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CLINICAL INVESTIGATION **Brain**

WHOLE BRAIN RADIOTHERAPY WITH HIPPOCAMPAL AVOIDANCE AND SIMULTANEOUS INTEGRATED BOOST FOR 1–3 BRAIN METASTASES: A FEASIBILITY STUDY USING VOLUMETRIC MODULATED ARC THERAPY

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Purpose: To evaluate the feasibility of using volumetric modulated arc therapy (VMAT) to deliver whole brain radiotherapy (WBRT) with hippocampal avoidance and a simultaneous integrated boost (SIB) for one to three brain metastases.

Methods and Materials: Ten patients previously treated with stereotactic radiosurgery for one to three brain metastases underwent repeat planning using VMAT. The whole brain prescription dose was 32.25 Gy in 15 fractions, and SIB doses to brain metastases were 63 Gy to lesions ≥2.0 cm and 70.8 Gy to lesions <2.0 cm in diameter. The mean dose to the hippocampus was kept at <6 Gy_2. Plans were optimized for conformity and target coverage while minimizing hippocampal and ocular doses. Plans were evaluated on target coverage, prescription isodose to target volume ratio, conformity number, homogeneity index, and maximum dose to prescription dose ratio.

Results: Ten patients had 18 metastases. Mean values for the brain metastases were as follows: conformity number = 0.73 ± 0.10, target coverage = 0.98 ± 0.01, prescription isodose to target volume = 1.34 ± 0.19, maximum dose to prescription dose ratio = 1.09 ± 0.02, and homogeneity index = 0.07 ± 0.02. For the whole brain, the mean target coverage and homogeneity index were 0.960 ± 0.002 and 0.39 ± 0.06, respectively. The mean hippocampal dose was 5.23 ± 0.39 Gy_2. The mean treatment delivery time was 3.6 min (range, 3.3-4.1 min).

Conclusions: VMAT was able to achieve adequate whole brain coverage with conformal hippocampal avoidance and radiosurgical quality dose distributions for one to three brain metastases. The mean delivery time was under 4 min. Crown Copyright © 2010 Elsevier Inc.

Volumetric modulated arc therapy, Whole brain, Brain metastases, Simultaneous integrated boost, Hippocampus.

INTRODUCTION

Brain metastases represent a significant clinical problem, occurring in 25–45% of cancer patients (1). In patients diagnosed with brain metastases, management with steroids and whole brain radiotherapy (WBRT) is common practice. The prognosis, however, remains poor, with a median survival of 2.4–4.8 months (2). Radiosurgery has been shown to improve outcomes. Radiosurgical boost after WBRT improves local control compared with WBRT alone (3, 4). For selected patients with a single brain metastasis, WBRT followed by a radiosurgical boost improves survival (3).

Several radiosurgical techniques have been developed to deliver highly conformal radiotherapy to discrete brain lesions with high precision. One technique uses multiple highly collimated cobalt sources, whereas others use a linear accelerator–based treatment delivery method. These highly precise treatments typically follow nonconformal WBRT, delivered using lateral-opposed fields, which do not permit selective sparing of intracranial structures. With newer techniques for planning and delivering WBRT, it is possible to selectively spare sensitive brain regions, such as the hippocampus. The use of WBRT with hippocampal sparing to preserve neurocognitive functioning is a novel concept (5–7). To explore the viability of hippocampal-sparing brain radiotherapy, Ghia *et al.* (5) reported on the distribution of brain metastases in relation to the hippocampi. Of 272 metastases, the incidence of metastases within 5 mm of the hippocampi was very low (3.3%), suggesting that hippocampal sparing would be unlikely to result in an inordinately high failure

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rate. Additionally, it may be advantageous to deliver a radiosurgical boost for gross disease simultaneously, rather than sequentially, to reduce tumor cell proliferation and accelerated repopulation as causes of treatment failure (8, 9).

The use of WBRT with simultaneous integrated boost (SIB) for brain metastases has been accomplished with image-guided intensity modulated radiotherapy (IMRT) and with helical tomotherapy (10, 11). More recently, the feasibility of delivering WBRT with hippocampal avoidance and SIB for brain metastases has been reported using tomotherapy (5, 7). The achievements in conformality and dose distribution quality with tomotherapy and IMRT, however, can come at the cost of prolonged treatment times, particularly when considering multiple treatment fractions.

Volumetric modulated arc therapy (VMAT) is a novel plan optimization platform that uses a single dynamically modulated gantry arc rotation of up to 360° to deliver a conformal three-dimensional (3D) dose distribution accurately and efficiently. The optimization algorithm, first described by Otto, is the predecessor to RapidArc (Varian Medical Systems Inc., Palo Alto, CA), and its dosimetric accuracy has been previously published (12). The technique is similar to tomotherapy in that a full 360° of beam directions are available for optimization, but is different in that the entire dose volume is delivered in a single gantry rotation as opposed to multiple slice-by-slice treatment delivery. Studies using VMAT and RapidArc treatment planning for prostate and cervical carcinomas have shown better conformity, more favorable dose distributions, and shorter treatment times compared with conventional IMRT (13, 14). The aim of this investigation was to determine whether VMAT could meet the treatment planning challenge of WBRT with hippocampal avoidance and SIB for as many as three brain metastases.

METHODS AND MATERIALS

With approval from our institutional review board, 10 patients previously planned with linear accelerator–based stereotactic radiosurgery (SRS) for one to three brain metastases underwent repeat planning with VMAT using the same normal structure and target contours as defined with computed tomography (CT)-magnetic resonance imaging (MRI) fusion. Planning CT scans were done on a Picker PQ 5000 CT scanner (Picker International Inc., Cleveland, OH) with an axial image slice thickness of 2 mm over the entire head region. The CT images were fused to a gadolinium-enhanced, T_1-weighted, magnetization-prepared rapid gradient-echo axial MRI acquired on a Siemens 1.5-T magnetic resonance scanner (Siemens AG, Munich, Germany) using a 1.2-mm slice thickness.

Anatomic contours and target metastases were delineated on the fused CT-MRI axial image sets in the Varian Eclipse External Beam Planning System, version 7.1 (Varian Medical Systems). The organs at risk included the eyes (whole globe), brainstem, and hippocampi. The hippocampi were contoured manually by a neuroradiologist. The hippocampal avoidance structure was generated using a computer-automated 5-mm 3D margin expansion of the contoured hippocampi. The gross tumor volume for each target metastasis was identified as the contrast-enhancing lesion on the T_1-weighted MRI. A planning target volume (PTV) for each metastasis was outlined using a computer-automated 2 mm 3D margin expansion of the gross tumor volume for each metastasis. The PTV of each metastasis was used as the target volume for the boosts. For the purposes of WBRT, the whole brain clinical target volume (CTV) was generated by contouring the whole brain and excluding the PTV for each metastasis and the hippocampal avoidance structure.

Gutiérrez *et al.* (7) derived a dose fractionation schedule from Radiation Therapy Oncology Group (RTOG) 0023 such that the expected acute complications were matched for the target volumes treated to the boost dose in RTOG 0023 (15). The same dose-fractionation schedule was used in this study. The prescription to the whole brain was 32.25 Gy in 15 fractions to 95% of the volume of the whole brain (whole brain CTV). The SIB doses in 15 fractions to the brain metastases were 63 Gy to 95% of the volume for lesions $\geq$2.0 cm in diameter and 70.8 Gy to 95% of the volume for lesions <2.0 cm in diameter. Normal tissue sparing was quantified using the mean normalized total dose, which is the total dose given in 2-Gy fractions that would give a biologically equivalent effect as the actual fractionation schedule (16). An α/β ratio of 2 Gy was assumed for the hippocampus and 3 Gy for the eyes (7). The dose constraint for the hippocampus was mean <6 Gy_2 and for the eyes was mean <10 Gy_3. Because the brainstem was part of the whole brain CTV, it was assigned the same dose as for the whole brain CTV.

The CT planning images and associated contours were transferred to the VMAT optimization planning system environment from the Eclipse treatment planning system using the digital imaging and communications in medicine (DICOM) format. Using the VMAT optimization algorithm published by Otto (12), VMAT treatment plans were generated for whole brain radiotherapy with conformal avoidance of the hippocampi and eyes and with boosts to the metastases. During planning, the user defines the prescription to the target structures and also the dose constraints to the organs at risk. The main planning objective was to reduce the mean dose for the hippocampi to <6 Gy_2 without compromising on coverage of the metastases and whole brain. A second planning objective was to optimize conformity while maintaining target coverage (TC) for the metastases. Dose calculations for VMAT optimization were performed using a pencil beam algorithm (17), the same algorithm used in the Eclipse, version 7.1, treatment planning system. The VMAT plans consisted of a single arc, starting at a gantry angle of 179° and rotating counterclockwise through 358° to stop at a gantry angle of 181°. During optimization, multileaf collimator (MLC)-shaped fields are progressively added throughout the arc. The gantry rotation speed and monitor units (MU)per gantry angle degree were optimized for a variable dose rate plan with a maximum dose rate of 400 MU/min.

Each VMAT treatment plan was delivered to a cylindrical solid water phantom to simulate treatment. In this treatment planning study, no patients underwent repeat irradiation. Plans were delivered using 6-mV photons with a maximum dose rate of 400 MU/min on a Varian CL21 EX linear accelerator with a Millennium 120-leaf MLC (Varian Medical Systems). The delivery time for each VMAT plan was measured.

To verify the delivery feasibility of the VMAT plan, quality assurance (QA) procedures were performed for each treatment plan. The VMAT treatment plans were delivered to an $18.6 \times 18.6 \times 18.6\ cm^3$ solid water phantom. The dose at isocenter was measured using a NAC 009T 0.01-cc farmer-type mini ion chamber (Victoreen Instruments Co., Cleveland, OH). The dose profiles on axial, coronal, and sagittal planes were measured using Kodak EDR2 film (Eastman Kodak, Rochester, NY). The quality of the VMAT plans was assessed according to the following measures: homogeneity index (HI), maximum dose to prescription dose ratio (MDPD),