CASE REPORT

Fractionated Helical Tomotherapy as an alternative to radiosurgery in patients unwilling to undergo additional radiosurgery for recurrent brain metastases

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ABSTRACT. Our clinic routinely treats brain metastases with stereotactic radiosurgery using a 6 megavoltage (MV) linear accelerator, cones, and a surgically attached head frame. Four patients declined repeat radiosurgery for new lesions due to their previous discomfort and a fifth patient could not complete radiosurgery because of uncontrolled nausea. Instead patients were treated with Helical Tomotherapy (HT). This report discusses the spatial dose distribution of HT as measured in a head phantom and the clinical course of these five patients. The planning target volume (PTV) was a 3 mm geometric expansion of the gross tumour volume (GTV). The prescribed dose to the PTV was 27 Gy in five daily fractions with the distribution optimised to deliver 30 Gy to the GTV. Patients were immobilised with a mask and the lesions were targeted by MV computerised tomography, an inherent feature of the system. One patient died six weeks later from systemic disease; the remaining patients survived eight to 16 months. No patient experienced an exacerbation of neurological symptoms following Helical Tomotherapy. These results suggest that fractionated Helical Tomotherapy for brain metastases may be a viable alternative to radiosurgery in patients unable or unwilling to undergo that procedure.

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Radiotherapeutic options are limited for patients with recurrent unresectable brain metastases. Radiosurgery is one approach that has been adopted for these individuals [1]. The technique in our clinic has been to immobilise the patient in a surgically attached frame and proceed with irradiation using a 6 megavoltage (MV) linear accelerator.

In patients unwilling or unsuitable for a surgically attached head frame, alternative means of providing conformal radiation treatments include the use of non-surgical relocatable head frames such as the Gill-Thomas-Cosman (GTC, Integra Radionics, Burlington MA) frame [2], implanted fiducials [3] or intensity modulated radiotherapy (IMRT) with kilovoltage (kV) computerised tomography (CT) or MVCT image guidance to provide anatomical verification before each treatment.

The TomoTherapy Hi-Art II System (TomoTherapy Inc, Madison, Wisconsin, USA), developed with the purpose of delivering IMRT and MVCT image guidance with one integrated machine [3], was used to treat the patients described in this report. Helical Tomotherapy (HT) has been

considered as a possible treatment for brain metastases [4–6] including single fraction treatments [5] and as whole brain treatment with a concomitant boost [6]. This report discusses the spatial dose distribution of HT as measured in a head phantom and the clinical course of five patients.

Methods and materials

TomoTherapy Hi-Art II System

The TomoTherapy Hi-Art II System consists of a small 6 MV linear accelerator mounted on a continuously rotating gantry. The couch moves the patient simultaneously through the radiation beam. Detectors for MVCT imaging are on the gantry opposite the radiation source. During therapy, a multi-leaf collimator dynamically modulates the radiation beam in the transverse plane and static jaws set the cranial-caudal beam thickness, called “field width”, to 1.05, 2.5 or 5.0 cm.

The manufacturer-supplied planning system is similar to standard IMRT platforms, where dose objectives are set for the tumour planning target volumes (PTVs) and dose limits to the organs-at-risk (OAR). Parameters unique to HT include the field width and the pitch (defined as couch movement during one gantry rotation/field width).

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Phantom study

A dosimetry study was performed using an anthropomorphic head phantom: a 1.6 cm diameter PTV was generated assuming a gross tumour volume (GTV) of 1.0 cm with a 0.3 cm uniform margin. To achieve good conformity a 1.05 cm field width was selected with a pitch of 0.2. Three artificial organs-at-risk (sculptors) were introduced in the IMRT optimisation objectives to achieve a rapid fall off of dose outside the PTV. One superior and one inferior sculptor were defined using the same area of the PTV on two transverse slices beginning 0.3 cm above and 0.3 cm below the PTV respectively. These confined the dose in the cranial-caudal direction. A third "ring" sculptor 0.5 cm in thickness was placed 0.5 cm from the PTV on all the transverse slices containing the PTV. The planning objectives were to reduce the dose in these sculptors, but maintain a high dose in the PTV.

To assess the accuracy of this dose calculation, Kodak EDR2 film was placed in the transverse slice through the centre of the PTV. The phantom was then aligned with MVCT and treated.

Patient selection and planning

Our radiosurgery patients are localised with a surgically attached head frame (CRW, Integra Radionics, Burlington MA) and irradiated with a 6 MV linear accelerator using cones and a non-coplanar multiple arc technique. Planning is also performed using the Integra Radionics XKnifeTM IMRT system. Non-spherical lesions are treated with several isocentres.

Five patients deemed suitable for radiosurgery who either declined (four patients) or did not tolerate the procedure (one patient) were offered HT as an alternative conformal radiation treatment. Four patients were unwilling to undergo radiosurgery due to discomfort with the surgical frame during previous treatment. In one further case radiosurgery was aborted (Case 3) because of uncontrolled nausea.

All patients were immobilised within a mask (Uni-Frame, Medtec Inc, Orange City, Iowa, USA). All metastases were delineated using gadolinium enhanced volumetric magnetic resonance imaging (MRI). After MRI-CT fusion, the images were transferred to the Tomotherapy planning station.

With a surgically affixed frame, usually no margin is added to the GTV to obtain the PTV. In these HT cases, a 3 mm margin on the GTV was added for the following reasons:

- According to TomoTherapy Inc.'s instructions in the acceptance document, the delivered dose is within 5% and/or 3 mm of calculated dose.
- Our quality assurance checks of plans using phantoms occasionally identified shifts of up to 3 mm using tomotherapy.
- The Uni-Frame masks do not have sub-millimeter accuracy in relocating patients [7]. To achieve acceptable precision it was necessary to make adjustments based upon the MVCT. However, there was no fine mechanism to adjust the position of the patient's head

for rotations in the sagittal plane or for large corrections in the coronal plane (yaw). Such corrections were performed manually.

- MVCT images are inferior to kVCT [3] in distinguishing minor variations in tissue density such as brain convolutions.

Surrounding each lesion, three sculptors were defined as per the phantom study. Normal tissues including the eyes, anterior visual pathways and brain stem were identified and had dose limits applied. In cases where there were two or more metastases, a separate plan was produced for each metastasis if the cranial-caudal separation exceeded 3 cm. All patients were planned with a field width of 1.05 cm.

The treatment beam-on time was typically 10 minutes (Table 1), due to small field width and the relatively low pitch needed to meet the conformal isodose requirements. Immediately before each irradiation, the MVCT image was reviewed by a radiation oncologist. Sagittal rotational misalignment was manually corrected.

The radiation dose prescription took into consideration the 3 mm expansion of the GTV to form the PTV, as well as normal tissue tolerance. A hypofractionated prescription equivalent to a generally accepted radical dose for late CNS effects was selected. This comprised a dose of 27 Gy in five fractions prescribed to the PTV with distribution optimised to deliver 30 Gy in five fractions (equivalent to 60 Gy in 30 fractions using the linear quadratic model and an α/β of 2 Gy) to as much of the GTV as was possible.

Results

Results in the head phantom

Only a transverse dosimetry film is available, since the phantom was physically sliced only in that plane. Figure 1 shows that the measured dose differed from the calculated dose by less than 2% and the positioning of the dose profiles exhibited a shift of 1.5–2.0 mm (lateral profile) or less (anterior-posterior profile) compared to calculations. The shift in the lateral profile is slightly larger than the ± 1 mm typical measurement error.

The HT delivery system is co-planar, resulting in a profile with a large penumbra ("wings") in the transverse plane. The cranial-caudal profile is comparatively

Table 1. Planning

Case	Number of metastases	Beam-on time (minutes)	Pitch	Gantry rotation period (seconds)
1	2	9.07	0.15	16
2	1	7.50	0.15	15
3	2	8.97	0.20	26
(1 plan per metastasis)		7.11	0.20	21
4	2	9.12	0.22	25
5	2	11.48	0.15	15

Figure 1. On the left, transverse and sagittal views of the phantom show 100%, 90%, 50% isodose lines. On the right, lateral and AP dose profiles through the isocentre in the transverse plane as measured with film (red) and compared to calculation (blue) from the Helical Tomotherapy planning system are shown. The calculated cranial-caudal profile is shown in the bottom right.

compact due to a) superior and inferior sculptors; b) co-planar dose delivery; c) small field width.

adjustment of the patient's head was required for ~40% of the fractions. No immediate toxicity to HT treatment was observed for any patient.

Case studies

A total of nine metastases in five patients were treated with Helical Tomotherapy. A summary of patient characteristics and survival following treatment is given in Table 2. The median follow-up is 11 months and two of nine metastases progressed following HT. All patients tolerated the mask well, although post-MVCT manual

Case 1

A 63-year-old woman with a more than two year history of low volume brain metastases from non-small cell carcinoma of the lung. **Previous radiation therapy:** whole brain radiotherapy (WBRT) (30 Gy in 10 fractions), partial brain radiotherapy (30 Gy in 10 fractions) to the temporal region and radiosurgery again to the temporal lobe (39 Gy in 3 fractions). **Presentation:** the

Table 2. Demographic summary of patients treated

Case	Primary disease site	Age (years)	ECOG PS	Active systemic disease	Location	Local relapse	Post HT survival (months)
1	NSCLC	63	2	No	Occipital cerebellar	Not available	14
2	Renal	77	0	No	Frontal	No	>16
3	NSCLC	62	2	No	Temporal	No	11
4	NSCLC	51	1	No	Frontal	No	
5	Renal	78	3	Yes	Parietal	Yes	8
					Frontal	Yes	
					Frontal	No	1.5
					Parietal	No	

Abbreviations, NSCLC: Non small cell lung cancer; ECOG PS: Eastern Cooperative Oncology Group performance status; HT: Helical Tomotherapy.

patient was found to have asymptomatic radiologically progressive metastases in the right occipital lobe and cerebellar hemisphere measuring 12 mm and 4 mm respectively. There was no clinical evidence of active extra cranial disease. **Following HT:** the patient subsequently declined to attend for follow-up and died in the community 14 months later.

Case 2

A 77-year-old woman with a seven year history of metastatic renal cell carcinoma (clear cell). **Previous radiation therapy:** her first brain metastasis developed five years previously, at which point she underwent complete resection of a single metastasis. In the absence of further intracranial metastases, and in view of her age, she did not receive any post-operative WBRT. On subsequent intracranial relapse within the frontal lobe she received radiosurgery (39 Gy in three fractions) using a linear accelerator. She had lung metastases, which had remained stable for the preceding three years. She had not received any systemic anticancer treatment before. **Presentation:** she presented with a new 9 mm metastasis in the right frontal lobe (Figure 2). **Following HT:** the patient experienced temporary localised epilation of the scalp. She received no further anti-cancer treatment and completed 16 months of follow-up. There was no evidence of intracranial disease progression or late radiotherapy toxicity.

Case 3

A 63-year-old woman with metastatic non-small cell carcinoma of the lung. **Previous radiation therapy:** she received WBRT (20 Gy in five fractions) for metastatic disease. The only other site of disease was within the left supraclavicular fossa, but this had remained stable for more than six months. **Presentation:** nine months after her WBRT, the patient developed two new intracranial metastases measuring 1.1 cm and 0.8 cm in the left occipital and right frontal lobes respectively. Radiosurgery was attempted to both the metastases but failed due to vomiting when she lay flat. Once the emesis had been controlled she did not want any further attempts at radiosurgery and was offered HT as an alternative. **Following HT:** follow-up CT of the brain six months after radiotherapy confirmed local control of the intracranial metastasis. Five months following HT, the patient suffered progressive bone metastases. She died due to systemic disease 11 months following HT, but with no evidence of intracranial disease progression or late radiation toxicity.

Case 4

A 51-year-old woman with metastatic non-small cell carcinoma of the lung. **Previous radiation therapy:** she first presented with a brain metastasis, which was treated with resection and postoperative WBRT. Staging investigations at presentation also confirmed lung metastases, for which she received four cycles of carboplatin and paclitaxol chemotherapy, followed by erlotinib. A subsequent brain metastasis was treated successfully with radiosurgery. **Presentation:** eighteen months after her WBRT, the patient presented with two progressing intracranial metastases, one within the right parietal lobe and the other in the right frontal lobe (Figure 3). **Following HT:** no immediate toxicity was experienced, but follow-up imaging at one month suggested disease progression at both sites. Further radiation was deemed inappropriate. An MRI four months later (Figure 3) showed a mixed picture of treated controlled (operated) and progressive (HT and radiosurgery) brain metastases, as well as new brain metastases. By then she had developed progressive extracranial disease, which was treated with palliative chemotherapy and radiotherapy. She died eight months following HT.

Case 5

A 78-year-old woman with a three-and-a-half-year history of metastatic renal cell carcinoma. **Previous radiation therapy:** her first intracranial metastasis was treated with radiosurgery. In the following nine months, three more isolated brain metastases were also successfully treated in two other sessions of radiosurgery. She also had bone metastases. She had already undergone systemic therapy with sunitinib, progressing following one-and-a-half-years of treatment, and interferon, progressing following six months of treatment. **Presentation:** eighteen months after her first intracranial metastases she presented with two new brain metastases. Although she had active systemic disease, it was felt that she was at risk of imminent neurological deficits and was offered further radiation. Her performance status (Eastern Cooperative Oncology Group 3) reflected multiple bone metastases. **Following HT:** the patient died due to systemic disease six weeks following HT.

Discussion

Due to improving systemic therapies, the challenge of relapsing intracranial disease is likely to become more

Figure 2. Contrast enhanced MRI of Case 2 before (left) and six months after (right) Helical Tomotherapy.

Figure 3. MRI scans showing the two metastases in case 4 before Helical Tomotherapy (left) and four months following (right). Follow-up at one month post-Helical Tomotherapy suggested disease progression at which point the patient was started on chemotherapy.

common. The evidence base for managing such patients is sparse. Such patients are often excluded from systemic therapy trials. Observation alone may lead to progression of symptoms that are likely to become more difficult to manage.

Craniotomy and resection may provide rapid relief of symptoms where required, but also carries significant risks and morbidity. Repeat WBRT or even partial brain radiotherapy is possible, but may be inappropriate for low volume disease and the dose that can be delivered is limited [8].

Guidelines support the use of radiosurgery for appropriately selected patients [9]. However, as described here, patients may have endured extensive prior treatment and may then decline radiosurgery due to the need for surgical immobilisation. HT provided a well tolerated alternative allowing conformal delivery of high radiation doses without the need for a surgical frame.

In the phantom study HT did not routinely match the accuracy of radiosurgery as achieved through surgical fixation and, in the case of the GammaKnife (Elekta AB, Stockholm, Sweden), fixed sources of radiation. HT positioning could be improved with a) implanted fiducial markers [10]; b) an adjustable headrest or couch [11]; c) a new couch bracket (Tomotherapy Inc.) for holding a GTC frame; d) better quality imaging.

Figure 4 shows the HT dose volume histogram (DVH) of a small brain lesion (Case 3) and the DVH of the same lesion calculated for our traditional non-coplanar 6 MV radiosurgery (1.75 cm cone). The 90% (PTV) volume is 1.5 cc for both techniques, but the volume of normal brain exposed to lower doses of radiation is larger with HT than with radiosurgery due to the coplanar nature of

HT (e.g. at 50%: 8.1 cc vs 4.6 cc). HT may therefore place the patient at greater risk of neurocognitive dysfunction than an equivalent treatment with radiosurgery.

Within this series one patient (case 4) had a restaging scan at one month, which showed progression and subsequently received systemic therapy. Optimal timing of imaging following radiosurgery, and response criteria, remain unknown. It is possible that the early imaging changes seen in this case would have stabilised without chemotherapy. Clinic policy was to offer patients frequent surveillance imaging following radiosurgery, allowing early detection and salvage of new sites of intracranial relapse, aiming to prevent neurological deterioration and preserve quality of life.

Two of the patients (case 2, aged 77 years and case 5, aged 78 years) in this series did not receive WBRT. Although shown to improve intracranial control of disease [12], concerns exist over toxicity with WBRT and some have moved towards omitting it in patients amenable to localised therapy [13].

In particular, elderly patients are more likely to suffer a decline in neurocognitive function following radiotherapy [14], which is known to correlate with quality of life [15]. Accordingly, elderly patients may be better served with local therapy alone. The debate over the role of WBRT continues and may be resolved by ongoing clinical trials.

One of the patients within this series died six weeks following HT (case 5). This patient had active extra-cranial disease and such patients are expected to have a worse outcome. Although the aim here was to prevent neurological deficits (which was achieved), appropriate patient selection based on performance status, age and absence of active extra-cranial disease remains important

Figure 4. Curves comparing dose volume histograms achieved with Helical Tomotherapy for one metastasis in this series (case 3) with radiosurgery for the same planning target volume. The radiosurgery technique is planned for a 6 MV linear accelerator using cones with Integra Radionics XKnifeTMRT planning software.

to avoid unnecessary interventions [16]. In addition, short survival limits subsequent assessment of late treatment effects. In this series, four out of five patients survived more than six months following HT and in these patients no late adverse sequelae were identified.

Conclusion

Unlike radiosurgery, HT avoids the need for a surgically applied head frame. Furthermore, it requires less exhaustive quality assurance, allows for fractionation and can easily be delivered during the normal working day within departments without dedicated neurosurgical support. Although radiosurgery with a surgical frame remains the current gold standard, IMRT with image guidance offers an attractive resource sparing alternative that warrants further investigation.

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