Journal of Neuro-Oncology
https://doi.org/10.1007/s11060-025-05053-6

EDITORIAL

Advancements in adaptive MR-guided radiotherapy for high-grade gliomas

Alexander S. Marwaha[1] · Matthew J. Shepard[2] · Stephen M. Karlovits[1] · John Herbst[3] · Rodney E. Wegner[1]

Received: 20 March 2025 / Accepted: 18 April 2025

Abstract

Glioblastoma multiforme (GBM) is the most common primary malignancy of the central nervous system, with a poor prognosis despite multimodal treatment approaches. With the development and integration of Magnetic Resonance-guided Linear Accelerator (MR-Linac) technology into the treatment paradigm for high-grade gliomas, there is promising potential for improved treatment precision and reduced side effects for patients diagnosed with this aggressive cancer. The MR-Linac combines high-resolution, real-time magnetic resonance imaging with precise linear accelerator-based treatment delivery, enabling adaptive radiotherapy that adjusts to anatomical changes during the treatment course. This technology offers the potential to refine target delineation, optimize treatment volumes, and reduce radiation exposure to healthy tissue. The editorial discusses the transformative potential of the MR-Linac in improving treatment personalization and outcomes for patients with high-grade gliomas, positioning it as a significant advancement in radiation oncology.

Introduction

Glioblastoma multiforme (GBM) is the most common primary malignancy of the central nervous system, characterized by its aggressive nature and poor prognosis. Standard treatment paradigms for GBM typically include a multimodality approach encompassing maximal safe surgical resection, radiation therapy, concurrent and adjuvant chemotherapy, and, more recently, tumor treating fields [1]. Among these modalities, radiation therapy remains a cornerstone, with treatment regimens ranging from as few as five fractions in hypofractionated protocols to conventional schedules comprising 15 to 30 fractions [2].

Treatment planning and volumes for radiation therapy have traditionally relied on standardized guidelines for target delineation, such as the two-stage volume approach recommended by the Radiation Therapy Oncology Group/National Radiation Group (RTOG/NRG), which uses relatively large margins [3]. However, more recent consensus guidelines, such as those from the European Society for Radiotherapy and Oncology (ESTRO), advocate for updated margins that are smaller and eliminate the need for a cone-down phase [4].

The advent of the Magnetic Resonance-guided Linear Accelerator (MR-Linac) technology represents a significant innovation in radiation oncology, offering the ability to integrate high-resolution, real-time magnetic resonance imaging with precise linear accelerator-based treatment delivery. This technology facilitates frequent imaging during treatment, enabling adaptive radiotherapy to adjust to anatomical changes over the treatment course dynamically. Because of this unique adaptive feature, the MR-Linac harnesses the possibility to redefine target margins, potentially optimizing treatment volumes while reducing dose to healthy tissue [5]. Furthermore, its ability to make real-time adaptations during the treatment course opens avenues for identifying biomarkers of response or progression, offering insights into GBM biology and treatment efficacy.

This article explores the integration of MR-Linac technology into the treatment paradigm for high-grade gliomas, highlighting its potential to refine target delineation, improve treatment personalization, and enhance outcomes in this challenging patient population.

✉ Rodney E. Wegner
Rodney.Wegner@ahn.org

[1] Allegheny Health Network Cancer Institute, Department of Radiation Oncology, Pittsburgh, PA, USA

[2] Allegheny Health Network, Department of Neurosurgery, Pittsburgh, PA, USA

[3] Allegheny Health Network Cancer Institute, Department of Neuro-Oncology, Pittsburgh, PA, USA

Published online: 24 April 2025

Discussion

An addition to the armamentarium for treatment of newly diagnosed glioblastomas is derived from a phase 3 randomized trial that evaluated the efficacy of Tumor Treating Fields (TTFields) delivered via the Optune device in conjunction with maintenance temozolomide. The trial demonstrated significant improvement in both progression free survival and overall survival in patients that received both the TTFields and temozolomide, compared to the temozolomide-only group. All patients in this trial had completed 45–70 Gy (Gy) of local radiation therapy. Of note, the radiation targets in this study were defined as the Gross Tumor Volume (GTV) being the post-surgical tumor bed and residual enhancing tumor, and appropriate Clinical Target Volume (CTV) (2–3 cm) and Planning Target Volume (PTV) (3–5 mm) margins [6]. The GTV represents the visible contrast-enhancing extent of the tumor on T1-weighted MRI, and the CTV and PTV represent dedicated margin expansions of the GTV to account for microscopic spread and movement errors, respectively. The original protocol from Stupp et al. in 2005 consisted of treating glioblastomas with 60 Gy of total radiation, where patients were getting 2 Gy daily for 6 weeks (Monday through Friday). Temozolomide was also given concurrently during radiation therapy as well as an adjusted adjuvant dose. This protocol resulted in a significant overall survival improvement at 2 years [7].

This topic brings in an important discussion about current guidelines to delineate margins and volumes for GBMs, provided by both the RTOG and European Organization for Research and Treatment of Cancer (EORTC). In well-known clinical trials such as RTOG 0525, NRG-BN007, and NRG-BN011, radiation therapy for glioblastoma followed specific target volume delineation protocols based on North American or European centers [3]. The RTOG recommends a two-phase treatment volume strategy. The first phase includes the T2/FLAIR signal abnormalities from the postoperative MRI, expanded with a 2 cm CTV margin and up to a 5 mm PTV margin. This volume receives 46 Gy in 23 fractions. The second phase included a smaller volume, which is a boost to the area of enhancement plus the cavity and similar CTV and PTV margins, receiving an additional 14 Gy in 7 fractions, totaling to 60 Gy [8]. In contrast, the EORTC uses a single, uniform planning volume that treats the enhancement and cavity with a 15 mm CTV margin, delivering the full 60 Gy in 30 fractions. Specifically, the GTV is defined by the intact contrast-enhancing tumor or resection cavity and residual contrast-enhancing regions on T1-weighted MRI. This approach avoids including T2/FLAIR abnormalities that represent edema but may be included in the CTV as they may represent non-enhancing tumor. The PTV should be no greater than 3 mm with the use of daily onboard imaging. Margins are reduced or excluded at natural barriers like the falx, ventricles, and skull, reflecting a strategy focused on limiting radiation toxicity while maintaining efficacy [4] (Table 1).

Table 1 Summarized RTOG and EORTC GBM contouring guidelines, adapted from Econtour.com [9]

Group	RTOG	EORTC
Phases	46 + 14 = 60 Gy	60 Gy (single phase)
GTV	GTV1: T1 + cavity (post-op) GTV2: GTV1 + T2/FLAIR	T1 + cavity
CTV	CTV1: GTV1 + 2 cm CTV2: GTV2 + 2 cm	GTV + 1.5 cm
PTV	PTV1: CTV1 + 3–5 mm PTV2: CTV2 + 3–5 mm	CTV + 2–5 mm

The advent of MR-guided radiation therapy (MRgRT) has facilitated the use of smaller target volumes. There are discussions about the transformative potential of MRgRT in central nervous system malignancies, highlighting its ability to provide real-time imaging and adaptive treatment capabilities. This technology allows for precise targeting of tumor tissues, potentially enabling the reduction of CTV margins without compromising treatment outcomes [10].

Using the example case in Fig. 1, we compare the treatment plans for a patient with GBM using contours from three different guidelines: EORTC, RTOG, and UNITED. In all three contours, the GTV consists of the T1-weighted contrast-enhancing tumor. The CTV and PTV margins are where the contours differ; the EORTC margins are relatively more conservative than the RTOG margins, focused on sparing surrounding healthy brain tissue, hence the smaller volume treated and less expansion into normal tissue. The UNITED guideline contours incorporate adaptive radiotherapy principles using the MR-Linac, with the goal of balancing effective tumor targeting with reducing toxicity to healthy tissue. Specifically, the UNITED contours introduce a reduced CTV margin of 5 mm, which are significantly smaller than what the RTOG and EORTC offer. It is important to understand, though, that the MR-Linac may not be essential to reducing margins depending on the results of ongoing studies which can help further confirm patterns of failures. The capabilities of the MR-Linac are certainly helpful though, with the onboard imaging to capture any significant changes which can allow for adaptation and the most accurate plan possible.

The impact on treatment plans is also evident given the differences in the guidelines. Adaptive radiotherapy technology allows the treatment volumes to be smaller, as seen in Fig. 1, while still maintaining proper coverage of the GBM. The UNITED contours offer a more personalized and patient-specific approach compared to the RTOG and EORTC contours, finding a good balance between treatment efficacy and toxicity reduction, using the MR-Linac

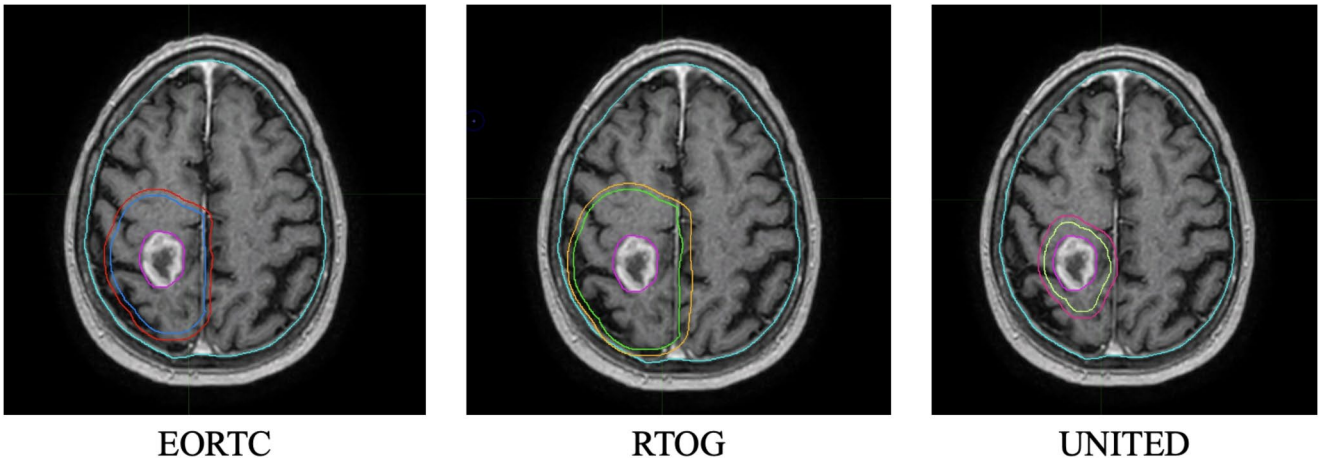

Fig. 1 Example case of a glioblastoma multiforme (GBM) with contours following 3 different guidelines. EORTC contours (left) showing GTV (purple), CTV (blue), and PTV (red). RTOG contours (middle) showing GTV (purple), CTV (green), and PTV (yellow). UNITED contours on an MR-Linac (right) showing GTV (purple), CTV (lime-green), and PTV (pink)

technology's real-time imaging capabilities to reduce radiation exposure to healthy tissue.

Recent research has explored the potential of reducing target volumes in glioma radiotherapy to minimize radiation-induced toxicity while maintaining treatment efficacy. This approach is supported by studies showing that the majority of glioma recurrences occur within the high-dose radiation region rather than distantly. For instance, a study analyzing patterns of failure in high-grade gliomas found that 69% of recurrences were central (within the high-dose volume), while only a small percentage (3.4%) were distant [11]. Another study on temporal lobe GBMs reported that most recurrences were at local or adjacent regional sites, with 74% of the failures occurring locoregionally [12]. These findings suggest that focusing on precise target delineation and adaptive radiotherapy can effectively manage gliomas while reducing unnecessary radiation exposure to healthy tissue.

A study from the MR-Linac International Consortium Research Group provided consensus contouring recommendations for glioma treatment, emphasizing the integration of advanced imaging modalities to enhance target delineation accuracy [13]. That study involved six experienced neuroradiation oncologists from five international institutions who contoured ten glioma cases, including both low-grade and high-grade tumors. Each case was contoured using MRI-only and CT-MRI workflows to assess inter-observer variability and the impact of imaging modalities on contouring accuracy. The findings demonstrated a high level of agreement in GTV and CTV contours across observers in the MRI-only workflow. Notably, the addition of CT information did not significantly alter this agreement, suggesting that MRI-alone may suffice for accurate target delineation in glioma radiotherapy. Furthermore, the study highlighted the importance of precise OAR delineation, particularly for structures like the cochlea, where the inclusion of CT data improved contouring agreement. These consensus recommendations aim to standardize glioma contouring practices, potentially allowing for reduced target volumes and, consequently, decreased radiation exposure to healthy brain tissue without compromising treatment efficacy by taking advantage of new technologies [13].

The UNITED Trial, a phase II study conducted in Toronto, investigated the feasibility and safety of weekly online adaptive radiotherapy for high-grade gliomas (HGGs) using MR-Linac (MRL) technology. The trial employed a reduced CTV margin of 5 mm, significantly smaller than the aforementioned traditional 20–30 mm margins, with the aim of sparing normal brain tissue while maintaining tumor control. This was a possibility given the adaptive nature of the treatment planning and delivery as well MR-imaging capabilities. The GTV was defined as the surgical cavity and residual tumor, with an additional PTV margin of 3 mm. Adaptive treatment plans were generated weekly using online MR imaging with gadolinium to account for changes in anatomy and tumor response during therapy [14].

The study, similar to the existing literature, demonstrated a low risk of marginal failure (4.1%, 95% CI: 1.6–10%), establishing non-inferiority compared to historical data with standard margins which showed an 11% risk of recurrence at the edge of the radiation target. Progression-free survival (PFS) and overall survival (OS) outcomes varied by treatment schedule. Patients treated with the long course (60 Gy in 30 fractions) achieved a median PFS of 11.6 months and a median OS of 18.5 months. In contrast, and not surprisingly, those receiving the short course (40 Gy in 15 fractions) had a median PFS of 6.8 months and a median OS of 10.6 months. Importantly, outcomes were stratified by

Table 2 Summary of research and clinical trials on MR-Linac technology in glioblastoma therapy (RT = radiation therapy, os = overall survival, pfs = progression free survival, lc = local control, TMZ = temozolomide)

Study/Trial	Goals or Key Findings	Status
MR-Linac International Consortium Research Group, Tseng et al. 2020 [13]	High level of agreement in GTV and CTV high- and low-grade glioma contours	Published
UNITED Phase II, NCT04726397 [14]	Significant reduction in CTV margins; Low risk of marginal failure (4%) without compromising OS or PFS	Published
UNITED2, NCT05565521	Oncologic outcomes in patients treated with concurrent dose-escalated chemoradiation with TMZ and MR-Linac with weekly adaptation	Ongoing
UNITED-3, NCT05720078	Comparing an adaptive RT, two-phase approach using an MR-Linac to standard non-adaptive RT on LC and other oncologic outcomes	Ongoing
Lawrence et al. 2023 [16]	MR-Linac diffusion MRI (DWI) changes in glioblastoma are prognostic	Published
NCT05565326	Response assessment during MR-guided RT for glioblastoma; Evaluating change in tumor volume over course of treatment	Ongoing
Tseng et al. 2022 [17]	First clinical series of HGG patients treated with RT on the MR-Linac; Clinically acceptable adapt-to-position workflow and treatment times.	Published
Guevara et al. 2023 [18]	Weekly adaptive plans on an MR-Linac reduce radiation dose to the hippocampi and brain when treating glioblastoma	Published

MGMT methylation status, with methylated tumors showing improved survival. These findings establish MR-Linac as a promising modality for integrating precise radiation delivery with adaptive workflows, potentially reducing radiation toxicity without compromising efficacy. The reason behind these similar findings stems from the daily MRI and adaptive planning that the UNITED study employed to take into account the tumoral changes during radiotherapy, which ranged from 20 to 30% in their cohort. The risk of missing the changing target with smaller CTV margin of 5 mm can be avoided with this daily imaging [14].

The UNITED-3 clinical trial, which is still accruing patients and based in Toronto, is investigating the efficacy of a two-phase, adaptive radiation therapy approach using MR-Linac technology for patients with high-grade gliomas. The primary objective is to assess whether this adaptive RT method improves local tumor control compared to standard non-adaptive RT. Non-adaptive RT relies on an MRI as a reference to treat glioblastomas, leading to larger margins (15–30 mm) on the same volumes for each treatment. By combining MR imaging with a Linac into one machine, this adaptive RT allows for a new MRI to be obtained prior to each treatment delivery. This enables changes to be made when visualizing the patient's anatomy and allows for lowering the margins to 5 mm. By utilizing MR-Linac's real-time imaging capabilities, the study aims to reduce treatment margins and adapt therapy to personal tumor changes, potentially enhancing treatment precision and patient outcomes. Secondary outcomes include evaluations of overall survival, progression-free survival, patterns of failure, toxicity, neurological function, and quality of life differences that may result when having smaller margins, controlling dose to real-time patient anatomy, and delivering less dose to healthy tissue [15] (Table 2).

Additionally, the utilization of advanced imaging sequences, such as diffusion weighted imaging (DWI) and dynamic contrast-enhanced (DCE) MRI, have been investigated for their role in assessing glioblastoma response [19, 20]. The ability to obtain MRI with other imaging strategies during radiation therapy can help individualize therapy by finding noninvasive biomarkers. Techniques such as DWI, DCE, and chemical exchange saturation transfer (CEST) can be more descriptive about properties like perfusion and metabolism that can also be correlated with features that are associated with radioresistance or radiosensitivity, also contributing to individualized therapy [20]. In fact, CEST-MRI has already been studied in patients with primary CNS tumors treated on an MR-Linac. One study found CEST changes in relation to time and tumor grade [21], showing promise and feasibility in using advanced imaging sequences during treatment.

This report has several limitations that must be acknowledged. Firstly, the sample size and diversity of the patient population of the clinical trials and studies mentioned may be limited, which may affect the generalizability of the findings. This report primarily referenced patients from specific clinical trials, and the possibly small and homogeneous groups may not fully represent the broader population of patients with primary brain tumors. Also, the lack of long-term data on survival rates and treatment effects after treatment for GBMs on an MR-Linac is a limitation that should be addressed. More extensive follow-up studies are needed to confirm the sustained efficacy and safety of this approach over time. Additionally, the implementation of advanced technologies such as the MR-Linac requires specialized expertise and resources, which may limit its widespread adoption across all treatment facilities. Addressing these limitations in future research will be crucial for validating

the findings and ensuring that the benefits of the MR-Linac can be broadly applied to diverse patient populations with high-grade gliomas.

The integration of MR-Linac technology into glioblastoma treatment represents a significant advancement, offering precise, adaptive radiotherapy that minimizes radiation exposure to healthy tissue while maintaining treatment efficacy. Ongoing clinical trials and research continue to demonstrate the potential of the MR-Linac to improve patient outcomes, highlighting its role in the future of radiation oncology for high-grade gliomas.

Acknowledgements Thank you to all the authors and my mentors in the Allegheny Health Network's Radiation Oncology and Neurosurgery departments for their invaluable mentorship and support throughout this learning experience.

Author contributions AM drafted the initial manuscript.RW, MS, SK, and JH created edits and changes to the drafts and helped finalize the manuscript. All authors reviewed the manuscript and contributed to writing and editing prior to submission.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

References

1. Rong L, Li N, Zhang Z (2022) Emerging therapies for glioblastoma: current state and future directions. J Exp Clin Cancer Res 41:142. https://doi.org/10.1186/s13046-022-02349-7
2. National Comprehensive Cancer Network (2025) NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancers. Version 1.2025. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf
3. Mark R, Gilbert et al (2013) Dose-Dense Temozolomide for newly diagnosed glioblastoma: A randomized phase III clinical trial. JCO 31:4085–4091. https://doi.org/10.1200/JCO.2013.49.6968
4. Niyazi M et al (2023) ESTRO-EANO guideline on target delineation and radiotherapy details for glioblastoma. Radiother Oncol 184:109663. https://doi.org/10.1016/j.radonc.2023.109663
5. Kutuk T, Detsky J, Sahgal A, Kotecha R (2024) MR-Linac-Guided adaptive radiotherapy for brain tumors. In: Das IJ, Alongi F, Yadav P, Mittal BB (eds) A practical guide to MR-Linac. Springer, Cham. https://doi.org/10.1007/978-3-031-48165-9_20
6. Stupp R, Taillibert S, Kanner A et al (2017) Effect of Tumor-Treating fields plus maintenance Temozolomide vs maintenance Temozolomide alone on survival in patients with glioblastoma: A randomized clinical trial. JAMA 318(23):2306–2316. https://doi.org/10.1001/jama.2017.18718
7. Stupp R, Mason W, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO, National Cancer Institute of Canada Clinical Trials Group (2005) Radiotherapy plus concomitant and adjuvant Temozolomide for glioblastoma. N Engl J Med 352(10):987–996. https://doi.org/10.1056/NEJMoa043330
8. Kruser TJ, Bosch WR, Badiyan SN, Bovi JA, Ghia AJ, Kim MM, Solanki AA, Sachdev S, Tsien C, Wang TJC, Mehta MP, McMullen KP (2019) NRG brain tumor specialists consensus guidelines for glioblastoma contouring. J Neurooncol 143(1):157–166. https://doi.org/10.1007/s11060-019-03152-9
9. Glioblastoma Multiforme Case #116 (2025) eContour. Duke University; https://econtour.org/cases/116. Accessed 6 Mar
10. Cao Y, Tseng CL, Balter JM, Teng F, Parmar HA, Sahgal A (2017) MR-guided radiation therapy: transformative technology and its role in the central nervous system. Neuro Oncol 19(suppl2):ii16–ii29. https://doi.org/10.1093/neuonc/nox006PMID: 28380637; PMCID: PMC5463498
11. Uehara K, Sasayama T, Miyawaki D, Nishimura H, Yoshida K, Okamoto Y, Mukumoto N, Akasaka H, Nishihara M, Fujii O, Soejima T, Sugimura K, Kohmura E, Sasaki R (2012) Patterns of failure after multimodal treatments for high-grade glioma: effectiveness of MIB-1 labeling index. Radiation Oncol (London England) 7:104. https://doi.org/10.1186/1748-717X-7-104
12. Jayamanne D, Wheeler H, Brazier D, Newey A, Kastelan M, Guo L, Back M (2018) Predicting patterns of failure in Temporal lobe GBMs: possible implications on radiotherapy treatment portals. Radiation Oncol (London England) 13(1):133. https://doi.org/10.1186/s13014-018-1078-y
13. Tseng CL, Stewart J, Whitfield G, Verhoeff JJC, Bovi J, Soliman H, Chung C, Myrehaug S, Campbell M, Atenafu EG, Heyn C, Das S, Perry J, Ruschin M, Sahgal A (2020) Glioma consensus contouring recommendations from a MR-Linac international consortium research group and evaluation of a CT-MRI and MRI-only workflow. J Neurooncol 149(2):305–314 Epub 2020 Aug 29. PMID: 32860571; PMCID: PMC7541359
14. Detsky J et al (2024) MR-Linac On-Line weekly adaptive radiotherapy for high grade glioma (HGG): results from the UNITED single arm phase II trial. Int J Radiat Oncol Biol Phys 120(2):S4
15. National Library of Medicine (US) (2023) UNIty-Based MR-Linac Guided Adaptive RadioThErapy for High GraDe Glioma-3 (UNITED-3). Identifier NCT05720078. https://clinicaltrials.gov/study/NCT05720078
16. Lawrence LSP, Chan RW, Chen H, Stewart J, Ruschin M, Theriault A, Myrehaug S, Detsky J, Maralani PJ, Tseng CL, Soliman H, Lim-Fat J, Das M, Stanisz S, Sahgal GJ, A., Lau AZ (2023) Diffusion-weighted imaging on an MRI-linear accelerator to identify adversely prognostic tumour regions in glioblastoma during chemoradiation. Radiotherapy Oncology: J Eur Soc Therapeutic Radiol Oncol 188:109873. https://doi.org/10.1016/j.radonc.2023.109873
17. Tseng CL, Chen H, Stewart J, Lau AZ, Chan RW, Lawrence LSP, Myrehaug S, Soliman H, Detsky J, Lim-Fat MJ, Lipsman N, Das S, Heyn C, Maralani PJ, Binda S, Perry J, Keller B, Stanisz GJ, Ruschin M, Sahgal A (2022) High grade glioma radiation therapy on a high field 1.5 Tesla MR-Linac - workflow and initial experience with daily adapt-to-position (ATP) MR guidance: A first report. Front Oncol 12:1060098. https://doi.org/10.3389/fonc.2022.1060098
18. Guevara B, Cullison K, Maziero D, Azzam GA, De La Fuente MI, Brown K, Valderrama A, Meshman J, Breto A, Ford JC, Mellon EA (2023) Simulated adaptive radiotherapy for shrinking glioblastoma resection cavities on a hybrid MRI-Linear accelerator. Cancers 15(5):1555. https://doi.org/10.3390/cancers15051555
19. Maziero D, Azzam G, de La Fuente M, Stoyanova R, Ford JC, Mellon EA (2023) Implementation and evaluation of a dynamic contrast enhanced MR perfusion protocol for glioblastoma using a 0.35T MRI-Linac system. arXiv. arXiv:2304.09128v2

20. Tseng C-L, Zeng KL, Mellon EA, Soltys SG, Ruschin M, Lau AZ et al (2024) Evolving concepts in margin strategies and adaptive radiotherapy for glioblastoma: A new future is on the horizon. Neuro Oncol 26(Suppl 1):S3–16. https://doi.org/10.1093/neuonc/noad258
21. Chan RW, Lawrence LSP, Oglesby RT, Chen H, Stewart J, Theriault A, Campbell M, Ruschin M, Myrehaug S, Atenafu EG, Keller B, Chugh B, MacKenzie S, Tseng CL, Detsky J, Maralani PJ, Czarnota GJ, Stanisz GJ, Sahgal A, Lau AZ (2021) Chemical exchange saturation transfer MRI in central nervous system tumours on a 1.5 T MR-Linac. Radiotherapy Oncology: J Eur Soc Therapeutic Radiol Oncol 162:140–149. https://doi.org/10.1016/j.radonc.2021.07.010