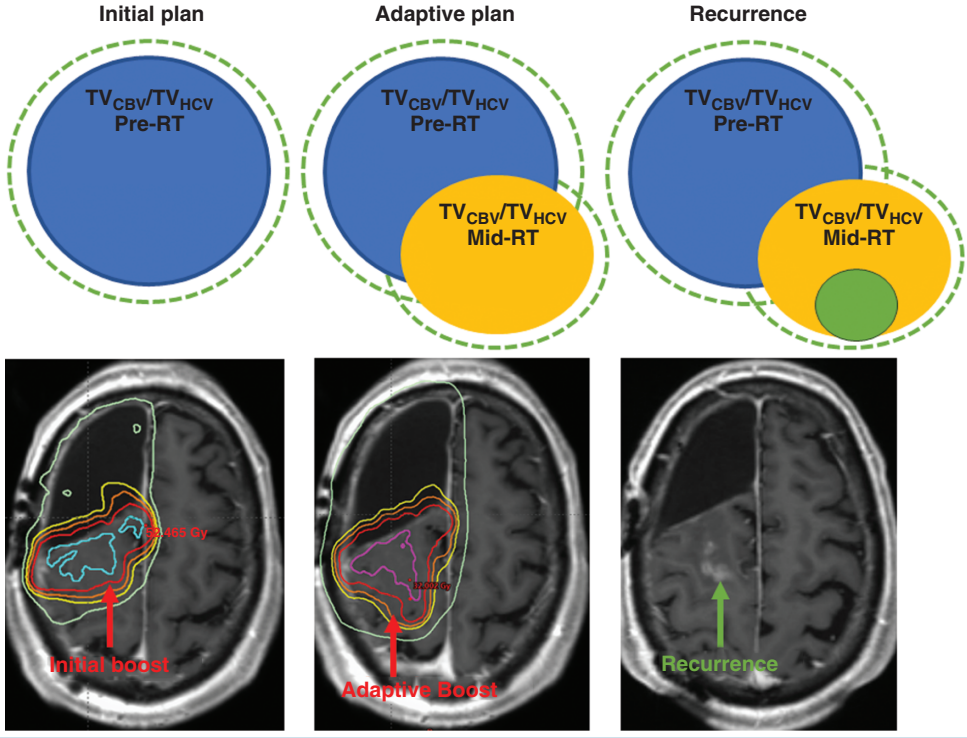

Figure 2. (Top row) A schematic illustration of residual hyperperfused (TV_{CBV}) and hypercellular (TV_{HCV}) tumor identified after resection and prior to radiotherapy using multiparametric perfusion and high b-value diffusion magnetic resonance imaging (MRI) (blue circle). The persistent and newly developing TV_{CBV}/ TV_{HCV} identified by mid-radiation is illustrated with the yellow circle, and ultimate area of tumor recurrence is illustrated in green. (Bottom row) In the far left panel, hypercellular and hyperperfused tumor was identified in a patient with an apparent gross total resection of a right frontal glioblastoma prior to radiotherapy (cyan structure overlaid on T1-weighted gadolinium-enhanced MRI). In the middle panel, an illustrative adaptive plan is shown encompassing the persistent but also newly developing TV_{CBV}/ TV_{HCV} identified by mid-radiation (magenta structure overlay). In this patient, tumor recurrence was ultimately demonstrated 12 months after treatment corresponding to the TV_{CBV}/ TV_{HCV} developing during radiation therapy.

thereby decreasing the total volume of brain irradiation and decreasing dose to adjacent brain substructures. This decrease in treatment volume particularly in the normal brain parenchyma treated may allow for safely shortening treatment courses with increased dose per fraction.[8,43,55,56] The numerous benefits of enabling safe hypofractionation of glioblastoma include the potential for improved outcomes, decreased lymphopenia, and improved integration with standard and investigational systemic therapies including immunotherapy, integration into the pre-operative setting, and importantly patient convenience and access to care.[57]

Conclusion

Advanced imaging using multiparametric MRI, spectroscopic MRI, and amino acid PET have demonstrated early promise in improving outcomes using biologically based radiation treatment for patients with glioblastoma. The development and successful conduct of multicenter prospective trials are needed to improve access to these novel technologies and to demonstrate their value in improving outcomes for patients.

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