Treatment planning and 3D dose verification of whole brain radiation therapy with hippocampal avoidance in rats

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Abstract. Despite increasing use of stereotactic radiosurgery, whole brain radiotherapy (WBRT) continues to have a therapeutic role in a selected subset of patients. Selectively avoiding the hippocampus during such treatment (HA-WBRT) emerged as a strategy to reduce the cognitive morbidity associated with WBRT and gave rise to a recently published the phase II trial (RTOG 0933) and now multiple ongoing clinical trials. While conceptually hippocampal avoidance is supported by pre-clinical evidence showing that the hippocampus plays a vital role in memory, there is minimal pre-clinic data showing that selectively avoiding the hippocampus will reduce radiation-induced cognitive decline. Largely the lack of pre-clinical evidence can be attributed to the technical hurdles associated with delivering precise conformal treatment to rats. In this work we develop a novel conformal HA-WBRT technique for Wistar rats, utilizing a 225kVp micro-irradiator with precise 3D-printed radiation blocks designed to spare hippocampus while delivering whole brain dose. The technique was verified on rodent-morphic Presage® 3D dosimeters created from micro-CT scans of Wistar rats with Duke Large Field-of-View Optical Scanner (DLOS) at 1mm isotropic voxel resolution. A 4-field box with parallel opposed AP-PA and two lateral opposed fields was explored with conformal hippocampal sparing aided by 3D-printed radiation blocks. The measured DVH aligned reasonably well with that calculated from SmART Plan Monte Carlo simulations with simulated blocks for 4-field HA-WBRT with both demonstrating hippocampal sparing of 20% volume receiving less than 30% the prescription dose.

1. Introduction
Therapeutic whole brain radiotherapy (WBRT) has been used to primary or metastatic brain tumors since the 1950s [1]. However, many patients experience some degree of neurocognitive decline after treatment [2]. Studies have shown that metastases to the limbic circuit – which includes the hippocampus – are rare, and hence can be spared during WBRT for improved brain functions [3, 4]. The potential value of hippocampal avoidance is supported by pre-clinical and clinical evidence showing that the hippocampus plays a vital role in memory. Yet there is minimal in-vivo pre-clinic data showing that selectively avoiding the hippocampus will reduce radiation-induced cognitive decline. Largely the lack of such evidence can be attributed to the technical hurdles associated with delivering precise conformal treatment to small animal to create an accurate model. Our group published the first rodent model of hippocampal avoidance where treatment planning incorporated MRI-based identification of the hippocampus as an avoidance structure and validated accurate treatment delivery dosimetrically and
with tissue immunostaining (Cramer et al. [5]). In brief, in this initial work, we developed lateral-opposed 2-field HA-WBRT plan in 8-week Wistar rats with two conformal lead hand-cut blocks held at a distance in front of the x-ray source shielding the hippocampus. Since then, we have replaced the hand-cut lead blocks with 3D-printed radiation blocks generated from tungsten-doped plastic filaments.

Precise, conformal irradiation of small targets in rodents is exceptionally challenging [5]. High-resolution 3D dosimetry is essential to ensure accurate treatment delivery [6]. Presage® (from John Adamovics, Heuris Inc.) is a 3D radiochromic (i.e. changing color when irradiated), tissue-equivalent solid plastic dosimeter which is ideal for these situations. Presage molding techniques allowed fabrication of rodent-morphic Presage dosimeters [7]. These are dosimeters with exact dimensions of a mouse or a rat. In this study, we generated a rodent-morphic Wistar rat dosimeter with the purpose of reconstructing 4-field conformal HA-WBRT dose delivered to a tissue-equivalent, geometrically accurate rat dosimeter on the small animal irradiator with 225kVp x-ray treatment beam.

2. Methods and Materials
In this section, we present methods used to verify that conformal 4-field HA-WBRT has indeed spared the hippocampus with a rodent-morphic dosimeter. All radiation experiments have been performed on Xrad 225Cx MicroCT irradiator from Precision X-ray, Inc. which has image-guided radiotherapy capabilities. All irradiation was performed at 225kVp with a 0.35mm copper filter. Dose read-outs from Presage dosimeter were performed with high-resolution Duke Large Field-of-View Optical Scanner (DLOS), which is an optical CT specifically designed for 3D quantitative reconstruction of Presage [8].

2.1. Conformal radiation therapy on Xrad 225Cx
Conformal radiation therapy was previously performed with Xrad 225Cx unit by attaching a lead radiation block onto a thin piece of paper suspended by 40x40mm² collimator and a 3D-printed block holder (Figure 1, left) intended to shield the hippocampus. For further details on our conformal radiation therapy method, the reader is referred to Cramer et al [5].

To improve conformality and remove human error from block fabrication, a metal-composite 3D printing material GMASS (Turner MedTech, Inc., Orem, UT) replaced the lead block. Intended for x-ray shielding, the high-density tungsten-composite ABS filament fit our purposes of performing conformal HA-WBRT. Hippocampal-sparing 3D-printed blocks for 4-field treatment with 1mm margin for each block were attached to our customized collimator attachment for treatment (Figure 1).

2.2. Verification of Radiation Block and 4-field HA-WBRT with Rodent-Morphic Dosimeters
Initial verification of radiation blocking properties of GMASS filament was done using a heart-shaped 3D-printed block with a GafchromicTM EBT3 film at radiation dose of 6 Gy. Film was sampled at 30 dpi to reduce micro-variations in film optical density. This was to ensure minimal primary radiation is passing through the dosimeter. Once this was verified, rodent-morphic dosimeters were fabricated.

Rodent-morphic dosimeters for this set-up were modelled after the CBCT of an 8-week old Wistar rat (Figure 2). The model of the rat was generated from this CBCT via surface rendering on itk-snap (www.itksnap.org) [9]. The model was then smoothed to exclude extraneous details that could
compromise the quality of the resulting Presage mold, then 3D-printed using PLA filament. The 3D-printed rat model was then used to mold and cast two rodent-morphic dosimeters.

The fabricated dosimeters were then subjected to an irradiation with 4-field box with parallel opposed AP-PA and two lateral opposed fields, with conformal hippocampal sparing aided by 3D-printed radiation blocks. The prescription dose for this HA-WBRT was 1 Gy for direct comparison with 1 Gy planning-dose SmART Plan simulation, a full Monte Carlo dose planning software for Xrad 225Cx irradiator [10]. The dose distribution was read out with DLOS at 1mm isotropic voxel resolution. We calculate and compare between dose volume histograms (DVHs) of measured and simulated dose distributions for the hippocampus (plus 1mm margin) and the brain without hippocampus to assess hippocampal sparing and dose agreement.

3. Results and Discussion

We present here the result of radiochromic film study and 4-field conformal HA-WBRT delivered to a rodent-morphic Presage dosimeter discussed in section 2.2.

Figure 3 demonstrates that very minimal dose (0.19 Gy for a 6.01 Gy treatment) passes through the 3D-printed blocks. The block edges are well-defined, with 80%-to-20% penumbra spanning less than 1mm.

Figure 4 (left) shows the results of the measured rodent-morphic Presage dose distribution for the 4-field HA-WBRT and SmART Plan simulated of HA-WBRT, overlaid on top of rat CBCT. Figure 4 (right) shows a dose volume histogram (DVH) calculated from this dose distribution. Rodent-morphic Presage verification of 4-field HA-WBRT shows significant agreement with the simulated SmART-plan results.

The 4-field DVHs show good agreement between the measured and simulated results. More importantly, both the measurement and the simulation agree that the hippocampus is spared at less than 20% of volume receiving less than 30% of the prescription dose. Slightly more volume of the brain
(without hippocampus) received 40% or more of the prescription dose for simulated DVH versus measured DVH. This is probably because of not accounting for divergence of the beam when fabricating the block and should be addressed in subsequent runs.

**Figure 4.** Left: Measured and SmART Plan Monte Carlo simulated dose distribution of 4-field HA-WBRT treatment. Right: Calculated DVHs for brain without hippocampus (brain wo hippo) and the hippocampus with 1mm margin (hippo+margin). Red and green lines were generated using the Presage dosimeter data and blue and green lines were generated via Monte Carlo simulation in SmART Plan.

**4. Conclusion**
The complex nature of conformal HA-WBRT on a small animal irradiator requires elegant dosimetry to ensure that the delivery is sound. The rodent-morphic Presage dosimeters have fulfilled this role and allowed us to make informed decisions on whether 4-field HA-WBRT is sufficiently hippocampal-sparing. Our planned future studies will further develop the 3D-printed radiation compensators to enable IMRT capabilities in micro-irradiator and verify the treatment once again with rodent-morphic dosimeters.

**5. References**
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