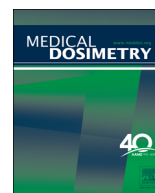




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## Treatment planning strategy for whole-brain radiotherapy with hippocampal sparing and simultaneous integrated boost for multiple brain metastases using intensity-modulated arc therapy

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### ABSTRACT

**Purpose:** To retrospectively evaluate the accuracy, plan quality and efficiency of intensity-modulated arc therapy (IMAT) for hippocampal sparing whole-brain radiotherapy (HS-WBRT) with simultaneous integrated boost (SIB) in patients with multiple brain metastases (m-BM).

**Materials and methods:** A total of 5 patients with m-BM were retrospectively replanned for HS-WBRT with SIB using IMAT treatment planning. The hippocampus was contoured on diagnostic T1-weighted magnetic resonance imaging (MRI) which had been fused with the planning CT image set. The hippocampal avoidance zone (HAZ) was generated using a 5-mm uniform margin around the paired hippocampi. The m-BM planning target volumes (PTVs) were contoured on T1/T2-weighted MRI registered with the 3D planning computed tomography (CT). The whole-brain planning target volume (WB-PTV) was defined as the whole-brain tissue volume minus HAZ and m-BM PTVs. Highly conformal IMAT plans were generated in the Eclipse treatment planning system for Novalis-TX linear accelerator consisting of high-definition multileaf collimators (HD-MLCs: 2.5-mm leaf width at isocenter) and 6-MV beam. Prescription dose was 30 Gy for WB-PTV and 45 Gy for each m-BM in 10 fractions. Three full coplanar arcs with orbit avoidance sectors were used. Treatment plans were evaluated using homogeneity (HI) and conformity indices (CI) for target coverage and dose to organs at risk (OAR). Dose delivery efficiency and accuracy of each IMAT plan was assessed via quality assurance (QA) with a MapCHECK device. Actual beam-on time was recorded and a gamma index was used to compare dose agreement between the planned and measured doses.

**Results:** All 5 HS-WBRT with SIB plans met WB-PTV  $D_{2\%}$ ,  $D_{98\%}$ , and  $V_{30\text{ Gy}}$  NRG-CC001 requirements. The plans demonstrated highly conformal and homogenous coverage of the WB-PTV with mean HI and CI values of  $0.33 \pm 0.04$  (range: 0.27 to 0.36), and  $0.96 \pm 0.01$  (range: 0.95 to 0.97), respectively. All 5 hippocampal sparing patients met protocol guidelines with maximum dose and dose to 100% of hippocampus ( $D_{100\%}$ ) less than 16 and 9 Gy, respectively. The dose to the optic apparatus was kept below protocol guidelines for all 5 patients. Highly conformal and homogenous radiosurgical dose distributions were achieved for all 5 patients with a total of 33 brain metastases. The m-BM PTVs had a mean HI =  $0.09 \pm 0.02$  (range: 0.07 to 0.19) and a mean CI =  $1.02 \pm 0.06$  (range: 0.93 to 1.2). The total number of monitor units (MU) was, on average,  $1677 \pm 166$ . The average beam-on time was  $4.1 \pm 0.4$  minute. The IMAT plans demonstrated accurate dose delivery of  $95.2 \pm 0.6\%$ , on average, for clinical gamma passing rate with 2%/2-mm criteria and  $98.5 \pm 0.9\%$ , on average, with 3%/3-mm criteria.

**Conclusions:** All hippocampal sparing plans were considered clinically acceptable per NRG-CC001 dosimetric compliance criteria. IMAT planning provided highly conformal and homogenous dose

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distributions for the WB-PTV and m-BM PTVs with lower doses to OAR such as the hippocampus. These results suggest that HS-WBRT with SIB is a clinically feasible, fast, and effective treatment option for patients with a relatively large numbers of m-BM lesions.

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## Introduction

Brain metastases are a common finding in patients with cancer and multiple treatment options are available for patients with limited (1 to 3) brain metastases. Whole-brain radiation therapy (WBRT) has been the historical standard of care to treat brain metastases and to prevent recurrences elsewhere in the brain.<sup>1</sup> In addition, stereotactic radiosurgery (SRS) to individual metastases has become an increasingly adopted approach. The addition of WBRT to SRS is associated with improved local control and reduces distant recurrence in the brain, but does not improve maintenance of functional status or overall survival.<sup>2</sup> Conversely, the addition of SRS after WBRT improves local control and potentially overall survival in selected patients.<sup>3</sup> Secondary analysis of a Japanese phase 3 clinical trial comparing SRS with and without WBRT in 88 non-small cell lung cancer patients with 1 to 4 brain metastases demonstrated significantly better median survival (MS) in patients with higher diagnosis-specific Graded Prognostic Assessment who received WBRT plus SRS (MS 16.7 months,  $p = 0.04$ ) as compared to those who received SRS alone (MS 10.6 months).<sup>4</sup> Nonetheless, WBRT remains the most commonly used approach in patients with multiple (>3) brain metastases (m-BM) as it is less complex than SRS and offers better intracranial control of disease. However, the primary shortcoming of WBRT has been neurocognitive toxicity. In one provocative study from MD Anderson,<sup>2</sup> the addition of WBRT to SRS significantly worsened memory at 4 months. Similar neurocognitive changes have been noted after prophylactic cranial irradiation with WBRT in a dose dependent manner compared to observation.<sup>5</sup>

Clinical and preclinical evidence suggests that the neurocognitive toxicity associated with WBRT may be the result of radiation-induced damage to the neural stem cell compartment of the hippocampus.<sup>3,6,7</sup> Accordingly, it has been hypothesized that preferential sparing of this region during WBRT may reduce neurocognitive decline. The phase II RTOG 0933 trial investigated the use of hippocampal sparing WBRT (HS-WBRT) and found reduced neurotoxicity compared to historical control.<sup>8</sup> This study has led to the current NRG-CC001 phase III study of HS-WBRT vs standard WBRT.<sup>9</sup>

Preferential avoidance of the hippocampus requires complex treatment planning and initial studies on this subject typically employed helical tomotherapy,<sup>10-12</sup> or linear accelerator-based intensity-modulated radiation therapy (IMRT).<sup>13-16</sup> In addition to hippocampal avoidance, the use of highly conformal intensity-modulated treatment also presents the opportunity to deliver focal dose escalation to radiographically apparent brain metastases. Dose escalation in this fashion may mimic SRS boost to WBRT without the need for additional sequential treatment. However, tomotherapy or linear accelerator-based IMRT requires a large number of total monitor units (MU) and relatively longer treatment times.<sup>10-16</sup>

Intensity-modulated arc therapy (IMAT) is a recently introduced rotational radiotherapy technique which allows for highly conformal radiation dose delivery by simultaneously modulating gantry rotation, dose rate and multileaf collimators (MLC) positions.<sup>17-19</sup> Conformal IMAT plans may decrease the dose to organs at risk (OAR) such as the hippocampus while providing conformal dose distributions to the whole-brain planning target volume (WB-PTV) and simultaneously allowing for dose escalated boost

to m-BM planning target volumes (PTVs). Herein we report our unique treatment planning strategy that applies bilateral orbit exclusion sectors and a 5-mm hippocampal avoidance zone (HAZ) to further assess the clinical potential of IMAT for fast and effective delivery of HS-WBRT with simultaneous integrated boost (SIB) in patients with a relatively large numbers of m-BM following the NRG-CC001 dosimetric compliance criteria.<sup>9</sup>

## Methods and Materials

### Patient simulation and target volume definition

A total of 5 patients were included in this retrospective planning study. All 5 patients had been diagnosed with cerebral metastatic melanoma and had previously been treated with conventional WBRT followed by SRS for m-BM. Computed tomography (CT) simulation was performed on a 16 slice Phillips Brilliance Big Bore CT Scanner (Phillips, Cleveland, OH) and the patient's head was immobilized using a thermoplastic mask which was fixed at the base to a stereotactic head and neck localization box (BrainLab Head&Neck Localization Inc., Heimstetten, Germany). The 3D-CT images were acquired with  $512 \times 512$  pixels at 0.75-mm slice thickness and 0.75-mm slice spacing. All DICOM 3D-CT datasets were then electronically transferred to the BrainLab iPlan treatment planning system (TPS) for contouring and SRS treatment planning.

Target volumes and OAR were delineated by an experienced radiation oncologist on T1/T2-weighted magnetic resonance images which had been registered to the 3D planning CT. Gross tumor volume was defined as the enhancing tumor on T1-weighted images. The m-BM PTVs were generated with a 1 to 2 mm uniform expansion around each gross tumor volume with tighter margins used near critical structures or in the buildup region. The total number of m-BMs ranged from 6 to 10 (average =  $6.6 \pm 2.1$ ). The summated PTV for m-BMs ranged from 1.2 to 18.0 cc (average =  $7.3 \pm 6.6$  cc). The OAR were delineated on magnetic resonance images which had been fused to the 3D planning CT and consisted of brainstem, optic apparatus (optic chiasm and bilateral optic nerves), eyes, and lenses.

### Clinical SRS planning and delivery process

For each m-BM, clinically optimal SRS treatment plans were generated as a hybrid plan using a combination of 3D conformal noncoplanar arcs and non-opposing static beams for the Novalis-TX linear accelerator (Varian Palo Alto, CA) with BrainLAB iPlan system (BrainLAB iPlan, Feldkirchen, Germany) consisting of high-definition MLC (HD-MLCs: 2.5 mm leaf width at isocenter) and 6 MV-SRS (1000 MU/min) beam. The prescription dose was 16 to 20 Gy in one fraction with at least 95% of the PTV receiving 100% of the prescription dose. No additional margin for dose buildup was applied at the edges of the MLC blocks beyond the m-BMs PTVs. Single fraction QUANTEC guidelines<sup>20</sup> were used to respect the OAR dose tolerances. The maximum dose to brainstem and optic apparatus was kept than 12.5 and 12 Gy, respectively. Also, the 50% isodose line should not touch the skin surface. All treatment plans were calculated using heterogeneity corrected pencil-beam algorithm with  $2.0 \times 2.0 \times 2.0$  mm<sup>3</sup> dose grid sizes.

For each m-BMs SRS treatment delivery, initial repositioning of the patient was achieved by using the stereotactic localization box on the treatment couch. A pair of oblique kilo-voltage x-ray images was acquired and automatic 2D-to-3D image registration was performed in the ExacTrac system. This was followed by onboard cone-beam CT scanning for each brain tumor for further improvement of target localization. Before delivering each SRS treatment, a daily quality assurance check on kilo-voltage to megavoltage imaging isocenter coincidence was performed, including Winston-Lutz test for precise and accurate target localization. All quality assurance procedures were in compliance for SRS treatment planning and delivery.

### Hippocampal sparing WB-IMAT with SIB planning

After obtaining institutional review board approval, all DICOM 3D-CT datasets and contoured structures were then electronically transferred from iPlan workstation to Eclipse TPS for the purpose of HS-WBRT with SIB treatment planning. The hippocampi were delineated per RTOG-0933/NRG-CC001 criteria.<sup>8,9</sup> The HAZ was defined as the bilateral hippocampi with a uniform 5-mm margin for dose reduction/optimization as per NRG-CC001/RTOG-0933 guidelines. The WB-PTV was defined as whole-brain parenchyma excluding the HAZ and m-BM PTVs.

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