Title

Minimizing normal tissue dose spillage via broad-range optimization of hundreds of intensity modulated beams for treating multiple brain targets.

Journal

Journal of radiosurgery and SBRT, 4(2)

ISSN

2156-4639

Authors

Dong, Peng
Hossain, Sabbir
Keeling, Vance
et al.

Publication Date

2016

Peer reviewed

Jour. of Radiosurgery and SBRT, Vol. 4, pp. 107–115
Reprints available directly from the publisher
Photocopying permitted by license only

Physics Contribution

Minimizing normal tissue dose spillage via broad-range optimization of hundreds of intensity modulated beams for treating multiple brain targets

Peng Dong[1,3], Sabbir Hossain[2], Vance Keeling[2], Salahuddin Ahmad[2], Lei Xing[3] and Lijun Ma[1]

[1]Department of Radiation Oncology, University of California San Francisco, San Francisco, CA 94143, USA
[2]Department of Radiation Oncology, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, USA
[3]Department of Radiation Oncology, Stanford University, Stanford, CA 94305, USA

Correspondence to: Lijun Ma, PhD, University of California San Francisco, 505 Parnassus Avenue, Room L-08, San Francisco, CA 94143, USA; Email: lijunma@radonc.ucsf.edu; Phone: +1 (415) 353-8932; Fax: +1 (415) 353-8679

(Received: November 15, 2015: Accepted: December 17, 2015)

Variable normal tissue dose and inter-target dose interplay effects have been reported in volumetric modulated arc therapy (VMAT) of multiple brain metastases. In order to minimize such adverse effects, a Broad-Range Optimization of Modulated Beam Approach (BROOMBA) was developed whereby hundreds of intensity-modulated beams surrounding the central axis of the skull were progressively selected and optimized. To investigate technical feasibility and potential dosimetric benefits of BROOMBA, we first developed such an approach on a standalone workstation and then implemented it for a multi-center benchmark case involving 3 to 12 multiple brain metastases. The BROOMBA planning results was compared with VMAT treatment plans of the same case using coplanar and non-coplanar arc beams. We have found that BROOMBA consistently outperformed VMAT plans in terms of low-level normal brain sparing and reduction in the dose interplay effects among the targets. For example, when planning simultaneous treatment of 12 targets, BROOMBA lowered the normal brain dose by as much as 65% versus conventional VMAT treatment plans and the dose interplay effects across 8 Gy to 12 Gy levels was reduced to be negligible. In conclusion, we have demonstrated BROOMBA as a powerful tool for improving the planning quality of multiple brain metastases treatments via modern high-output linear accelerators.

Keywords: intensity-modulated arc therapy, dose interplay, brain metastases, beam optimization

1. INTRODUCTION

Recent advancements in early diagnosis and systematic therapy have made multiple brain metastases one of the leading indications managed with single-fraction or hypofractionated high-dose radiation therapy (1). The role of such focal radiation therapy in managing limited number ($N \leq 3$) of brain metastases as well as a relatively large number of brain metastasis ($N>3$) is rapidly evolving. Recent meta-analysis of three randomized clinical trial has pointed to quality-of-life and survival benefits of focal radiation therapy for younger and high performing patients (2). In addition, technical advancements such as the introduction of volumetric modulated arc therapy (VMAT) delivery via state-of-the-art high output, flattening-filter-free digital linear accelerators have enabled rapid irradiation of $N>3$ brain metastases with a beam-on time of 15-20 minutes or less.

One of the key issues in managing N>3 brain metastases is how to spare the normal brain (3, 4). Recent studies have observed a significantly increased normal tissue spillage dose associated with digital linear accelerators in particular the VMAT delivery techniques for treating brain metastases (4-6). Initial multi-institutional benchmark study has pointed to inter-target dose interplay (i.e. dose interference from one target affecting another one) as a contributive factor for increased normal brain spillage dose (6). By default, such a dose interplay effect was unique for the multiple target treatments and the effect was found to increase precipitously with the increasing number of targets.

Based on the results of these studies, we hypothesize that a new treatment planning optimization approach is needed for planning multiple lesions versus solitary targets. The conventional treatment planning approaches via pre-arranged beam configurations such as axial/parasagittal arcs or manually selected fixed beam angles are likely suboptimal in finding a solution for multiple brain metastases treatment given the fact that multiple targets tend to distribute randomly throughout the brain parenchyma. Therefore, the goal of our study is to develop a patient-specific beam arrangement approach that effectively minimizes the dose-interplay effects thus reduce the normal brain spillage dose for simultaneous focal irradiation of multiple intracranial targets.

For such a purpose, a Broad Range Optimization Of Modulated Beam Approach (BROOMBA) has been developed in this study whereby two basic principles are applied: (1) the total number of beams are expanded by multiple folds surrounding the central skull axis when irradiating multiple targets (N≥3) (2) beam angle selection and intensity levels are simultaneously optimized throughout the planning process. As a proof of these principles, the BROOMBA has first been developed on a standalone workstation and then implemented for a multi-institutional benchmark case (6), where the BROOMBA results are compared with the conventional VMAT planning approach involving coplanar as well as non-coplanar arc beams.

2. MATERIALS AND METHODS

The data set for the benchmark case was derived from a patient study treated with stereotactic radiosurgery(5). The data set was anonymized and consisted of CT and MR images, and DicomRT contours of 12 brain tumors. The largest tumor measured approximately 1.0 cm in diameter and the smallest tumor had 0.3 cm in diameter with a mean target volume of 0.45±0.34 mL. Consistent with the benchmark study requirements, a combination of N= 3, 6, 9 and 12 targets were used for BROOMBA and VMAT treatment planning comparisons.

For general BROOMBA treatment planning of brain metastases, 1162 non-coplanar beams were first placed surrounding the central axis of the skull with 6 degrees of separation between two adjacent beams. All the beams were isocentrically placed with the isocenter at the center of mass of all the targets under consideration. First of all, we eliminated all the beams that are either physically inaccessible by the hardware such as those aiming superiorly close to the central axis of the skull etc, or passing through the patient body contour in the first and last of the available CT slices. The remaining beams were then subdivided into 2 mm x 2 mm beamlets, and the dose distribution matrices of each beamlet were calculated using a previously published collapsed-cone convolution algorithm with 6-MV x-ray polyenergetic kernels (7). The dose calculation was also matched to a generic 6-MV machine commissioning data. For this study, the dose grid was interpolated to less than 0.5 mm^3. Collimator angle is set a fixed 0 degree.

The BROOMBA optimization routine was formulated as follows,

$$\begin{aligned} &Minimize\ F(z)\ subject\ to: \\ &dose\ for\ voxel\ j: z_j = \sum_{b \in B} \sum_{i \in B_b} D_{bij} x_{bi} \end{aligned} \tag{1}$$

where D_{bij} is the dose delivered to a voxel j from beamlet i∈N of beam b∈B, F(z) is the objective function which we will discuss later, and x_{bi} is the beamlet intensity to be optimized.

During the optimization, a greedy algorithm was applied iteratively to determine the beam orientation while explicitly taking into account the treatment plan quality. The process started from an empty solution set, and for each iteration, a new beam from the remainder of the candidate beam pool was added to the selected beam set for solving the free modulation optimization (FMO) problem, i.e., the problem of determining the optimal beamlet intensity levels for the given fixed beam angles. The iterative process continued until the desired number of beams, which is limited by delivery efficiency, was reached or the objective function plateaued. To select a new beam, brute-force solving the FMO problem with all potential beam candidates and choosing one beam that had the lowest objective function value possible, the computation time would be clinically impractical. In practice, the benefit of adding a beam was predicted

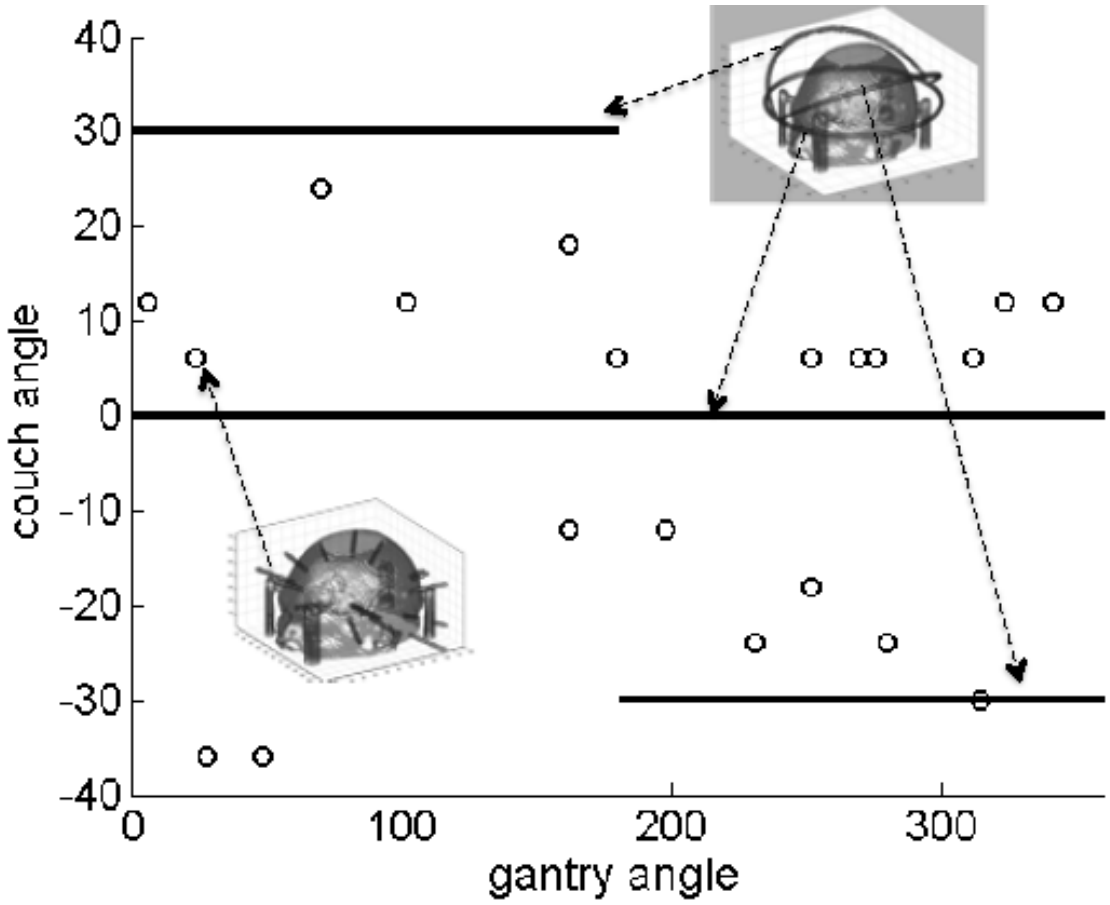

Figure 1. Illustration of beam/arc orientations and pathways in terms of gantry and couch angels for a treatment planning case (n=3 targets) between the noncoplanar VMAT results and the noncoplanar BROOMBA results (1) shows the BROOMBA beam configurations (N=20), (2) shows a 4-arc VMAT beam arrangement.

in BROOMBA rather than explicitly computed. The first-order information known as the shadow price in constrained optimization was used to select the new beam. The shadow price is the instantaneous change, per unit of the constraint, in the objective value of the optimal solution of an optimization problem obtained by relaxing the constraint. In our problem, the constraint is Equation 1. Each new beam will add values to those constraints. The beam with largest shadow price was selected.

We used an objective function F(z) that is based on a linear approximation of an equivalent uniform dose.

$$G_s(z) = \gamma_s mean(z_j) + (1-\gamma_s) max(z_j) \; for \; OARs$$

$$G_r(z) = \gamma_r mean(z_j) + (1-\gamma_r) min(z_j) \; for \; PTVr$$

$$F(z) = \sum_{m \in s,r} \alpha_m G_m(z)$$

where $\alpha_m < 0$ for PTV and $\alpha_m > 0$ for OARs. γ_s and γ_r are the importance factors for the r_{th} OAR or PTV among multi-objectives α_m that were fine-tuned to reach individual planning objectives.

The assignment of a voxel that lay within multiple OARs was given the greatest optimization priority to minimize the dose interplay effects. A ring OAR structure, uniformly expanded from all the PTV by 1.2 cm, was manually created to minimize the mean dose to its voxels in order to lower the peripheral normal brain dose. CPLEX (Academic Research Edition 12.2) was used to solve the final linear optimization problem.

To evaluate the BROOMBA planning results, the VMAT treatment plans for the benchmark cases were created as follows: All the VMAT treatment plans were developed on a clinical treatment planning system (Eclipse Progressive Resolution Optimizer Version 11.0, Varian Oncology, Palo Alto, CA). Both coplanar and non-coplanar 6 MV flattening-filter-free (FFF) beams were applied for VMAT treatment plan-

ning. For coplanar treatment planning, one transverse arc spanned 358° at the couch angle of 0° was used. For non-coplanar treatment planning, the one 358° transverse coplanar arc and 2 parasagittal arcs were employed. The non-coplanar parasagittal arcs were both 179.9° arcs with the couch angle of ±30°, respectively. To minimize the digitization effect of finite leave width for the multi-leaf collimator, the collimator was rotated either 30° or 45° for the parasagittal arcs. The choice of variable VMAT beam arrangements, particularly with increasing number of arc beams are described in detail in a separate study (8). The above-described beam configurations are representative of these studied VMAT techniques. For final analysis, the treatment planning results of BROOMBA and VMAT were all exported via DicomRT protocol into a single dose analysis workstation for comparisons (MiMVista, Cleveland, OH). For consistent analysis, all the treatment plans were normalized such that a dose of 20 Gy was prescribed to cover at least 99% of each individual target volume.

3. RESULTS

An illustration of final optimized BROOMBA beam angles versus a VMAT arc beam configuration is plotted in Figure 1. Significant discrepancy between the BROOMBA beam orientations and the beam paths of the VMAT technique were noted. As expected, the BROOMBA beam arrangement was found to depend on the total number of targets and patient-specific target locations while the beam paths for VMAT were prefixed for the planning process.

On average, BROOMBA and VMAT produced equivalent target dose coverage of all the targets

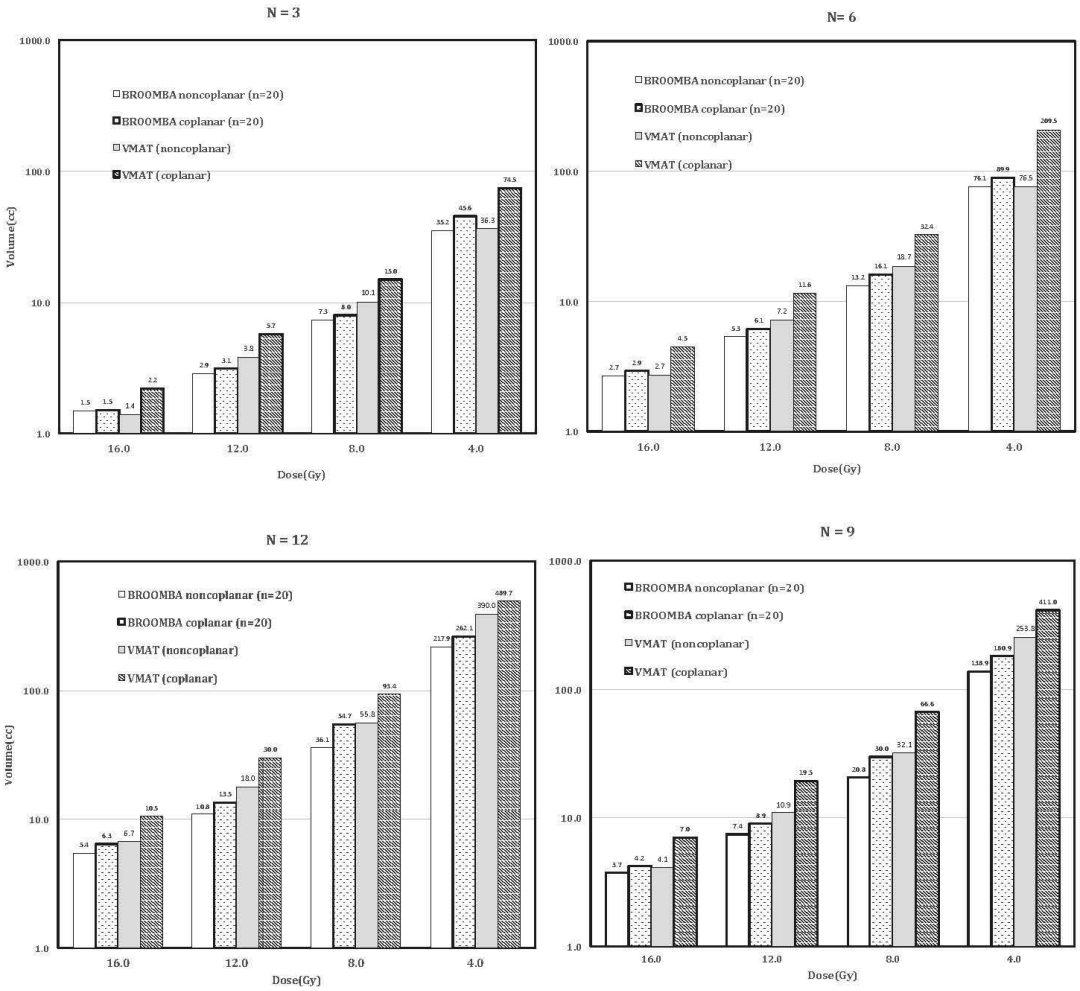

Figure 2. Comparison of normal brain at different peripheral isodose levels between coplanar and non-coplanar BROOMBA and VMAT techniques for increasing target numbers (e.g., N=3, 6, 9, and 12, respectively).

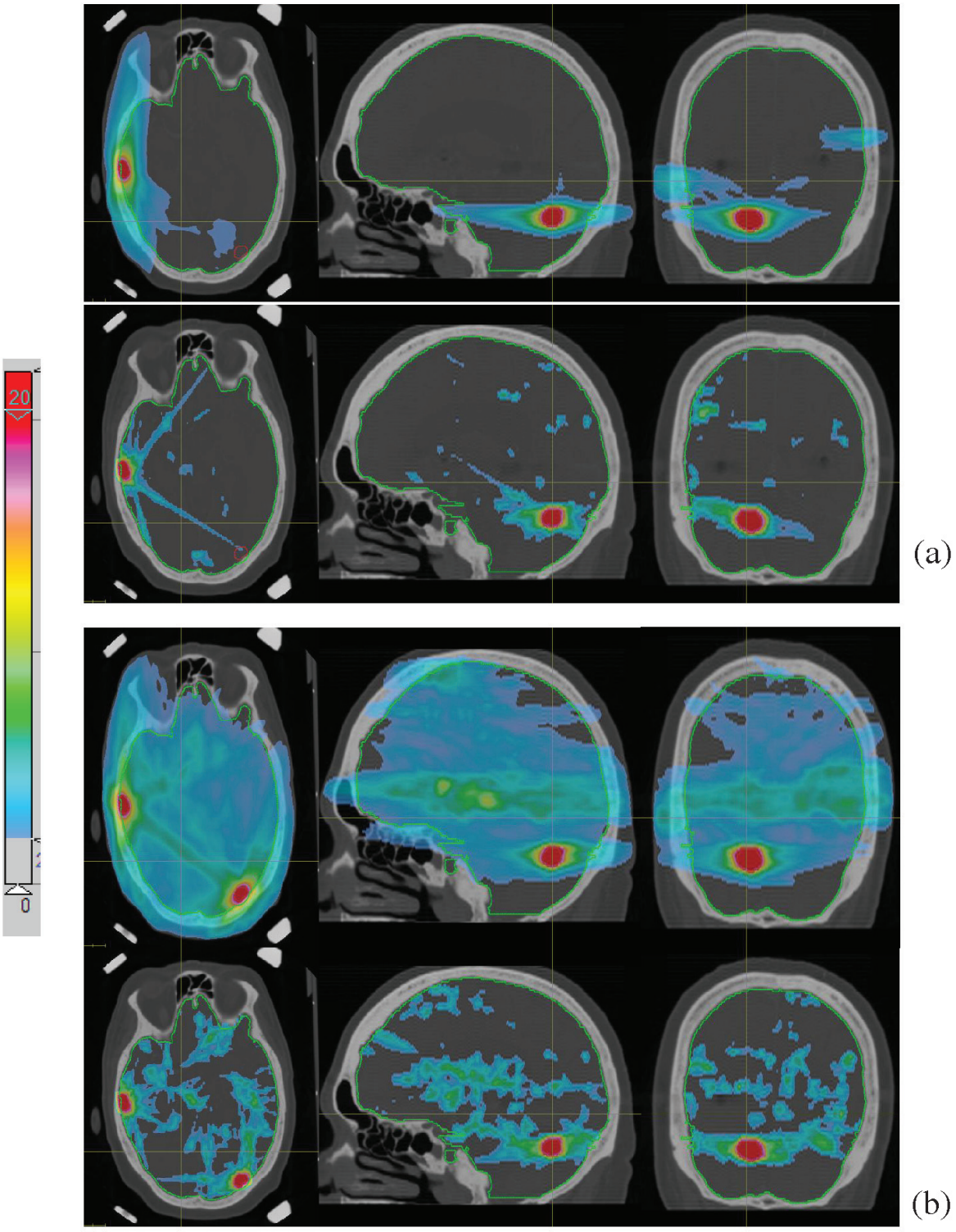

Figure 3. Comparison of low-level normal brain spillage isodose distributions for the case of N=3 (panel a) and N=12 (panel b) for the 6 MV x-ray treatment plans. In both panel (a) and (b), the top figures are the noncoplanar 4-arc VMAT treatment plans and bottom figures are the BROOMBA treatment plans via 20 non-coplanar beams. Note the area difference in the low dose levels between the two techniques.

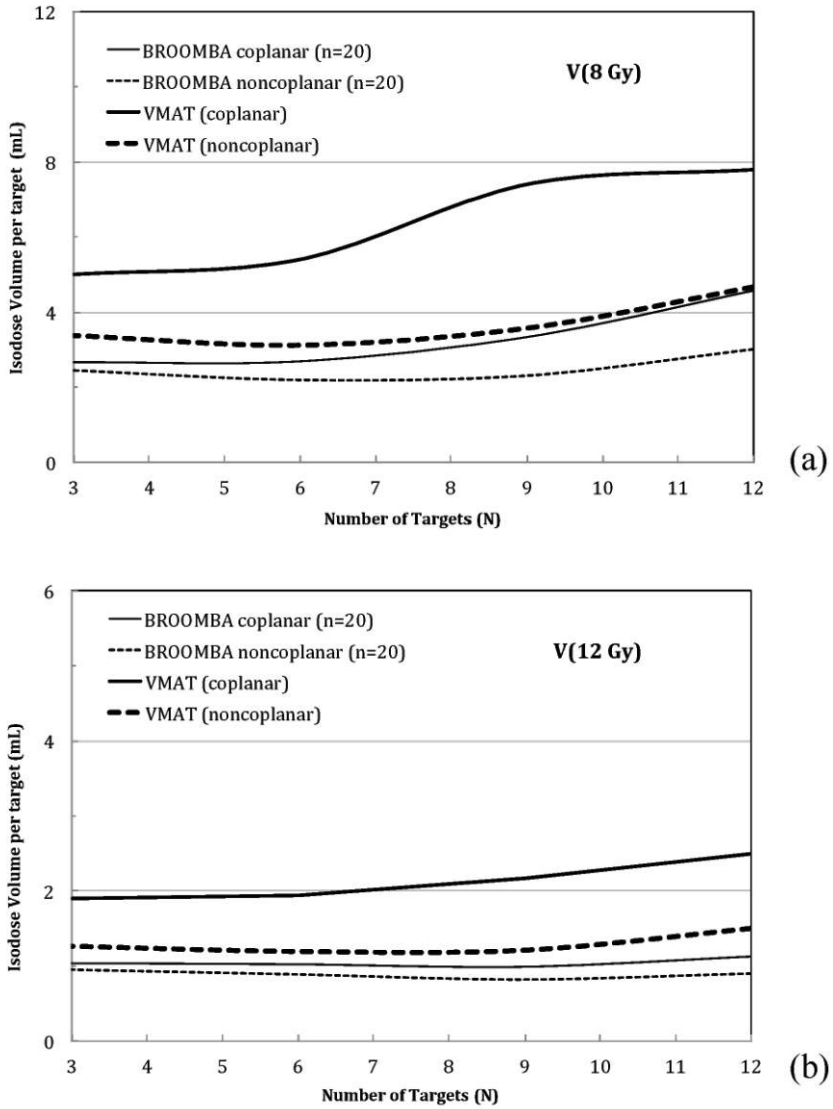

Figure 4. Dependence of dose interplay effects (i.e. mean isodose volume per target with increasing number of targets) at the 8-Gy and the 12-Gy isodose levels. Note the differences in the y-intercepts and slopes among these curves and the lowest values produced by the non-coplanar BROOMBA technique.

(V100 > 99%) and achieved comparable dose conformity in terms of Paddick dose conformity indices with the mean values of 0.84±0.04, 0.84±0.04, 0.80±0.04, 0.78±0.04 for N=3, 6, 9, and 12 target treatment plans respectively (p> 0.90; paired two-tailed t-test). For the 12 target cases, homogeneity index (HI) of the BROOMBA is 17.4 and VMAT is 47.5, where HI = (D2-D98)/Dp×100, D2 = minimum dose to 2% of the target volume, D98 = minimum dose to the 98% of the target volume and Dp = prescribed dose. However, when comparing the dose spillage to the normal brain, large differences were observed between BROOMBA and VMAT results. This is shown in Figure 2, where peripheral normal brain volumes at different isodose levels, i.e., from 16 Gy (i.e. 80% of the prescription dose) to 4 Gy (20% of the prescription dose) are shown. Note that vertical axis of the plot is in the logarithmic scale.

From the results of Figure 2, non-coplanar BROOMBA beams produced the lowest peripheral normal brain dose for all the cases. The improvements at the 8 Gy and 12 Gy isodose levels were particularly noteworthy with increasing number of targets. For example, when compared with the VMAT plans, the 12-Gy normal brain isodose volumes were lowered by 32.8%, 34.4%, 47.6% and 65.6% for N=3, 6, 9, and 12 targets respectively. Similarly, the 8-Gy normal brain isodose volumes

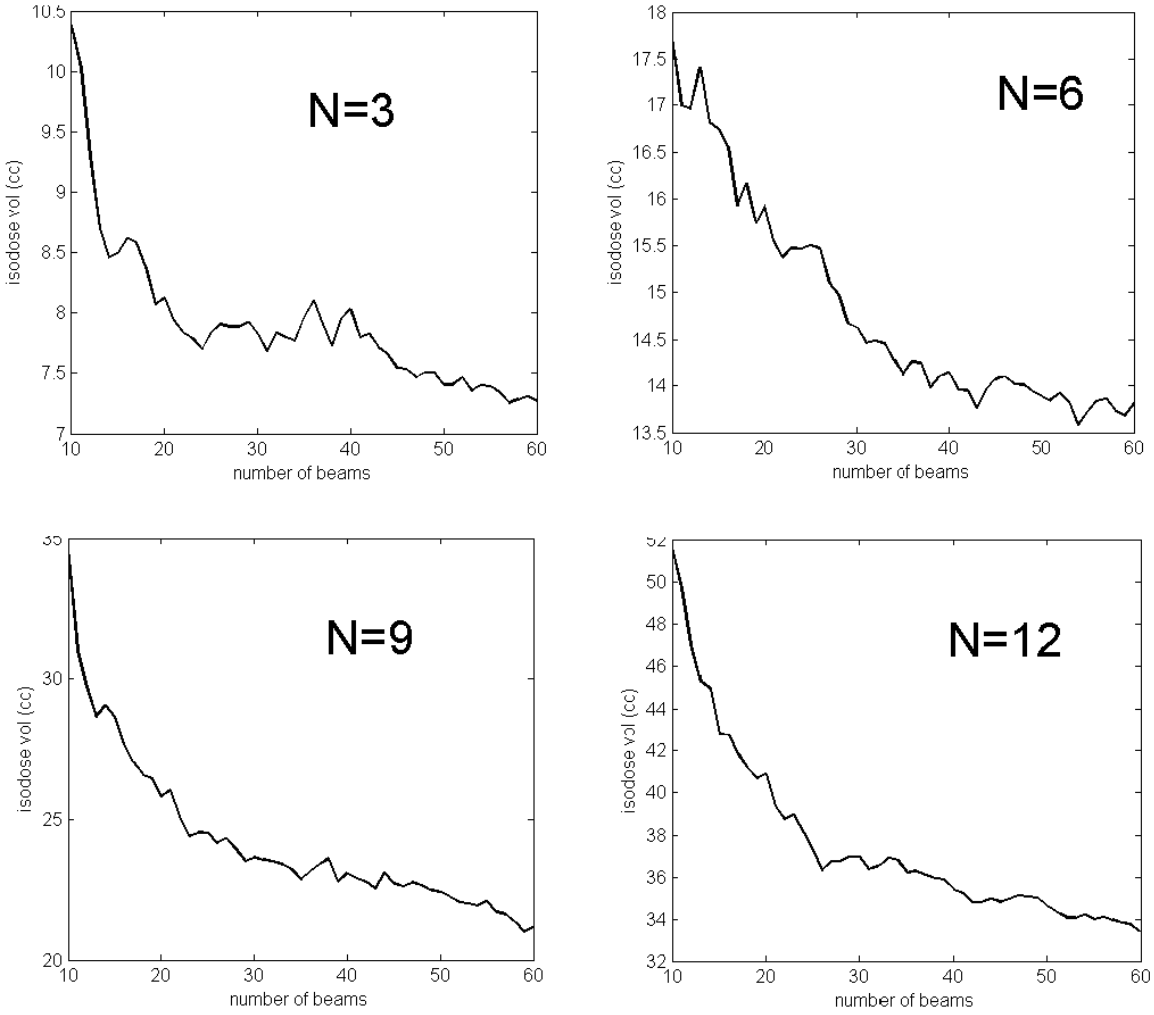

Figure 5. Example of the peripheral 8-Gy isodose volume dependence on the increasing number of beams as determined by the BROOMBA for treating different number of targets of N=3, 6, 9, and 12. The curve continuously decreased with increasing number of beams for BROOMBA and the maximum gain was approximately reached near 20-30 beams depending on the number of targets under consideration.

were lowered by 37.9%, 42.2%, 54.7% and 54.8% for N=3, 6, 9, and 12 targets, respectively. This is further illustrated in Figure 3 where planar isodose distributions for BROOMBA versus VMAT for N=3 (top panel) and N=12 (bottom panel) targets were shown. Note the significant differences in the low-level isodose areas between the two techniques on the axial images.

The dose interplay effect improvements with BROOMBA were further evidenced in Figure 4, where averaged isodose volume per target is plotted against increasing number of targets for 8-Gy and 12-Gy isodose levels. From the results of Figure 4, BROOMBA dramatically lowered the ambient background dose contribution (as indicated by the y-intercept values) of the curves when compared to the VMAT treatment plans. BROOMBA also reduced the trending slopes of these curves, suggesting effectiveness of the technique in curtailing dose interplay as zero slope values would indicate the ideal situation of no interference among the targets. As an IMRT based treatment, our BROOMBA method will consume ~ 50% more total monitor units, hence ~50% more beam on time.

4. DISCUSSIONS

Cross-firing beams from many directions is a classical technique in radiotherapy treatment plan-

ning. When dealing with multiple (N≥3) brain metastases, however, our study is the first in demonstrating the advantages of a high number of optimized beams in minimizing the inter-target dose interplay effects and lowering the dose spillage to the normal brain. Applying a large number of beams for spillage dose reduction seems counter-intuitive in the sense that more beams might be thought to irradiate larger volume of normal brain. However, patient-specific optimizations such as BROOMBA had effectively countered such a concern by drastically lowering the spillage dose near the neighborhood of individual targets at the critical levels such as 20%-80% of the prescription dose.

Although no general guideline has been established on normal brain spillage dose for multiple brain metastases treatments, several retrospective studies (9-12) have correlated that near-target peripheral isodose volumes such as the 8-Gy to 12-Gy isodose volumes with the incidence of symptomatic adverse radiation effects (AREs). QUANTEC guideline (10) has also recommended minimizing peripheral isodose volumes near the target for reducing AREs. In practice, a user always attempts to keep the normal brain spillage dose as low as possible and for this reason, near-target normal brain dose has been the key parameter in measuring and scoring the planning quality for treating multiple brain metastases.

Despite BROOMBA is capable of optimizing thousands of beams without a theoretical limitation for delivery, we have capped the total number of beams at 20 for efficiency and clinical implementability consideration for the study. The dependency of the peripheral isodose volume with increasing number of beams was also explored for the studied cases. Figure 5 illustrated the relationship between increasing number of beams for BROOMBA affecting the peripheral dose volumes with increasing number of targets. A continuous decrease in the peripheral normal brain volumes was observed for most situations although some leveling off of the curves was detected around 20-30 beams.

Evidently more studies are warranted to determine the trade-off between the treatment planning quality and efficiency of delivering a high number of beams for a BROOMBA treatment in clinical settings. It is evidently inefficient to deliver a large number of beams at different couch angles with the current linear accelerator that requires multiple manual setups. It is however expected that with high output x-ray beams and digitally controlled maneuverability, delivering tens and hundreds of intensity-modulated beams will be turnkey solution and supported by the modern digitally controlled linear-accelerator technology.

Patient specific QA for BROOMBA treatment is suggested to be split into two parts. First, all selected gantry and couch angles have to be checked in the treatment room for potential machine and patient collisional hazard. Second, dose verification should be the same as any other nonplanar IMRT plans, overriding couch kicks while measuring dose with diode arrays or ionization chamber arrays.

In summary, we have developed and demonstrated technical feasibility of BROOMBA in treating multiple brain metastases. We have found that progressively selecting and optimizing intensity-modulated beams of several folds of conventional IMRT beam numbers can significantly reduce inter-target dose interplay effects and improve normal brain sparing for treating multiple brain metastases. In summary, BROOMBA can be a powerful tool in minimizing adverse radiation effects associated with the normal brain spillage dose for treating multiple brain metastases (13).

Authors' disclosure of potential conflicts of interest

The authors reported no conflict of interest.

Author contributions

Conception and design: Peng Dong; Sabbir Hossain, Lijun Ma
Data collection: all authors
Data analysis and interpretation: Peng Dong; Sabbir Hossain, Lei Xing, Lijun Ma
Manuscript writing: all authors
Final approval of manuscript: all authors

REFERENCES

1. Sahgal A, Ma L, Chang E, et al. Advances in technology for intracranial stereotactic radiosurgery. Technol Cancer Res Treat. 2009 Aug;8(4):271-80.
2. Sahgal A, Aoyama H, Kocher M, et al. Phase 3 trials of stereotactic radiosurgery with or without whole-brain radiation therapy for 1 to 4 brain metastases: individual patient data meta-analysis. Int J Radiat Oncol Biol Phys. 2015 Mar 15;91(4):710-7.
3. Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. The Lancet Oncology. 2014 Apr;15(4):387-95.
4. McDonald D, Schuler J, Takacs I, Peng J, Jenrette J, Vanek K. Comparison of radiation dose spillage from the Gamma Knife Perfexion with that from volumetric modulated arc radiosurgery during treatment of multiple brain metastases in a single fraction. J Neurosurg. 2014 Dec;121 Suppl:51-9.
5. Ma L, Petti P, Wang B, et al. Apparatus dependence of normal brain tissue dose in stereotactic radiosurgery for multiple brain metastases. J Neurosurg. 2011 Jun;114(6):1580-4.

6. Ma L, Nichol A, Hossain S, et al. Variable dose interplay effects across radiosurgical apparatus in treating multiple brain metastases. International journal of computer assisted radiology and surgery. 2014 Apr 20.

7. Dong P, Lee P, Ruan D, et al. 4pi noncoplanar stereotactic body radiation therapy for centrally located or larger lung tumors. Int J Radiat Oncol Biol Phys. 2013 Jul 1;86(3):407-13.

8. Hossain S, Keeling V, Kimberly H, et al. Normal Brain Sparing With Increasing Number of Beams and Isocenters in Volumetric-Modulated Arc Beam Radiosurgery of Multiple Brain Metastases. Technol Cancer Res Treat. 2015; PMID: 26596914, in press.

9. Korytko T, Radivoyevitch T, Colussi V, et al. 12 Gy gamma knife radiosurgical volume is a predictor for radiation necrosis in non-AVM intracranial tumors. Int J Radiat Oncol Biol Phys. 2006 Feb 1;64(2):419-24.

10. Lawrence YR, Li XA, el Naqa I, et al. Radiation dose-volume effects in the brain. Int J Radiat Oncol Biol Phys. 2010 Mar 1;76(3 Suppl):S20-7.

11. Chin LS, Ma L, DiBiase S. Radiation necrosis following gamma knife surgery: a case-controlled comparison of treatment parameters and long-term clinical follow up. J Neurosurg. 2001 Jun;94(6):899-904.

12. Blonigen BJ, Steinmetz RD, Levin L, Lamba MA, Warnick RE, Breneman JC. Irradiated volume as a predictor of brain radionecrosis after linear accelerator stereotactic radiosurgery. Int J Radiat Oncol Biol Phys. 2010 Jul 15;77(4):996-1001.

13. Sneed PK, Mendez J, Vemer-van den Hoek JG, et al. Adverse radiation effect after stereotactic radiosurgery for brain metastases: incidence, time course, and risk factors. J Neurosurg. 2015 Aug;123(2):373-86.