

# MRI Guided Adaptive Radiation Therapy of Glioblastoma

Subjects: [Radiology](#), [Nuclear Medicine & Medical Imaging](#)

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Magnetic resonance imaging linear accelerators (MRLINAC) technology allows clinicians to leverage imaging information gathered during radiation therapy to adapt therapy for a patient while actively undergoing treatment. There is a significant need to understand how imaging changes may correlate to outcomes during treatment for glioblastoma (GBM) as these tumors have a poor prognosis and treatment tailored to the tumor characteristics may improve outcomes. Some of the advantages of MR guided therapy include facilitating a more detailed study of tumor and normal tissue response during chemo-radiation therapy, providing a mechanism to adapt therapy based on imaging changes, identifying new imaging biomarkers for tumor response as well as normal tissue response. These avenues could provide a more tangible way to evaluate pseudoprogression and radiation necrosis with radiogenomics as a mechanism to correlate imaging findings to genomic biomarkers.

GBMs

radiotherapy

MRI

## 1. Molecular Basis of Glioblastoma (GBM)

Prior to the World Health Organization (WHO) Classification of Tumors of the Central Nervous System (CNS) fourth edition, molecular characteristics were not a major factor in the classification of tumors as histological features dictated tumor grading. In 2016, when the fourth edition was released, molecular characteristics were integrated into the classification system. Previously, histological features were sufficient to deem a tumor as grade 4 and classify it as a GBM, regardless of isocitrate dehydrogenase (*IDH*) status. With the new 2021 classification system (WHO fifth edition), *TERT* promoter mutation, *EGFR* amplification, and +7/-10 copy number changes in *IDH*-wildtype diffuse astrocytomas are awarded a glioblastoma, *IDH*-wildtype CNS WHO grade 4 designation despite harboring histological features that would previously be rated as a lower grade. This change in classification criterion was made to adequately group patients with the poorest prognosis <sup>[1]</sup>.

Several other molecular biomarkers of prognostic significance have been identified. Both the telomerase reverse transcriptase (*TERT*) promoter and epidermal growth factor receptor (*EGFR*) have been shown to have a prognostic significance among patients with GBM. *TERT* promoter mutation vs. *TERT* promoter wild type has been found to be associated with an older age (median 59.6 vs. 53.6 years), and with a poorer prognosis in *IDH* wild type GBMs with an overall survival of 13.7 vs. 17.5 months. Additionally, there appears to be an interplay between *TERT* and *EGFR*. Patients with a *TERT* promoter wild type and *EGFR* wild type tumor had approximately double the overall survival of patients harboring a *TERT* promoter wild type tumor with *EGFR* alteration, with an overall

survival of 26.6 vs. 13.3 months. To further complicate this, in *EGFR* altered tumors, *TERT* promoter mutation was associated with a longer survival than *TERT* promoter wild type. Finally, patients harboring neither mutation had the best prognosis [2].

The Cancer Genome Atlas (TCGA) has also examined molecular characteristics of GBM and has shown that multiple genes (*ERBB2*, *NF1*, *TP53*, *PIK3R1*, *PDGFRA/IDH1*, etc.) and pathways possess aberrations that may be clinically relevant [3][4]. Molecular analysis of transcription levels, genetic alterations, and DNA methylation has also allowed for further subtyping of GBM into 4 classes, proneural, neural, classical, and mesenchymal [4][5][6]. Response to treatment differs among subtypes with the classical subtype receiving the greatest benefit from treatment and the proneural subtype showing little to no benefit [4]. Additionally, *MGMT* promoter methylation status may serve as a predictive biomarker to treatment response in the classical subtype and not the proneural subtype [7]. These findings reinforce the notion that molecular testing plays a critical role in elucidating prognosis as there is a complicated interplay between multiple genes and pathways.

## 2. Role of Radiotherapy in GBM

Prior autopsy studies have underlined the infiltrative tendencies of GBM and have shown microscopic extension up to 2.0 cm from the border of the resection cavity, indicating that there continues to be a significant risk even after maximal safe resection [8]. External beam radiotherapy continues to be a mainstay of treatment to address this concern. A series of historical studies, the Brain Tumor Study Group protocols (BTSG 66-01, 69-01, 72-01), have established a dose-effect relationship and have shown that higher doses of adjuvant radiotherapy improve survival [9][10][11][12]. These three studies enrolled a total of 621 patients who had undergone resection with histologically confirmed GBM, prior to the molecular understanding of this disease. After resection, the patients received either no radiotherapy or adjuvant therapy to either  $\leq 45.0$  Gy, 50.0 Gy, 55.0 Gy, or 60.0 Gy given in doses of 171–200 cGy daily with five fractions per week. Median survival for these patients was 18.0 weeks, 13.5 weeks, 28.0 weeks, 36.0 weeks, and 42.0 weeks, respectively. These results showed that there was an improved median survival with dose escalation to 60 Gy [9]. Subsequently, multiple dose escalation studies including the most recent NRG trial BN001 have been performed but have thus far failed to show survival improvement with dose regimens above 60 Gy [13][14][15][16][17]. The current standard of care entails forming a clinical target volume (CTV) that includes the surgical resection cavity, residual contrast enhancing tissue, associated peritumoral hyperintensity based on T2-FLAIR signal, along with a 2.0 cm margin to cover for microscopic extension, and treating to 46 Gy. A 2 cm margin has been empirically determined, as over 80% of recurrences have been found within 2 cm of the contrast-enhanced lesion [18][19]. This initial treatment is then followed by a sequential boost of 14 Gy to a total dose of 60 Gy to treat a clinical target volume which includes only the resection cavity, residual contrast enhancing tissue, and a 2.0 cm margin. In summary, the 46 Gy field will cover the resection cavity plus regions of T2-FLAIR along with a 2.0 cm margin, while the 60 Gy field will omit regions of T2-FLAIR and target only the resection cavity with a 2.0 cm margin. This standard of care treatment protocol has been established based on NRG trial guidelines and the consensus of a panel of CNS radiation oncologists [20].

### 3. Types of Radiotherapy Devices for GBM

The role of radiotherapy as a cornerstone of treatment for GBM after surgical resection has been well established. There are multiple techniques available to deliver radiation that have been explored over the years.

**LINAC**—The most common technique utilized is external beam radiotherapy through the use of a linear accelerator (LINAC). LINAC based treatments provide photon radiation. Typical LINACs have on-board imaging capabilities which allow verification with a cone beam CT or kV X-ray image. The on-board imaging is utilized for confirming patient positioning and verifying treatment field shape, is not of diagnostic quality, is low resolution, and is not ideal for visualizing soft tissue such as brain. However, LINAC based treatment remains the standard of care at this time.

**IORT**—Intraoperative radiotherapy (IORT) is a method of radiotherapy that delivers a large single dose of radiation directly to the tumor tissue and resection cavity. In several small and limited studies IORT has been utilized to provide dose escalation, delivering 12–20 Gy intraoperatively with patients subsequently receiving adjuvant radiotherapy as well. The most recent studies in the TMZ era have been relatively small, consisting of approximately 15–50 patients. While these studies have shown manageable rates of toxicity and verified the safety of IORT, they have failed to show meaningful improvements in patient outcomes such as PFS or OS improvements [21][22]. As such, IORT is not considered a standard of care practice for patients with GBM.

**GammaTile**—GammaTile brachytherapy (GT) is a bioresorbable 3D-collagen tile embedded with Cesium-131 sources which is implanted in the final stages of tumor resection. GT is a relatively new method to treat recurrent brain tumors. A recent study in *IDH* wildtype GBM treated with maximal safe resection and GT at the time of recurrence demonstrated an overall survival of 20 months for *MGMT* promoter unmethylated patients and 37 months for *MGMT* promoter methylated patients. GT safety profile is comparable to patients undergoing repeat surgery without GammaTile [23].

**SRS**—Stereotactic radiosurgery (SRS) is another method of radiotherapy that entails high dose per fraction irradiation. SRS may be performed with a LINAC or a cobalt source platform that utilizes multiple beams that converge in three dimensions on a small target. Through this technique, a much higher dose may be delivered, which leads to a more ablative treatment, causing higher rates of cell kill and significant damage to tumor vasculature [24][25]. Since a much higher dose is being utilized, it is critical to ensure accurate target localization and tight margins. Due to this, greater spatial resolution is required; therefore, it is recommended that magnetic resonance imaging is co-registered to aid in target volume delineation [26].

At present, stereotactic radiosurgery is commonly utilized in the treatment of brain metastases. There have been multiple prior attempts to establish a role for SRS in the treatment of GBMs, such as in the Radiation Therapy Oncology Group (RTOG) 9305 trial which compared postoperative resection cavity SRS plus external beam radiotherapy vs. resection plus external beam radiotherapy. Unfortunately, there were no significant survival differences or pattern of failure differences between the two arms [27]. As such, the role of SRS for the treatment of GBMs remains controversial and limited. Currently, SRS is most commonly utilized in the setting of recurrent GBM

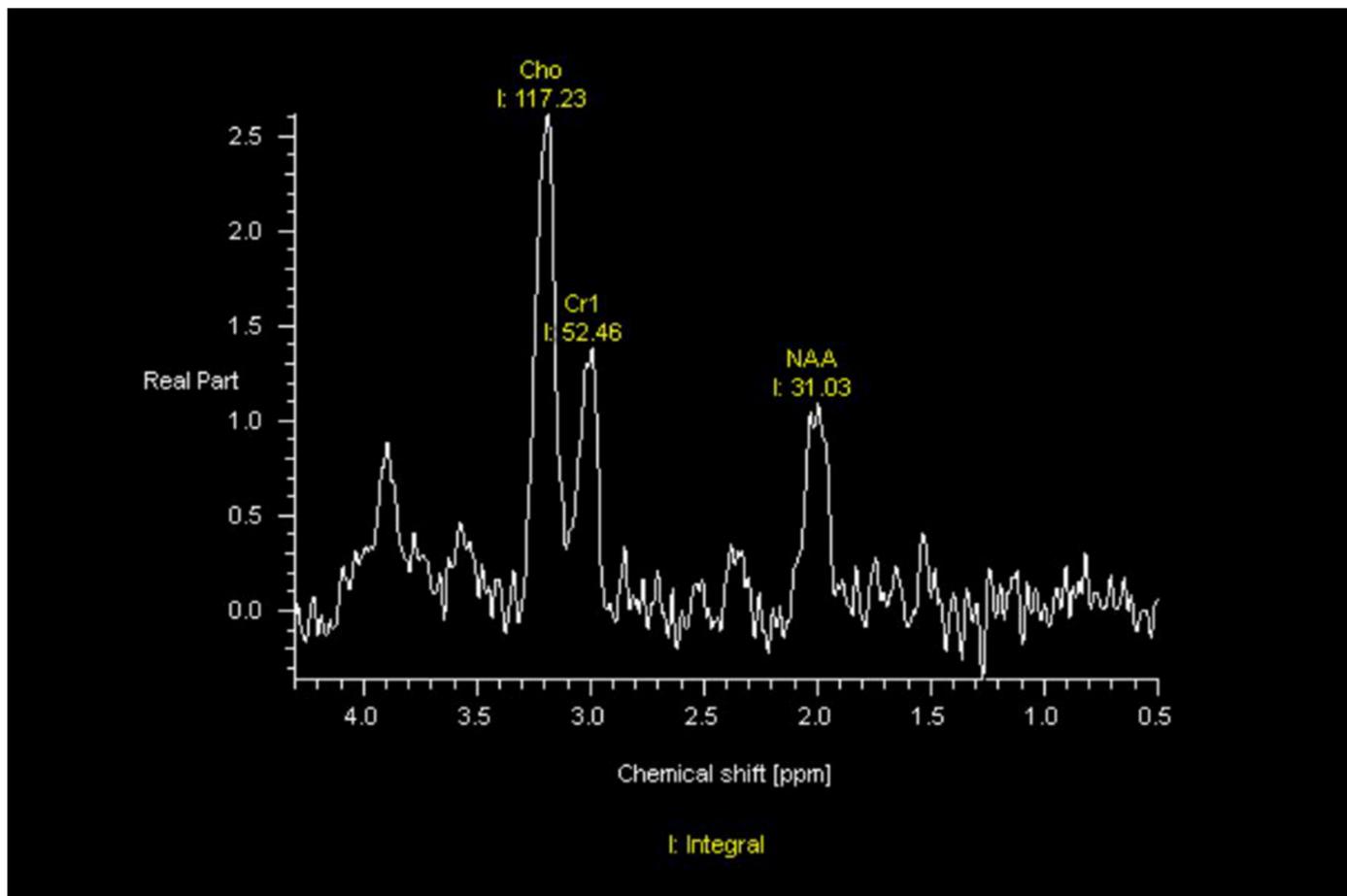
for patients with a high-performance status, a good response to the initial chemoradiotherapy treatment, a prolonged interval to recurrence, and limited volume disease [28].

**Protons**—Charged particle therapy, particularly proton therapy, has been gaining popularity in the last decade. Proton based radiation imparts a dosimetric benefit, allowing for a more favorable dose distribution, which in turn may reduce patient morbidity. A retrospective analysis comparing photon and proton treatment plans showed that proton therapy provided a dosimetric advantage by reducing dose to organs at risk [29]. Although proton therapy provides a more favorable dosimetry, it is unclear if this translates into improved clinical outcomes or reduced late toxicity. A recent prospective phase II randomized controlled trial compared proton therapy vs. intensity modulated radiotherapy for patients with newly diagnosed GBMs and utilized first cognitive failure as a primary endpoint. Despite the more favorable dosimetry, there were no significant differences in cognitive failure between the treatment arms. Additionally, there were no significant differences in progression free survival or overall survival [30]. Pending results from the NRG BN001 trial [Clinical Trial NCT02179086] will also allow a comparison between proton- and photon-based radiotherapy in the treatment of GBM. Thus far, proton therapy has not yet demonstrated improved treatment efficacy nor reduction in toxicity in the treatment of GBM.

**MRI guided machine**—Soft tissue imaging is critical for successful volume definition in GBM. As already mentioned, for GBM treatment it is necessary to co-register MRI scans to the radiotherapy planning scan in order to have the necessary spatial resolution to properly define the target volume and organs at risk. Furthermore, as image guided radiotherapy has become a mainstay of treatment, there has been a need for better soft tissue image guidance. This has led to the development of MRI guided radiotherapy machines.

## 4. Imaging Characteristics of GBM on MRI

**MRI**—On MRI, GBMs typically demonstrate contrast-enhanced T1-weighted heterogeneous enhancement and irregular borders, central necrosis, and significant surrounding T2/FLAIR hyperintensity. The increased FLAIR signal in the peritumoral habitat reflects not only edema but also nonenhancing infiltrative tumor. The increased cellularity of these tumors often appears heterogeneously relatively T2-hypointense and may be associated with restricted diffusion. However, a minority of GBMs will manifest as ill-defined nonenhancing, T2/FLAIR hyperintense masses that are difficult to differentiate from low-grade gliomas or as smaller homogeneously enhancing well-defined masses that can be mistaken for metastases. GBMs at the corpus callosum can be difficult to differentiate from lymphoma. Tumefactive multiple sclerosis, infection, and subacute infarcts also can be difficult to differentiate from GBMs or other neoplasms. GBMs typically result in significant mass effect. GBMs can demonstrate increased corrected relative cerebral blood volume (rCBV) on dynamic susceptibility contrast (DSC) MR perfusion, increased permeability on dynamic contrast-enhanced (DCE) MR perfusion, and an abnormal tumor spectrum on MR spectroscopy, with reversal of Hunter's angle—meaning increased choline (Cho), decreased creatine (Cr) and decreased N-acetyl-aspartase (NAA) (**Figure 1**).



**Figure 1.** MR Spectroscopy shows reversal of Hunter’s angle with elevated choline (Cho), decreased creatine (Cr), and decreased N-acetyl-aspartase (NAA) in a patient with GBM status post radiation therapy, temozolomide, and tumor treating fields.

## 5. Radiomic and Radiogenomic Differentiation of Molecular Markers, Sex Differences, and Morphologic Subtypes of GBMs

Radiomics is the quantitative analysis of radiologic images, using statistics or machine learning/artificial intelligence, to correlate features on a large scale to underlying biologic processes or diagnoses. Radiogenomics is the correlation of these imaging features with gene expression patterns and mutations.

*IDH* wild type—Before the patient’s treatment plan can be formed, it must know whether the tumor is *IDH* wild type or mutated. Many groups have developed a variety of machine learning tools to predict the *IDH* status noninvasively, but recent deep learning models using convolutional neural networks have achieved high accuracy, sensitivity, specificity, and Dice scores (Dice coefficient indicates how closely a segmentation matches the ground truth) in automatically color coding and predicting *IDH* mutation status by analyzing only T2-weighted MRI—without contrast-enhanced MRI sequences—apparently obviating the administration of contrast material [31][32].

*MGMT* promoter methylation—Machine learning models have been able to noninvasively detect *MGMT* promoter methylation on MRI analysis, with varying degrees of success. Recently, the same model described above that demonstrated high accuracy in detecting *IDH* mutation status also was used to detect and segment the *MGMT* promoter methylated tumor on MRI with an accuracy of 94.73%, sensitivity of 96.31%, specificity of 91.66%, and mean AUC of 93%. The Dice score for segmenting the tumor on MRI was 82%. This model again was successful using only T2-weighted images, possibly eliminating the need to administer contrast material [33].

*EGFR* alteration—One of the best-known drivers of aggressive behavior in GBMs is *EGFR* alteration, in specific, *EGFRvIII* mutation. Akbari et al. showed that multiparametric machine learning modeling could be used to detect *EGFRvIII* alteration with 85.3% accuracy, 86.3% specificity, 83.3% sensitivity, 85% AUC [34].

*BRAF-V600E* Mutation—While the cases of *BRAF-V600E* mutated GBMs are too few for studies to demonstrate statistical significance and power, the potential for increased survival with targeted treatment merits discussion of the radiologic features of *BRAF-V600E*-mutated tumors. *BRAF-V600E* mutation, associated with epithelioid GBM, can be targeted by BRAF and MEK inhibitors such as dabrafenib and trametinib, which can lead to longer survival in some cases. However, some epithelioid GBMs result in shorter survival despite treatment, and investigation of additional molecular markers such as *TERT* promoter mutation and *CDKN2A/B* homozygous deletion is needed to predict which tumors will progress despite targeted therapy.

## 6. MRI Guided Machines

Imaging component—Magnetic resonance imaging linear accelerators (MRLINAC) provide improved soft tissue imaging, allowing for superior image guidance and adaptive treatment planning. Combining an MRI system and LINAC is an arduous task with numerous logistical obstacles. Firstly, the MRI imaging system relies on a high-powered magnet, which produces a magnetic field that may hamper the function of the multi-leaf collimator (MLC) of the LINAC [35]. Additionally, a magnetic field may influence the motion of electrons as they travel through the accelerating waveguide [36]. Furthermore, the presence of a LINAC near an MRI system may lead to interaction between the treatment beam and RF receiver coil, causing image quality degradation [37]. There are several different methods of overcoming these obstacles.

Currently there are two commercial systems available, with more to come in the future. The Elekta Unity utilizes a 1.5 T magnet, which is the highest-powered magnet commercially available in today's MRLINACs. To overcome interference from this magnet the photon beam is placed on a rotating gantry which passes a superconducting cryostat configured to avoid angles that will interfere with imaging quality. Additionally, the electron gun is housed in a zero-field zone and utilizes specific shim settings to minimize image degradation [38].

Treatment planning systems are fully integrated into both the Unity and MRIdian, allowing for on-table treatment plan adaptive radiotherapy. This allows treatment to be re-planned in the event of organ motion or with target volume alteration during the course of treatment. In these systems, each daily scan is registered to the primary planning image along with the initial target volumes and organ at risk contours. These volumes can then be

adjusted as appropriate. The original treatment plan is subsequently recalculated with an updated Monte Carlo dose calculation that is calibrated to account for the magnetic field as well. The software will provide a dose volume histogram (DVH) comparison of both plans. The user can then determine which plan is preferred, providing the patient with superior target coverage and sparing of organs at risk [\[39\]\[40\]](#).

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