Chapter 7

A phase I trial of simultaneous infield boost with helical tomotherapy for patients with 1-3 brain metastases

Rodrigues G¹, Yartsev S¹, Yaremko B¹, Perera F¹, Dar AR¹, Hammond A¹, Lock M¹, Yu E¹, Ash R¹, Caudrelier JM², Khuntia D³, Bailey L¹, Bauman G¹

1. Department of Oncology, University of Western Ontario and London Regional Cancer Program, London Health Sciences Centre, London ON, Canada

2. Department of Radiation Oncology, University of Ottawa, Ottawa ON, Canada

3. Department of Human Oncology, University of Wisconsin, Madison WI, USA

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ABSTRACT

Purpose
Stereotactic radiosurgery is an alternative to surgical resection for selected intracranial lesions. Integrated image-guided intensity modulated capable radiotherapy platforms such as helical tomotherapy (HT) could potentially replace traditional radiosurgery apparatus. The study objective was to determine the maximally tolerated dose (MTD) of simultaneous in-field boost (SIB) integrated with whole brain radiotherapy for the palliative treatment of patients with 1-3 brain metastases using HT.

Methods and Materials
Inclusion/exclusion criteria and endpoints were consistent with the RTOG 9508 radiosurgery trial. Cohorts were constructed with a 3+3 design; however, additional patients were enrolled in lower-dose tolerable cohorts during toxicity assessment periods. Whole brain radiotherapy (WBXRT) of 30 Gy in 10 fractions was delivered with a 5-30 Gy (total lesion dose of 35-60 Gy over 10 fractions) SIB delivered to the metastases. The MTD was determined by the frequency of neurologic grade 3-5 NCICTC v3.0 dose limiting toxicity (DLT) events within each phase I cohort.

Results
Forty-eight patients received treatment on the 35 Gy (n=3), 40 Gy (n=16), 50 Gy (n=15), 55 Gy (n=8), and 60 Gy (n=6) cohorts. No patients experienced DLT events in any trial cohorts. Three month RECIST assessments available in 32/48 patients demonstrated CR in 2, PR in 16, SD in 6, and PD in 8 patients.

Conclusions
The delivery of 60 Gy in 10 fractions to 1-3 brain mets synchronously with 30 Gy WBXRT was achieved without dose limiting CNS toxicity as assessed three months post treatment. This approach is being tested in a Phase II efficacy trial.
INTRODUCTION

Brain metastases are a common cancer problem and the patient outcome with currently available therapies remains poor. The majority of patients with brain metastases are managed with whole brain radiotherapy (WBRT). Clinical trials have suggested selected subgroups of patients (i.e. younger age, good performance status, extra-cranial metastases absent or controlled, and/or single brain metastatic site [1, 2]) may benefit from more aggressive local treatment of their intracranial disease with surgery or with radiosurgery often in combination with WBRT [3, 4].

Helical tomotherapy combines intensity modulated fan-beam radiotherapy delivery with megavoltage computed tomography (MVCT) imaging for integrated patient positioning and treatment delivery [5, 6]. Such a combination provides a potential alternative to conventional [7] stereotactic frame systems for precision radiotherapy. Dosimetric comparisons of serial tomotherapy or HT delivery for primary and metastatic brain tumors have suggested comparable normal tissue sparing and target coverage compared to other precision radiotherapy techniques [8-12]. HT (as well as other forms of intensity modulated radiotherapy delivery) lends itself to synchronous boost strategies as multiple targets can be easily treated to different dose (and dose per fraction) levels in the course of the intensity modulated radiation delivery. Therefore, HT could potentially allow for radiosurgery-type boost treatments to be given synchronously with standard whole brain radiotherapy component and in this way the system can be used to efficiently boost multiple brain metastases without the need for separate stereotactic procedures. We previously reported the dosimetric feasibility of using HT to deliver a synchronous boost with WBRT to achieve intra-lesional biologically effective doses (BED) similar to single fraction stereotactic radiosurgery [12] and others have recently reported the use of volumetric arc therapy [13, 14]. Here, we describe results of a phase I dose escalation trial of HT for the treatment of 1-3 brain metastases using a whole brain treatment with simultaneous in-field boost technique (HT-SIB).

MATERIALS AND METHODS

Clinical Trial

The phase I trial was approved by the Institutional Review Boards at the participating institution and registered (Ontario Clinical Trials Registry OCT 1145 TOMO-B) as per CONSORT guidelines. Patient eligibility for the trial was as follows: histologically proven cancer, imaging and clinical presentation consistent with brain metastases; 1-3 brain metastases on pretreatment contrast enhanced CT or Magnetic Resonance Imaging, lesion size > 5mm and < 3cm in diameter, > 5mm from brainstem optic
or optic apparatus, Karnofsky Performance Status > 70, extracranial disease absent, controlled or planned to be treated (in the case of synchronous presentation) anticipated survival greater than 3 months, no prior cranial radiotherapy. Patients were allowed to have prior craniotomy provided there was residual tumor or additional unresected lesions on postoperative imaging. The trial was designed according to typical phase I dose escalation rules with 5 dose levels for the SIB boost: 35, 45, 50, 55, and 60 Gy. The original trial was designed to accrue 3 patients at each dose level with a subsequent escalation if no dose limiting toxicity (DLT) was seen at 3 months with a further 3 patients to be enrolled if one patient experienced DLT. Dose limiting toxicity was as defined by the National Cancer Institute Common Toxicity Criteria v3.0 as grade 3-5 central nervous system toxicity including necrosis (symptomatic and interfering with ADL, life threatening requiring intervention or fatal). Once the trial commenced, it became evident that there was considerable loss of patients to inter-current illness and systemic disease progression (despite eligibility criteria) before the 3 month assessment and the trial was modified to allow 6 patients to be accrued at each dose level to ensure adequate numbers of patients available for the 3 month assessment to ensure timely completion of the trial. During the three-month waiting period for the dose level under assessment we allowed enrollment at the previously evaluated dose level one step below the current dose level. Patients were excluded from the DLT analysis if three-month assessments for toxicity were unavailable, if patients refused treatment after enrollment, or if they did not complete all radiotherapy treatments as planned. The status of patients who were not evaluable at three months was confirmed with primary care physicians in order to assess the reason for the lack of the three-month assessment. This follow-up was utilized to ensure early treatment related toxicity was not responsible for the non-evaluable status. Use of anticonvulsants and steroids were at the discretion of the attending oncologist.

Toxicity was monitored weekly during treatment and every month for 3 months post treatment then every 3 months for one year. Response on imaging at 12 weeks post treatment was assessed. Patients were accrued at 3-6 patients per dose level and escalation to the next dose level occurs if no limiting (grade 3 or greater) toxicity was observed in more than 1 of 3 or 2 of 6 patients by three months post treatment. This endpoint was designed to be similar to the RTOG 9005 radiosurgery dose finding study [15]. Patients were also monitored for long-term toxicity, understanding that the treatment paradigm being explored is novel and that important CNS toxicity endpoints, such as radionecrosis may manifest after the initial three-month observation point. In the case of patients who were not able to attend for imaging and/or clinical assessment at the three month follow-up due to physical decline or death, primary care physicians were contacted and medical records (hospital admission notes, death summaries, laboratory and imaging reports) were obtained to ascertain whether the reason for early decline could be due to treatment related toxicity. The attending Radiation Oncologist was consulted
and reviewed the information and the available information was reviewed independently by one of the study principal investigators (GSB) for determination of possible treatment related toxicity.

Selection of optimization criteria

Selection of the dose and fractionation prescription for the trial was based on prior reported experience with single fraction radiosurgery alone or combined with whole brain radiotherapy for treatment of patients with oligometastatic disease to brain. Using the synchronous boost technique, we calculated that a total intra-lesion dose of 60 Gy/10 fractions delivered with a surrounding whole brain dose of 30 Gy/10 fractions would provide a similar BED to a radiosurgery boost of 18 Gy in 1 fraction combined with whole brain radiotherapy to 30 Gy / 10 fractions [16, 17]. Thus we set 60 Gy / 10 fractions as the target maximum SIB dose levels with interim SIB dose levels of 35, 45, 50, and 55 Gy for this Phase I trial. A maximum dose (D1) of 35 Gy in 10 fractions for brainstem and chiasm in the SIB treatment was estimated assuming a tolerance of 50 Gy / 25 fractions and this dose was used as a dose constraint for these critical structures in the inverse planning.

Treatment planning and delivery

All patients had a custom head and neck thermoplastic shell (S-frame, CIVCO, Iowa USA) constructed for simulation and treatment. A planning CT (Phillips Healthcare) through the whole head and upper neck was obtained with a 3 mm slice thickness. Patients without a recent (< 3 weeks) contrast enhanced diagnostic CT or MRI had CT contrast at the time of simulation; otherwise, the diagnostic scan was fused with the planning scan for treatment planning purposes. The individual contrast enhancing lesions only were contoured as the SIB targets without margin and the whole cranial contents with a 3mm 3D margin was contoured as the target for the whole brain treatment.

Planning parameters [18] used for the tomotherapy plans were fan beam thickness: 2.5 or 5.0 cm; pitch: 0.287-0.43; modulation factor: 3.0; normal calculation grid (1.8×1.8×3 mm3). Plans were generated for the dose level under evaluation as well as the next higher dose level to provide a running assessment of the feasibility of proceeding to the next level. Treatment planning constraints specified for the inversely planned HT SIB technique are outlined in Table 1 and have been described elsewhere [12]. An example of isodose curves and dose-volume histograms for a 60 Gy / 10 fraction SIB case is illustrated in figures 1 and 2, respectively. For optimization and reporting purposes, maximum doses to organs were specified as maximum dose to a minimum, but still clinically significant volume. For example, maximum dose to whole brain was specified as maximum dose to a minimum volume of 1% of
the total brain volume (D1). By specifying a minimum volume, spurious results due to isolated dose peaks within clinically insignificant volumes (such as a single calculation voxel) were avoided.

Figure 1. Sample 60 Gy / 10 fraction SIB Treatment Isodose Curve

Figure 2. Sample 60 Gy / 10 fraction SIB Dose-Volume Histogram Dosimetry. ON=optic nerve, Lt=left, Rt=right, GTV=gross tumor volume.
Table 1. Helical Tomotherapy Planning Constraints

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<th>Dmax Pen</th>
<th>DVH Vol</th>
<th>DVH Dose</th>
<th>DVH Pen</th>
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<td>95</td>
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PTV: Planning target volume; Lt, Rt: Left, Right; OAR: Organ at risk; Dmax: Maximum dose constraint structure; Dmax Pen: Penalty weighting for violating the Dmax dose constraint; DVH Vol: Dose volume histogram volume objective for structure; DVH Dose: Dose volume histogram dose objective for structure; DVH Pen: Penalty weighting for violating the DVH dose constraint for structure; Dmin: Minimum dose constraint for structure; Dmin Pen: Penalty weighting for violating the minimum dose constraint for structure.

All plans were verified in-phantom on the HT unit prior to any commencement of treatment. Patients were treated using the thermoplastic mask immobilization used for simulation with positioning based on co-registration of the simulation KVCT with an MVCT acquired on the HT unit immediately before treatment. Initial automated MVCT co-registration using the bone and soft tissue setting on the HT unit was used with manual refinements by the therapists prior to treatment. An attending Radiation Oncologist verified all MVCT co-registrations on day one of treatment.

RESULTS

Patient Population

A total of sixty patients were registered for potential treatment in the phase I trial. Twelve patients (20%) were excluded from this analysis, due to treatment refusal (n=6), ineligibility to receive treatment due to decline in performance status due to progressive disease (n=4), or subsequent loss to follow-up after treatment (n=2). Both patients lost to follow-up were treated on the 2nd dose level (40Gy/10 intra-lesional boost). Therefore, a total of 48 (80%) treated patients are included in this report. The mean age of patients on protocol was 65.0 years (range 39 - 90 years). Thirty (63%) patients were male and median Karnofsky performance status was 80 (range 70 -100). Thirty-four patients (71%) had systemic disease at the time of brain radiotherapy. A total of 24 (50%) of patients were diagnosed with a lung primary (23 non-small cell lung cancer, 1 small cell lung cancer). Other cancers included kidney (n=7), breast (n=4), rectum (n=3), bladder (n=2), thyroid (n=2), sarcoma (n=2), and other (n=4). A total of 70 lesions were
treated with 3 patients having 3 lesions, 16 patients with 2 lesions, and 29 patients with solitary lesions. Brain lesions were found in the frontal lobes (n=22), parietal lobes (n=15), cerebellum (n=8), occipital lobes (n=6), temporal lobes (n=6), and other locations (n=13). Lateralized tumors were right sided in 31 and left sided in 18 lesions. Median lesion size was 1.38 cm (range 0.5-3cm).

A total of 32/48 (66%) of cases were evaluable at three months post treatment with imaging; 29/48 (60%) had their planned 3 month clinical visit as well. Of the sixteen patients (33%) non-evaluable 14 patients had clinical documentation of decline or death due progressive systemic cancer or complications of cancer (i.e. pneumonia or pulmonary embolism) 4/14 had imaging at the time of deterioration that confirmed stable or improved intra-cranial disease. Two of the sixteen patients were non-evaluable at three months due to early intracranial recurrence: one had progression at the site of the boosted lesion; the other had new intracranial metastases outside of the boosted lesion. Of those patients with imaging but no clinical follow-up at 3 months (n=3), reasons for no clinical follow-up included two patients with physical decline due to documented extra-cranial progression and one patient with combined intracranial/extra-cranial progression. In terms of dose level and availability for evaluation, all three level one (35 Gy) cases were evaluable by imaging at three months. Five of 16 (31%) level two (40 Gy) cases, 4/15 (27%) level three cases (50 Gy), 4/8 (50%) level four (55 Gy) cases and 1/6 (17%) level five (60 Gy) were found to be non-evaluable by imaging at three months. No statistical association between dose level and non-evaluation rate was found to exist in this patient population (chi square p = 0.60). That is, a similar proportion of patients were non-evaluable at each dose level, decreasing the probability that there was an underestimation of dose limiting toxicity due to a difference in early patient attrition at the dose levels examined. There were 2/4 patients treated at the highest dose level (level five, total of 60 Gy lesion dose) who were not evaluable at 3 months. One patient did have a follow-up MRI scan prior to the 3-month mark, which demonstrated progressive CNS disease that accounted for his death prior to the three-month clinical follow-up. The other patient had documented progressive extracranial metastatic disease prior to death with no neurologic signs or symptoms to suggest treatment related toxicity.

No cases of grade III-V DLT were found to possibly, probably, or definitely to be attributable to protocol treatment in any of the study cohort levels. Therefore, the maximally tolerated dose has not been reached. The following grade 1 and 2 toxicities likely related to radiotherapy were frequently (> 5% of patient population) reported by patients during their follow-up: fatigue (22/48), alopecia (8/48), headache (12/48), taste alteration (6/48), skin reaction (3/48), anorexia (3/48), vision changes (3/48). Median survival of all patients was 5.29 months (range 0.49 – 31.2 months). Seven patients were still alive at the time data analysis. Median follow-up of all living patients was 7.72 months (range 3.4 – 24.2 months). Of the 32 patients radiologically assessed at three months; 2 patients experienced a CR, 16 a
PR, 6 demonstrated SD, and 8 had PD, for a crude rate of stable or responding disease of 75% (24/32). Of the 8 progressing patients, 4 patients had local progression in the SIB treated lesions, 2 patients had intracranial but non-local CNS progression (i.e. outside of the SIB treated lesions), and another 2 patients had both local and CNS progression on 3 month imaging.

Technical parameters

Median value of D1 (maximum dose) to the metastatic lesions was 51.47 Gy (range 35.5 – 64.8 Gy) and D95 (prescription dose) of 50 Gy (35-60 Gy). Median maximum (D1) doses were calculated for the brain (51.6 Gy), eye (17.9 Gy), brainstem (32.61 Gy) and spinal cord (29.1 Gy). Average image-guidance shifts were 0.87 mm (range -2.43 to 4.46 mm, SD = 0.60) in the lateral direction, -1.27 mm (range -6.15 to 4.56 mm, SD = 1.26) in the superior-inferior direction, and 3.00 mm (range -3.60 to 8.83 mm, SD = 0.77) in the anterior-posterior direction.

DISCUSSION

Traditionally, treatment for patients with metastatic disease has been palliative whole brain radiotherapy alone [19]. Over the last 10 years, introduction of focal treatments (surgery or radiosurgery) for selected patients with metastatic disease has been explored in clinical trials and institutional series. The treatment of patients with metastatic disease to brain now may include one or more of the following interventions: best supportive care, palliative whole brain radiotherapy, radiosurgery, or surgical resection with the goals of management being effective palliation of symptoms, preventing intracranial progression, preserving neurologic function and quality of life. Typically, patients who are suitable for more aggressive, multi-modality therapies are those with oligometastatic disease (1-3 metastases), controlled extracranial disease, and good performance status [2, 20]. Randomized studies have demonstrated local control and neurologic progression free survival benefits for surgery or radiosurgery added to whole brain radiotherapy in this population compared to whole brain radiotherapy alone, radiosurgery, or surgery [3, 4].

Radiosurgery delivered as a single fraction to individual intracranial lesions has been established as a safe alternative to surgical resection [21]. The RTOG 9502 established radiosurgery doses recommendations of 15 – 24 Gy for individual lesions up to 4 cm based on observed CNS toxicity at 3 months post treatment [15]. This approach has subsequently been shown to be safe and effective in numerous single institution and multi-institution reports and trials [4]. Logistically, radiosurgery requires separate localization and treatment procedures that add some inconvenience and cost for patients,
providers and caregivers. Depending on the radiosurgery system used, invasive immobilization devices may be necessary which add to patient discomfort [7]. Single fraction treatments do not permit the exploitation of the potential radiobiologic benefits of reassortment and reoxygenation that may occur with a fractionated radiotherapy course. Hall et al. [17] have argued that fractionated stereotactic radiotherapy may be more efficacious in the treatment of neoplastic disease compared to single fraction radiosurgery. Tumor cell repopulation or sublethal damage repair may occur if there is a significant break between the radiosurgery and whole brain radiotherapy sessions. Finally, depending on the radiosurgery system used, treatment of more than 3 metastases may involve prohibitively long treatments, requiring multiple sessions or omission of radiosurgery entirely.

From a dosimetric standpoint, the ability to incorporate boost contributions to larger field lower dose volumes as part of the optimization process is an advantage of the simultaneous boost strategy (22) over radiosurgery. Radiosurgery dose is added to the previously delivered whole brain dose without opportunity for optimization of these two components resulting in unintended increased dose to the brain. In the case of the treatment of brain metastases using the SIB technique the lower isodose “spill” from the SIB can be incorporated as a component contributing to the whole brain radiation dose allowing the simultaneous optimization of both components and improved dosimetry compared to sequential whole brain and radiosurgery boosts [12, 13]. Finally, while our strategy has been to exploit the ability to simultaneously boost brain lesions, conformal avoidance with intensity modulated radiotherapy techniques is equally feasible. This strategy has been proposed as a method to reduce potential morbidity of whole brain radiotherapy by the avoidance of sensitive structures such as the hippocampus and other critical tissues [14, 23].

We sought to investigate whether a hypofractionated stereotactic simultaneous in-field boost approach using a non-invasive stereotactic localization with on-board image guidance would be a safe alternative to sequential whole brain and single fraction stereotactic radiosurgery. We have previously reported our development and early treatment experience using this form of simultaneous in-field boost treatment with HT (HT-SIB) [5]. Since our initial report, others have reported on modelling or early clinical experience using an SIB technique [13]. In our phase I trial we were able to achieve our target dose of 30 Gy WBRT with a simultaneous boost of individual lesions up to 60 Gy, both delivered over 10 fractions. Treatment planning and treatment delivery of this approach was demonstrated to be feasible. No dose limiting toxicity at the 3-month assessment was noted at any of the dose levels and among the subset of patients living beyond 3 months no treatment related late toxicity was noted. A number of patients enrolled on our trial missed complete follow-up (due to lack of imaging or clinical assessment) at the three-month point primarily due to extracranial, intracranial progression or intercurrent disease. In all
cases, it was determined, to the best of our ability that this early deterioration was not due to treatment related toxicities. It is important to note that most of the patients in our trial had single brain metastasis and patients with lesions over 3 cm in size or in close proximity to the brainstem were excluded. Thus it is possible our phase I study may have underestimated the potential toxicity of this approach in patients with multiple metastases. Offsetting this somewhat is the fact that patients with multiple metastases were represented at all dose levels. Specifically at the highest dose level 2/6 patients had multiple metastases treated (2 and 3 metastases respectively). A similar proportion of patients with multiple metastases versus single metastasis were treated at the lower dose levels.

In terms of patient outcome, partial responses were seen at all dose levels, without a clear increase in response rate with increasing SIB dose and overall, our intracranial control rate was inferior to that noted in prospective trials of whole brain radiotherapy with radiosurgery boost [24, 25]. Numbers of patients treated per cohort are small and only 6 patients were treated at the highest dose level. Thus it is difficult to draw any firm conclusions regarding the relative efficacy regarding the fractionated stereotactic infiel boost technique at highest tolerated dose as delivered in this phase I dose escalation study. A limitation of our study is the high early patient attrition due to intercurrent illness and systemic disease progression and the limited number of patients studied at the highest dose level. In addition, patients with imaging evidence of local intracranial progression were not routinely investigated with functional imaging (i.e. thallium single positron emission tomography or Magnetic Resonance Spectroscopy) to rule out necrosis compared to local tumor progression thus there is a risk that we underestimated the true incidence of treatment related toxicity. In addition, outcomes such as overall survival and late neurocognitive effects cannot be fully assessed in conjunction with a phase I safety/feasibility study, thus our observations in this regard must be viewed as preliminary results only. A multi-institutional phase II trial powered to permit an assessment of this approach in terms of non-inferiority for intra-cranial control compared to traditional radiosurgery techniques is underway and includes secondary endpoints of survival and quality of life.

CONCLUSIONS

We have confirmed the feasibility and safety of using the a simultaneous infiel boost approach in this phase I clinical trial using 30 Gy whole brain radiotherapy with intra-lesional boosts to 60 Gy over 10 fractions. We plan to evaluate this approach in a larger multi-institutional cohort of patients to evaluate efficacy of this treatment with primary endpoints of overall survival, intracranial and local lesion control and toxicity. Other research directions could also include investigations of alternate fractionation schemes [13]; incorporation of additional avoidance structures [14, 23], the treatment of patients with
more than three brain metastases who otherwise meet the criteria for aggressive management (controlled systemic disease and good KPS) [26] and the use of other platforms (i.e. linear accelerator based with volumetric arc or multiple static IMRT fields combined with on-board imaging) [13, 14]. Ultimately, randomized trials or carefully constructed cohort comparisons will be necessary to determine the relative efficacy of the fractionated SIB approach compared to conventional approaches with radiosurgery or surgery of oligometastatic disease.

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REFERENCES


