Clinically Delivered Treatment for Glioma Patients on a Hybrid Magnetic Resonance Imaging (MRI)-Linear Accelerator (MR-Linac) and a Cone Beam CT (CBCT)-Guided Linac: Dosimetric Comparisons with In Vivo Skin Dose Correlation

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Research Article

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Abstract

Background

Magnetic Resonance Imaging (MRI)-Linear Accelerator (MR-Linac) radiotherapy requires special consideration for secondary electron interactions within the magnetic field, which can alter dose deposition at air-tissue interfaces.

Methods

Thirty-seven consecutive glioma patients treated during their radiotherapy course with at least one fraction delivered on MR-Linac or Cone Beam CT (CBCT)-guided Linac, were analyzed. Treatment planning for both systems were completed prior to radiotherapy initiation and approved for clinical delivery using commercial treatment planning systems (TPS): a Monte Carlo calculation-based or convolution calculation-based TPS for MR-Linac or CBCT-Linac, respectively. Dosimetric parameters for planning target volume (PTV), organs-at-risk (OARs), and air-tissue interface were compared. In vivo skin dose during a single fraction of MR-Linac and CBCT-Linac treatment was measured using an Optically Stimulated Luminescent Dosimeter (OSLD) and correlated with TPS skin dose.

Results

Monte Carlo-based MR-Linac plans and convolution-based CBCT-Linac plans exhibited minimal differences in PTV and OAR parameters. However, MR-Linac plans had greater doses within tissues surrounding air cavities (1.52 Gy higher mean Dmean, $p < 0.0001$) and skin (1.10 Gy higher mean Dmean, $p < 0.0001$). In vivo OSLD skin readings were 14.5% greater for MR-Linac treatments ($p = 0.0027$), and were more accurately predicted by Monte Carlo-based calculation ($\rho = 0.95$, $p < 0.0001$) vs. convolution-based ($\rho = 0.80$, $p = 0.0096$).

Conclusions

The magnetic field's dosimetric impact was minimal for PTV and OARs in glioma as compared to standard CBCT-Linac treatment plans. However, skin doses were significantly greater with the MR-Linac and correlated with in vivo measurements. Future MR-Linac planning processes are being designed to account for skin dosimetry and treatment delivery.

Introduction

Modern radiotherapy with selective incorporation of Magnetic Resonance Imaging (MRI) during the treatment course has shown promise for evaluating glioma tumor dynamics [1], predicting glioma

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ns for dose escalation based on functional imaging. Typically,

no more than 2 to 3 MR images were obtained during a 6-week radiation treatment course due to practicalities and cost of obtaining repeat MRIs. With the advent of integrated MRI-linear accelerator (MR-Linac) delivery systems, this technology has the potential for the first time to allow daily acquisition of high field strength (1.5 Tesla) diagnostic quality MRI to enable adaptive radiotherapy, to individualize the radiation treatment plan and to incorporate functional imaging. At our institution, we have been developing the application of the Unity MR-Linac (Elekta AB, Stockholm, Sweden) to brain tumors, and have treated ~ 150 glioma patients with either 3 or 6 weeks of daily fractionated standard radiotherapy with concurrent temozolomide.

The challenge of delivering radiation within a high MRI field strength environment is the influence of the Lorentz force on dose deposition. The Electron Return Effect (ERE) refers to secondary electrons exiting tissue into air being curved back to deposit dose at the tissue surface due to the Lorentz Effect, which results from the presence of the strong magnetic field placed perpendicularly to the beam direction [3–11].

Until now, the ERE has been investigated in phantom studies [12], as well as in simulated dosimetric studies [13–17] with research versions of MR-Linac planning software prior to the release of the current clinical treatment planning version. The purpose of the current study is to report on those glioma patients treated on the MOMENTUM prospective registry study (Clinicaltrials.gov: NCT04075305) [18] who received at least one fraction of radiotherapy on both the MR-Linac and a Cone Beam CT (CBCT)-guided Linac: 1) the dosimetric impact of the magnetic field on the target, organs-at-risk (OARs), skin and tissues surrounding air cavities, and; 2) to compare skin dose modelled from the treatment planning software with in vivo skin dose measurements.

Materials And Methods

Patient Population

This consecutive case series of glioma patients treated between July 2019 and February 2021 consented to the institutional research ethics board approved prospective MOMENTUM trial. Patients were treated on the Unity MR-Linac (Elekta AB, Stockholm, Sweden) and our practice was to create a clinical backup conventional CBCT-Linac plan during treatment planning. On days when the MR-Linac was scheduled for maintenance or had a service issue such that treatment would otherwise be delayed, patients were irradiated on an Elekta CBCT-Linac (Elekta AB, Stockholm, Sweden) for that particular radiotherapy fraction. Thirty-seven glioma patients treated with at least one fraction on both the MR-Linac and CBCT-Linac for their adjuvant radiotherapy at our institution met these criteria. All patients completed maximal safe surgical resection followed by either 3 or 6 weeks of adjuvant radiotherapy according to standard practices [19–20].

Radiotherapy Simulation and Target Definition

All patients were simulated with a treatment planning CT (Brilliance, Philips Healthcare, Best, Netherlands) with a slice thickness of 1.0 mm, and immobilized with a thermoplastic head immobilization device (CIVCO Medical Solutions, Kalona, Iowa, USA). MRI simulation at 1.5 Tesla (Ingenia, Philips Healthcare, Best, Netherlands) was also performed in the treatment position with the immobilization device applied. Standard volumetric axial T1 gadolinium-enhanced and T2 FLAIR sequences with a slice thickness of 1.0 mm were acquired. CT images and MRI sequences were registered and fused based on rigid mutual information registration within a region of interest box defined around the tumor [21].

Delineation of OARs, gross tumor volume (GTV), and clinical target volume (CTV) were defined based on glioma consensus contouring guidelines [22]. Planning target volume (PTV) was generated as a 0.4-cm isotropic expansion of the CTV.

Radiotherapy Planning

Treatment planning for the MR-Linac was completed on the Monaco treatment planning system (TPS) (Monaco v5.40, Elekta AB, Stockholm, Sweden). The Monte Carlo algorithm [23] accounts for magnetic field effects for the MR-Linac. A TPS based on a convolution-superposition dose calculation algorithm (Pinnacle v9.8, Philips Healthcare, Eindhoven, Netherlands) was used for planning on the CBCT-Linac (Fig. 1). All MR-Linac plans used ≥ 9 coplanar non-opposing Intensity-Modulated Radiation Therapy (IMRT) beams, and were optimized to achieve at least 90% of the prescription dose covering 99% of PTV ($D_{99\%} > 90\%$), less than 5% of PTV getting 105% of the prescription dose ($V_{105\%} < 5\%$), and less than 110% of the prescription dose to 0.1cc volume of PTV ($D_{0.1cc} < 110\%$), as outlined by the MR-Linac consortium clinical treatment planning document. All CBCT-Linac plans used ≥ 7 coplanar non-opposing IMRT beams, and were optimized to achieve at least 95% of PTV covered by 95% of the prescription dose ($V_{95\%} \geq 95\%$), and at most 1% of PTV getting 105% of the prescription dose ($V_{105\%} \leq 1\%$). Dose to OARs were constrained according to our institutional protocols (Supplementary Material, Table 1).

Table 1
Patient Characteristics

Characteristic	Total (N = 37)
Age	22 (59.5%)
<i>cript</i> > 60 years	7 (18.9%)
60–69 years	8 (21.6%)
≥70 years	
Gender	25 (67.6%)
Male	12 (32.4%)
Female	
WHO Grade	9 (24.3%)
II	4 (10.8%)
III	24 (64.9%)
IV	
Prescription	8 (21.6%)
40 Gy in 15 fractions	15 (40.5%)
54 Gy in 30 fractions	13 (35.1%)
60 Gy in 30 fractions	1 (2.7%)
59.4 Gy in 33 fractions	

Radiotherapy Plan Evaluation

MR-Linac Monaco plans and CBCT-Linac Pinnacle plans for each patient were evaluated using cumulative dose-volume histogram (DVH) (Fig. 2) parameters chosen a priori. For targets, dosimetric parameters of interest were extracted and compared from reference plans for the PTV, CTV and GTV, including: 1) Volumes of tissue receiving at least 100%, 95%, 50% of the prescription dose (V100%, V95%, V50%); and 2) Minimum doses to 2%, 5%, 50%, 95%, 98% of the target volume (D2%, D5%, D50%, D95%, D98%). Dose homogeneity was assessed using Homogeneity Index (HI; Supplementary Material, Eq. 1), with lower HI values (closer to 1.0) indicating more homogeneous dose distribution. Dose falloff outside of the target was assessed using Gradient Index (GI; Supplementary Material, Eq. 2), with lower GI values characterizing a sharper dose falloff outside of the target. Dose conformity was assessed using Conformity Index (CI; Supplementary Material, Eq. 3), with CI values closer to 1.0 signifying better conformity. OARs for each patients' clinical treatment plans were extracted and compared including: Maximum dose to 0.03cc volume of Lens, Globe, Optic chiasm, Optic nerve (Lens D0.03cc, Globe D0.03cc, Optic chiasm D0.03cc, Optic nerve D0.03cc), Maximum dose to 0.01cc volume of Brainstem

(Brainstem D0.01cc), and Mean dose to each cochlea (Cochlea Dmean). The maximum dose to a small but finite volume of an OAR was defined so as to partially manage the statistical noise inherent in a Monte Carlo TPS.

Skin Dosimetry Assessment

Skin volumes were generated as a 5 mm rim of tissue contracted from the patient body surface (Supplementary Material, Fig. 1). Tissues around air cavities were generated as a 5mm rim of tissue expanded from air cavity volumes (e.g. nasopharynx, paranasal sinuses). Dosimetric parameters analyzed included: Mean dose and Maximum dose to 2cc volumes of tissues surrounding air cavities and skin contours (Air cavity Dmean, Air cavity D2cc, Skin Dmean, Skin D2cc), as well as the volume of skin receiving 20 Gy (Skin V20Gy).

For 10 randomly selected patients, in vivo skin dose measurements during one fraction of MR-Linac treatment and one fraction of CBCT-Linac treatment were obtained using Optically Stimulated Luminescent Dosimeters (OSLDs; nanoDots, Landauer, Glenwood, IL, USA) placed in a defined location on the patient's skin near the PTV (Supplementary Material, Fig. 2). OSLD dose point in the TPS was defined as the placement location on the treatment unit, at 0.6 mm depth from the patient surface. In the TPS, the patient surface was defined as the 0.6 g/cc boundary between tissue and air. The 0.6 mm depth is the water equivalent depth of an OSLD taking into account its plastic casing, and the accuracy was rated to be $\pm 3\%$ [12]. Dose delivered to skin, as measured by the OSLD, were correlated to both corresponding clinical treatment plans to determine which TPS best predicted the in vivo dose measurement.

Statistical Analysis

Descriptive statistics were used to summarize the dosimetric parameters. Assumption of normality was assessed using the Smirnov-Kolmogorov test. Student's t-paired test or Wilcoxon signed-rank test, as appropriate based on normality assumption, were used to compare dosimetric parameters between MR-Linac plans and CBCT-Linac plans. Spearman's correlation was used to assess the relationship between in vivo OSLD measurements and TPS skin dose. All statistical tests were two-sided, and threshold used for statistical significance was $p < 0.05$. Statistical analyses were performed using version 9.4 of the SAS system for Windows (2002–2012 SAS Institute, Inc., Cary, NC, USA).

Results

Target Volumes and Organs at Risk

Thirty-seven glioma patients treated with at least one fraction on both the MR-Linac and CBCT-Linac were analyzed (Table 1). Comparisons of PTV dosimetric parameters between MR-Linac and CBCT-Linac are detailed in Table 2a. There is no statistical difference in PTV V100%, V95%, V50%, D98%, and D95% ($p > 0.05$). Small but statistically significant differences were observed in mean PTV D50% ($p < 0.0001$), D5%

Loading [MathJax]/jax/output/CommonHTML/jax.js MR-Linac plans compared with CBCT-Linac. MR-Linac dose

distributions had higher HI ($p = 0.0007$), better CI ($p = 0.0064$), and equivalent GI ($p > 0.05$) compared to CBCT-Linac.

Table 2

a. Dosimetric impact of magnetic field on target volume parameters in treated glioma patients

PTV	MR-Linac (Mean $\pm$ ME)	Conventional Linac (Mean $\pm$ ME)	Paired Difference (Mean $\pm$ ME)	P value
V100% (cc)	265.94 $\pm$ 41.15	265.28 $\pm$ 41.43	0.66 $\pm$ 3.87	0.9705
V95% (cc)	278.48 $\pm$ 42.19	269.44 $\pm$ 43.00	9.04 $\pm$ 14.54	0.2920
V50% (cc)	280.07 $\pm$ 42.19	279.96 $\pm$ 42.17	0.11 $\pm$ 0.18	0.5000
D98% (Gy)	52.19 $\pm$ 2.46	51.57 $\pm$ 2.43	0.62 $\pm$ 0.66	0.5786
D95% (Gy)	53.11 $\pm$ 2.50	52.67 $\pm$ 2.47	0.44 $\pm$ 0.46	0.1090
D50% (Gy)	54.67 $\pm$ 2.57	54.39 $\pm$ 2.57	0.27 $\pm$ 0.10	< 0.0001
D5% (Gy)	55.92 $\pm$ 2.63	55.17 $\pm$ 2.60	0.75 $\pm$ 0.12	< 0.0001
D2% (Gy)	56.28 $\pm$ 2.65	55.42 $\pm$ 2.61	0.86 $\pm$ 0.12	< 0.0001
Homogeneity Index	1.05 $\pm$ 0.01	1.05 $\pm$ 0.02	0.01 $\pm$ 0.01	0.0007
Gradient Index	1.07 $\pm$ 0.04	1.22 $\pm$ 0.33	-0.14 $\pm$ 0.29	0.8303
Conformity Index	0.87 $\pm$ 0.02	0.83 $\pm$ 0.03	0.04 $\pm$ 0.03	0.0064
ME = Margin of error for 95% CI				
Paired difference = MR-Linac – Conventional Linac				

Table 2

b. Dosimetric impact of magnetic field on organs-at-risk (OARs) in treated glioma patients

OARs	MR-Linac (Mean $\pm$ ME)	Conventional Linac (Mean $\pm$ ME)	Paired Difference (Mean $\pm$ ME)	P value
Brainstem D0.1cc (Gy)	47.27 $\pm$ 4.48	46.72 $\pm$ 4.58	0.55 $\pm$ 0.79	0.0307
Optic Chiasm D0.03cc (Gy)	43.88 $\pm$ 4.78	42.78 $\pm$ 5.24	1.11 $\pm$ 1.17	0.5635
Optic Nerve Right D0.03cc (Gy)	35.47 $\pm$ 5.64	35.36 $\pm$ 6.09	0.11 $\pm$ 1.38	0.1804
Optic Nerve Left D0.03cc (Gy)	34.29 $\pm$ 5.87	34.64 $\pm$ 6.14	-0.35 $\pm$ 1.26	0.4858
Globe Right D0.03cc (Gy)	24.90 $\pm$ 4.51	21.87 $\pm$ 4.61	3.03 $\pm$ 1.69	0.0009
Globe Left D0.03cc (Gy)	22.26 $\pm$ 3.54	18.56 $\pm$ 3.48	3.70 $\pm$ 1.98	0.0005
Cochlea Right Dmean (Gy)	18.25 $\pm$ 6.70	18.56 $\pm$ 6.53	-0.30 $\pm$ 1.78	0.5597
Cochlea Left Dmean (Gy)	15.52 $\pm$ 6.94	16.39 $\pm$ 7.05	-0.87 $\pm$ 1.80	0.5046
Lens Right D0.03cc (Gy)	7.15 $\pm$ 0.79	5.25 $\pm$ 0.79	1.89 $\pm$ 0.67	< 0.0001
Lens Left D0.03cc (Gy)	7.43 $\pm$ 0.75	5.29 $\pm$ 0.85	2.14 $\pm$ 0.71	< 0.0001
ME = Margin of error for 95% CI				
Paired difference = MR-Linac – Conventional Linac				

Comparison of OAR dosimetric parameters between MR-Linac and CBCT-Linac are shown in Fig. 2a, and summarized in Table 2b. There was no statistical difference in the D0.03cc for the optic chiasm and optic nerves ($p > 0.05$), and no statistical difference in the mean dose to each cochlea ($p > 0.05$). Small but statistically significant differences were observed in clinically delivered D0.03cc for brainstem ($p = 0.0307$), D0.03cc for each globe ($p < 0.0010$), and D0.03cc for each lens ($p < 0.0001$) for the MR-Linac.

Tissues around Air Cavities and at Skin Surface

The difference in dosimetric parameters for tissues surrounding air cavities and skin between MR-Linac and CBCT-Linac are shown in Fig. 2b, and summarized in Table 3a. For tissues surrounding air cavities, MR-Linac treatments had statistically significant higher Dmean ($p < 0.0001$) and D2cc ($p = 0.0007$) compared to CBCT-Linac. For skin tissues, MR-Linac treatments had statistically significant higher Dmean ($p < 0.0001$) and V20Gy ($p = 0.0001$) compared to CBCT-Linac, but no difference in D2cc ($p = 0.7975$).

Table 3

a. Dosimetric impact of magnetic field on tissues surrounding air cavities and at skin surface in treated glioma patients

Tissues Surrounding Air Cavities and at Skin Surface	MR-Linac (Mean $\pm$ ME)	Conventional Linac (Mean $\pm$ ME)	Paired Difference (Mean $\pm$ ME)	P value
Air Cavity Dmean (Gy)	12.05 $\pm$ 2.27	10.53 $\pm$ 2.08	1.52 $\pm$ 0.60	< 0.0001
Air Cavity D2cc (Gy)	41.78 $\pm$ 6.10	40.55 $\pm$ 6.44	1.23 $\pm$ 0.98	0.0007
Skin Dmean (Gy)	8.64 $\pm$ 1.99	7.54 $\pm$ 2.00	1.10 $\pm$ 0.54	< 0.0001
Skin D2cc (Gy)	45.55 $\pm$ 2.80	45.45 $\pm$ 3.67	0.11 $\pm$ 0.85	0.7975
Skin V20Gy (cm ³)	85.59 $\pm$ 13.70	66.55 $\pm$ 12.16	19.04 $\pm$ 11.45	0.0001
ME = Margin of error for 95% CI				
Paired difference = MR-Linac – Conventional Linac				

Table 3

b. Comparison of predicted skin dose from TPS software and delivered skin dose measured from OSLD

Skin Dose	MR-Linac (Mean $\pm$ ME)	Conventional Linac (Mean $\pm$ ME)	Mean Difference (Mean $\pm$ ME)	P value
TPS (Gy)	35.0 $\pm$ 7.7	27.2 $\pm$ 6.8	7.8 $\pm$ 4.1	0.0020
OSLD (Gy)	36.3 $\pm$ 9.6	31.7 $\pm$ 8.8	4.6 $\pm$ 2.5	0.0027
Mean Difference	1.4 $\pm$ 2.1	4.0 $\pm$ 5.2		
P value	Spearman ρ = 0.9500, p < 0.0001	Spearman ρ = 0.8000, p < 0.0096		
ME = Margin of error for 95% CI				

Differences between predicted skin dose from the TPS and delivered skin dose measured from OSLD are quantified in Table 3b. Mean skin dose as determined by the TPS was 7.8 Gy greater on MR-Linac plans (95% CI 3.7–11.8 Gy) compared with CBCT-Linac (p = 0.0020). Mean in vivo OSLD skin readings were 4.6 Gy greater (14.5% higher) on MR-Linac treatments (95% CI 2.1–7.1 Gy) compared with CBCT-Linac (p = 0.0027). There was a 1.4 Gy mean difference between MR-Linac Monaco modelled skin dose and in vivo OSLD skin dose. In contrast, there was a 4.0 Gy mean difference between CBCT-Linac Pinnacle modelled skin dose and in vivo OSLD skin dose. Furthermore, MR-Linac Monaco predicted in vivo OSLD skin dose

more accurately (Spearman's correlation $\rho = 0.9500$, $p < 0.0001$). By comparison, there was a weaker association between CBCT-Linac Pinnacle modelled skin dose and in vivo OSLD skin dose (Spearman's correlation $\rho = 0.8000$, $p < 0.0096$).

Discussion

We demonstrate that Monaco is able to accurately generate safe MR-Linac radiotherapy treatment plans for glioma patients that achieve planning objectives. We observed that for coplanar beam arrangements, MR-Linac treatments have lower homogeneity, but higher dose conformity and equivalent dose falloff outside of the target, when compared with CBCT-Linac. Conventional CBCT-Linac with non-coplanar beams can potentially achieve better dose falloff than MR-Linac, but only coplanar beam arrangements were used to standardize comparisons. MR-Linac treatment plans had more heterogeneous dose distributions, which is consistent with the observed small but statistically significant increase in PTV D50%, D5%, and D2%. This is also consistent with previous reports showing higher heterogeneity and higher median V100% for MR-Linac plans compared with CBCT-Linac [24]. Similarly, a very small but statistically significant increase in Brainstem D0.1cc, each Globe D0.03cc, and each Lens D0.03cc was observed in MR-Linac plans. Over the course of a patient's entire radiotherapy regimen, the absolute summed dose difference was < 1 Gy for PTV parameters, < 1 Gy for brainstem, approximately 3 Gy for each globe, and approximately 2 Gy for each lens. Since MR-Linac treatment plans are adapted to position every fraction [25], the exact location of these minimally higher dose regions varies geospatially every fraction, which may negate their effects when accumulated over the treatment course. Nonetheless, all MR-Linac treatments achieved standard planning objectives and dose constraints, and it is unlikely that these small differences translate into clinically relevant outcomes.

We also quantitatively characterized the impact of the MR-Linac's magnetic field on delivered dose to skin and tissue surrounding air cavities. Compared to CBCT-Linac, we observed that MR-Linac treatments showed 1.52 Gy higher Dmean ($p < 0.0001$), and 1.23 Gy higher D2cc ($p = 0.0007$) for tissues surrounding air cavities. Skin D2cc was not statistically different ($p > 0.05$), skin Dmean was 1.10 Gy higher ($p < 0.0001$), and skin V20Gy was 19.04 cm³ higher ($p = 0.0001$) with MR-Linac treatment. This is consistent with recent preliminary studies investigating the effect of the MR-Linac's magnetic field on radiotherapy treatment [12–17]. Tseng et al. used Monaco to retrospectively generate MR-Linac plans with 9 coplanar non-opposing IMRT beams on 24 patients with intact single brain metastases, and found MR-Linac had 0.08 Gy higher Dmean and 0.6 Gy higher D2cc for skin, and 0.07 Gy higher Dmean and 0.3 Gy higher D2cc for tissues around air cavities [13]. Schrenk et al. used an open-source Monte Carlo-based TPS to retrospectively generate plans in the presence of a magnetic field with ≥ 7 coplanar non-opposing 3D-CRT and IMRT beams on 4 patients with non-small cell lung cancer, and found that the presence of the perpendicular magnetic field increased mean dose to tissues surrounding the lung air cavity by 0.5 Gy (18.5%) [14]. Nachbar et al. used Monaco to prospectively generate a MR-Linac plan with 7 coplanar non-opposing IMRT beams on 1 breast cancer patient, and found MR-Linac had 0.3 Gy higher D2cc and 15.3% higher V35Gy for skin tissue [15]. Xia et al. used Monaco to retrospectively generate MR-Linac

cancer, and found MR-Linac had 1.30–1.81 Gy higher Dmean and 1.68–5.43 Gy higher Dmax for skin, and no difference in dose to tissues surrounding air cavities except for higher Dmax to larynx and trachea [16]. Boldrini et al. used MRIdian TPS to retrospectively generate MR-Linac plans with 7 coplanar non-opposing equally-spaced IMRT beams on 10 patients with locally advanced rectal cancer, and found MR-Linac had higher skin dose and higher PTV V105% (14.8%) compared with CBCT-Linac VMAT with two full coplanar arcs (5.0%) and CBCT-Linac IMRT using 5 coplanar beams (7.3%) [17]. Taken together, these studies demonstrated that MR-Linac plans have small increases in dose to skin and tissues surrounding air cavities, and are consistent with our findings. However, the present study is unique in that the selected patient population represents a large cohort of glioma patients who received at least one fraction on both MR-Linac and CBCT-Linac based on clinically approved radiotherapy plans. Second, the plans were prospectively generated prior to treatment and delivered on both MR-Linac and CBCT-Linac, in contrast to previous studies of simulated plans that were retrospectively generated for dosimetric comparison. Lastly and importantly, we performed in vivo measurements to correlate the skin dose calculated on Monaco and Pinnacle, with measured patient skin dose via OSLD on MR-Linac and CBCT-Linac.

A potential limitation of our study is the variability in dose fractionations used. However, plan evaluation was performed with pairwise comparisons between MR-Linac and CBCT-Linac treatments for each patient and are independent of absolute values. Second, there may be potential uncertainty in OSLD measurements caused by placement, air gaps, and surface effects. To mitigate this, a single OSLD measurement was obtained from each patient's MR-Linac and CBCT-Linac treatments using standardized technique [12], although we acknowledge that reproducibility could be assessed by performing additional measurements. Third, since there are differences in how each TPS models patient surface, calculates surface dosimetry, and uses voxel sizes for TPS dose evaluation, we recognize the difficulty in quantifying the magnitude of these effects and their contribution to the dose differences observed. Finally, each patient's clinically delivered treatment plan was analyzed on the latest version of clinical Monaco TPS, and we acknowledge that future iterations of clinical Monaco may have even better dose optimization, dose engines, and dose modelling.

Potential strategies to mitigate skin dose in MR-Linac treatment include increasing the number of beam angles [26–28], using opposing beam configurations [29], using VMAT [30], using partial arcs [31], using smaller margins on target volumes [32], and specifically using a skin objective during planning optimization to minimize skin dose. Kim et al. investigated the effects of different beam arrangements on skin dosimetry for partial breast radiotherapy using MR-Linac, and demonstrated an 11–18% increase in skin D1cc and an 146–149% increase in skin V30 with the addition of the magnetic field. However, increasing the number of beam angles, and going from IMRT to VMAT reduced the skin dose in the presence of the magnetic field [27]. Bainbridge et al. investigated the effect of a PTV margin reduction from 7 mm to 3 mm on skin dosimetry for lung cancer radiotherapy using MR-Linac. They demonstrated that MR-Linac plans with 7 mm margins had 0.4 Gy higher Dmean skin dose and 1.7 Gy higher D2cc skin dose compared to CBCT-Linac plans with 7 mm margins. However, MR-Linac plans with a reduced margin (3mm) alleviated this issue, while also decreasing other OAR metrics, and allowed isotoxic dose

Loading [MathJax]/jax/output/CommonHTML/jax.js trial used a reduced 5 mm CTV margin with hypofractionated

regimens and demonstrated survival outcomes similar to that of historical control [33]. Therefore, MRI-guided treatment of gliomas with a reduced CTV margin and an adaptive framework not only potentially mitigates skin dose effects on the MR-Linac, but may allow for opportunities to decrease toxicities and incorporate boost strategies based on functional imaging. Finally, since this study demonstrates that Monaco's Monte Carlo dose algorithm can accurately model the near-surface dose, using the TPS IMRT optimizer with skin as an avoidance structure can reliably decrease skin dose. Future work to incorporate skin dose mitigation strategies into planning processes are being developed. Further studies investigating favorable clinical scenarios where higher dose is required to skin and superficial targets are warranted as well.

Conclusion

This is the first prospective dosimetric comparison of glioma patients clinically treated with at least one fraction on both MR-Linac and CBCT-Linac, combined with in vivo correlation to delivered dose on each platform. The dosimetric impact of the MR-Linac's magnetic field was minimal for target volumes and standard OARs. However, higher doses to tissues at skin surface and surrounding air cavities were observed for clinically delivered MR-Linac treatments. In vivo correlation of delivered skin dose was more accurately predicted by Monaco. Future MR-Linac planning processes are being designed to account for skin dosimetry and treatment delivery.

Declarations

Funding:

The authors did not receive financial support from any organization for the submitted work.

Conflicts of Interest:

MR is a co-inventor/owns intellectual property specific to the image-guidance system

on the Gamma Knife Icon outside the submitted work.

HS has received travel accommodations/expenses and honoraria from Elekta AB outside the submitted work.

SM has provided research support to Novartis AG and has received honoraria from Novartis AG and Ipsen and travel accommodations/expenses from Elekta outside the submitted work.

BK has received previous grant funding from Elekta AB outside of the submitted work and has also received travel accommodations/expenses from Elekta AB outside of this work.

AS is an advisor/consultant for AbbVie, Merck, Roche, Varian, Elekta AB, BrainLAB, and VieCure; is a board member of the International Stereotactic Radiosurgery Society; is cochair of the AO Spine

Knowledge Forum Tumor; has conducted educational seminars for Elekta AB, Accuray Inc, Varian, BrainLAB, and Medtronic Kyphon; has received research grants from Elekta AB and travel accommodations/expenses from Elekta AB, Varian, and BrainLAB; and is a member of the Elekta MR-Linac Research Consortium, Elekta Spine, Oligometastases, and Linac-based SRS Consortia.

CLT has received travel accommodations/expenses and honoraria from Elekta AB and belongs to the Elekta MR-Linac Research Consortium.

The remaining authors reported no disclosures or conflicts of interest.

Availability of Data and Material:

Data will be made available on request to the corresponding author following institutional ethics committee protocols.

Author Contributions:

Conceptualization: MW, AK, MR, AS, CLT

Methodology: All authors

Formal analysis and investigation: All authors

Writing - original draft preparation: MW, AS, CLT

Writing - review and editing: All authors

Project administration and supervision: AS, CLT

All the authors are in agreement and accountable for all the aspects of the work.

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Figures

Figure 1

Clinically delivered treatment plans for a representative study patient diagnosed with glioblastoma, and prescribed 60 Gy in 20 fractions. Top row depicts MR-Linac axial (a), coronal (b), and sagittal (c) dose

distributions from Monaco. Bottom row depicts conventional Linac axial (d), coronal (e), and sagittal (f) dose distributions generated from Pinnacle. PTV is depicted in blue colorwash. Isodose lines are quantified in cGy

Figure 2

Dose-Volume Histograms of Planning Target Volume and Organs-at-Risk (a), as well as tissues surrounding air cavities and at skin surface (b) for a representative study patient. Delivered MR-Linac treatment (solid lines) is compared with conventional Linac treatment (dashed lines)

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