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Highly Conformal Radiation Planning of Orthotopic Glioblastoma Model in Mice Using 9.4T MRI Scans to Simulate Human Treatment

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ABSTRACT

Glioblastomas (GBM) are nearly uniformly fatal tumors. Preclinical GBM models are crucial for the development of novel therapeutic strategies to improve outcomes for this disease.

One major limitation of existing preclinical models is the significant disparity in the radiotherapy (RT) methodology employed in the laboratory for small rodent models compared to that used for human patients in the clinic. The delivery of highly conformal, conventional fractionation RT forms the basis for standard-of-care RT in human GBM.

However, most preclinical RT approaches utilize large, whole-brain fields and extreme hypofractionation limiting translational potential. Therefore, this study was designed to improve preclinical translation through the development of a novel, standardized technical procedure for highly conformal, preclinical RT planning in a murine model of GBM using ultra-high field 9.4T magnetic resonance (MR) imaging.

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METHODS AND MATERIALS

- Eight 7-week-old C57BL/6J mice, 4 female and 6 males, were implanted with approximately 50,000 SB28 GBM cells into the right hemisphere stereotactically.
- Tumor growth was monitored through BLI.
- MR images were obtained for the mice using the 9.4T scanner 9 days post implantation based on tumor kinetics.
- Axial and sagittal multislice T2-w TurboRARE sequences were acquired (slice thickness 0.8 mm) using either quadrature surface or volume saddle RF coils with an in-plane resolution of 78 µm.
- The MRI images were registered to CBCT images acquired on the Xstrahl Small Animal Radiation Research Platform (SARRP) using the Muriplan TPS, enabling rapid delineation of target volumes and organs at risk (OARs).
- Radiation plans were generated using a prescription consisting of 40.05 Gy in 15 fractions at 2.67 Gy/fx.
- Acceptable plans required that the prescribed dose covered 95% of the planning target volume. Dose calculation and verification was performed through a Monte Carlo algorithm.

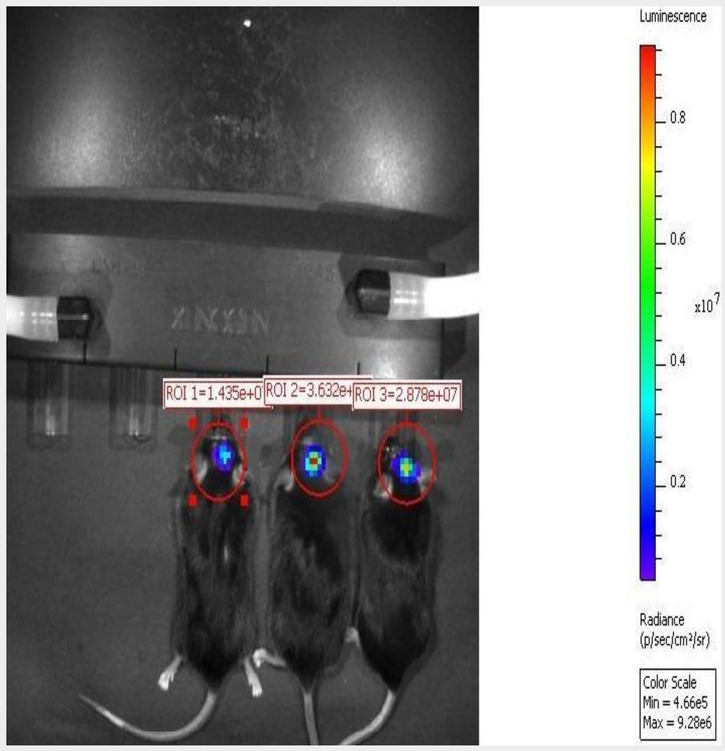


Figure 1 (Above): Bioluminescent imaging using an In-Vivo Imaging System to monitor tumor kinetics to plan the MRI scans.

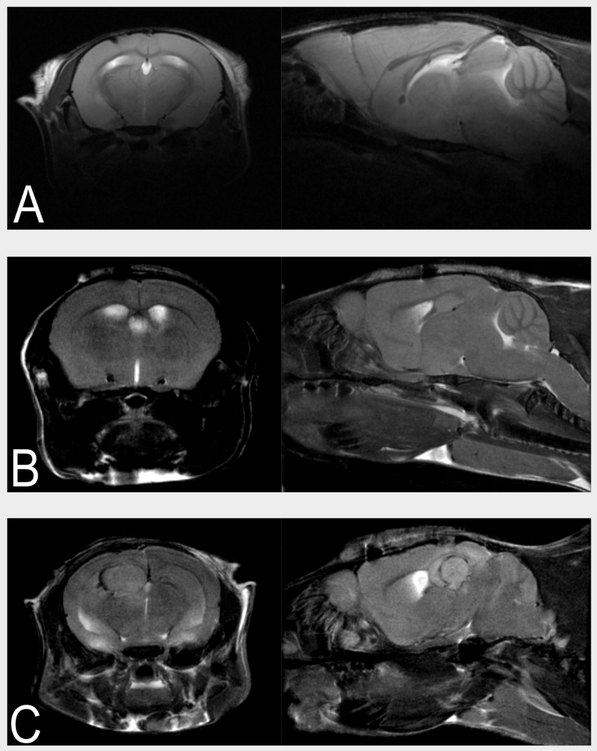


Figure 2 (Above): T2-w TurboRARE MRI images in axial and sagittal orientations obtained for RT treatment planning
A) Control animal - quadrature RF coil
B) Control animal - volume saddle RF coil
C) Animal with tumor - volume saddle RF coil

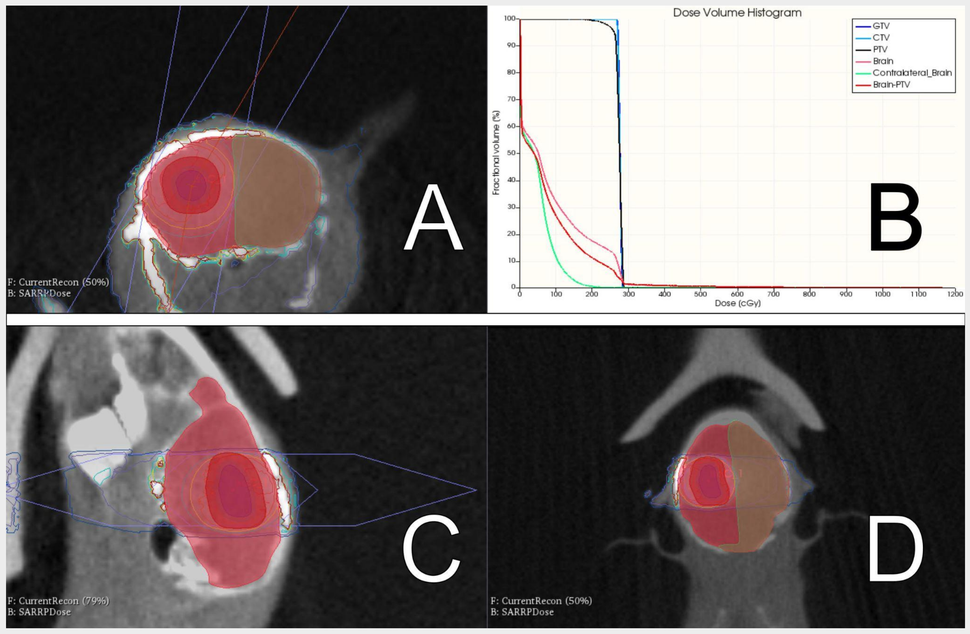


Figure 3 (Above): MRI and CBCT fusion shown with super-imposed contouring and isodose lines

Figure 4 (Left): Example treatment plan for tumor bearing mouse.

A) Axial slice of RT plan
B) Dose volume histogram
C) Sagittal slice of RT plan
D) Coronal slice of RT plan

Mouse	Dose (cGy) D95 PTV	D99 CTV	D99 GTV
A1	262.3	269.4	271.0
A2	192.6	236.6	276.3
A4	268.2	269.6	271.4
B1	269.6	272.5	275.2
B2	228.8	264.4	274.6
C1	185.0	245.2	269.8
Per-fraction dose (cGy)			
Mean	234.4	259.6	273.1
σ	38.41	14.98	2.67
Total dose (Gy)			
Mean	35.16	38.94	40.96
σ	5.76	2.25	0.40

Table 1: The doses covering 95 and 99 percent of a respective tumor volume used for planning.

Mouse	Dose (cGy) $D_{98\%}$	$D_{2\%}$	D_{mean}	$D_{50\%}$
A1	243.1	291.5	280.6	282.3
A2	237.7	319.9	300.4	300.9
A4	246.9	302.6	286.6	286.9
B1	239.5	304.1	287.0	290.5
B2	210.4	308.5	292.0	286.5
C1	243.1	357.2	280.0	276.8
Per-fraction dose (cGy)				
Mean	240.6	314.0	287.8	287.3
σ	17.9	23.1	7.64	8.14
Total dose (Gy)				
Mean	36.09	47.09	43.16	43.10
σ	2.68	3.47	1.15	1.22

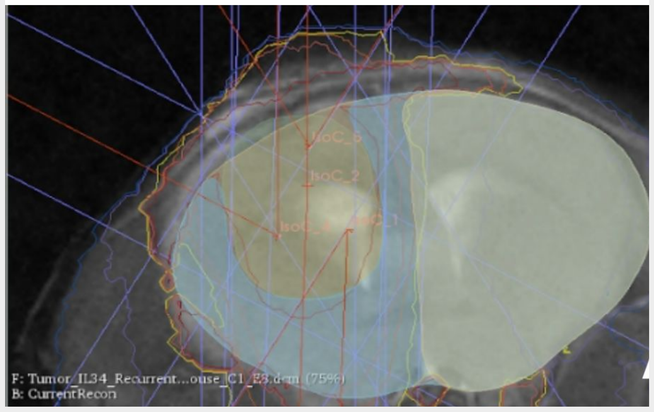
Table 2: The min, max, mean, and median dose delivered to the PTV.

Mouse	Dose (cGy) D_{mean} NB	D_{mean} CB	$D_{2\%}$ NB	$D_{2\%}$ CB
A1	84.12	51.45	302.3	177.5
A2	100.5	60.98	307.3	260.1
A4	104.9	71.13	295.3	276.1
B1	116.7	70.97	300.5	265.1
B2	102.8	83.70	283.5	281.1
C1	102.4	73.55	286.6	271.9
Per-fraction dose (cGy)				
Mean	101.9	68.63	295.9	255.3
σ	10.46	11.11	9.30	38.85
Total dose (Gy)				
Mean	15.28	10.29	44.39	38.30
σ	1.57	1.67	1.40	5.83

Table 3: The mean and max doses for the OARs including normal brain (NB) and contralateral brain (CB).

RESULTS

- Registered 9.4T MR and CBCT images allowed precise delineation of target volumes and OARs in an orthotopic mouse model.
- Highly conformal dose distributions could be generated using static and/or dynamic beams, using multiple isocenters and collimator sizes, similar to human GBM RT planning.
- D99 and D95 values used determined for RT planning [Table 1].
- The mean values for the 6 treated mice for near-minimum (D98%), near-maximum (D2%), mean (Dmean) and median (D50%) PTV doses were were calculated [Table 2].
- Mean and near-minimum dose values were calculated for the OARs also [Table 3].



CONCLUSIONS

- The use of 9.4T MR images has not been described for preclinical murine irradiation yet enables precise visualization and delineation of implanted GBM tumors.
- Moreover, combining 9.4T MR images with highly conformal planning techniques on the SARRP permits target coverage while reducing NB irradiation despite the small size of the brain and targets.
- Importantly, planning dose and plan quality indices are similar to those reported for GBM patients, thus maximizing the translational potential of preclinical data.

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