2021

DEVELOPMENT OF A ROBUST LINAC-BASED RADIOSURGERY PROGRAM FOR MULTIPLE BRAIN METASTASES & ESTIMATION THE RADIOBIOLOGICAL RESPONSE OF INDIRECT CELL KILL

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Digital Object Identifier: https://doi.org/10.13023/etd.2021.039

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DEVELOPMENT OF A ROBUST LINAC-BASED RADIOSURGERY PROGRAM FOR MULTIPLE BRAIN METASTASES & ESTIMATION THE RADIOBIOLOGICAL RESPONSE OF INDIRECT CELL KILL

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Medicine
at the University of Kentucky

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ABSTRACT OF DISSERTATION

DEVELOPMENT OF A ROBUST LINAC-BASED RADIOSURGERY PROGRAM FOR MULTIPLE BRAIN METASTASES & ESTIMATION THE RADIOBIOLOGICAL RESPONSE OF INDIRECT CELL KILL

Accurate and precise delivery of Stereotactic Radiosurgery (SRS) using Gamma Knife (GK) unit by Leksell is a gold standard for multiple intracranial lesions. SRS provides less brain toxicity compared to whole brain radiotherapy techniques historically used. However, these treatments are limited in availability and are accompanied by long treatment times with painful, intolerable headframe fixation. With advancements in linear accelerator (Linac) based SRS, multiple brain lesions can be treated separately with individual isocenters or, more recently, altogether with a single isocenter multi-target (SIMT) volumetric modulated arc therapy (VMAT) technique. SIMT methods reduce the challenges of treating patients with GK by significantly decreasing treatment times, improving patient comfort and clinic workflow. This dissertation explores the usability of SIMT VMAT and presents potential solutions to the challenges of treating multiple brain lesions using Linac-based SRS.

Treating multiple brain lesions simultaneously with a SIMT VMAT plan is an efficient treatment option for SRS; however, it does not account for patient setup uncertainty, which degrades treatment delivery accuracy. This dissertation quantifies the loss of target coverage by simulating patient setup errors that would be seen on daily cone beam CT imaging during patient set up and verification. These simulations resulted in dosimetric discrepancies up to 70% (average, 30%), providing suboptimal SRS treatments. It was also found that small tumors were more susceptible to these setup uncertainties and would experience greater losses of target coverage. This means SIMT-VMAT, in its current use, is not an accurate SRS treatment modality for brain metastases. This dissertation aims to provide potential solutions to minimize these spatial uncertainties discussed. First, a novel risk-adapted correction strategy was explored where dose is escalated for small targets at a large distance from the isocenter. These treatments with up to ±1°/1 mm set up errors in all 6-directions demonstrated promising plan quality and

treatment delivery accuracy with less spread of intermediate dose to the normal brain. Second, a dual isocenter planning strategy that groups lesions based on brain hemisphere location was proposed. These plans provided similar target coverage and dose conformity as compared to the SIMT plans with less low and intermediate dose to the brain and less dose to surrounding critical organs. These techniques could potentially improve target localization accuracy and be delivered within a standard treatment slot.

Though these SIMT VMAT treatments for multiple brain metastases could be at risk of detrimental spatial uncertainties, recent clinical outcome studies suggest high rates of tumor local-control and positive treatment outcomes. In this dissertation, this is explained through a combination of both direct and indirect cell kill. A single dose of 15 Gy or more will cause damage to the weak cellular vasculature of the brain tumors, ultimately resulting in secondary cell death. By inducing clinically observable systematic set up errors, the role of secondary cell death is modeled to define the relationship between achieving required target coverage and spatial uncertainty. For 20 Gy prescription, it was found that patient set up errors of 1.3 mm/1.3°in all 6-directions must be maintained in order to achieve a target dose of 15 Gy or higher with no additional brain toxicity. At this range of uncertainty, devascularization would occur resulting in positive tumor local control, providing guidance to treating physicians for clinically acceptable patient setup errors and perhaps resulting acceptable treatment outcomes. A prospective clinical trial is necessary to further validate this radiobiological model, incorporating secondary cell death with direct cell kill using a single-isocenter VMAT plan for multiple brain lesions.

KEYWORDS: Single Isocenter VMAT, Patient Setup Errors, Multiple Brain Metastases, Stereotactic Radiosurgery, Indirect Cell Kill

Allison Nicole Palmiero

3/15/21

Date

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ACKNOWLEDGMENTS

When I began my time at the University of Kentucky 9 years ago, I never imagined I would leave with a doctoral degree in Medical Physics. When I joined the Medical Physics program as a master's student, I joined a remarkable team. I have received guidance and support from nearly every faculty and staff member in the Department of Radiation Oncology here at UK. It was only for this team that I was able to complete my dissertation and successfully move on to residency.

I would like to express my deepest appreciation to my committee chair and mentor Dr. Damodar Pokhrel. His enthusiasm and passion for Medical Physics has kept me constantly engaged with my research and made my time at UK enjoyable. Without his guidance, this dissertation would not have been possible. His commitment to his students is unwavering. He has taught me many skills, both clinically and academically, that I can take with me in the next steps of my career.

I would like to thank Dr. Janelle Molloy and Dr. Marcus Randall for allowing me to complete my PhD here at UK. They created an opportunity that I never dreamed of having and I am honored to be among the first graduates of the PhD program. Dr. Dennis Cheek has also done a great job inheriting this program and pushing it to be better for students to come. I would also like to thank Dr. William St. Clair for guidance on the dissertation subject matter and his clinical expertise. I would also like to thank my other committee members Dr. Jie Zhang and Dr. Guoqiang Yu for their support. Their guidance through the qualification and dissertation process was helpful for our new program and paved the way for future students to come. Finally, I would like to thank Dr. Sheng who has kindly agreed to be the external examiner for my final thesis examination.

I also would like to extend my appreciation to my fellow PhD students, Justin Visak, Lana Critchfield and Aaron Webster. Their encouragement has been especially valuable. Finally, I would like to acknowledge Dr. Lee Johnson for being one of the greatest teachers I have had. He taught me nearly everything I have learned in medical physics. He has guided me through the entire graduate school process with patience and exemplified the future professor that I would eventually like to be.

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CHAPTER 1. INTRODUCTION

1.1 An Overview of Brain Metastases

Multiple brain metastases are common, occurring in 20-40% of cancer patients.[1] The development of multiple brain metastases usually indicate a poor overall prognosis of a patient.[2] There is potential for serious complications due to the neurologic symptoms they cause and can result in death by compression of the normal brain against the nonexpendable skull.[3] Presenting symptoms depend on the surrounding anatomic structures of the lesions. Symptoms range from a minor as a headache or cognitive dysfunction to hemorrhaging, resulting in comas or neurological seemingly stroke-like complications.[3]

Posner and Chernik produced a comprehensive study at Memorial Sloan-Kettering Cancer Center (New York, USA) performing 2375 brain autopsies in the 1970's. Lung cancer was found to be the most common primary malignancy occurring in 18 to 63% of the cases studied. Other cancers with potential development of brain metastases included breast (2 to 21%), melanoma (4 to 16%), and colorectal cancers (2 to 11%).[4] Brain metastases are diagnosed with contrast-enhanced magnetic resonance imaging (MRI), though, with an unknown primary malignancy a pathology report via biopsy is necessary for confirming the diagnosis.[1] In the MRI scans, gadolinium-based contrast agents are used to highlight the brain metastases through disruption of the blood-brain barrier.

To maximize survival benefits, prognostic factors must be assessed where both demographic and clinical variables are involved. These factors include age, Karnofsky Performance Status (KPS) score, number of brain metastases, primary tumor type and systemic activity.[5] The highest determinant for survival is treatment regimen and KPS score as second. KPS score is an indication of how sickly and capable a patient is to care

for themselves. These factors were categorized with a Radiation Therapy Oncology Group (RTOG) database using recursive partitioning analysis (RPA). The RPA class combined with course of treatment is used to estimate median survival.[5] Through history, improvements have been made in the diagnosis and treatment of brain metastases to better prognosis. This topic is still the forefront of research to best manage these patients giving the longest and most quality life that medicine can provide.

1.2 Treatment of Multiple Brain Metastases

Historically, multiple brain metastases have been treated with whole brain radiotherapy (WBRT). With this treatment technique, survival increased by median 3-4 months, which is an increase from the 1-month survival without treatment.[5] Tumor response is found in approximately 60% of patients where symptom maintenance occurs at the same rate, though is vaguely studied.[6-7]Fractionation schemes for the WBRT treatments are employed to best limit risk of neurotoxicity. Most commonly 30 to 35 Gy in 10 to 14 fractions is delivered.[2] WBRT, currently, is mostly reserved for patients with multiple brain metastases who do not qualify for surgical resection or stereotactic radiosurgery (SRS). The risk for neurotoxicity resulting in complications like memory loss makes it a non-ideal method for treating multiple brain metastases.

With the increased availability of imaging techniques, the use of surgery for resection of brain metastases became a primary treatment option for one or two brain metastases. Surgery can be beneficial for rapid relief or neurological symptoms and can establish local tumor control.[8] Surgery is of very limited use for patients with multiple brain metastases and is limited to dominant, symptomatic or life-threatening lesions.[5] Only a

highly selected group of patients with a few metastases are able to benefit from surgical resection. Instead, SRS is a noninvasive (or minimally invasive) treatment option for multiple brain metastases, even for tumors unable to be removed surgically.

SRS delivers a single, high dose of radiation to a small tumor volume using multiple converging beams. There are multiple modes of SRS delivery with frame-based Gamma Knife (GK), cone or MLC based linear accelerators (Linacs) and cyclotron proton beams. According to RTOG 90-05 protocol, maximum tolerable prescription doses of 15 to 24 Gy are used based on increasing tumor size and location.[9] One-year local control rates range from 71 to 79% for single-lesion and multiple brain metastases. Larger tumor sizes (generally > 3 cm in diameter) are not ideal candidates for single dose brain SRS due to increased risk of brain radionecrosis.

Chemotherapy mostly plays a limited role for treatment of brain metastases and is mostly reserved for patients that have failed other treatment options. The amount of the chemotherapy drug to pass the blood brain barrier is difficult to estimate.[10] There are also treatment options that are a combination of these methods. Surgery followed by WBRT to single brain metastases found to have better local control rates but no benefit to overall survival, though they were less likely to die of neurologic causes.[11] SRS boost to residual tumors after WBRT is a treatment option to improve local control, but have shown no effect on overall survival benefits.[12] The same result was evident for SRS to brain lesions followed by WBRT.[13] WBRT still presents concern with dose to brain resulting in radionecrosis. This is apparent in a randomized trial performed by MD Anderson Cancer Center (Houston, TX) on SRS of multiple brain metastases patients. They compared SRS patients with and without WBRT. Patients that received WBRT in addition to SRS

demonstrated inferior neurocognitive results compared to those that did not receive WBRT. This must be considered when determining the best treatment option for multiple brain metastases on a per patient basis.[14]

1.3 Modes of SRS to Brain Metastases

SRS to multiple brain metastases offers a precise and accurate delivery of a single large dose of radiation to small tumor volumes and provide better local control rates. The patient is positioned with very high precision using headframe fixation or a tight mask-based system. Treatment delivery accuracy is of paramount importance for the patient safety. It provides a concentrated dose in the lesion with steep dose gradients outside of the tumor volume in an effort to spare adjacent critical organs. There is a wide array of modes used for SRS of multiple brain tumors including x-rays, gamma rays and proton beams.

SRS was first introduced by a neurosurgeon, Lars Leksell in 1951 (in Sweden).[15] To this day, GK SRS is considered the gold standard for treating intracranial lesions. It consists of 192 Co-60 sources in a hemispherical orientation and are collimated to focus at a single point at the target. It requires stereotactic head frame fixation to prevent patient motion in order to localize the target accurately.[16] In GK SRS, dose is prescribed to the 50% isodose line, providing it a high hotspot in the center of a lesion with a high dose fall-off outside the target, sparing adjacent critical organs and normal brain. This gives GK the advantage of having a high biological effective dose (BED) to the tumor. Though there are benefits of high local control when using GK SRS, there are some issues to consider. GK SRS is not readily available to all patients, where it is only included in 26% of all 428 dedicated SRS systems in the United States of America.[17] The treatment times of this

technique are long with painful, intolerable headframe fixation, where patients with large or multiple craniotomy sites are often not qualified. Those with superficial tumors would also not qualify due to collision issues. Coordination with anesthesiologists is required for the patients who may not tolerate headframe fixation. Lastly, because of it is a Co-60 unit, it requires more stringent radiation safety program in placed with tighter regulatory requirements and specialized manpower. These challenges along with the supporting evidence of SRS outcomes has stimulated the development of new treatment technologies to bring these treatments to more clinics around the globe.

Linac-based SRS has been of interest due to its availability in many radiation therapy centers. A recent treatment unit is CyberKnife (Accuray Inc., Sunnyvale, CA) used for radiosurgery of both intracranial and extracranial lesions. It is a compact linear accelerator mounted to an arm that can move in all 6 degrees of freedom (6DOF), although no posterior beams are available. Pencil beams of radiation are delivered as the robotic arm moves around the patient. This treatment method also has even longer treatment times than that of GK SRS.[18] Ring mounted linear accelerators, specifically helical Tomotherapy (Accuray Inc., Sunnyvale, CA) have also been investigated in the treatment of multiple brain metastases. With this technique, a fan beam of radiation rotates around the patient in a helical path. In addition to co-planner beam geometry, this technique still had less ideal treatment times, though less than that of GK and CyberKnife SRS. With coplanar beam geometry, a conformal dose to the target was possible, however dose fall-off outside of the target was not clinically optimal.[19]

C-arm Linac-based SRS to multiple brain metastases began with the use of dynamic conformal arcs (DCA)-based treatment plans. This method is useful for treating small

lesions where cones or multileaf collimators (MLC) are used to conform to the target and move dynamically with gantry rotation at different couch positions.[20] With this original DCA method, the isocenter was placed at the center of each lesion with each target being treated separately. Treatment planning and delivery were based on the number of lesions present and number of arcs used per lesion. Multiple isocenter DCA methods was followed by the use of intensity modulated arc therapy (IMRT) treatment. This method uses multiple non-coplanar static beams with MLC modulation for each treatment field. MLC positions are optimized with inverse planning methods. In inverse planning approaches, many control points are created and an iterative least squares algorithm is used to generate a fluence map at each point, optimizing the MLC positions.[21] IMRT methods created a more conformal dose distribution than that of DCA, but with the trade-off of low dose spread and relatively longer treatment times.[22] Later, volumetric modulated arc therapy (VMAT) was introduced where gantry speed, MLC aperture and dose rate varied during treatment delivery.[23, 24] VMAT planning uses an inverse optimization technique similar to IMRT, though the solution is the optimization of MLC aperture rather than fluence maps. MLC position adjustments along with gantry rotation and dose rate variability are used to generate a highly conformal dose distribution.[21] VMAT was developed to achieve the same coverage as IMRT with reduced treatment times due to a decrease in total monitor units (MU). VMAT also has fewer couch kicks are required with less intermediate dose spread.[25]

Traditionally, VMAT methods were developed to treat tumors individually, similar to DCA or IMRT methods, where there was a single isocenter per target. With multiple isocenter methods, the patient is aligned to each isocenter and therefore each lesion is imaged, matched and treated seperately.[26] Because of these long treatment times, it has

been of great interest to evaluate the feasibility of a single isocenter, treating multiple lesions simultaneously with a single VMAT plan. Single isocenter multi target (SIMT) methods have several variations. Huang et al. developed a single isocenter DCA-based radiosurgery technique for multiple brain metastases using high-definition MLC.[27] This was adopted by Brainlab (Feldkirchen, Germany) for multi-lesion treatments and commercially known as Multiple Metastases Elements (MME) in BrainLab treatment planning system (TPS). Alternatively, VMAT planning approaches use a multi-arc, non-coplanar geometry with a single isocenter placed at the center of all targets. VMAT optimization is then used as described above. Varian adopted this methodology and automated the treatment planning and delivery process as a new module in the Eclipse TPS (Varian Medical Systems, version 15.6, Palo Alto, CA) known as HyperArc VMAT.[16] This method automates the isocenter placement at the geometric center of all lesions and chooses the best collimator angles to each arc to reduce dose to the normal brain. HyperArc VMAT is frameless, user and patient friendly and simplifies the treatment planning and delivery.[28, 29] There is also a new option to use a hybrid approach using DCA-based VMAT optimization with a user defined MLC aperture controller. This approach used a DCA base dose calculation and then slightly optimizes the treatment plan to further improve plan quality, reduce intermediate dose spill and increase delivery accuracy.[30] With this method, Eclipse users can control the MLC field aperture shape and create a 3D dose distribution using DCA planning before VMAT optimization. For utilization of DCA-based VMAT planning, commissioning and validation of photon optimizer (PO)-MLC algorithm in Eclipse TPS is required. Although, a few investigators have studied the clinical use of PO-MLC algorithm for VMAT lung SBRT plan optimization, the usefulness of DCA-based

VMAT planning in the treatment of multiple brain metastases has not yet been reported.[30-32]

Most recently, several researchers have performed comparison studies of single-isocenter VMAT plans with all other modes of SRS treatment to multiple brain metastases. SIMT VMAT plans have similar conformity and whole brain V12Gy to that of GK SRS with significantly reduced treatment times.[33] Tomotherapy SRS plans were less conformal due to the coplanar beam arrangements with longer treatment planning and delivery times compared to single isocenter VMAT plans.[19] SIMT VMAT plans provided better conformity and V12Gy with the sacrifice of dose fall-off compared to CyberKnife radiosurgery.[34] Multiple isocenter plans have a higher dose fall-off outside the target, but have significantly longer treatment time compared to single isocenter VMAT plans, though dose conformity showed to be comparable between the two plans.[35] SIMT VMAT plans have higher conformity and brain V12Gy with shorter beam on times compared to BrainLab Element, but with a tradeoff of low dose spread and mean brain dose.[36]

Though single isocenter VMAT plans increase clinic efficiency and patient tolerability there is a tradeoff when treating multiple targets simultaneously. Multiple small brain lesions cannot be seen on a daily conebeam CT (CBCT) to insure proper alignment. Instead, alignment is done bony landmarks, making true individual tumor-to-tumor localization nearly impossible. As a result, treatment delivery inaccuracies could be caused by residual patient setup errors. Studies have shown localization and delivery inaccuracies when treating multiple brain metastases using single SIMT VMAT plan to best deliver safe and accurate treatments for these complex patients.

1.4 Radiobiology of Stereotactic Radiosurgery

Based on current clinical data of SRS, large doses per fractions produce high rate of tumor cells death.[45] Traditionally, conventionally fractionation schemes were used to achieve high sparing of normal tissues around the tumor. Dose escalation with SRS and SBRT has increased with increasing technology of image guidance and advanced radiation therapy techniques to achieve high doses in the tumor and high dose falloff to limit dose to normal tissues outside of the target. Classic radiobiology is described through the 5 R's: repair of sublethal cellular damage, repopulation of cells after radiation, redistribution of cells within the cell cycle, reoxygenation of surviving cells and radiosensitivy.[46,47] Radiobiological response models have been generated to model cell survival and to measure cell killing for specific doses and tumor types. The linear quadratic (LQ) model describes cell kill by either single or double DNA strand breaks. This model has become adopted in many clinics to determine changes in treatment regiments and dose per fractionation.[48] This model has been used for many clinical trials to best estimate the risk to normal tissues and tumor response. It is inherent in this model that reoxygenation is accounted for between each fraction. When considering single high doses, there is a lack of reoxygenation that is not accounted for. It would then be assumed that high doses of radiation would produce less tumor cell kill for the same normal tissue damage.[50] This is not evident through current clinical follow-up results.[51-55] The LQ model must not be properly predicting tumor cell kill for these high doses of radiation. This model clearly overestimates the tumor control rates with SRS techniques. Normal tissue doses may be less than projected, which would allow for larger doses than predicted to be used. The LQ survival cell curve bends continuously downward with increases in radiation dose with increased contribution of the quadratic component of the model.[56] This could be further

explained through antitumor effects that are not predictable with classic radiobiology as explained, specifically secondary cell kill effects.

There are three types of indirect cell killing to consider: strand breaks by free radicals, cell signaling of antitumor immunologic rejection and devascularization.[46] Tumor cells have weak, disorganized, fragile vasculature, making them sensitive to high dose radiation damage. For this reason, literature suggests that devascularization as the mode of secondary cells death.[46,57-58] Previous studies show that irradiation of tumors with doses higher than 15 Gy per fraction cause major vascular damage accompanied by deterioration of intratumor microenvironment resulting in secondary cell death.[59-61] This is further seen by the inverted "hockey-stick" phenomena of the cell survival curve.[61] In this cell survival curve, the beginning part of the curve represents the death of oxygenated cells. As radiation dose increases, the curve is less steep representing the death of hypoxic cells. As the dose is increased even further, above 15 Gy, cell death increases due to that of vascular damage. This bending of the curve and increases in cell death at higher doses of radiation is known as the "hockey-stick" phenomena.[61] Further understanding the radiological response of high dose per fraction SRS, specifically how it relates to patient set up errors while using a SIMT VMAT, is imperative when determining the usefulness of this treatment technique.

There are many advantages of treating multiple brain metastases using single isocenter VMAT plan as discussed above. The usefulness and limitations of single isocenter methods are still in need of investigation. There are still many questions left unanswered, for example, how do we know patients are accurately setup when using a single-isocenter plan? Patients are setup to the daily cone beam CT where the lesions are not clearly visible, therefore alignment is done by matching the skull-based bony anatomy.

What is the result if they are slightly misaligned? How can misalignments be managed? How does target coverage change as a function of set up errors and what is the radiobiological tumor response due to secondary cell death? What are the clinically acceptable limits for patient's set up errors considering indirect cell kill? These questions must be answered in order for guidance to be provided to the treating physicians and physicists to use this treatment technique more effectively in academic and the community centers.

1.5 Purpose of Dissertation

SIMT VMAT is an efficient treatment modality for multiple brain metastases patients, but does not account for isocenter misalignment, degrading treatment delivery accuracy. **The purpose of this dissertation is to evaluate the clinical usefulness and limitations of SIMT VMAT as a treatment option for stereotactic radiosurgery for multiple brain metastases patients.** The suggestions described in this dissertation will provide guidelines and some patient setup correction strategies for treating physicians and physicists for generating Linac-based SRS protocol for the fast, safe, accurate and effective treatment delivery of multiple brain metastases with SIMT VMAT plans.

1.6 Clinical Innovations and Impact

Clinical Innovation #1: Quantification of patient setup uncertainty in all six dimensions, including the affect misalignment has on normal tissue organs.

Chapter 2 evaluates the limitations of SIMT VMAT treatments of multiple brain metastases in its current clinical practice by investigating the dosimetric effects of rotational and translational patient setup uncertainties. Multiple small brain lesions are not

visible on a daily CBCT scan, making alignment to lesions a difficult task. Instead, registration must be done to bony landmarks, leaving room for patient setup uncertainty. Literature shows that SIMT VMAT could deliver suboptimal stereotactic treatment to multiple brain metastases. Sagawa et al. looked at CBCT registration information to quantify 3-dimensional rotational setup uncertainty. They concluded that significant under dosing was evident due to the rotational setup errors.[43] This work along with others exclusively evaluates the detriment of rotational errors in this setting.[35-45]While treating multiple brain lesions simultaneously, patient setup uncertainty is likely largely due to contributions of translational errors as well. This means that single isocenter VMAT SRS is an efficient treatment modality; however, due to small residual setup errors, single isocenter VMAT, in its current use, is not an accurate SRS treatment modality for multiple brain metastases. This study expanded on the effects of patient setup uncertainty when treating with SIMT VMAT by quantifying loss of target coverage due to clinically observable rotational and translational errors along with potential collateral damage to adjacent normal tissues organs. **We hypothesized that there would be a geometric relationship between isocenter to tumor distance, tumor size and loss of target coverage with potentially increased dose to surrounding critical structures.** To explore the hypothesis, small residual setup errors in all 6 DOF was induced and the effect on target coverage was evaluated along with the change in dose to critical structures.

Clinical innovation #2: Utilization of user defined aperture controller and DCA-based VMAT optimization to improve the plan quality, treatment delivery efficiency and accuracy compared to standard SIMT VMAT plan.

Chapter 3 describes and compares DCA-based VMAT and standard single-isocenter VMAT approaches for SRS of multiple brain lesions. Small field dosimetry errors are prevalent when using small beamlets in the delivery of highly modulated single isocenter VMAT. These errors are due to the high modulation of MLC, creating beamlets to treat multiple lesions simultaneously.[62] These small field dosimetry errors must be considered when using traditional single isocenter VMAT. Huang et al. first introduced the use of single isocenter DCA (SIDCA) for the treatment of multiple brain lesions. This reduced total number of monitor units for single isocenter VMAT plans, reducing the treatment time, and therefore improving treatment efficiency and compliance.[27] Traditional VMAT approaches use flattening filter free (FFF) beams to allow for higher dose rates, reduced lateral beam hardening and to reduce leakage and out of field dose from lateral scatter and electron contamination.[63-65] However, DCA-based approaches cannot utilize FFF beams due to their non-uniform dose profile.[66-67] With the development of the aperture controller feature of the photon optimizer (PO)-MLC algorithm in the Eclipse TPS, a hybrid of the two methods became possible with the development of DCA-based VMAT approach.[30,68] A 3D-DCA base dose is calculated before VMAT optimization. This has been investigated for single dose of lung SBRT plans for improved plan quality and treatment delivery efficiency and accuracy, but the usefulness of this approach in terms of brain metastases is first reported in this thesis.[30] **It was hypothesized that utilizing that DCA-based VMAT planning reduces MLC modulation through the multiple targets and improve the plan quality, treatment delivery efficiency and accuracy compared to traditional SIMT VMAT plans.** To explore this hypothesis, a comparison study between a novel DCA-based VMAT and traditional single isocenter VMAT plans was

performed. This study sparks potential for incorporating DCA-based VMAT optimization in single isocenter methods, similar to HyperArc VMAT, and warrants future investigation.

Clinical innovation #3: Creation of a novel risk adapted SIMT VMAT planning approach for multiple brain metastases to minimize spatial setup uncertainties.

Chapter 4 introduces a novel correction strategy for patient setup errors using a risk adapted planning approach where variable doses are prescribed based on distance to isocenter, tumor size and proximity of the dose limiting organs at risk (OAR). It was described in Chapter 2, that single isocenter VMAT treatments are prone to patient rotational and translational positioning errors, generating large dosimetry disparity.[35-45] Dr. Ezzell from University of Minnesota analyzed the spatial accuracy of single isocenter treatments using image guidance and concluded that spatial accuracy degrades at large distances from the isocenter.[42] Most current correction strategies, including suggestions by Dr. Ezzell, involve adding an additional margin around the target. [37-45] Though this should increase the delivery accuracy of these plans, this comes at high risk of high doses to the normal brain tissue as well. To address this issue, this chapter introduces a new correction strategy using variable prescriptions to multiple brain lesions. **We hypothesized that by escalating the prescription dose to 24 Gy, the loss of target coverage to small lesions away from isocenter could be alleviated without adding additional margin around the target(s).** Similarly, prescribing 18 Gy to large tumors located near dose limiting OAR would alleviate risk in a palliative setting. A plan comparison study was done between this risk adapted planning approach and original DCA-VMAT style plans. With this method, lesions at a large distance from isocenter can be managed while maintaining similar plan quality with lower dose to OAR including normal brain tissue. This proposed solution

would allow for SIMT VMAT to be both an efficient and accurate treatment modality for patients with multiple brain metastases.

Clinical innovation #4: Creation of a novel dual isocenter VMAT SRS planning approach for the management of multiple brain metastases that improves the plan quality and minimize patient setup uncertainties.

Chapter 5 introduces a novel dual isocenter VMAT technique to alleviate the dosimetric discrepancies of single isocenter VMAT for the management of multiple brain metastases, as quantified in Chapter 2.[35-45] Many researchers have made efforts to mitigate this uncertainty, mostly through the use of added margins.[44,69] In addition to the dosimetric discrepancies due to patient rotational and translational errors, there is also an issue of island blocking. This is when more than one lesion shares the same MLC pair. This creates gaps between the lesions, allowing for low and intermediate dose spill, increasing the dose to the normal brain and adjacent OAR. Treatment techniques, like HyperArc VMAT, attempt to mitigate this issue using collimator optimization to each arc based on tumor shape and configuration. Ohira et al. dosimetrically compared a collimator optimized HyperArc VMAT plan to a non-collimator optimized VMAT plan. They concluded that the collimator optimization did reduce dose to normal brain.[70] Other research made the similar effort through optimization of beam geometry.[71] Collimator optimization could help improving the plan quality, but cannot fully alleviate the issue of island blocking, especially with a large number of targets involved. To overcome the issue of dosimetric uncertainty and island blocking, Prentou et al. first introduced a dual isocenter planning technique. They used two isocenters to limit the distance from isocenter to decrease the spatial uncertainty. Decreases in spatial uncertainty for patients with less than 4 lesions

was apparent, though no conclusions were made on the effect of normal tissue doses.[72] It was necessary for this planning technique to be simplified with a defined delivery strategy along with the investigation of the role of island blocking in terms of sparing normal tissue structures. Therefore, **we hypothesized by grouping lesions in halves based on brain hemisphere location, MLC travel can be limited along with dose bridging due to island blocking, sparing OAR and reducing brain dose while maintaining optimal plan quality.** A comparison study of the single isocenter VMAT and dual isocenter VMAT plans was performed to investigate this hypothesis. With the a simplified dual isocenter method, it was expected that complex patients with many brain metastases could be treated with similar plan quality and more accurate treatment delivery accuracy while limiting dose to normal tissue compared to a single isocenter VMAT delivery.

Clinical innovation #5: Quantification of the role of indirect cell death in dosimetric errors due to patient setup uncertainty using radiobiology models in a SIMT VMAT setting.

Chapter 6 quantifies the role of secondary cell death in the treatment of multiple brain metastases with SIMT VMAT and defines the relationship it has with patient setup uncertainty. Recent clinical outcome studies show high rates of local tumor control for single isocenter VMAT treatments, even with the presence of setup uncertainty discussed in Chapter 2.[51-55] For example, Alongi et al did a follow up observation of 43 patients with multiple brain metastases at 6 months (average) from their SRS treatment. They observed 60% of patients had complete or partial response to radiation and 40% with stable control. Though overall survival was not reported, positive local control rates are apparent. This can be explained though effects of indirect cell kill. Specifically, doses higher than 15 Gy

per fraction cause major vascular damage in the tumor accompanied by deterioration of intratumor microenvironment resulting in secondary cell death.[56-61] **We hypothesized that in addition to direct cell kill, the effect of indirect cell kill could be playing a major role in SRS treatments, resulting in positive local control rates.** This biological modeling was used to find a clinical threshold of patient setup errors to be maintained to achieve tumor coverage for indirect cell killing to occur along with effects on normal brain toxicity. By understanding the radiobiological concepts of secondary cell death on single isocenter multi-lesion SRS treatments, physicians could have the opportunity to better decide on the effectiveness of this treatment modality for multiple brain metastases.

Finally, **Chapter 7** discusses the summaries and conclusions of each chapter, limitations of this study and future research directions to utilize the innovative methods and tools created in this study in the management of complex patients with multiple brain metastases.

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CHAPTER 2. SINGLE ISOCENTER VMAT RADIOSURGERY FOR MULTIPLE BRAIN METASTASES: POTENTIAL LOSS OF TARGET COVERAGE DUE TO ISOCENTER MISALIGNMENT

To fully understand the usability of SIMT VMAT SRS in the treatment of multiple brain lesions, we must first be able to understand its limitations. Patient positioning errors are possible when treating with a single isocenter. It was necessary to quantify the effect these patient setup errors had on tumor coverage, dose to critical structures and plan quality. The results of this chapter exemplified the risk of treating multiple brain lesions with a single isocenter, calling for methods of improvement. The following chapter has been adopted from a published manuscript: Palmiero A, Critchfield L, St. Clair W, Randall M and Pokhrel D. "Single-Isocenter VMAT Radiosurgery for Multiple Brain Metastases: Potential Loss of Target(s) Coverage due to Isocenter Misalignment." Cureus, 2020. 12(10):e11267.

Abstract

Purpose: A single-isocenter volumetric modulated arc therapy (VMAT) treatment to multiple brain metastatic patients is an efficient stereotactic radiosurgery (SRS) option. However, current clinical practice of single-isocenter SRS does not account for patient setup uncertainty, which degrades treatment delivery accuracy. This study quantifies the loss of target coverage and potential collateral dose to normal tissue due to clinically observable isocenter misalignment.

Methods and Materials: Nine patients with 61 total tumors (2-16 tumors/patient) who underwent Gamma Knife SRS were replanned in Eclipse using 10MV-FFF bream (2400 MU/min), using a single-isocenter VMAT plan, similar to HyperArc VMAT plan.

Isocenter was placed in the geometric center of the tumors. The prescription was 20 Gy to each tumor. Average gross tumor volume (GTV) and planning target volume (PTV) were 1.1 cc (0.02–11.5 cc) and 1.9 cc (0.11–18.8 cc), respectively, derived from MRI images. Average isocenter to tumor distance was 5.5 cm (1.6–10.1 cm). Six-degrees of freedom (6DoF) random and systematic residual set up errors within [±2 mm, ±2º] were generated using an in-house script in Eclipse based on our pre-treatment daily conebeam CT imaging shifts and recomputed for the simulated VMAT plan. Relative loss of target coverage as a function of tumor size and distance to isocenter were evaluated as well as collateral dose to organs-at risk (OAR).

Results: Average beam-on time was less than 6 minutes. However, loss of target coverage for clinically observable setup errors were, on average, 7.9% (up to 73.1%) for the GTV ($p < 0.001$) and 21.5% for the PTV (up to 93.7%) ($p < 0.001$). Correlation was found for both random and systematic residual setup errors with tumor sizes; there was a greater loss of target coverage for small tumors. Due to isocenter misalignment, OAR doses fluctuated and potentially receive higher doses than the original plan.

Conclusion: A single-isocenter VMAT SRS treatment (similar to HyperArc VMAT) to multiple brain metastases was fast with < 6 min of beam-on time. However, due to small residual set up errors, single-isocenter VMAT, in its current use, is not an accurate SRS treatment modality for multiple brain metastases. Loss of target coverage was statistically significant, especially for smaller lesions, and may not be clinically acceptable if left uncorrected. Further investigation of correction strategies is underway.

2.1 Introduction

Multiple brain metastases are common among cancer patients. Twenty to fifty percent of cancer patients develop brain metastases with the most common primary malignancies being lung cancer, breast cancer, and melanoma.[1] Historically, this was treated with whole brain radiotherapy (WBRT), which resulted in normal tissue toxicities such as memory loss, hair loss, pituitary dysfunction and diminished hearing, and positive treatment outcomes were not achieved (with 100% failure at one year).[2] More recently, stereotactic radiosurgery (SRS) has gained popularity due to its high precision and accuracy in a single treatment, providing good tumor local control rates and sparing critical organs.[3,4] For instance, a randomized trial from the MD Anderson Cancer Center on SRS of multiple brain metastases patients with or without WBRT demonstrated inferior neurocognitive results in the cohort who had received WBRT in addition to SRS.[3] Of the stereotactic treatment modalities for treating multiple metastases, Gamma Knife (GK) radiosurgery is a gold standard.[5] However, GK patients face many challenges such as incredibly long treatment times, painful headframe placement, inability to affix the headframe to craniotomy sites, and difficultly arranging anesthesia time for claustrophobic patients. Though alternative treatment modalities such as robotic CyberKnife and ring-mounted accelerators are available, long treatment times and inferior plan quality can be problematic.[6]

Linac-based SRS treatments is an option to provide frameless SRS to brain metastatic patients. This began through multiple isocenter dynamic conformal arcs (DCA) or VMAT-based treatment planning where each target was planned and treated individually. Isocenters were placed at the center of each tumor and setup and imaged

individually, allowing for corrections of residual setup errors around each isocenter. Traditional Linac-based SRS treatments can impede clinic workflow due to individual patient setup and conebeam CT (CBCT) imaging of each isocenter and long treatment times. A new treatment planning and delivery approach is to treat multiple lesions simultaneously using a single-isocenter VMAT plan, allowing for increased clinic efficacy and tolerability.[7] Varian recently introduced a Truebeam Linac-based (or superior) single-isocenter VMAT platform known as HyperArc as a module in the Eclipse treatment planning system (TPS, Varian Medical Systems, Version 15.6) to mitigate all of these challenges mentioned above.[6,8,9] HyperArc (HA) VMAT can rapidly deliver treatment to multiple brain metastates and improve patient compliance and comfort.

However, there is a tradeoff when treating multiple targets simultaneously using a single-isocenter VMAT plan, similar to HyperArc plan. First, small multiple brain metastases cannot be seen on a daily single CBCT to ensure proper target alignment. Instead, alignment must be made by rigid registration to bony anatomy. As a result, treatment delivery inaccuracies that could come with residual patient setup errors could increase. Second, lining up multiple brain tumors accurately using a single daily CBCT is almost impossible. Studies have shown localization and treatment delivery inaccuracy when treating multiple brain lesions using HyperArc VMAT.[9-11] For example, Sagawa et al. used CBCT registration information to induce a 3-dimensional rotational setup uncertainty.[9] They concluded that non-negligible under dosing to the PTV was due to residual rotational set up errors. Although they successfully explain the presence and dosimetric effects of rotational set up uncertainties, their work excludes consideration of small translational effects in addition to the rotational errors. This study is innovative in

the sense that it includes setup uncertainties in all 6DOF to further quantify the treatment delivery inaccuracy of HyperArc style single-isocenter VMAT plan. This work was performed in a clinically representative manner for the commissioning of single-isocenter VMAT treatments. The Eclipse TPS was used entirely and isocenter misalignments were randomly induced errors to mimic representative patient positioning uncertainties for SRS treatments using an in-house script. Thus, the main purpose of this study is to fully quantify the dosimetric effects resulting from clinically attainable residual patient set up errors in all 6-directions for single-isocenter/multi-lesions technique. Relative loss of target coverage as a function of tumor size and distance from isocenter was investigated. Additionally, collateral dose to the adjacent organs-at-risk (OAR) was evaluated.

2.2 Materials and Methods

2.2.1 Patient images and contouring

After obtaining an Institutional Review Board (IRB) approval, nine patients with multiple brain metastases (all lung primary) were included in this retrospective study. These patients were previously treated with frame-based GK radiosurgery using high-resolution double contrast MPRAGE MRI imaging (Siemens MAGNETOM, 1.5T MRI System, Ferndale, MI). The MRI images were 512×512 pixels and 1 mm slice thickness with no gap between the slices. These DICOM MRI datasets were transferred from the GK planning station into Varian Eclipse TPS for contouring and planning. The target volumes were delineated by an experienced radiation oncologist on the MRI and the gross tumor volumes (GTVs) were defined by the visible tumor in the MRI images. The planning target volumes (PTVs) were created using a uniform 1.0 mm margin around each GTV. There were 2-16 lesions per patient with total 61 lesions. The tumor characteristics are

summarized in Table 1. The OAR's were delineated including: optics apparatus (both optics nerves plus chiasm), brainstem, eyes and lenses, normal brain (brain minus PTVs) and hippocampi (left and right hippocampus). The hippocampi contours were done following RTOG-0933 atlas.[12] Since no planning CT images were available for these patients, for treatment planning purposes, a homogenous medium was assigned to the body contour in Eclipse TPS with a CT value of 0. Distance to isocenter was calculated by finding the coordinates of the PTV geometric center and determining the distance from the isocenter coordinates for each lesion.

Table 2.1 Main tumor characteristics of the patients included in this study.

Parameters	Mean ± STD (range)
Total tumors (n = 9 patients)	61 (2–16/patient)
GTV (cc)	1.06 ± 1.85 (0.03–11.5)
PTV (cc)	1.88 ± 2.86 (0.11–18.8)
Prescribed dose to each lesion	20 Gy in 1 fraction (70-80% isodose line)
Isocenter to tumors distance (cm)	5.50 ± 1.80 (1.58–10.15)
Tumor location (bi-lateral brain)	(all patients)
Normal brain (cc) = Whole brain minus PTVs	1517 ± 198 (1213–1705)

2.2.2 Original VMAT plans

HyperArc (HA) style single-isocenter VMAT SRS plans were generated in the Eclipse TPS for the Truebeam Linac (Varian Medical Systems, Palo Alto, CA) with standard millennium MLCs and 10MV-FFF beam (maximum achievable dose rate of 2400 MU/min). The plans mimicked HyperArc VMAT geometry with the use of 4-5

noncoplanar arc arrangements, replicating gantry rotation and couch kicks. Isocenter was placed at the approximate geometric center of all the tumors. The collimator angles were chosen manually to minimize island blocking and dose outside of the target. Dose was 20 Gy to each lesion prescribed to the 70-80% isodose line. The plans were optimized so that 95% of each PTV received at least 100% of the prescription dose with the hotspot at the center of the GTV. The dose was calculated with Anisotropic Analytic Algorithm (AAA) (Eclipse, version 15.5) with 1.25 mm calculation grid size. Inverse optimization was performed with the photon optimizer (PO) MLC algorithm with individual dose steering ring structures to each target. Jaw tracking and normal tissue objective (NTO) was used to control the dose fall-off outside of each target for better dose conformity and to spare adjacent OAR. Planning objectives followed RTOG 0933 guidelines for hippocampal sparing that were converted to SRS dose constraints using biological effective dose, allowing maximal dose to hippocampus to be < 6.5 Gy.[12,13] Other OAR followed QUANTEC guidelines for single fraction treatments such as maximal dose to optic apparatus < 8.0 Gy.[14] Average beam on time for original VMAT plans was recorded 5.20 ± 0.97 min (range, 3.01–6.02 min). Beam-on time was calculated by taking the total monitor units divided by the maximum dose rate setting of 2400 MU/min for 10 MV-FFF beam.

2.2.3 Simulated VMAT plans

A novel in-house method was developed to simulate clinically realistic residual setup errors by inducing uncertainties within a range of ±2 mm and ±2° in all 6DoF. These induced uncertainties were chosen randomly to mimic prospective daily CBCT setup errors obtained at the machine in a clinically realistic setting based on previous SRS patient's

data. The residual translational errors were defined for isocenter displacements. The rotational errors were defined for patient rotations relative to the isocenter around the right-left (pitch), anterior-posterior (yaw) and superior-inferior (roll) directions. After the single-isocenter VMAT plans were generated, the patient MRI images were duplicated and co-registered to the original MRI. The image registration DICOM file was exported from the Eclipse TPS and imported into an in-house MATLab script that generated random rotational ($\Delta\alpha$, $\Delta\beta$, $\Delta\gamma$) and translational (Δx, Δy, Δz) errors within [±2°, ±2 mm] in each direction. These matrices were then applied to the reference frame, and the output was a new image registration file with a simulated shift in 6DoF. The image registration DICOM file was imported back into the Eclipse TPS with the new transformation matrix applied to the registered MRI images. The single-isocenter VMAT plan was then overlaid on to the new registered image and dose was re-calculated with the only difference in the plans being the shift in the isocenter. For better statistics, each patient's original plan was simulated 10 times and all the output data averaged. A visual scripting tool (Varian Medical Systems, Palo Alto, CA) (see Appendix 2) was used to export relevant dosimetric parameters for plan comparison. This process provides all dosimetric parameters including OAR doses using the same dose calculation algorithm as the original plan.

This same method was used to systematically induce setup uncertainties. Instead of randomly generating the translational and rotational matrices, they were set to [±0.5 mm, ±0.5°]; [±1 mm, ±1°] and [±2 mm, ±2°] in each direction, systematically. With these systematic errors, the image registration was then repeated and the original single-isocenter VMAT plan was overlaid on to the new image set for comparison as described above.

2.2.4 Plan comparison and data analysis

The simulated VMAT plans with isocenter misalignment were compared to the original single-isocenter VMAT plans. The visual scripting tool (see Appendix 2) exported dose volume histogram (DVH) parameters used to evaluate the plan quality. The minimum, mean and maximum doses to GTV were evaluated between the plans. The PTV coverage was assessed by a comparison with original PTV D95% coverage. The OAR's were evaluated using maximal doses to hippocampi, brainstem, and optics apparatus. Dose to the normal brain was assessed using mean brain dose (MBD), V12 and V16.[15] For each target, heterogeneity index (HI), Paddick conformation number (CN), and under-treatment ratio (UR) were evaluated.[16] The HI is the ratio between the maximum dose in the target target (D_{Max}) and the prescription isodose (D_{RX}). A HI value of less than 2.0 meets protocol guidelines. The Paddick CN is defined as the ratio of the target volume covered by the prescription isodose (TV_RX) to the product of the target volume (TV) and the total volume covered by the prescription isodose (VRX). This parameter accounts for the position of the prescription isodose relative to the target volume. Additionally, the Paddick CN was evaluated via the under-treatment ratio (UR), where a value of 1.0 represents a fully covered or overly treated lesion and less than 1.0 represents an undertreated lesion. Loss of target coverage for both randomly generated and systematically induced setup uncertainties were evaluated as a function of target volume and distance to isocenter. A paired two-tail student's t-test (Microsoft Excel, Microsoft Corp., Redmond, WA) was used to compare the data for the original VMAT vs simulated VMAT plans for all dosimetric parameters of target coverage and to the OAR. A value of $p < 0.05$ was used as a cutoff for statistically significant.

2.3 Results

2.3.1 Simulated random errors

The analysis of target coverage for all nine patients (61 lesions) randomly simulated 10 times each is shown in Table 2. Simulated VMAT plans showed an average loss of PTV coverage of 21.5 ± 13.6% (range, 0.4–94.7%) compared to the original VMAT plans. After applying clinically observable random transformations, major loss in PTV coverage, CN, UR and HI were observed. The severe loss in the average values of CN ($p < 0.001$) and UR ($p < 0.001$) for the simulated VMAT plans suggests that the prescription isodose volume did not cover the PTV as planned originally. The minimum and mean doses to GTVs were decreased by an average of 3.6 Gy and 1.5 Gy, signifying underdosing of the GTVs.

Table 2.2 Analysis of the loss of target coverage for each plan

Target (s)	**Parameter**	**Original VMAT plans**	**Simulated VMAT plans**	***p*-value**
GTVs	Max dose (Gy)	25.4 ± 0.5 (24.5–26.1)	25.3 ± 0.51 (24.3–26.1)	p = 0.385
	Min dose (Gy)	21.9 ± 0.65 (20.8–23.3)	18.3 ± 2.2 (14.3–21.3)	***p* < 0.001**
	Mean dose (Gy)	24.0 ± 0.47 (23.2–24.8)	22.6 ± 1.4 (19.8–24.6)	***p* < 0.001**
PTVs	% Volume covered by Rx dose (%)	98.7 ± 1.4 (95.0–100.0)	77.2 ± 13.7 (5.0 – 99.7)	***p* < 0.001**
	CN	0.70 ± 0.11 (0.35–0.91)	0.43 ± 0.18 (0.04–0.89)	***p* < 0.001**

Table 2.2 (Continued)

	UR	0.95 ± 0.15 (0.13–0.913)	0.75 ± 0.16 (0.13–1.0)	***p* < 0.001**
	HI	1.3 ± 0.03 (1.1–1.3)	1.2 ± 0.04 (1.0–1.3)	***p* = 0.04**

Figure 2.1 shows an axial, coronal, and sagittal view of the original and simulated VMAT plans for an example patient with 16 tumors (not all tumors are seen). With induced random setup uncertainties within [-2.0, +2.0] mm and [-2.0, -2.0] degrees in all 6DOF, major loss of both GTV and PTV coverage was observed. In the simulated VMAT plan, loss of target coverage was evident due to the visible difference in overlap of the PTV (orange) and the prescription isodose lines (green).

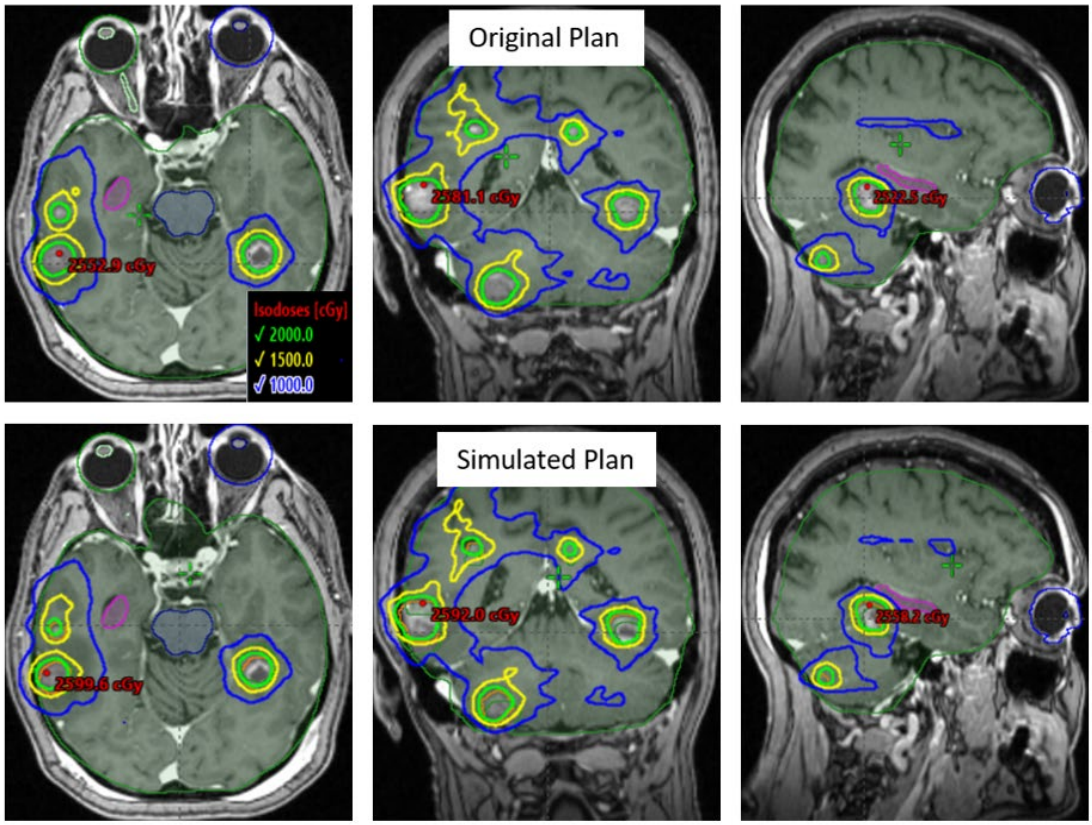


Figure 2.1 Example of loss of coverage seen in patient with 16 tumors.
An axial, coronal and sagittal view of an example case with 16 tumors: Original VMAT plan (upper panel) and simulated VMAT plan (lower panel) with randomly induced residual set up errors of ±2.0 mm and ±2.0° in each direction. The prescription isodose line (green) conformed to each lesion as in original plan. Loss of target coverage is seen in the simulated VMAT plan (see lower panel) and shifted the higher isodose line closer to the hippocampus.

This is further illustrated in the DVH (see Figure 2.2) with the original VMAT plan (triangle) and simulated VMAT plan (square). The blue arrow shows the original intended coverage for all targets (> 95% of PTVs receiving 20 Gy dose). Loss of PTV (orange) coverages were observed up to 45% and loss of GTV (red) coverages of up to 25% in some lesions. OAR doses fluctuated depending on the random uncertainty induced to the simulated VMAT plans, and in some cases resulting in substantial increases to OAR doses. Figures 2.1 and 2.2 demonstrate the example case of an increased dose to the hippocampus

(pink color). In the original plan, the maximal dose to hippocampi was kept below 6.3 Gy.[13] With induced random errors in the simulated VMAT plan, maximal dose to hippocampi was 8.1 Gy, exceeding the protocol requirement of 6.5 Gy. This was visible in the sagittal image of the Figure 2.1 above where the 50% isodose line (10 Gy) was perturbed towards the hippocampus (pink contour) and also shown in DVH (see figure 2.2).

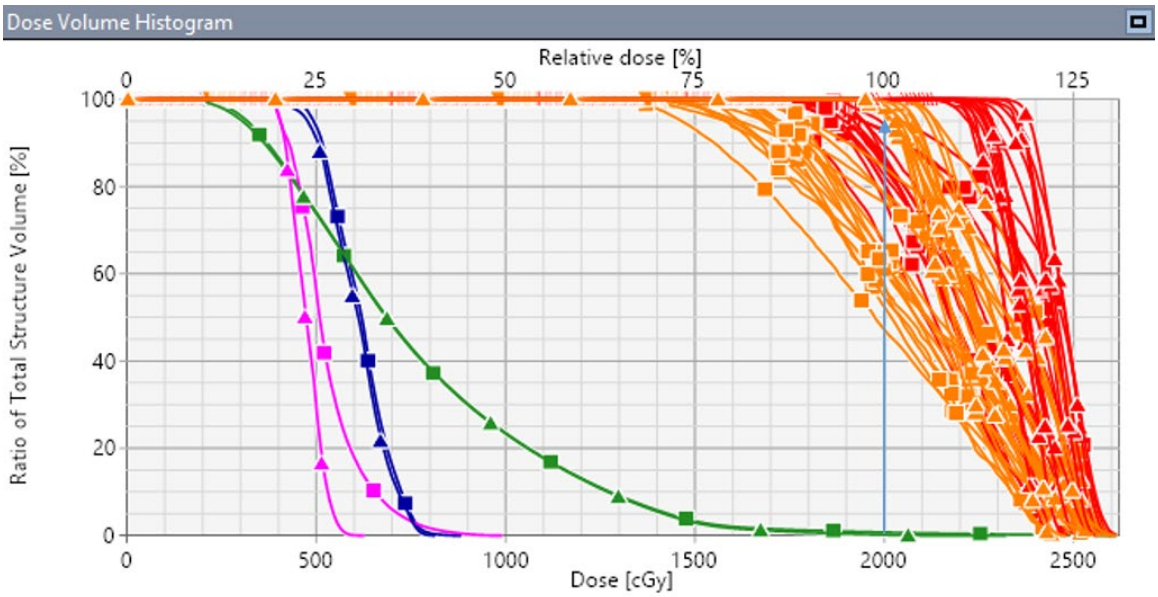


Figure 2.2 Comparison of DVH for iriginal VMAT plan (triangle) and simulated VMAT plan (square)
Comparison of dose volume histogram (DVH) for the original VMAT plan (triangle) and the simulated VMAT plan (square) with randomly induced residual set up error in 6DoF. Vertical blue arrow shows the original planned coverage to all PTV. Brainstem (blue) and normal brain (green) are shown. Due to small, clinically observable residual patient setup errors, unacceptable loss of target coverage was observed along with increased dose to hippocampi (pink).

An analysis of loss of coverage for all nine patients with setup uncertainty is displayed in Figure 2.3. The probability distribution function of coverage loss due to GTVs and the PTVs is shown. The number of occurrences of a particular coverage loss was binned in the histograms for all 10 iterations of the simulation for all nine patients (61 original targets, total 610 simulated targets). The red line represents the distributions

correlating to the histogram with relative target coverage losses for GTVs and PTVs with the average values of 7.9 ± 11.1% and 21.5 ± 13.6%, respectively. This means for a typical single-isocenter VMAT plan, predictively, a loss of coverage of this magnitude would potentially exist during multiple brain metastases SRS treatment.

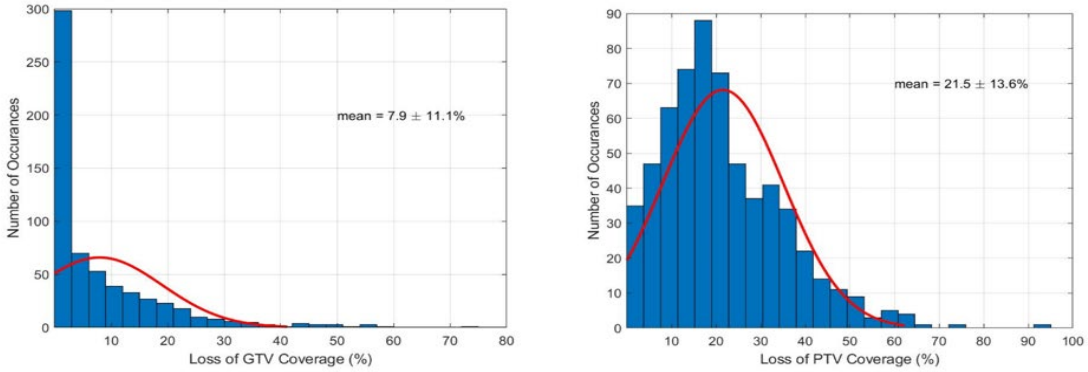


Figure 2.3 Probability distribution functions demonstrating the loss of coverage for all 9 patients.
Probability distribution functions demonstrating the loss of coverage for both the GTVs (left) and PTVs (right) of all nine patients (61 tumors), randomly repeated each patient over 10 times (610 iterations). Residual set up errors between [± 2.0 mm, ± 2.0º] were applied in all 6DoF to replicate the day-to-day clinically representative residual set up errors. Due to these small set up errors, clinically unacceptable loss of target coverage was observed, which projects the magnitude of loss that would be seen in a typical single-isocenter VMAT treatment.

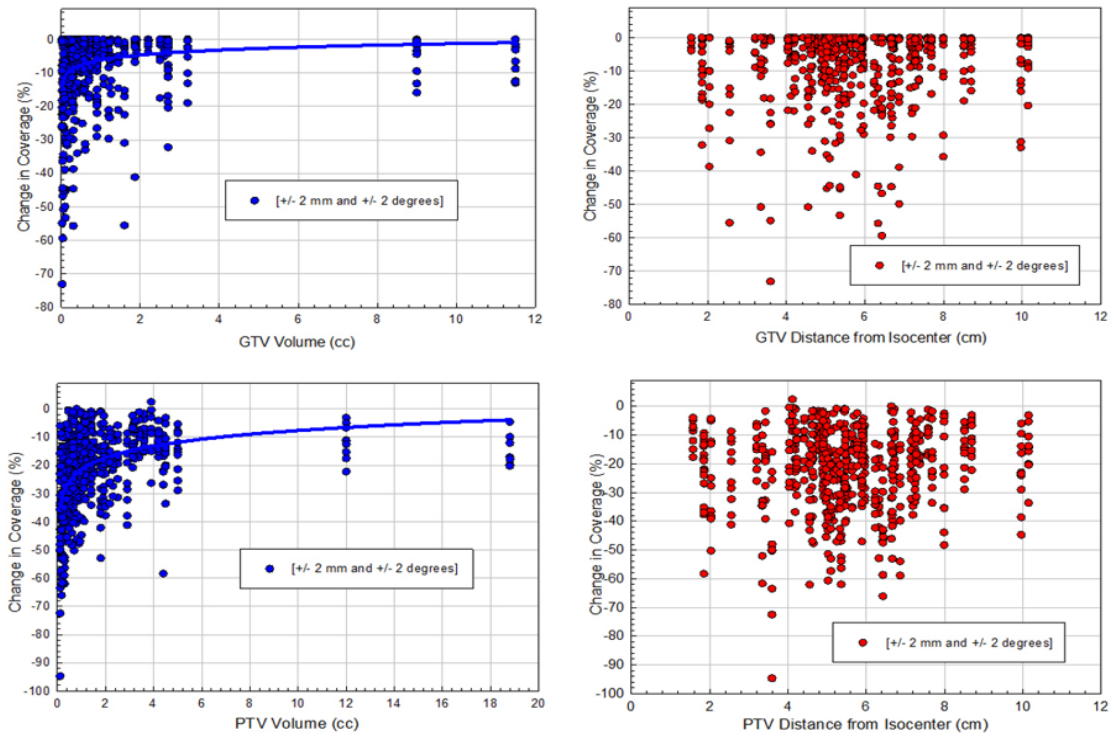


Figure 2.4 Scatter plots of loss of target coverage as a function of tumor volume and distance to isocenter.
Scatter plots of the relative dose errors of target coverage due to random residual set up errors as a function of tumor volume and distance to isocenter for both GTVs (upper panel) and PTVs (lower panel) were shown. Greater loss of target coverage for smaller tumor sizes was correlated for both GTVs and PTVs. However, no obvious trends were seen when comparing loss of coverage and distance from isocenter while simulating all 6DoF residual set up errors.

The loss of target coverage due to random residual set up errors in 6DoF as a function of tumor size and distance to isocenter for the both GTVs and PTVs are shown in Figure 2.4. A clear trend was evident that with a smaller GTV and PTV, there was increased loss of target coverage (see left panel). However, there was no correlation between loss of coverage and distance to isocenter (right panel). This could be due to randomly generated clinically realistic translational error of ±2 mm (in each direction) dominating small but clinically observed rotational error of ±2° (in each direction). The variation in patient

parameters such as tumor number, size and distance to isocenter could make such a trend difficult to detect.

Regarding normal brain dose, no statistically significant difference was observed for MBD ($p = 0.41$), V12 ($p = 0.97$), V16 ($p = 0.79$). However, in some cases the maximal difference was up to 1.0 Gy, 5.2 cc and 5.9 cc. In the Linac-based SRS treatments, Blonigen et al. reported that normal brain V8 to V16 were the best predictors for radio-necrosis. Therefore, we caution that in some cases, maximal difference in V16 up to 5.9 cc could be detrimental to the normal brain.[17] Maximal dose increase of brainstem, optic apparatus and hippocampi were < 2.0 Gy, < 0.4 Gy, and < 2.7 Gy, respectively.

2.3.2 Simulated systematic errors

To evaluate worst-case scenarios, we simulated single-isocenter VMAT plans with systematically assigned rotational and translational errors in all six-directions. This was performed by inducing systematic ±0.5 mm, ±1 mm, and ±2 mm, and ±0.5°, ±1°, and ±2° errors in all 6DoF; results are shown in Figure 2.5. These simulations compared the results of relative loss of PTV coverage for all 61 tumors. Loss of target coverage was a function of both the magnitude of induced uncertainty and tumor volume. The loss of target coverage due to systematic residual set up errors for 0.5 mm, 1 mm, and 2 mm, and 0.5°, 1°, and 2° errors were 6.0 ± 3.1% (range, 0.5–15.6%), 18.2 ± 6.9% (range, 6.6–34.1%) and 42.9 ± 15.0% (range, 16.2–87.7%), respectively. Similar results were obtained for the negative direction (see Figure 2.5).

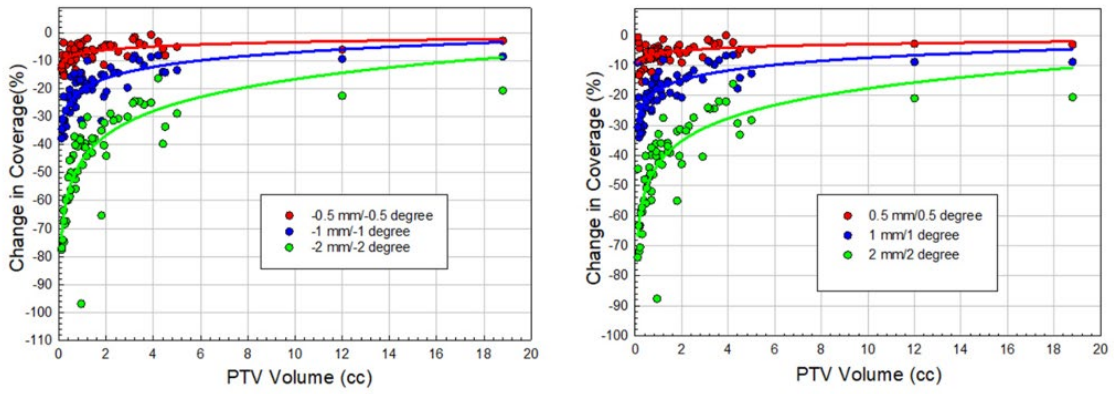


Figure 2.5 Loss of coverage as a function of PTV volume for systematic errors
Scatter plots of loss of target coverage as a function of PTV volume is shown for all 61 targets. All systematically induced errors were within [±2 mm, ±2°] in all 6DoF. There was greater loss of target coverage for smaller tumors with the larger residual set up errors (green).

2.4 Discussion

In this clinically representative simulation study, the dosimetric impact of clinically observable 6DoF residual setup errors in HyperArc style single-isocenter VMAT plans in the treatment of multiple brain metastases have been evaluated. Clinically unacceptable loss of target coverage for smaller tumors was observed when simulating residual isocenter misalignments. After applying clinically achievable random translational errors of ±2 mm and rotational errors of ±2° in each direction, the dramatic loss of the PTV coverage was observed with an average relative dose error of 21.5 ± 13.6% (up to 94.7% in some lesions) ($p < 0.001$). This suggests that this technique could have major limitations treating multiple brain lesions synchronously. Minimum dose to GTVs was lower by almost 4.0 Gy, on average, suggesting potential underdosing of small tumors.

Due to faster treatment delivery, Linac-based VMAT SRS is becoming increasingly utilized, specifically using single-isocenter SRS.[18] Average beam on time was less 6 minutes. Varian developed a novel technology to automate this process using single-

isocenter HyperArc VMAT for multiple lesions brain SRS.[19] Localization of each lesion is of utmost importance when escalating dose to a small region. This is a difficult task, especially when treating multiple brain metastases simultaneously via a single-isocenter VMAT plan, including HyperArc VMAT. Patients are setup using a daily single CBCT to align bony anatomy; targets are not visible on daily CBCT, so targets are not localized individually. Small patient misalignments result in clinically significant loss of coverage and could deliver a very high dose adjacent to the tumor. This finding is of utmost importance because the HyperArc style single-isocenter VMAT could potentially deliver dosimetrically unacceptable treatments to patients through a near or complete geometric miss of the small brain lesions and increase damage to the adjacent critical structures. Major loss of dose conformity, lower GTV dose, higher relative dose errors for smaller lesions, and potentially higher doses to OAR's including hippocampi and normal brain V12 and V16 have been demonstrated.

Other researchers have studied the loss of target coverage due to residual patient setup errors.[9,20-25] Sagawa et al. reported that due to rotational set up errors there was non-negligible underdosing of PTV coverage and significant increase of normal brain V10 to V16 for multiple brain metastases patients with HA-VMAT plans. Uncertainties were simulated using a 3rd party software (MIM Maestro, MIM software Inc., USA) that could add additional source dosimetric errors.[11] Rotational set up errors were up to ± 3° in each direction. Roper et al. systematically induced rotational errors of 0.5°, 1.0°, and 2.0° using Velocity AI (Velocity Medical, Atlanta GA) registration software.[24] They demonstrated a correlation between diminishing PTV coverage and distance from isocenter; however, their study was performed only using systematic rotational setup errors in single-isocentric

VMAT plans consisting of only two lesions. Their results showed that PTVD95% values worsened up to 60% of the prescribed dose in systematic rotations of 2° about all three axes. However, they did not include potential translational pretreatment set up errors and did not report the impact on OAR doses. In contrast, this study included all 6DoF residual set up errors for patients with multiple brain lesions (up to 16) and reported changes in OAR's.

This investigative approach is more consistent with clinical realities by including all 6DoF residual patient set up errors and resulted in an even greater loss of target coverage than what other studies have shown. An innovative aspect of this study is that it uses computer generated random uncertainties in all rotational and translational directions (in Eclipse) to apply to isocenter to simulate patient setup errors. This successfully simulates the types of errors encountered in a clinical setting without using a third-party software, which avoids adding other sources of dosimetric discrepancy. Another novelty in this study is the diversity of patients. Most similar studies used patients with few tumors whereas patients in this study had up to 16 tumors (average 7) and a total of 61 lesions. Unlike other studies, the simulations and treatment planning were all done within the Eclipse TPS, minimizing other sources of error and making it more clinically representative. This tool can be used for both intracranial as well as extracranial multi-lesions and single-lesion stereotactic treatments settings.

There are some limitations of this study. First, due to the lack of HyperArc planning license, HyperArc style single-isocenter VMAT plans were simulated. Although, the arc geometry of HyperArc was kept the same, collimator optimizations were done manually to minimize the out of field dose on a per-patient basis. Second, this is a retrospective study

of previously treated frame-based GK radiosurgery patients using high-resolution MRI imaging. Therefore, we did not have an appropriate planning CT imaging for heterogeneity corrections. For this simulation study, homogenous dose to the brain was calculated assigning a CT value equal to water. However, in a Monte Carlo study by Pokhrel et al. with fractionated-SRS treatments of cavernous sinus tumors, it was demonstrated that dose discrepancy is less than 2% in the brain with pencil-beam algorithm.[26] Although, a homogenous medium is used in routine GK radiosurgery treatments, we acknowledge that heterogeneity corrections will introduce most likely a small dosimetric errors in the brain compared to these large discrepancies due to residual set up errors. In the future, planning CT images will be used for actual patient treatment via single-isocenter VMAT, co-registering MRI for tumors and OAR delineation. Due to the proximity of multiple brain lesions and island blocking problems (two or more lesions sharing the same MLC pairs), the spread of 50% isodose lines created higher dose bridging in between/among the tumors. This created a major difficulty in calculating gradient indices for each lesion (results not shown here). Another limitation to the study is using standard MLCs of 5 mm width. Single-isocenter VMAT for multiple brain lesions is primarily limited to linear accelerators utilizing 2.5 mm high-definition MLCs. However, a recent study from Duke demonstrated that for radiosurgery of multiple brain metastases using a single-isocenter VMAT plan, 5 mm MLCs can produce similar target conformity with slightly increased 30-50% isodose spillage, but this can be minimized by adding one or two more VMAT arcs.[27]

In summary, a single-isocenter VMAT treatment similar to HyperArc VMAT for multiple brain metastases can reduce treatment time significantly and improve treatment tolerability and clinic workflow. However, due to small but clinically relevant residual set

up errors an unacceptable loss of target coverage is observed. This could increase dose to OAR including normal brain. It is therefore very important for any HyperArc style VMAT users to quantify these dosimetric discrepancies and develop correction strategies to minimize the dosimetric effects. Potential correction strategies are possible. First, institute an asymmetric margin around the GTV as a function of target volume and distance to isocenter. Second, assign risk-adapted prescriptions up to 24 Gy (rather than 20 Gy) to small lesions away from the isocenter and no critical structures around the tumor. Third, create dual-isocenter VMAT plans, rather than single-isocenter plan, for a large number of multiple brain metastases as a function of distribution of the lesions in the brain, dividing the brain into two equal volumes. Any of these correction strategies could potentially compensate for the loss of target coverage and could be adopted on a patient-specific basis.

2.5 Conclusion

Rapid treatment of multiple brain lesions using a single-isocenter VMAT is possible; however, small setup errors can result in large deviations from the planned target coverage, specifically for the smaller targets. This loss of target coverage due to small isocenter misalignment cannot be ignored for single-isocenter VMAT plan, similar to HyperArc VMAT plan. In some cases, large increases of normal brain dose V12 and V16 and maximal dose to OAR including hippocampi could be harmful. Further investigation of correction strategies is warranted.

CHAPTER 3. A NOVEL DYNAMIC CONFORMAL ARC-BASED SINGLE ISOCENTER VMAT PLANNING FOR RADIOSURGERY OF MULTIPLE BRAIN METASTASES

Upon the confirmation of risks target coverage loss due to patient positioning uncertainty when treating with SIMT VMAT, improvements in plan quality was warranted. A DCA base VMAT hybrid planning approach was developed to minimize small field dosimetry errors and improve overall plan quality compared to traditional SIMT VMAT methods. These results gave insight to alternative methods for the fast and more accurate treatment of multiple brain metastases with single isocenter Linac-based stereotactic radiosurgery. The following chapter has been adopted from a recently accepted article: Pokhrel D, Palmiero A, Bernard M, and St Clair W. "A Novel Dynamic Conformal Arcs-based Single Isocenter VMAT Planning for Radiosurgery of Multiple Brain Metastases." *Med Dosim,* 2020; 1-6 (Article in Press) Elsevier.

Abstract

Purpose: Multiple small beamlets in the delivery of highly modulated single-isocenter HyperArc VMAT plan can lead to dose delivery errors associated with small-field dosimetry, which can be a major concern for stereotactic radiosurgery (SRS) for multiple brain lesions. Herein, we describe and compare a clinically valuable dynamic conformal arc (DCA)-based VMAT (DCA-VMAT) approach for SRS of multiple brain lesions using flattening filter free (FFF) beams to minimize this effect.

Methods: Original single-isocenter HyperArc style VMAT and DCA-VMAT plans were created on 7 patients with 2-8 brain lesions (total 35 lesions) for 10MV-FFF beam. 20Gy was prescribed to each lesion. For identical planning criteria, DCA-VMAT utilizes user-controlled field aperture shaper before VMAT optimization. Plans were evaluated for

conformity and target coverage, low- and intermediate dose spillages to brain volume that received more than 30% (V30%) and 50% (V50%) of prescription dose. Additionally, mean brain dose (MBD), V8, V12 and maximal dose to other adjacent organs-at-risk (OAR) including hippocampi were reported. Total monitor units (MU), beam modulation factor (MF) and treatment delivery efficiency and accuracy were recorded.

Results: Comparing with original VMAT, DCA-VMAT plans provided similar tumor dose, target coverage and conformity, yet tighter radiosurgical dose distribution with lower dose to normal brain V30% ($p = 0.009$), V50% ($p = 0.05$) and other OAR. Lower total number of monitor units and smaller beam modulation factor reduced beam on time by 2.82 min ($p < 0.001$), on average (maximum up to 3.8 min). Beam delivery accuracy was improved by 8%, on average ($p < 0.001$) and maximum up to 13% in some cases for DCA-VMAT plans.

Conclusions: This novel DCA-VMAT approach provided excellent plan quality, reduced dose to normal brain and other OAR while significantly reducing beam-on time for radiosurgery of multiple brain lesions –improving patient compliance and clinic workflow. It also provided less MLC modulation through the targets –potentially minimizing small field dosimetry errors as demonstrated by quality assurance results. Incorporating DCA-based VMAT optimization in HyperArc module for radiosurgery of multiple brain lesions value future investigation.

3.1 Introduction

Traditional Linac-based stereotactic radiosurgery (SRS) treatment to multiple brain lesions requires an individual plan to each lesion with a separate isocenter placed in the

center of each lesion. Currently many clinics around the globe use this technique by using circular arcs with stereotactic cone-mounted linac or multileaf collimators (MLC)-based 3D dynamic conformal arc (DCA), intensity modulated radiosurgery and volumetric modulated arc radiosurgery plan placing the Linac isocenter at each target. [1, 2]For multiple brain lesions, this requires huge treatment planning effort, prolonged patient set up to each isocenter and overall longer treatment time as well as patient collision issues with the cone-mounted linac heads. To overcome this difficulty, Huang et al. developed a single-isocenter dynamic conformal arcs (SIDCA) based radiosurgery technique for multiple brain lesions using high-definition MLC. [3] In a SIDCA plan, there is a single-isocentere position at the geometric center of all the lesions, while each lesion is treated with DCA . This SIDCA approach was later adopted by BrainLAB AG (Feldkirchen, Germany) system for multiple brain lesions as Multiple Metastases Elements (MME). The main benefits of SIDCA planning being: reduction of treatment planning and treatment delivery time due to single-isocenter setup, fewer conebeam CT scans, fewer treatment fields, and less number of total monitor units (MU), improving treatment efficiency and patient compliance. However, this approach could work well for traditional flattened beams but it may not be very suitable with flattening filter free (FFF) beams due to their unflattened dose profiles. [4, 5]Compared to the traditional flattened beams, FFF beams have certain advantages for radiosurgery treatment, including higher dose rates, reduced lateral beam hardening, and reduced leakage and out-of-field dose due to less lateral scattering and electron contamination, without increasing tissue toxicity and gaining whispered popularity in the clinic for single and multiple lesion stereotactic treatments. [6-8]

Recent advances in technology have allowed for the use of volumetric modulated arc therapy (VMAT) in the treatment of multiple brain lesions using a single-isocenter technique with single or multiple arcs. [9-13] For instance, Clark et al from the University of Alabama at Birmingham were the first to demonstrate the feasibility of using single-isocenter VMAT for multiple brain lesions. [9] To further improve the plan quality by minimizing the inter-planners variability and to fully automate the treatment planning and delivery, Varian recently introduced a Truebeam Linac-based (or superior) single-isocenter VMAT platform known as HyperArc (Varian Medical Systems, Palo Alto, CA) as a module in the Eclipse treatment planning system (TPS). This module is generating a global clinical interest in the treatment of multiple brain lesions simultaneously. [14-17] This new treatment planning and delivery module allows for treatment of multiple brain lesions simultaneously using a single-isocenter VMAT plan, allowing for an increased clinic efficiency and tolerability for the multiple brain metastatic patients. However, unlike SIDCA plans, extremely modulated HyperArc VMAT plans that are highly susceptible to delivery uncertainties due to small-field dosimetry errors.[18] That is due to MLC modulation of multiple beamlets through the multiple small targets simultaneously. To minimize MLC modulation effects and further improve the plan quality Varian Eclipse TPS has recently implemented a new multileaf collimator (MLC) optimization algorithm, called Photon Optimizer (PO). [19]PO offers a new MLC aperture shaper controller. With this new feature, Eclipse users can control the field aperture shape and create a 3D dose distributions using DCA before VMAT optimization. Although a few investigators have studied the clinical use of PO-MLC algorithm for VMAT lung SBRT plan optimization, [20-22]the dosimetric effects and treatment delivery complexity of this planning approach with a FFF-beam in

the treatment of multiple brain lesions using a HyperArc style VMAT plan has not yet been reported.

Thus, as a part of our Linac-based stereotactic radiosurgery commissioning of Eclipse TPS (Version 15.6), it is important to highlight the importance of investigating new planning features to provide the highest quality plan and the most efficient and accurate treatment delivery. When using a highly modulated single-isocenter VMAT plan for multiple small brain lesions, the MLCs must travel a longer distance to provide adequate coverage to each lesion simultaneously. Moreover, dose to radiosensitive organs including nontarget normal brain is a major concern in treating multiple brain lesions synchronously using a single-isocenter VMAT plan. [23-29]Therefore, in this report we have retrospectively evaluated this new feature on seven patients with multiple brain metastases for improving plan quality and treatment delivery efficiency and accuracy. For comparison, the original HyperArc style VMAT plans were re-optimized using a DCA-based VMAT (DCA-VMAT) planning approach with identical beam geometry, dose calculation algorithm, grid size, planning objectives and parameters. The DCA-VMAT plans utilized DCA-based dose with the high strength of field-aperture shaper control priority before VMAT optimization– therefore, less beam modulation through the multiple targets is expected. The original VMAT plans and re-optimized DCA-VMAT plans were compared for target coverage and conformity, low- and intermediate- dose-spillage to normal brain and dose to OAR. Additionally, treatment delivery efficiency and accuracy were reported.

3.2 Materials and methods

3.2.1 Patient population

Seven patients with a range of 2-8 brain metastases (all lung primary) were included in this retrospective study approved by our institutional ethic committee. These patients were previously treated through single fraction SRS in our institution using a high-resolution double contrast MPRAGE MRI imaging (Siemens MAGNETOM, 1.5T MRI System, Ferndale, MI) on GammaKnife. The MRI images were 512×512 pixels and 1 mm slice thickness with no gap in between the slices. These DICOM MRI datasets were transferred into Varian Eclipse TPS for targets and critical structures contouring. The target volumes were delineated by an experienced radiation oncologist on the MRI and the gross tumor volumes (GTVs) was defined by the visible tumor in the MRI images. The planning target volumes (PTVs) were created using a uniform 1.0 mm margin around each GTV using a departmental SRS protocol. There were 2-8 lesions per patient with a total of 35 lesions. The tumor characteristics are summarized in Table 1. The OAR were delineated including: optics apparatus (both optics nerves plus chiasm), brainstem, eyes and lenses, normal brain (brain minus PTVs) and hippocampi (left and right hippocampus). The hippocampi contoured was done following RTOG-0933 atlas. [24] Distance to isocenter was calculated by finding the coordinates of the PTV geometric center and determining the 3D Euclidian distance from the isocenter coordinates for each lesion.

Table 3.1 Tumor characteristics of the patients included in this study

Patient no.	No. of lesions	Average distance from isocenter (cm)	Volume of each lesion (cc)	Total PTV (cc)
I	2	2.5	2.94, 4.37	7.37
II	3	5.8	1.82, 0.28, 0.65	2.76
III	4	6.4	18.79, 1.04, 1.90, 4.17	25.91
IV	5	8.9	12.05, 1.98, 5.00, 4.48, 1.04	24.54
V	6	5.5	3.56, 3.42, 1.49, 1.43, 1.13, 1.35	12.38
VI	7	5.1	3.88, 1.81, 1.40, 0.92, 0.73, 0.57, 0.85	10.16
VII	8	4.3	0.49, 0.94, 1.23, 3.19, 0.33, 0.93, 0.61, 0.46	8.18

3.2.2 Original VMAT plans

Clinically optimal HyperArc style single-isocenter VMAT SRS plans were generated in the Eclipse TPS for the Truebeam Linac (Varian Medical Systems, Palo Alto, CA) with standard millennium MLC and 10MV-FFF beam (maximum achievable dose rate of 2400 MU/min). The plans mimicked HA-VMAT geometry consisting of 4 VMAT arcs: one 360º axial arc and three 180º non-coplanar half arcs at couch positions of 45º, 90º, and 315º (IEC convention). [9]The isocenter was placed at the approximate geometric center of all the tumors. The collimator angles were chosen manually to minimize island blocking and dose outside of the target. Dose was 20 Gy to each lesion prescribed to 70-80% isodose line. The plans were optimized so that 95% of each PTV received at least

100% of the prescription dose with the hotspot at the center of the GTV. The dose was calculated with Anisotropic Analytic Algorithm (AAA) (Eclipse, version 15.6) with 1.25 mm calculation grid size. Inverse optimization was performed with the photon optimizer (PO) MLC algorithm with individual dose steering ring structures to each target. Jaw tracking and normal tissue objective (NTO) was used to control the dose fall-off outside of each target for better dose conformity and sparing the adjacent OAR. Planning objectives followed RTOG 0933 guidelines for hippocampal sparing that were converted to SRS dose constraints using biological effective dose, allowing maximal dose to hippocampus to be a max dose of < 6.5 Gy . [24-25]Other OAR followed QUANTEC guidelines for single fraction treatments such as maximal dose to optic apparatus < 8.0 Gy. [26]

3.2.3 DCA-VMAT plans

For comparison, the original VMAT plans for all patients were retrospectively re-planned (in Eclipse version 15.6) using a new feature (MLC aperture controller) with DCA-based dose calculation followed by VMAT optimization (DCA-VMAT). Figure 3.1 shows the proposed treatment planning workflow of this novel approach.[22] For the DCA-VMAT plans (with identical beam geometry), first 1mm of the MLC aperture around the combined PTV is automatically generated and maintained dynamically around the targets during arc rotation. The MLC fitting was observed to dynamically conform to the beam's-eye-view (BEV) projections of the combined PTV for each arc. Second, a high priority in the MLC aperture shape controller was selected (a new feature in Eclipse v15.6, PO MLC algorithm in calculation models) and proceeded to calculate a DCA-based 3D dose distribution. This 3D dose distribution was then used as a based-dose for VMAT optimization. This was followed by VMAT optimization with identical planning objectives, dose calculation

algorithm, grid-size and convergence mode identical to the original VMAT plan, including the normal tissue objectives (NTO) parameters and ring structures.

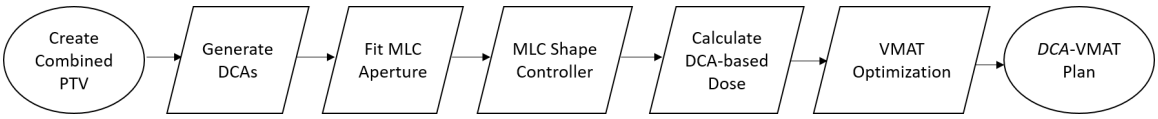


Figure 3.1 Treatment planning workflow of DCA-VMAT method for multiple brain metastases

3.2.4 Plan evaluation and data analysis

This study was a retrospective planning study and none of the patients were treated with the DCA-VMAT or original VMAT plans. The DCA-VMAT plans were compared to the original VMAT plans for minimum, mean and maximum dose to each GTV. The combined PTV coverage was assessed by comparing with original PTV D95% coverage and conformity index (CI). The low and intermediate dose-spillage to the normal brain was evaluated by V30% and V50% for brain minus combined PTV in addition to mean brain dose (MBD), V8Gy and V12Gy. V30% and V50% were defined as the volume of brain minus combined PTV receiving greater than or equal to 30% and 50% of the prescribed dose, respectively. The OAR were evaluated using their maximal doses to hippocampi, brainstem, and optics apparatus. Comparing total number of monitor units (MU), beam modulation factor (MF) and total beam on time (BOT) evaluated the treatment delivery efficiency. The MF was defined as the ratio of total number of total MU to the prescription dose in cGy. The BOT was recorded during VMAT quality assurance (QA) phantom measurement at the machine for both plans. Dosimetric verification of the both plans were performed by using portal dosimetry (PD) QA procedure established in our clinic.[30] The electronic portal imaging device (EPID, aS1200 flat panel detector, Varian Medical

Systems) mounted on the Truebeam Linac was used. The detector has an active area of 400 mm × 400 mm with a very high resolution pixel size of 0.34 mm. A paired two-tail student's t-test (Microsoft Excel, Microsoft Corp., Redmond, WA) was used to compare the data for the original VMAT vs DCA-VMAT plans for all dosimetric parameters of target coverage, dose to OAR and treatment delivery parameters. A p-value below 0.05 was considered to indicate statistically significant.

3.3 Results

3.3.1 Target coverage and dose to normal brain

Compared to original VMAT plans, DCA-VMAT plans provided similar tumor conformity, target coverage and comparable dose to GTV; all exhibited no statistical significance differences. However, DCA-VMAT plans shows smaller values of V30% (p = 0.009) and V50% (p = 0.043) as demonstrated by the values of low and intermediate dose-spillage to the normal brain (Table 3.2), systematically lower for all patient's plans.

Table 3.2 Evaluation of target coverage and dose spill for all 7 patients

	Parameters	**Original VMAT**	**DCA-VMAT**	***p*-value**
Combined PTV	% Volume covered by Rx dose (%)	98.2 ± 0.9 (97.3–99.3)	97.8 ± 0.6 (96.8–98.6)	*p = 0.261*
	CI	1.23 ± 0.1 (1.15–1.29)	1.25 ± 0.1 (1.14–1.31)	*p = 0.228*

Table 3.2 (Continued)

Low/intermediate dose-spillage	**V30% (cc)**	**352.7 ± 202.2 (58.7–557.5)**	**267.2 ± 146.8 (59.4–414.9)**	***p = 0.009***
	V50% (cc)	104.3 ± 56.7 (21.6–182.3)	88.9 ± 50.7 (19.6–164.0)	***p = 0.043***
GTV	D_{min} (Gy)	21.4 ± 0.73 (18.9–22.4)	21.2 ± 0.94 (18.7–22.8)	*p = 0.762*
	D_{max} (Gy)	26.4 ± 4.6 (24.5–52.7)	25.7 ± 0.56 (24.7–26.8)	*p = 0.469*

Figure 3.2 shows an example case of radiosurgical dose distribution of a patient with 6 brain lesions in the axial, coronal, and sagittal views comparing the DCA-VMAT (left panel) and the original VMAT (right panel). It was observed that clinically desirable tighter 50% isodose distribution was obtained with DCA-VMAT (see blue 10 Gy isodose lines) compared to the original VMAT plan. DVH parameters (top middle panel) are shown for the GTVs, combined PTV coverage, and dose to OAR for DCA-VMAT plan vs the original VMAT, suggesting that DCA-VMAT plan was dosimetrically superior. The combined PTV size was 12.38 cc. In this case, the PTV coverage, CI, V30%, and V50% were 98.6% vs 98.6%, 1.27 vs 1.25, 362.2 cc vs 512.4 cc and 87.9 cc vs 139.5 cc for DCA-VMAT vs original VMAT plan, respectively. Moreover, V8Gy, V12Gy and MBD were 160.8 cc vs 255.5 cc, 39.7 cc vs 55.3 cc and 4.42 Gy vs 5.34 Gy for DCA-VMAT vs original VMAT plan –all dosimetric parameters favoring the DCA-VMAT plan.

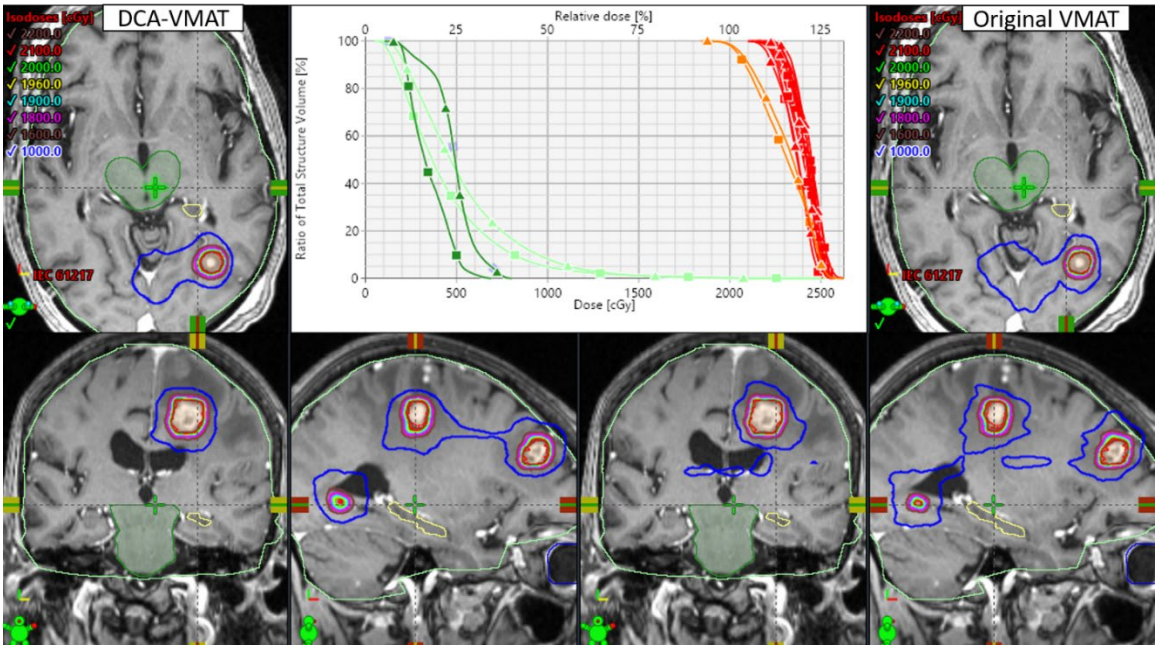


Figure 3.2 Comparison of DCA-VMAT and original VMAT dose distributions for example case #5

Side-by-side comparison of DCA-VMAT (left panel) and original VMAT (right panel) planned dose distributions on axial, coronal and sagittal views for an example case #5 with 6 brain lesions. Each lesion was prescribed for 20 Gy to the PTV. Hippocampi (yellow) contour and Middle: DVH of combined PTV (orange), 6 GTVs (red), brainstem (green) and normal brain tissue (sea blue) for both plans is shown. Triangle shows the original VMAT and square shows the DCA-VMAT plan. Identical target coverage, yet lower dose to normal brain was achieved with DCA-VMAT plan; it provided lower values of V30% and V50%, a shorter treatment time, and perhaps more accurate treatment delivery.

Figure 3.3 depicts the ratio of MBD, V8 and V12 between original VMAT and DCA-VMAT plans. For all parameters, DCA-VMAT was favorable over original VMAT plans and it was lower by 1.0 Gy (MBD), 44.5 cc (V8) and 4 cc (V12), on average, respectively. Additionally, the maximal dose differences between the original VMAT and DCA-VMAT plans for the OAR (optics apparatus, brainstem and hippocampus) were found to be very small (not shown here) and therefore are not expected to be clinically significant.

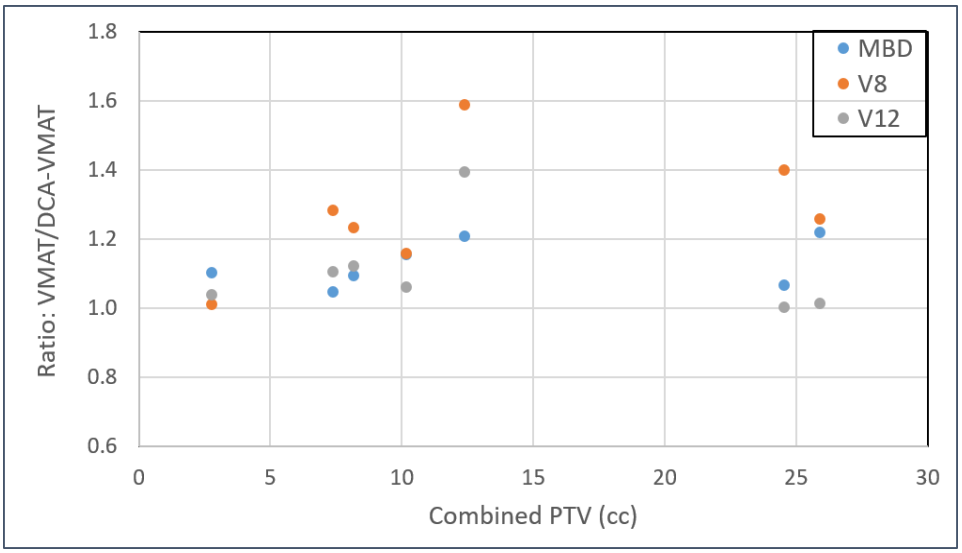


Figure 3.3 Comparison of MBD, V8 and V12 between original VMAT and DCA-VMAT
Ratio of MBD, V8 and V12 between the original VMAT and DCA-VMAT plans. MBD, V8 and V12 improved by a 13%, 28% and 10%, on average respectively, corresponds to 1.0 Gy, 44.5 cc and 4.0 cc lowered with DCA-VMAT plan.

3.3.2 Treatment delivery efficiency and accuracy

Dose delivery efficiency was accessed by comparing total number of MU and estimated beam on time while delivering QA plans at the machine. Compared to original VMAT plans, DCA-VMAT plans show fewer total MU and less beam modulation. Mean values of total MU and MF were 12498 and 6.3 for original VMAT plans vs 5742 and 2.9 for DCA-VMAT plans. The MF and the beam-on time for original VMAT vs DCA-VMAT plans is shown in Figure 3.4. For the given DCA-VMAT plans, the total number of MU was reduced significantly (by a factor of 2.2, on average, and systematically lower for all patients) while using DCA-based dose before VMAT plan optimization, suggesting that the DCA-VMAT plan had much smaller MF ($p < 0.001$). Because of this, the average beam-on time for DCA-VMAT plan was 2.82 min less ($p < 0.001$) (maximum up to 3.8 min) than original VMAT plan (mean value, 6.21 min) due to less beam modulation

through the multiple targets. With DCA-VMAT plan, single-dose of 20 Gy SRS treatment to multiple brain lesions can be delivered in less than 3 min, on average. The lower beam-on time will reduce the time the patient is on the treatment table, thus improving patient compliance and potentially improving the clinic workflow.

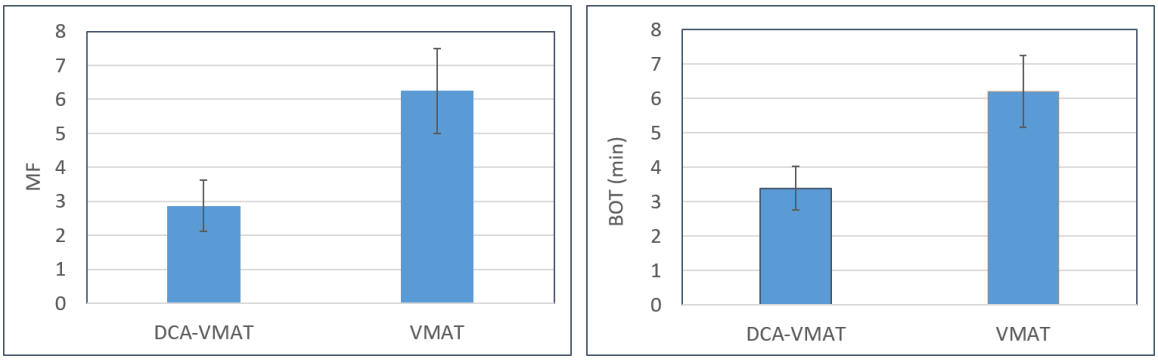


Figure 3.4 Comparison of treatment parameters for original VMAT and DCA-VMAT

Left panel: MF for DCA-VMAT vs original VMAT plans for all 7 patients with 2-8 multiple brain lesions (total 35 lesions). Mean values of MF for DCA-VMAT and original VMAT plans were 2.87 ± 0.75 (ranged, 1.95–4.19) and 6.15 ± 1.25 (ranged, 3.62–7.22) respectively. Right panel: The corresponding BOT for both plans. Mean values of BOT for DCA-VMAT vs original VMAT plans were 3.39 ± 0.63 min (ranged, 2.63–4.49 min) and 6.21 ± 1.05 min (ranged, 4.01–7.86 min) respectively, with DCA-VMAT plans beam-on time improve by an almost a factor of 2.0.

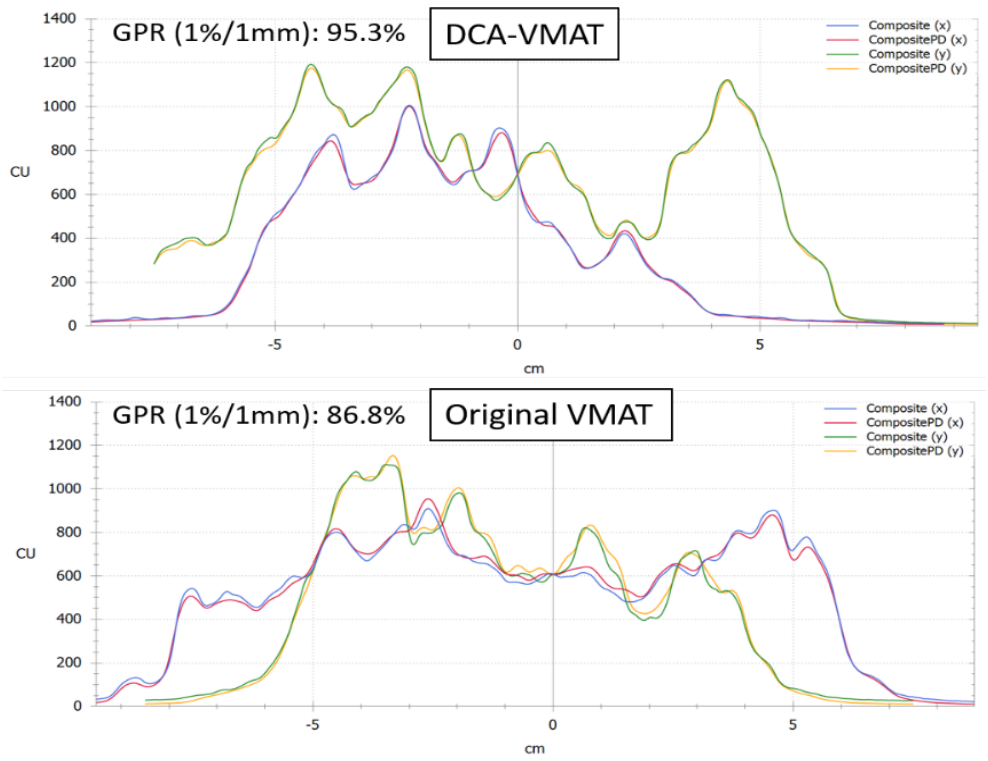


Figure 3.5 Portal dosimetry QA results for original VMAT plan and DCA VMAT plan for patient #5
Measured (red and orange) and calculated (blue and green) composite 2D profiles and gamma pass rate (GPR) on portal dosimetry QA results of DCA-VMAT and original VMAT plan for an example patient #5 who presented with 6 brain lesions. In this case, 8.5% improvement in GPR for 1%/1mm criteria with DCA-VMAT plan suggesting that more accurate treatment delivery.

Treatment delivery accuracy was evaluated by delivering both plans at Truebeam Linac in the QA mode using the EPID device and measuring the portal dosimetry QA data (see example case #5 in Figure 3.5). The dose delivery accuracy of these original VMAT plans, and the corresponding DCA-VMAT plans were 87.5 ± 4.3% (ranged, 81.9–94.7%) and 95.4 ± 2.5% (ranged, 90.6–98.0%), on average respectively with 1%/1mm global gamma passing rate criteria with a low-dose threshold of 10%. Due to the small pixel size of aS1200 EPID detector (0.34 mm), the 2%/2mm gamma criteria was not very useful to see the dosimetric differences for these small brain lesions, therefore our departmental policy is to use 1%/1mm gamma criteria. One of seven cases met our departmental QA

pass criteria of greater than 90.0% gamma pass rates for original VMAT plans, whereas all seven cases met that criteria for DCA-VMAT plans, suggesting significantly improving dose delivery accuracy for small brain lesions. In some cases (for small lesions) dose delivery accuracy was improved by up to 13.6% with DCA-VMAT plans–suggesting that significant dose deviation ($p < 0.003$) can be seen with highly modulated original VMAT plans compared to DCA-VMAT plans.

3.4 Discussion

We have presented a novel and clinically attractive DCA-based single-isocenter VMAT planning approach for multiple brain lesions. The new DCA-VMAT plans achieved similar conformity and target coverage (see table 3.2) compared to original VMAT plans. For all patients, the DCA-VMAT plans provided lower values of low and intermediate dose spillage to normal brain, significantly reducing V30% and V50%. Additionally, MBD, V8 and V12 were systematically lower with DCA-VMAT plans including maximal doses to brainstem, optic apparatus and hippocampi. The DCA-VMAT plans required less total number of MU to deliver the same total prescribed dose due to less beam modulation through the multiple small brain lesions. Thus the BOT was reduced significantly (average beam on time 3.0 minutes) demonstrating the clinical efficiency of DCA-VMAT plans for treating multiple brain lesions simultaneously in this cohort. Moreover, the treatment delivery accuracy was improved significantly with measured data analyzed at 1%/1mm gamma passing-criteria, suggesting better delivery accuracy.

Liu et al presented dosimetric comparison of two competing technologies BrainLAB MME vs Varian HyperArc VMAT for multiple brain metastases in a most

recent study. [17]Thirty patients with 4-10 metastases were used. Both techniques used single-isocenter with 2.5 mm high-definition MLC (HD-MLC). MME plans used 4-9 non-coplanar DCAs with 6MV-FFF beam where as HyperArc used 2-4 non-coplanar VMAT arcs with 10MV-FFF beam. They have concluded that HyperArc VMAT favors better target conformity and high- to moderate dose levels compared to MME DCA plan while MME DCA gave slightly favorable low isodose spills. Approximate average beam on time for both techniques was reported, however they did not mention how this was achieved. 6MV-FFF beam of non-uniform dose profiles was managed while calculating MME DCA plan. Our clinical experience is generating DCA plans for multiple brain lesions with 6MV-FFF beam will be very challenging to get the highly conformal dose distribution around the targets due to uneven dose profiles. Moreover, the MLC complexity and the QA pass rates for HyperArc VMAT were not reported. Similar to HyperArc plans, we used 10MV-FFF beam but in contrast, we have presented the better treatment delivery efficiency and accuracy by delivering each DCA-VMAT plan with PD QA at the treatment machine.

Multiple researchers have studied the sparing of normal brain V8-V12 dose [25] and other OAR including hippocampi for SRS treatment of multiple brain metastases with or without WBRT and simultaneous integrated boost dosing. [24, 27-29]For instance, Birer et al. demonstrated lower maximal dose to hippocampi (< 6.5 Gy) can be achieved while re-optimizing previously treated SRS patients with 4-10 lesions via single-isocenter VMAT plan and potentially improve neurocognition deficit. In this setting, incorporating this novel DCA-VMAT approach can further minimize normal brain dose and other OAR including the hippocampi. However, there are few limitations of this retrospective study need to mention. First, due to the lack of HyperArc planning license, we have created HyperArc

style VMAT plans using a single-isocenter VMAT technique. Although, the arc geometry of HyperArc was kept identical, collimator optimizations were done manually to minimize the out of field dose on a per-patient basis. Second, HyperArc VMAT for multiple brain lesions is primarily used to linear accelerators utilizing 2.5 mm HD-MLC. Due to the unavailability of HD-MLC, our HyperArc style single-isocenter VMAT plans were generated using standard millennium 5 mm width MLC at Truebeam Linac. However, multiple recent studies [31, 32] have demonstrated that for radiosurgery of multiple brain metastases using a single-isocenter VMAT plan with 5 mm MLC can produce similar target conformity of HD-MLC with a slight increase in 30-50% isodose spillage, but can be managed by adding one or two more VMAT arcs. [31]

In summary, the potential benefit of utilizing DCA-based planning for HyperArc style single-isocenter VMAT for multiple brain lesions has been presented. With this approach, DCA-based plan optimization potentially reduces MLC complexity and beam-on time while providing similar target coverage to multiple lesions and lower dose to normal brain and other OAR in the brain. Therefore, to minimize MLC complexity and subsequently improve treatment delivery efficiency and accuracy we strongly recommend utilizing DCA-VMAT approach (if available) for single-isocenter/multi-lesions VMAT optimization, thereby reducing the total number of MU, MLC leakage and transmission and potentially lowering unwanted dose to the patients. The lower BOT will reduce the time the patient is on the treatment table, thus improving patient compliance and potentially improving the clinic workflow. Our future research incudes incorporating this novel DCA-based approach for generating better quality HyperArc VMAT plans for multiple brain lesions.

3.5 Conclusions

Our results clearly indicates that the advantages of using DCA-based approach in VMAT optimization for single-isocenter HyperArc style planning in the treatment of multiple brain lesions in terms of generating low- and intermediate dose to normal brain. With DCA-VMAT plan, the total number of MU, complexity of MLC patterns, and beam-on time was reduced significantly. Higher QA pass rates indicates that safe and more accurate treatment can be delivered. Incorporating DCA-based dose method in HyperArc module in future could further improve plan quality, treatment delivery efficiency and accuracy of multiple brain metastatic patients and hence improving the patient comfort and clinic workflow.

CHAPTER 4. A NOVEL RISK ADAPTED SINGLE ISOCENTER VMAT PLANNING TECHNIQUE FOR RADIOSURGERY OF MULTIPLE BRAIN LESIONS TO MINIMIZE SPATIAL SETUP UNCERTAINTIES

Due to the dosimetric errors due to patient positioning uncertainty discussed in Chapter 1 and 2, correction strategies to improve accuracy in the SIMT VMAT setting was explored. A risk adapted treatment technique was introduced to accomplish this goal. With this technique, small lesions at high risk due to their distance to isocenter would receive a higher prescription dose (24 Gy), where lesions close to critical structures would receive a lower prescription (18 Gy). Other lesions would receive a nominal prescription dose (20 Gy). The results of this chapter provided a treatment method to help improve the accuracy of SIMT VMAT techniques. This chapter has been adopted from the recently submitted manuscript for peer review by: Palmiero A, St. Clair W, Randall M and Pokhrel D. "A Novel Risk Adapted Single Isocenter VMAT Planning Technique for Radiosurgery of Multiple Brain Lesions to Minimize Spatial Setup Uncertainties. *J Appl Clin Med Phys*. (Under Review, Submitted November 2020)

Abstract

Purpose: Treating multiple brain lesions synchronously using a single-isocenter volumetric modulated arc therapy (VMAT) stereotactic radiosurgery (SRS) plan could significantly improve treatment delivery efficiency, patient compliance and clinic workflow. However, due to spatial set up uncertainty, aligning multiple brain lesions on a single daily conebeam CT (CBCT) is associated with unacceptable loss of target(s) coverage. To date, this issue has been managed by adding additional margin around the tumors, however this could increase dose to organs-at-risk (OAR) and the risk of brain toxicity. In contrast, we propose a novel risk-adapted correction strategy: an alternative

treatment planning approach that escalates dose to tumors away from the isocenter, compensating for setup errors. This planning method utilizes user defined aperture shape controller and dynamic conformal arcs-based dose calculation before VMAT optimization.

Methods: Seven difficult cases with 3-16 lesions (57 tumors) were planned with a single-isocenter VMAT-SRS (original VMAT) using a 10MV-FFF beam for a nominal single-dose of 20 Gy to each lesion. To compensate for the loss of target(s) coverage due to geometric setup errors and spare the OAR, each plan was re-planned using a risk-adapted approach (risk-adapted VMAT), utilizing 3-prescription (18 Gy, 20 Gy and 24 Gy) based on: distance to isocenter, tumor size and proximity to the OAR.

Results: Compared to original VMAT, risk-adapted VMAT plans provided similar target coverage and dose conformity and lower dose to normal brain and adjacent OAR. Most importantly, it compensated for the loss of target(s) coverage for small lesions (17 of 57 tumors) away from isocenter and provided a nominal dose of 20 Gy or higher to each lesion.

Conclusion: With less spread of intermediate dose to normal brain and similar treatment delivery parameters, the risk-adapted VMAT plan with up to 1°/1 mm set up errors in all 6 directions demonstrated promising plan quality and treatment delivery accuracy for patients with multiple brain lesions.

4.1 Introduction

Studies have demonstrated the feasibility of treatment of multiple intracranial lesions using single-isocenter volumetric modulated arc therapy (VMAT) stereotactic radiosurgery (SRS).[1-4] To automate SRS treatment delivery, Varian introduced a Truebeam

Linac-based (or superior) single-isocenter VMAT platform known as HyperArc as a module in the Eclipse treatment planning system (TPS, Varian Medical Systems, Version 15.6).[5-10] The major advantages of single-isocenter VMAT-SRS are reduction of treatment times and improvement of patient comfort and clinic workflow. The main challenge of this approach for treatment of multiple brain lesions is patient positioning and spatial uncertainty during treatment. This geometric uncertainty due to rotational and translational errors can generate a large dosimetric disparity on the total delivered dose compared to traditional multi- isocenter methods as previously demonstrated.[11-20] For instance, Palmiero et al. performed a dosimetric study evaluating clinically observable treatment delivery inaccuracies in all six-degrees-of-freedom (6DOF) of the couch, demonstrating potential to under dose the target(s) up to 72% and increase dose to adjacent organs-at-risk (OAR).[20] To resolve the issue, researchers have suggested adding an additional margin around the lesions, including an asymmetric margin.[11-18,19] For example, Ezzell analyzed the feasibility and spatial accuracy of single-isocenter non-isocentric treatments to multiple brain lesions using two image-guidance systems.[16] As expected, spatial accuracy degrades at large distances from isocenter and an additional tumor margin 1 mm at least 5 cm away from the isocenter was recommended. However, adding additional margin around multiple tumors could dose to OAR and increase toxicity.[22-25] For linac-based SRS, frameless thermoplastic mask systems are be viable options intracranial radiosurgery by immobilizing the patient within 1 mm accuracy.[26] However, this does not correct for geometric set up errors. Moreover, small brain lesions cannot be seen on daily conebeam CT images, and alignment must be made by rigid registration to bony landmarks. Aligning

each lesion perfectly to the planning CT images is nearly impossible, creating dosimetric deviation from the plan.

To tackle this problem, a novel correction strategy using a risk-adapted planning approach is described where variable prescriptions are prescribed based on distance to isocenter, tumor size. and proximity of the dose limiting OAR such as optic apparatus, brainstem and hippocampus. The hypothesis is that by escalating prescription dose to 24 Gy, the loss of target(s) coverage to small lesions away from isocenter could be alleviated without adding additional margin around the target(s). Similarly, prescribing 18 Gy to larger tumors located near dose limiting OAR could be safer in the palliative multi-lesion SRS setting, while other tumors could potentially receive higher doses. This can be accomplished dynamic conformal arcs (DCA) based dose calculation and user defined aperture shape controller features before VMAT optimization.[27] The aim of this manuscript is to demonstrate proof-of-concept of this novel correction strategy to minimizing the dosimetric impacts of geometric errors in the treatment of multiple brain lesions using single-isocenter VMAT.

4.2 Materials and Methods

4.2.1 Patient images and contouring

Seven previously treated SRS patients with multiple brain metastases were included in this retrospective study with Institutional Review Board approval. Patients were immobilized in the supine position with a thermoplastic mask and hands on chest. Patients were imaged with a GE Lightspeed 16 slice CT scanner (General Electric Medical Systems, Waukesha, WI) with a 512 × 512 pixel size and 1.25 mm slice thickness. Planning CT

images were co-registered with high-definition (1 mm cuts) MPRAGE sequence MRI images (Siemens MAGNETOM, 1.5T MRI System, Ferndale, MI) for target(s) and OAR delineation. An radiation oncologist delineated the gross tumor volumes (GTVs) on the MRI images co-registered to the planning CT images. The planning target volumes (PTVs) were created as a 1 mm symmetric margin around the GTVs. There were 3 to 16 lesions per patient and a total of 57 tumors. The OAR included the optic apparatus (optic nerves and optic chiasm), brainstem, hippocampi (left and right hippocampus), and normal brain tissue (brain minus PTVs). The hippocampi were contoured following RTOG 0933 guidance.[22] Distance to isocenter was calculated by measuring the 3-dimentional Euclidean distance with the coordinates of the geometric center of each PTV with respect to the single-isocenter coordinates in Eclipse TPS.

4.2.2 Original VMAT plans

Single-isocenter VMAT SRS plans were generated in Eclipse TPS for the Truebeam Linac (Varian Medical Systems, Palo Alto, CA) with standard millennium MLC and 10 MV-FFF beam (maximum dose rate of 2400 MU/min). Four non-coplanar arcs were used to mimic HyperArc style VMAT geometry. One full 360^{o} arc and 3 non-coplanar partial arcs were used to replicate the gantry motion and couch rotations. The single isocenter was placed at approximately the geometric center of all the targets. Collimator angles were manually chosen to minimize island blocking and low dose spillage.[28,29] Twenty Gy to the 70-80% isodose line for each lesion; at least 95% of each target received 100% of the prescribed dose and the hotspot was at the center of the each GTV. All plans were created with a DCA-based VMAT planning technique using the new MLC aperture controller features in Eclipse as mentioned above.[27] The combined PTV was created by

summing all the PTVs. A 1 mm MLC aperture was first automatically formed around the combined PTV and dynamically maintained during arc rotation, as observed in the beam's eye view (BEV) projection. A high priority aperture shape controller strength was then assigned (Eclipse v15.6, Photon Optimizer (PO) MLC algorithm). The DCA-based dose was calculated before VMAT optimization for appropriate target coverage and OAR sparing. The dose was calculated with Anisotropic Analytic Algorithm (AAA) (Varian Eclipse TPS, version 15.6) with the smallest calculation grid size (CGS) of 1.25 mm. On the PO MLC configuration, individual ring structures for each target were used for dose steering. Steep dose fall-off was enhanced by utilizing the jaw tracking option and normal tissue objective (NTO). Hippocampi were spared by using planning objectives in RTOG 0933 corresponding to the effective biological single-fraction dose tolerances of < 6.5 Gy.[22-23]All other OAR tolerances followed QUANTEC guidelines for single-dose treatments with a maximal doses to the optic apparatus and brainstem < 8.0 Gy and < 12.0 Gy, respectively.[24]

4.2.3 Risk Adapted VMAT plans

For comparison, all original VMAT plans were re-planned using risk-adapted variable prescriptions based on distance to isocenter, target size and proximity to adjacent OAR. Beam geometry was identical to the original VMAT plans including isocenter location and the DCA-based planning approach with an identical strength of a user defined aperture shape controller. Three prescriptions were utilized in this planning strategy; 18 Gy, 20 Gy and 24 Gy. For lesions, at risk of underdosage, the prescription dose was escalated to 24 Gy if they met 3 criteria: greater than 5 cm away from the isocenter, smaller than 5 cc volume and not proximate to a dose limiting OAR. Lesions close to OAR and

bigger than 5 cc were prescribed a lower dose of 18 Gy. All other tumors were prescribed a nominal 20 Gy to each lesion. In this patient cohort, 17 targets received 24 Gy, 11 received 18 Gy, and 29 received 20 Gy. These prescriptions were implemented in the inverse optimization system using separate objectives for each target. The hot spots in the center of the GTV and dose fall-off via ring structures were scaled according to the prescription of the each target. All plans were re-optimized, so that at least 95% of each target volume received 100% of the respective prescription dose, similar to the original VMAT plan. The dose calculation algorithm, CGS, jaw tracking option and normal tissue objective (NTO) were kept identical to the original VMAT plan.

4.2.4 Simulation of setup uncertainty

To quantify the dosimetric impacts of set up errors, the original VMAT and the risk-adapted VMAT plans were simulated with induced patient setup uncertainties of 0.5°/0.5 mm, 1°/1 mm and 2°/2 mm in all 6 degrees-of-freedom (6DOF). The residual translational errors were defined for isocenter displacements and the rotational errors were defined for patient rotations relative to the isocenter position around the anterior/posterior (pitch), left/right lateral (yaw) and superior/inferior (roll) directions. The simulation of set up uncertainties was introduced using an in-house simulation method developed in MATLAB (Mathworks Inc., WA, USA). All planning CT images were duplicated and co-registered to the original CT images, The image registration DICOM file was exported from the Eclipse TPS and imported to a MATLAB script that generated all 3-rotational ($\Delta\alpha$, $\Delta\beta$, $\Delta\gamma$) and translational (Δx, Δy, Δz) errors of 0.5°/0.5 mm, 1°/1 mm and 2°/2 mm. These matrices were applied to the reference frame, simulating isocenter displacement in all 6DOF. The new registration image DICOM file was imported into Eclipse. The original

VMAT and risk-adapted VMAT plans were overlaid onto the new registered images and dose was recalculated, with the only differences being the isocenter shift in all 6-dimensions.

4.2.5 Plan evaluation

In this proof-of-concept retrospective study, none of the SRS patients were treated with the original VMAT plan or the risk-adapted VMAT plan. Dosimetric impacts of geometric set up errors was determined by comparing the target coverage and dose to OAR between the original and the simulated plans. Differences in PTVD 95% coverage between the plans determined the loss of target(s) coverage. The loss of target coverage between the original VMAT and the risk-adapted VMAT plans were then compared. The minimum, mean, and maximum doses to the GTV were evaluated and compared between the two plans. The PTV and GTV coverages were assessed by the relative volume covered by the prescription isodose line. Tumor dose heterogeneity index (HI) and conformity index (CI) were calculated for each lesion per RTOG guidelines. The HI is the ratio between the maximum dose in the target and the prescription dose to each lesion. A HI of less than 2.0 meets protocol guidelines. The CI is the ratio of the volume of the prescription isodose and the volume of the PTV. A CI of 1.0 indicates superior plan conformity. The OAR doses were evaluated by examining the maximal dose to the optic apparatus, brainstem and hippocampi. Dose to normal brain was assessed for V8Gy, V12Gy, V16Gy and mean brain dose (MBD) between the plans. Treatment deliverability was assessed by comparing the total number of monitor units (MU), beam modulation factor (MF), total beam on time (BOT) and estimated treatment time. The MF is the ratio of the total number of monitor units to the prescription dose in cGy. The BOT was calculated as a ratio of the total MU

and the maximum dose rate setting (2400 MU/min) for the 10 MV-FFF beam on Truebeam Linac. The estimated treatment time accounted for daily single conebeam CT imaging, image matching, couch kicks, beam preparation and BOT for each plan. It is assumed that the 10 minutes for patient setup, conebeam CT time, and applying shifts and 5 minutes for couch rotation time including therapists entering the treatment room. Statistical analysis was performed using Microsoft Excel (Microsoft Corp, Redmond WA) program. Mean, standard deviation (SD) and range values for each of the dose metrics were compared for both plans.

4.3 Results

Differences in the target coverage for GTVs and PTVs are demonstrated in Figure 4.1. This result contains the targets that received 24 Gy (17 targets of 57) to observe minimizing the risk of loss of target coverage due to isocenter misalignment. Coverage loss was fully minimized for set up errors up to 1°/1 mm in any direction and could potentially deliver nominal dose of 20 Gy those lesions. Coverage loss was greatly reduced for errors up to 2°/2 mm for both the GTV and PTV (Figure 4.1). For 0.5°/0.5 mm induced setup errors, the original loss of average target coverage was 0.04 ± 0.08% (0–0.2%) for GTV and 8.2 ± 4.7% (0.93–15.8%) for the PTV and the corresponding risk-adapted plans had no loss of target coverage ($p < 0.001$) for both the GTV and PTV. For 1°/1 mm induced setup errors, the original plans had an average coverage loss of 5.5 ± 5.3% (0–16.8%) for the GTV and 20.8 ± 11.4% (2.1–35.3%) for the PTV. The corresponding risk adapted plan had no loss for the GTV ($p < 0.001$) and relatively smaller average loss of 3.4 ± 2.6% (0–7.8%) ($p < 0.001$) for the PTV. However, for the induced 2°/2 mm setup errors, the original VMAT plan showed an clinically unacceptable loss of 40.5 ± 24.6% (6.0–72.0%) for the

GTV and 48.6 ± 17.1% (1.4–53.0%) for the PTV. For those larger shifts, the corresponding risk adapted plans slightly improved the target coverage but still presented significant dosimetry errors of 15.6 ± 13.2% (0–40.4%) ($p < 0.001$) for the GTV and 27.1 ± 17.1% (1.4–53.0%) ($p < 0.001$) for the PTV, respectively. Significant differences were observed in the loss of coverage for all induced setup uncertainties with any errors larger than 1°/1 mm.

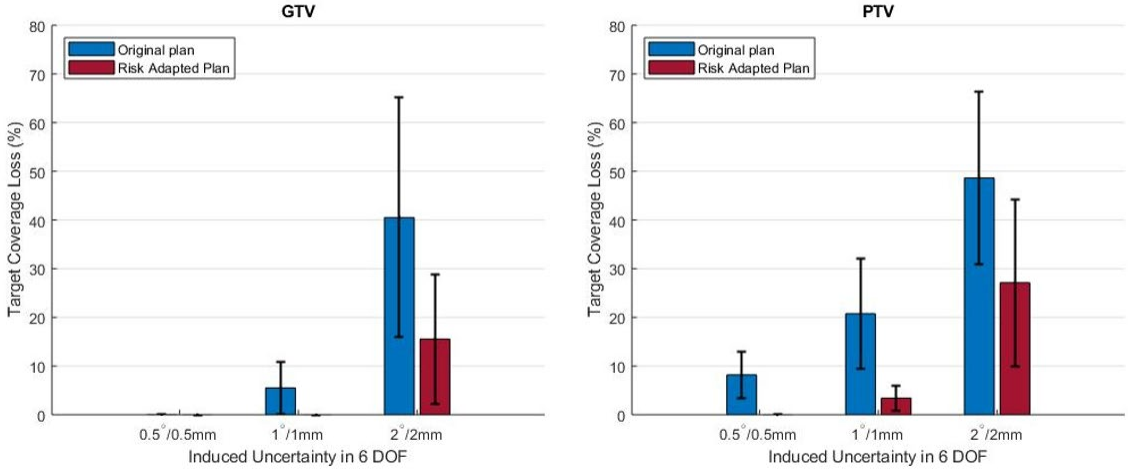


Figure 4.1 Loss of target coverage for induced uncertainty in all 6DOF
Loss of target coverage with induced uncertainties of 0.5°/0.5 mm, 1°/1 mm, and 2°/2 mm in all 6-directions. This cohort consists of 17 vulnerable targets receiving 24 Gy prescription. The blue is the original VMAT and the red is the risk-adapted VMAT plans with standard deviation error bars. Original, uncorrected VMAT plans showed clinically unacceptable loss of target coverage for 1°/1 mm or less set up errors while the risk adapted approach showed an improved coverage providing at least nominal dose of 20 Gy or higher to each lesion.

Compared to the original VMAT, for similar PTV coverage, target conformity and dose heterogeneity, the risked-adapted VMAT plans showed slightly increase maximum, minimum and mean dose to the to the GTV, considered desirable in many SRS treatments. With risk-adapted plan there was a significant reduction of V8Gy, V12Gy and MBD by

107 cc, 28 cc and 1.0 Gy, on average, respectively, while providing similar V16Gy that was due to escalated tumor dose to those small lesions farther away from the isocenter (see Table 4.1).

Table 4.1 Target coverage and dose to normal brain for all 7 patients

Target(s)	Parameter	Original VMAT	Risk-adapted VMAT
GTVs (n = 57)	Maximum dose (Gy)	24.9 ± 1.3 (22.3–26.8)	26.4 ± 2.5 (20.4–29.0)
	Minimum dose (Gy)	21.6 ± 0.59 (20.3–22.8)	22.5 ± 2.5 (18.0–26.7)
	Mean dose (Gy)	23.6 ± 0.88 (21.7–24.9)	24.9 ± 2.4 (20.3–29.0)
PTVs (n = 57)	% Volume covered by RX dose (%)	98.4 ± 1.1 (95.0–100.0)	97.9 ± 1.6 (95.0–100.0)
	CI	0.98 ± 0.09 (0.90–1.2)	0.98 ± 0.09 (0.91–1.2)
	HI	1.2 ± 0.7 (1.1–1.3)	1.1 ± 0.09 (1.02–1.3)
Normal brain	V8Gy (cc)	239.7 ± 221.8 (34.9–558.9)	132.6 ± 84.0 (53.6–249.0)
	V12Gy (cc)	68.1 ± 58.3 (9.3–147.7)	40.7 ± 20.7 (16.5–71.3)
	V16Gy (cc)	11.7 ± 6.0 (2.4–19.6)	13.5 ± 5.4 (6.0–20.9)
	MBD (Gy)	4.8 ± 2.3 (2.4–8.0)	3.9 ± 1.5 (1.9–5.7)

Table 4.2 shows the number of lesions per patient and the average 3D Euclidian distance between the target and the single isocenter for each patient ranged from 4.5 cm to 5.5 cm. In this cohort, 11 of 57 targets were determined to be proximal to the OAR (optic

apparatus, brainstem and hippocampus). With risk-adapted planning approach, for each patient the dose to OAR was reduced systematically and kept below the SRS protocol requirements.

Table 4.2 Maximum dose to adjacent critical isocenter and tumor distance to isocenter

Patient no.	**No. of lesions**	**Average distance to isocenter (cm)**	**Dose limiting OAR**	**Maximal dose to adjacent OAR**	
				Original VMAT (Gy)	Risk-adapted VMAT (Gy)
I	3	4.6	Hippocampi	10.6	6.2
II	4	4.7	Optic apparatus	11.3	6.4
III	5	3.5	Hippocampi	6.1	5.6
IV	8	5.4	Optic apparatus	10.2	6.7
			Hippocampi	6.6	5.1
V	11	5.5	Brainstem	15.9	11.8
			Hippocampi	15.3	7.1
VI	11	5.0	Hippocampi	15.4	8.2
VII	16	5.4	Optic apparatus	7.2	4.7
			Hippocampi	10.6	6.2
			Brainstem	11.6	8.1

Figure 4.2 shows an example (case #5) of the original VMAT plan of a patient who presented with 11 brain lesions. Dose distributions are displayed in axial, coronal and sagittal views. This can be compared to the same dose distributions for the risk-adapted VMAT plan, shown in Figure 4.3. The original VMAT plan had a single prescription dose of 20 Gy to all lesions, whereas the risk-adapted VMAT plan was generated for 3 prescriptions as described above, which is evident in the isodose color wash. Both the coronal and axial views in Figure 4.3 show a lower isodose spread into the hippocampus and brainstem, explaining the decreases in dose to critical structures in the risk-adapted VMAT plans as compared to the original VMAT plan (see Figure 4.2). Lesions at a farther distance from isocenter is displayed in the all 3 views, providing an example of the lesions that would have an escalated prescription dose of 24 Gy in the risk-adapted VMAT plan. The higher level of intermediate dose bridging that is obvious in the coronal view of the original VMAT plan, was mitigated with a tighter 50% isodose distribution is evident in the risk-adapted approach.

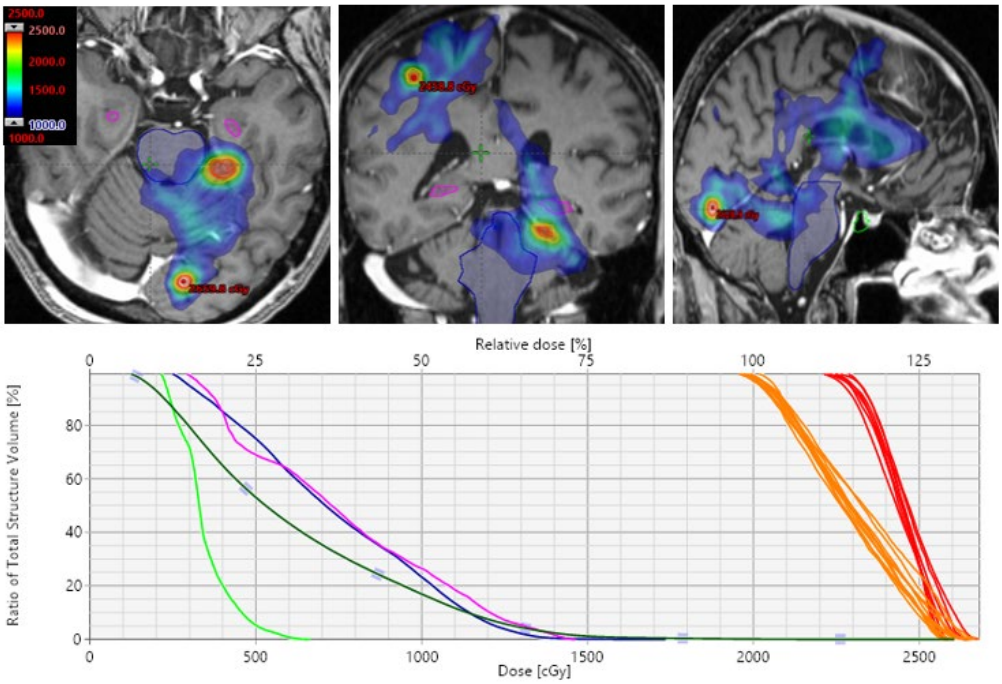


Figure 4.2 Example patient #5 single prescription plan
Example of the original VMAT plan with a nominal single-dose of 20 Gy to each lesion for an patient #5. The top panel shows the isodose colorwash in axial, coronal and sagittal views. The bottom panel contains the DVH for all PTVs (orange), GTVs (red), and the OAR: hippocampus (pink), brainstem (blue) and optic apparatus (light green) including normal brain (dark green).

Figures 4.2 and 4.3 can also be analyzed by their respective DVH for target coverage and dose to OAR. Differences in prescription are evident for each lesion. The original VMAT plan (Figure 4.2) has a single prescription of 20 Gy with all PTV (orange) receiving at least 95% of the prescription dose with the GTV (red) consisting of a 120% hotspot as described above. The risk-adapted plan has a lesion receiving 18 Gy (green arrow) prescription dose due to the proximity of brainstem and hippocampus. Four of 11 lesions were planned for the nominal dose of 20 Gy (blue arrow). Six lesions had an escalated prescription dose of 24 Gy (black arrow) due to distance from isocenter of > 5 cm. Additionally, dose to optic apparatus (green), brainstem (blue) and hippocampus (pink)

were reduced significantly compared to Figure 4.2 (see Table 4.2). The maximum dose to the optic apparatus, brainstem and hippocampus were 6.5 Gy, 15.9 Gy and 15.3 Gy for the original VMAT, respectively, and 3.5 Gy, 11.8 Gy and 7.1 Gy for the risk-adapted VMAT plan, respectively. Dose to normal brain was also reduced. Brain V8, V12 and MBD were 18.4 cc, 5.3 cc and 4.8 Gy, respectively, for the original VMAT plan, while the risk adapted plans were 9.4 cc, 3.0 cc, and 3.9 Gy, respectively.

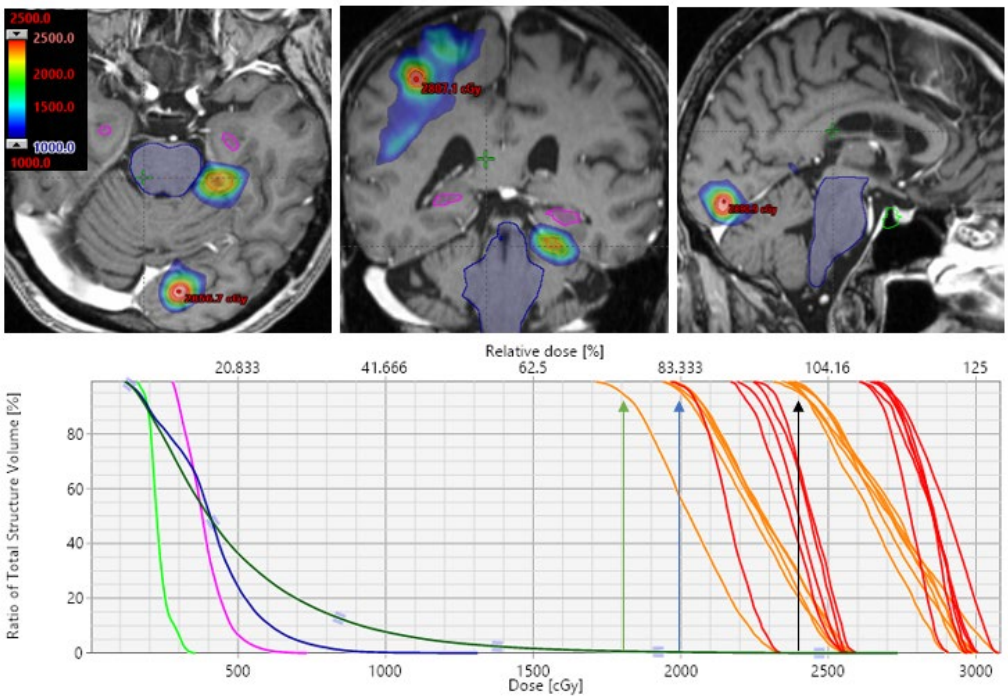


Figure 4.3 Example patient #5 with risk adapted plan
Example of the risk-adapted VMAT plan with 3 prescriptions (same patients with 11 lesions shown in Figure 4.2). Dose distributions on the axial, coronal and sagittal views are displayed (top panel) corresponding to the DVH (bottom panel). The PTVs (orange), GTVs (red), hippocampus (pink), optic apparatus (green) and brainstem (blue) including normal brain (dark green) are shown, demonstrating sparing of OAR with acceptable target coverage. Normal brain receives less dose than the original VMAT plan (Figure 4.2).

Table 4.3 shows the comparison of the treatment delivery parameters for the two plans. The risk-adapted VMAT had similar total MU, beam MF, BOT and estimated overall treatment time.

Table 4.3 Treatment delivery parameters for all 7 patients

Treatment delivery parameters	Original VMAT	Risk-adapted VMAT
Total MU	90182 ± 2741 (5400–13064)	8959 ± 2879 (5247–12444)
Modulation factor (MF)	4.6±1.4 (2.7–6.5)	4.3 ± 1.3 (2.4–5.7)
Beam-on time (min)	3.8 ± 1.1 (2.3–5.4)	3.7 ± 1.2 (2.2–5.2)
Treatment time (min)	18.8 ± 1.1 (17.3–20.4)	18.7 ± 1.2 (17.2–20.2)

4.4 Discussion

A novel and clinically useful risk-adapted single-isocenter VMAT planning approach is presented to minimize the effects of set up errors for targets at some distance from the isocenter and without adding additional tumor margin. Utilizing a DCA-based approach, risk-adapted VMAT plans provided better plan quality, lower dose to normal brain and spare relevant critical structures. Escalating dose to small targets that are prone to uncertainty improves target coverage, providing at least a nominal prescription dose of 20 Gy for spatial uncertainties up to 1°/1 mm, and greatly improves coverage for those up to 2°/2 mm. However, larger set up errors of 2°/2 mm, repositioning the patient, repeating the conebeam CT scan and realigning the lesions is preferred. In addition to more

appropriate doses to the GTVs (due to the escalated prescription), the risk-adapted VMAT plan provided lower MBD, V8Gy and V12 Gy, potentially reducing brain toxicity.[25]

Researchers have studied potential correction strategies for dosimetric uncertainties that come with treating multiple brain metastases with single-isocenter SRS techniques.[20-21] Most strategies suggest adding additional margin to compensate for inaccuracies, but this has potential to increase brain necrosis.[25]A risk-adapted approach, as evaluated in this study, is an alternative approach to compensate the loss of target coverage while limiting dose to normal brain and other OAR. By correcting for these geometric inaccuracies and minimizing dose to normal tissues, linac-based single isocenter VMAT SRS becomes a safe, efficient, and effective treatment for selected patients with multiple brain metastases.

There are limitations to this study's conclusions and applicability. Similar to HyperArc VMAT geometry a problem of island blocking is presented while treating large numbers of multiple brain lesions via a single isocenter VMAT plan, due to proximity of the brain lesions. This means that two or more lesions share the same MLC pairs.[28, 29] This increases the spread of the low and intermediate dose, creating dose bridging between targets. In the method reported here, this is minimized by manually choosing the best collimator angle applied to each arc, but with a large number of lesions there is no currently available way to completely alleviate this problem. Minimizing the spread of low and intermediate dose-spillage in the treatment of multiple brain lesions via dual-isocenter VMAT plans merits further investigation.[31] Utilizing risk-adapted approach on dual isocenter VMAT plans for treating left-sided vs right-sided brain lesions and only utilizing the corresponding partial arcs would help minimize intermediate dose bridging. However, dual-isocenter VMAT plans will increase planning time and approximately double the

treatment time. Another limitation is that this study uses standard millennium MLCs (5 mm), whereas micro MLCs (2.5 mm) are recommended for best practice of linac based SRS. [30] Utilizing a micro-MLC on risk-adapted VMAT plans with DCA-based approach could generate highly conformal dose distribution, reduce dose bridging, and spare dose to OAR in the treatment of multiple brain lesions, allowing dose escalation to smaller lesions farther away from isocenter in single isocenter VMAT setting.

4.5 Conclusion

The results of this study support the use of a risk-adapted planning approach for single-isocenter VMAT treatments for multiple brain metastases by accounting and correcting for geometric set up errors. With this risk-adapted method, patients with larger number of multiple brain lesions at reasonable distances from isocenter can be managed, while maintaining similar plan quality, lower dose to normal brain and OAR. By incorporating micro-MLC in the risk-adapted method, single-isocenter VMAT-SRS can provide high quality SRS treatments to patients in an efficient manner.

CHAPTER 5. MANAGEMENT OF MULTIPLE BRAIN METASTASES VIA DUAL ISOCENTER VMAT STEREOTACTIC RADIOSURGERY

To manage the complex patients with a large number of brain metastases, another correction strategy was introduced to minimize the dosimetric errors due to patient positioning uncertainty in the SIMT VMAT approaches as discussed previously. Rather than the traditional single isocenter plan to treat all lesions together, this novel dual isocenter technique utilizing DCA-based VMAT optimization was introduced to selectively treat lesions in groups to improve accuracy and plan quality of these treatment techniques. Moreover, This technique was created to limit MLC travel distance by restricting the tumor to isocenter distance, improve localization by reducing the region of interest for CBCT matching and reducing dose to brain by minimizing island blocking. The results of this chapter provide recommendations to physicians to manage difficult patients with a large number of brain lesions. This chapter has been adopted from the recently accepted manuscript by: Palmiero A, Fabian D St. Clair W, Randall M and Pokhrel D. "Management of Multiple Brain Metastases via Dual Isocenter VMAT Stereotactic Radiosurgery." *Med Dosim*; 2020:1-7 (Article in Press)

Abstract

Single-isocenter volumetric modulated arc therapy (VMAT) stereotactic radiosurgery (SRS) techniques to treat multiple brain metastases simultaneously can significantly improve treatment delivery efficiency, patient compliance and clinic workflow. However, due to large number of brain metastases sharing the same MLC pair causing island blocking. This provides higher low and intermediate dose spillage to the brain and higher dose to organs-at-risk (OAR). To minimize this problem and improve plan

quality, this study proposes a dual isocenter planning strategy that groups lesions based on hemisphere location (left vs right sided) in the brain parenchyma, providing less island blocking reducing the MLC travel. This technique offers simplified planning while also increasing patient comfort and compliance by allowing for large number of brain metastases to be treated in two groups. Seven complex patients with 5-16 metastases (64 total) were planned with a single-isocenter VMAT SRS technique using a 10MV-FFF beam with a prescription of 20 Gy to each lesion. The isocenter was placed at the approximate geometric center of the target. Each patient was re-planned using the dual isocenter approach, generating 2 plans and placing each isocenter at the approximate geometric center of the combined targets of each side with corresponding non-coplanar partial arcs. Compared to single isocenter VMAT, dual isocenter VMAT plans provided similar target coverage and dose conformity with less spread of intermediate dose to the normal brain with reduction of dose to OAR. Reduction in total monitor units and beam on time was observed, but due to the second isocenter setup, overall treatment time was increased. Dual-isocenter VMAT-SRS planning for large number of multiple brain metastases is a simplified approach that provides superior treatment options for patient comfort and compliance who may not tolerate longer traditional treatment time as with individual isocenters to each target. This planning technique significantly reduces the amount of low and intermediate dose spillage, further sparing OAR and normal brain, potentially improving target accuracy though localization of left vs right sided tumors for each isocenter.

5.1 Introduction

Single isocenter volumetric modulated arc therapy (VMAT) stereotactic radiosurgery (SRS) has gained popularity due to its fast and effective treatment for management of multiple brain metastases.[1-4] Varian developed the HyperArc module in the Eclipse (Varian Medical Systems, Version 15.6) treatment planning system (TPS) on the Truebeam Linac based automated treatment method for multiple brain metastases patients.[5-10] Single isocenter SRS provides reduction of treatment times, improving patient comfort and clinic workflow. There are challenges when treating multiple brain metastases with single isocenter VMAT. There is a degree of patient positioning spatial uncertainty during treatment due to rotational and translational errors, generating a large dosimetric disparity compared to that of multi-isocentric methods.[11-21] Many correction strategies consist of increasing the margin around the tumors to compensate for setup uncertainty, but this presents major concerns with brain dose.[11-25] There are also issues with island blocking where multiple lesions share the same MLC pairs causing a higher level of low and intermediate dose spill.[26] Ohira et. al performed a study dosimetrically comparing a collimator optimized HyperArc VMAT plan and a non-collimator optimized HyperArc VMAT plan.[27] They determined that the collimator optimized plan reduced dose to brain tissues with comparable OAR doses. Though researchers have suggested mitigating island blocking via collimator angle optimization, it cannot be fully be alleviated when considering a large number of targets for a single-isocenter plan. To overcome both mentioned challenges for treating multiple brain metastases, Prentou et. al first introduced a two isocenter planning technique using traditional VMAT planning methods. This planning technique limits the distance to isocenter and showed to decrease spatial uncertainty for less than 4 lesions, though ability to spare normal structures was

inconclusive.[28] There is room to further investigate and provide a simplified treatment planning and delivery strategy using dual isocenter approach to reduce island blocking, potentially leading to less low and intermediate dose spillage, spare OAR and reduce dose to normal brain. The use of dynamic conformal arc (DCA)-based VMAT optimization with user defined aperture controller strength have shown improve plan quality, reduce intermediate dose spillage and increase delivery efficiency.[30] Combining a dual isocenter approach with non-coplanar partial arcs and DCA-VMAT could potentially improve plan quality, reduce dose bridging between the tumors, spare OAR and improve target localization accuracy of multiple brain lesions.

To alleviate the issues discussed of this many body problem, a novel dual isocenter VMAT technique has been developed to manage multiple brain metastases. In this novel approach, lesions are grouped and treated in halves based on hemisphere location (right- vs left-sided) in the brain parenchyma, utilizing appropriate non-coplanar partial arcs on each side. By grouping the lesions and treating separately, MLC does not need to excessively travel on each plan and the dose bridging due island blocking can be limited, sparing OAR and reducing brain dose while maintaining optimal plan quality. As described above, this technique incorporates DCA based dose calculation and user defined aperture shape controller features before VMAT optimization, improving plan quality and reducing the overall plan complexity resulting in a decrease monitor units (MU).

Rather than matching the entire skull on a single daily cone beam CT (CBCT), selectively matching regions of interest (ROI) defined by hemispheres of the brain can improve target localization accuracy. Treating with two isocenters can increase overall

treatment time; however, each lesion groups can be treated separately to improve patient compliance and maintain an efficient clinic workflow and reduce brain toxicity.

5.2 Materials and Methods

5.2.1 Treatment planning datasets

Seven previously treated SRS patients with 3 to 16 lesions per patient (64 total) were chosen for this retrospective study with Institutional Review Board approval. The average gross tumor volume (GTV) and planning tumor volume (PTV) size of 0.84 cc (range: 0.02-9.0 cc) and 1.5 cc (range: 0.11-12cc). Patients were immobilized with a thermoplastic mask in the supine position. Patients were imaged with a GE Lightspeed 16 slice CT scanner (General Electric Medical Systems, Waukesha, WI) with a 512 × 512 pixel size and 1.25 mm slice thickness. These images were then registered with MPRAGE sequence MRI images (Siemens MAGNETOM, 1.5T MRI System, Ferndale, MI) with 1 mm slice thickness. The MRI images were used for GTV and OAR delineation performed by a radiation oncologist along with OAR. The PTVs were created as a 1 mm symmetric margin around the GTVs. The OAR of interest to this study were optic apparatus (optic nerves and optic chiasm), brainstem, hippocampi (left and right hippocampus) and normal brain tissue (brain minus PTVs). The hippocampi were contoured following RTOG 0933 protocol guidance.[22] The PTVs were grouped and combined based on location in either the left or right hemisphere of the brain. Distance to isocenter was calculated by measuring the 3-dimentional Euclidean distance with the centers of the targets and isocenter.

5.2.2 Single isocenter VMAT plans

The original single-isocenter VMAT SRS plans were generated in the Eclipse TPS for the Truebeam Linac (Varian Medical Systems, Palo Alto, CA) with standard millennium MLC and 10MV-FFF beam (maximum dose rate of 2400 MU/min). HyperArc style VMAT geometry was mimicked with one full arc and 3 partial noncoplanar arcs to replicate gantry motion and couch arrangements with the isocenter at the approximate geometric center of all targets giving an average distance of 5.3 cm (range: 0.05-8.5 cm). Collimator angles were chosen to best alleviate affects of island blocking.[26-27] The prescription to each lesion is 20 Gy to the 70-80% isodose line and optimized so that at least 95% of the target volume receives 100% of the dose. All plans were created with a DCA-based VMAT hybrid technique. A 1mm MLC aperture was generated around a combined PTV structure. The aperture shape controller (Eclipse v15.6, Photon Optimizer (PO) MLC algorithm) was assigned a high priority and the DCA-based dose was calculated before VMAT optimization. [30] The dose was calculated with Anisotropic Analytic Algorithm (AAA) (Varian Eclipse TPS, version 15.6) with the smallest calculation grid size (CGS) of 1.25 mm. Dose steering and fall-off was maintained by ring structures, jaw tracking and normal tissue objective (NTO). Hippocampi was spared following RTOG 0933 protocol corresponding to effective biological single fraction maximum dose of < 6.5 Gy.[22-23] The optic apparatus and brainstem were spared following QUANTEC guidelines of < 8 Gy and < 12 Gy, respectively.[24]

5.2.3 Dual isocenter VMAT plans

The single isocenter VMAT plans were all replanned using a Dual-isocenter technique. This method is outlined in Figure 5.1. Targets were divided based on their hemisphere (left or right) location in the brain. Combined PTV structures were made for both the left and right sides (combined left PTV and combined right PTV). Separate plans were generated for both the left and right sided combined PTVs with an isocenter placed at the geometric center of each side with an average distance to isocenter of 4.7 cm (range: 1.4-8.0).

Each plan consisted of 3 non-coplanar partial arcs corresponding to the left or right side of the brain. The optimal collimator angle was chosen for each plan to further minimize island blocking. The MLC shaper controller and DCA-dose was calculated as described above. The left isocenter plan was then optimized with ring structures, jaw tracking and NTO as mentioned previously. The combined left PTV plan was then used as a based plan when optimizing the combined right PTV plan and a final dose calculation was generated. Finally, both plans were combined and renormalized into a Dual-isocenter VMAT plan sum (see Figure 5.1).

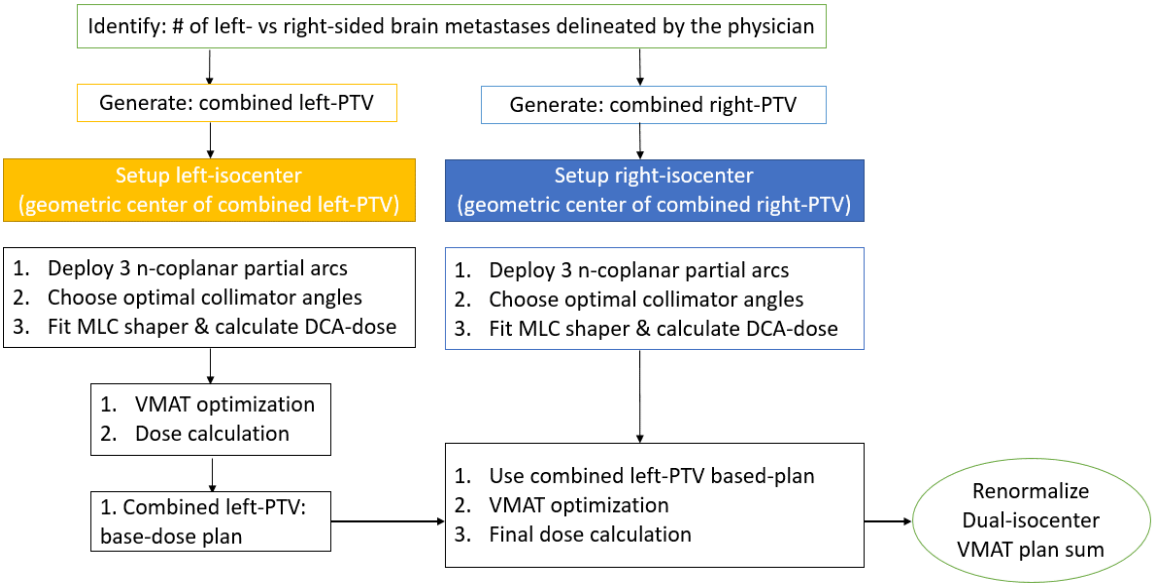


Figure 5.1 Treatment planning work flow for dual isocenter VMAT planning

5.2.4 Plan comparison

This is a retrospective study and none of the SRS patients were treated with the single or dual isocenter VMAT plans. The minimum, mean and maximum dose of the GTV were evaluated between the two planning methods. The PTVs were compared as functions of D99 (Gy), maximum dose (Gy), mean dose (Gy) and conformity index (CI). The CI is the ratio of the prescription isodose volume and the volume of the PTV where a value of 1.0 is considered superior plan conformity. The OAR were assessed using the maximal dose to the optic apparatus, brainstem, and hippocampi. The dose to the brain was evaluated with V8Gy, V12Gy, and mean brain dose (MBD). Additionally, V30% and V50% were documented. Deliverability of the plans were compared using the total number of monitor units (MU), the modulation factor (MF), beam-on time (BOT) and overall treatment time. BOT was calculated using the ratio of the total MU and the maximum dose rate setting (2400 MU/min). The overall treatment time was estimated including patient set

up time, conebeam CT scanning time for each isocenter, image matching, couch kicks, beam preparation and BOT. It is assumed that it takes about10 minutes for patient setup and conebeam CT time, so 10 minutes for a single isocenter and 20 minutes for dual-isocenter plan. Couch rotations from inside the room are estimated to be about 5 minutes. Statistical analysis was performed using Microsoft Excel program (Microsoft Corp, Redmond WA). Mean, standard deviation (SD) and range values for each of the metrics were compared in each plan.

5.3 Results

Figures 5.2 and 5.3 show an example case of a patient that presented with 16 brain lesions. In figure 5.1, the dose distribution is displayed in the axial, coronal, and sagittal views. The top panel contains the single isocenter plan and the bottom is the dual isocenter plan. In the coronal and sagittal views, the single isocenter plan shows higher dose spread into the brainstem and hippocampi. All 3 views show a tighter 50% isodose distribution signifying lower intermediate dose spillage. This is all further shown in the DVH (see figure 5.3) of both the single isocenter plan (triangles) and the dual isocenter plan (squares) superimposed on one another. There are decreases in dose to hippocampi, optics apparatus, brainstem and normal brain. For this example patient's single isocenter plan, the maximal dose to the hippocampi, optic apparatus and brainstem were 10.6 Gy, 9.6 Gy and 11.3 Gy with a normal brain V8Gy, V12Gy and MBD of 402.3 cc, 47.0 cc and 5.2 Gy, respectively. For the dual isocenter plan, the maximal dose the hippocampi, optics apparatus and brainstem were 6.8 Gy, 5.1 Gy, and 8.3 Gy with a normal brain V8Gy, V12Gy and MBD of 153.3 cc, 45.0 cc and 4.2 Gy, respectively. The PTVs were divided based on the left

(purple) and right (orange) hemispheres of the brain. All PTVs received at least 95% of the prescription dose with a 120% hot spot to each lesion (see figure 5.3).

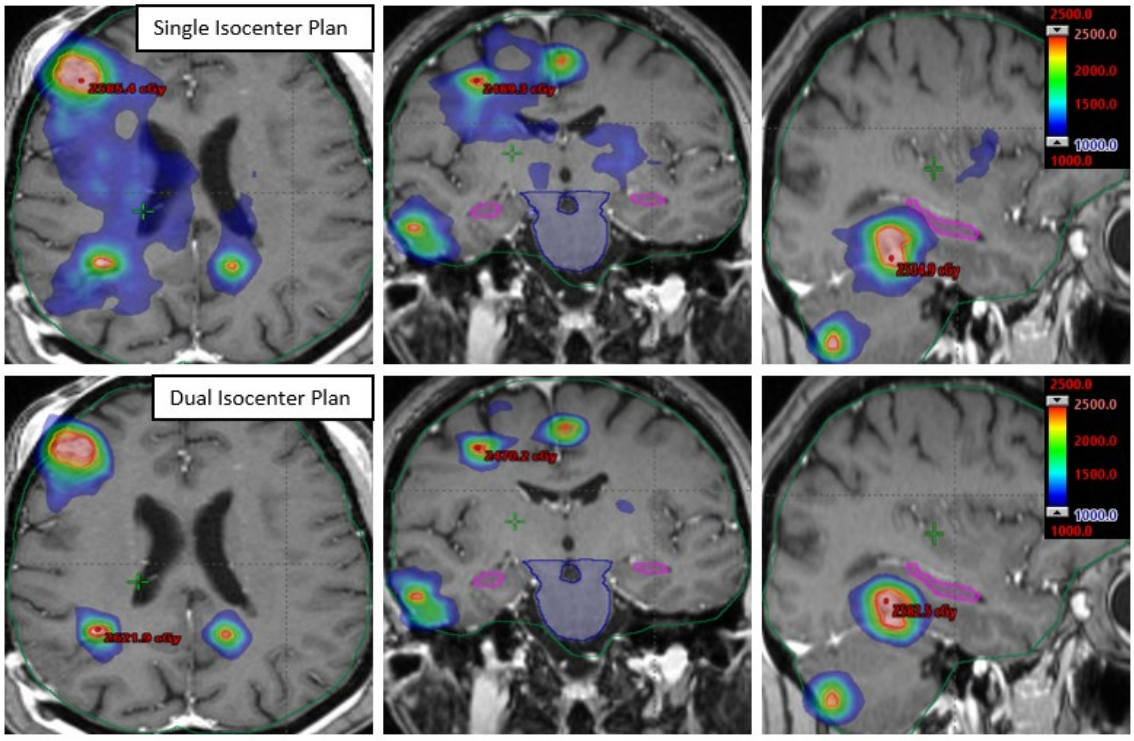


Figure 5.2 Example case with 16 lesions.
Example case with 16 lesions with a prescription of 20 Gy to each lesion. The top panel shows the isodose color wash (50 to 125%) in the axial, coronal and sagittal views for the single isocenter plan. The bottom panel contains the isodose color wash in the same 3 views for the dual isocenter plan. The dual isocenter plan demonstrates better sparing of hippocampi (pink), brainstem (dark blue) and normal brain (dark green) with a lower intermediate dose spread.

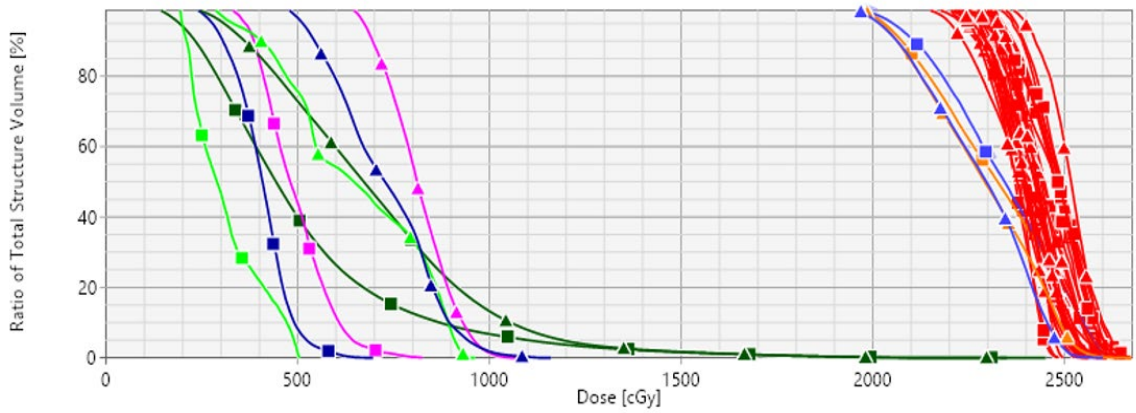


Figure 5.3 DVH of example patient with 16 lesions
DVH of same example patient with 16 lesions for both the single isocenter plan (triangles) and dual isocenter plan (squares). The combined-left PTV (purple) and combined-right PTV (orange) received at least 95% of the prescription dose (20 Gy); all GTVs (red) received higher dose. Decreases in maximal dose to hippocampi (pink), optics apparatus (light green) and brainstem (dark blue) is evident. Major reduction of normal brain (dark green) dose < 12 Gy is clearly demonstrated. The dual isocenter plan demonstrates better sparing of OAR and decreases to dose normal brain while maintaining target coverage.

Compared to the single isocenter VMAT plan, the dual isocenter plan showed similar minimum and mean dose to the GTV, with a slightly increased maximum dose, which is advantageous to SRS plans. The dual isocenter also showed to have similar target coverage, similar near minimum dose PTVD99%, maximum dose, mean dose and target conformity of the PTV compared to the single isocenter plan (see Table 5.1).

Table 5.1 Evaluation of plan quality for all 7 patients for both single and dual isocenter VMAT plans

Target(s)	Parameter	Single isocenter VMAT	Dual isocenter VMAT
GTVs	Maximum dose (Gy)	24.9 ± 1.3 (22.2–26.8)	25.3 ± 1.0 (21.3–25.7)
(n = 64)	Minimum dose (Gy)	21.4 ± 0.69 (20.3–23.3)	21.6 ± 0.72 (20.2–23.5)
	Mean dose (Gy)	23.4 ± 0.9 (21.6–25.1)	23.8 ± 0.81 (21.3–25.7)

Table 5.1 (Continued)

PTVs (n = 64)	**% Volume covered by RX dose (%)**	**98.6 ± 1.2 (95.0–100.0)**	**98.1 ± 1.8 (95.0–100.0)**
PTVs (n = 64)	D99% (Gy)	19.8 ± 0.18 (19.6–20.1)	19.8 ± 0.38 (19.1–20.3)
	Maximum dose (Gy)	25.3 ± 1.3 (23.4–26.8)	25.9 ± 0.77 (24.4–27.2)
	Mean dose (Gy)	22.4 ± 0.66 (21.4–23.2)	22.8 ± 0.39 (21.9–23.3)
	CI	0.98 ± 0.01 (0.97–0.99)	0.97 ± 0.03 (0.91–1.01)

Differences in OAR doses between the single isocenter VMAT and the dual isocenter VMAT plans can be seen in figure 5.4. All plans were optimized based on RTOG-0933 protocol for hippocampal sparing with a converted effective biological single-fraction maximum dose of < 6.5 Gy and QUANTEC guidelines for brainstem and optics apparatus doses of < 8 Gy and < 12 Gy, respectively. The result contains maximum doses to the brainstem, optics apparatus and hippocampi for all patients. The maximum dose to the brainstem for the single isocenter VMAT was 13.1 ± 7.2 Gy (2.2–21.8 Gy) and 11.9 ± 7.5 Gy (2.8–21.5 Gy) for the dual isocenter plans. In this cohort, maximum dose to the optics apparatus was 6.0 ± 3.7 Gy (2.2–12.4 Gy) for the single isocenter plans and 4.5 ± 1.6 Gy (2.4–7.4 Gy) for the dual isocenter plans. Similarly, the maximum dose to the hippocampi was 10.4 ± 4.5 Gy (6.1–19.1 Gy) for the single isocenter plans and 9.3 ± 5.3 Gy (4.3–19.9

Gy) for dual isocenter plans. The dual isocenter plans clearly resulted in sparing OAR compared to the single isocenter VMAT plans.

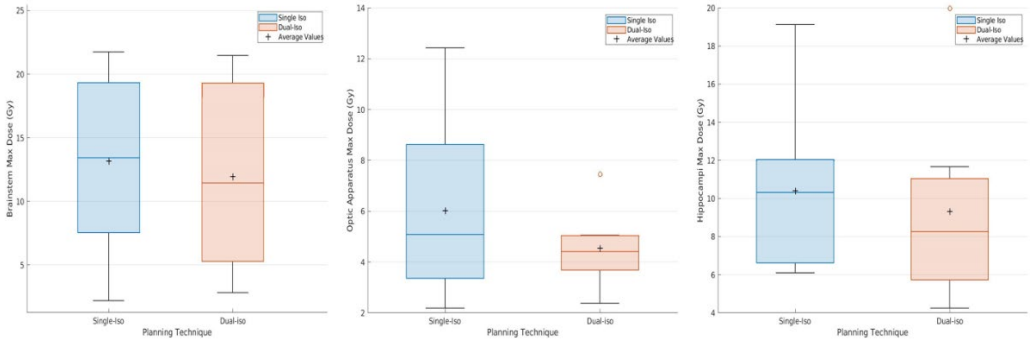


Figure 5.4 Box plots of maximum dose to OAR for all 7 patients.
Box plot of maximum dose to OAR for all 7 patients. The left panel (brainstem), middle panel (optics apparatus) and the right panel (hippocampi). The blue box plot represents the single isocenter VMAT and the orange box plot represents the dual isocenter VMAT plan. The black crosshair signifies the average value for each specific set. Overall, the dual isocenter plan showed better sparing of the critical structures.

Differences in normal brain dose between the single isocenter VMAT plans and the dual isocenter VMAT plans can be seen in figure 5.5. With the dual isocenter plans, there was a significant reduction of V8Gy, V12Gy and MBD compared to the single isocenter plans. Average V8Gy among all patients was 226.7 ± 135.4 cc (90.1–412.9 cc) for the single isocenter plans and 147.2 ± 43.1 cc (86.9–209.7 cc) for the dual isocenter plans. For all patients, V12Gy was 56.5 ± 34.8 cc (32.0–131.0 cc), on average for the single isocenter plans and 147.3 ± 16.4 cc (32.3–81.1 cc) for the dual isocenter VMAT plans. Similarly, MBD was reduced from 5.2 ± 1.4 Gy (4.1–7.3 Gy) to 4.2 ± 0.79 Gy (3.4–5.6 Gy) for the dual isocenter vs dual isocenter VMAT plans.

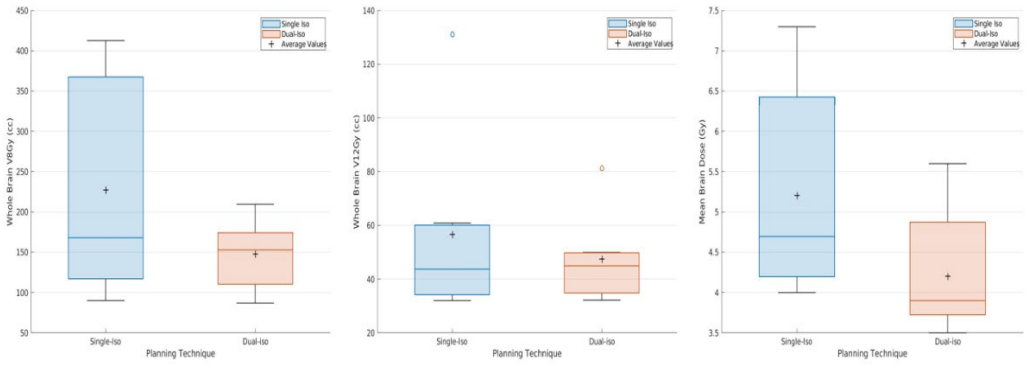


Figure 5.5 Box plot of dose to normal brain.
Box plot of dose to normal brain. The left panel (V8Gy), middle panel (V12Gy) and the right panel (MBD). Blue box is the single isocenter plans and the orange is the dual isocenter plans. The black crosshair is the average values for each parameter. The dual isocenter plans resulted in significant decreases in V8Gy, V12Gy and MBD compared to the single isocenter plan.

The reduction of OAR maximal doses and normal brain doses with dual isocenter planning can be attributed to a decreased intermediate and low dose spillage as seen in figure 5.6. Low and intermediate dose spillage is defined by V30% and V50%. For the single isocenter plan, average V30% was 494.2 ± 242.5 cc (246.0–839.7 cc) and V50% was 133.7 ± 75.3 cc (67.2–261.3 cc). For the dual isocenter plans, the average V30% was 333.6 ± 83.4 cc (201.9–414.9 cc) and V50% was 101.9 ± 30.8 cc (65.2–148.6 cc), reducing intermediate dose spillage by a factor of 1.5. Island blocking in single isocenter VMAT treatments for brain metastases is of major concern because it can cause low and intermediate dose spillage increasing the dose to normal brain. The dual isocenter plans could minimized this problem.

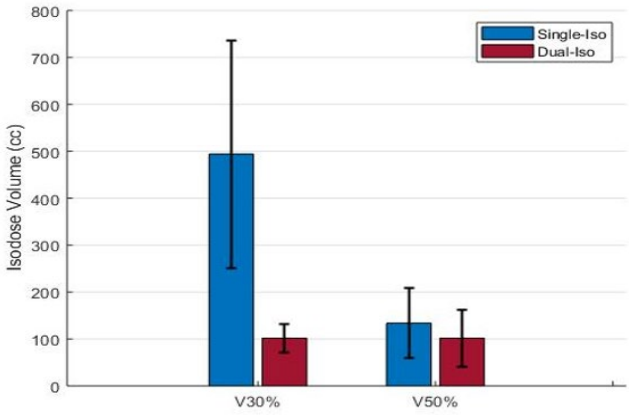


Figure 5.6 Low and intermediate dose spill for all 7 patients.
Low and intermediate dose spillage of all 7 patients. The blue bar represents the single isocenter VMAT plan and the red bar represents the dual isocenter VMAT plan with standard deviation error bars. Low and intermediate dose spillage are defined by the average V30% and V50% among all patients. Significant improvements in the low and intermediate spillage with the dual isocenter plans compared to the single isocentr plans is obvious.

Figure 5.7 shows the comparison of treatment delivery parameters between the single isocenter VMAT and dual isocenter VMAT plans. The dual isocenter showed to have a decrease in total MU and MF. The single isocenter plans had an average total MU of 12497 ± 2925 (9277–17687) and the dual isocenter plan had 10608 ± 1856 (7790–12468) and the corresponding average MF of 6.2 ± 1.5 (4.6–8.8) and 5.3 ± 0.93 (3.2–5.2), respectively. The BOT was only slightly decreased for the dual isocenter plan, but the overall treatment time increased, as expected. That is because with a dual isocenter plan, there are 2 isocenters to setup and verification, 2 conebeam CT scans, and image alignment that has to be done, increasing the total treatment time. The BOT and overall treatment time for the single isocenter plan was 5.2 ± 1.2 min (3.9–7.4 min) and 20.2 ± 1.2 (1.9–22.4 min), respectively. For the dual isocenter plan, the BOT and overall treatment time were 4.4 ± 0.77 min (3.2–5.2 min) and 29.4 ± 0.77 min (28.2–30.2 min).

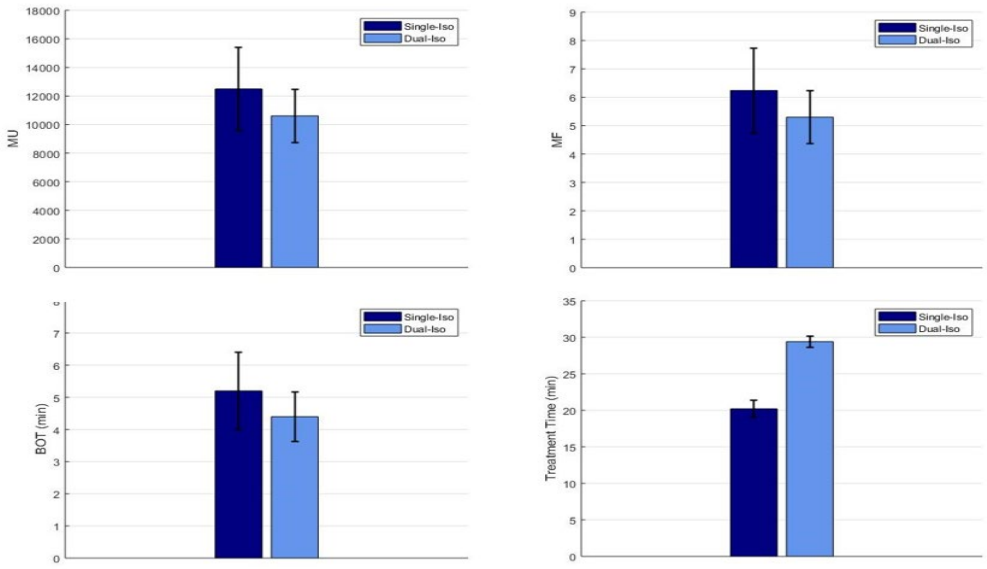


Figure 5.7 Evaluation of treatment delivery parameters for all 7 patients.
Evaluation of treatment delivery parameters for all 7 patients with multiple brain metastases (64 total lesions) for both the single isocenter plans (dark blue) and dual isocenter plans (light blue). The dual isocenter plans resulted in slightly decreased total MU and MF (top panel) compared to the single isocenter plans. There was also only a slight decrease in BOT (bottom left), but an increase, as expected, in total treatment time (bottom right). This is due to the patient setup and verification for each of the two isocenters.

5.4 Discussion

A clinically useful and patient friendly dual isocenter VMAT planning strategy has been exhibited to minimize the effects of island blocking and improve target localization accuracy. Additionally, this planning approach utilizes DCA based VMAT planning, providing better plan quality while limiting brain toxicity and dose to OAR. By using two isocenters and grouping the targets based on the brain hemisphere, a smaller number of lesions will share the MLC pairs, limiting the bridging of low and intermediate dose spills, further lowering doses to normal brain and adjacent OAR. This was demonstrated by lower MBD, V8Gy and V12Gy and could potentially reduce brain necrosis.[24] Superior plans can be achieved all while maintaining optimal plan quality with fewer number of total MU and

slightly higher doses to the GTV. This technique makes planning process simple for the SRS planner by providing guidance on how to handle even the most complex types of patients. The workflow for treatment by the therapists is also simplified to effortless as described in figure 5.8. For instance, the left brain lesions are setup, imaged and treated independently of the right brain lesions. This simplified workflow allows for each isocenter to be set up independently on a daily conebeam CT, reducing the ROI for image matching at the console, which would potentially reduce target localization spatial uncertainty. While utilizing non-coplanar partial arcs in the treated side will minimize dose to the other side of the brain. Although, a dual isocenter workflow comes with relatively longer overall treatment times compared to that of a single isocenter treatment. However, this provides an opportunity for the treating physician and the patients who cannot handle longer treatment times to be treated on two different days, improving patient compliance and potentially reducing the brain toxicity.

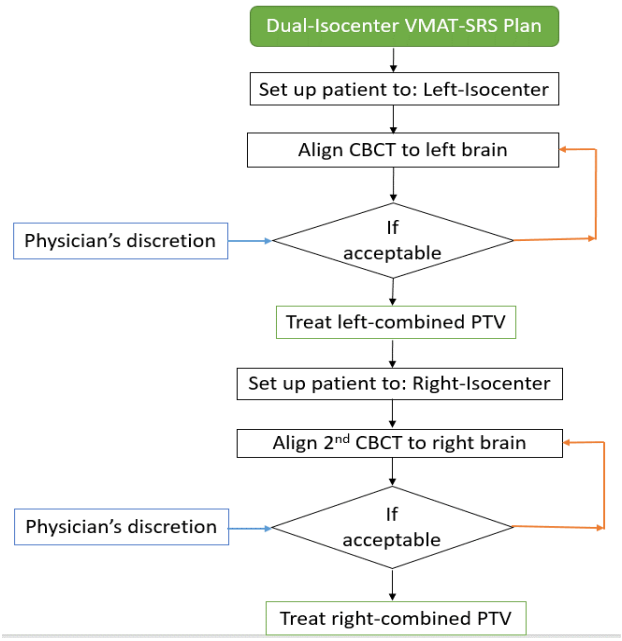


Figure 5.8 Propose dual isocenter VMAT treatment delivery workflow.
The proposed dual-isocenter VMAT-SRS treatment delivery workflow for large number of multiple brain metastases patients. The physician has the option to set up left and right sided brain parenchyma to line up each group of the tumors one at a time, potentially improving targeting accuracy.

As discussed previously, many researchers have worked to overcome the challenges of target localization accuracy and minimize the island blocking that comes with treating Linac-based SRS for patients with many lesions.[18-19]Efforts for mitigating this low dose spillage has mostly been through Linac geometry optimization. [27] For example, Kang et al. performed a computational study to develop a beam projection method to determine suitable table and collimator angles to best minimize MLC leaf sharing between lesions. They concluded that their optimization method minimized island blocking for their 3 example cases.[26] This methodology does great work to minimize or eliminate island blocking for patients with few lesions, but begins to fall apart for more complex patients with a large number of tumors where eliminating shared MLC pairs is nearly impossible.

This type of optimization is a good compliment in addition to the proposed dual isocenter method in this study to manage the most complex of brain metastases patients and reduce the effects of low and intermediate dose spillage due to island blocking. In addition, Chang et al. created a DCA planning technique with a variable number of isocenters (1-3) depending on the distribution and number of targets. They intended to use create an approach with a shortened treatment time that still achieved the plan quality of that with multiple targets. They concluded that their restricted isocenter method could produce satisfactory SRS plans, but resulted in increased dose to OAR and normal brain.[31] By using exclusively DCA approaches, there is less modulation, which can lead to better target conformity, but will not as successfully block normal tissue structures. Single isocenter DCA approaches proved to be a solution to the long treatment times of multi-isocenter based SRS.[29] However, DCA approaches are not very suitable for flattening filter free (FFF) beams because of their unflattened beam profiles. FFF beams provide a higher dose rate, decrease lateral beam hardening and reduce out of field dose because of less lateral scatter, giving them an advantage for stereotactic treatments. The novel dual isocenter approach in this study uses a DCA-VMAT hybrid method to best reduce the effects of low and intermediate dose spillage, perhaps reducing brain toxicity.

Though this study is a step forward for management of large number of multiple brain metastases, it does present with some limitations. As mentioned before, compared to a single isocenter VMAT, there is an increase in overall total treatment time due to two separate isocenters setup and CBCT verification. Though the overall treatment time is increased, it also opens an opportunity for the attending physician to treat lesions in halves on two separate occasions, keeping up the clinic workflow. This opportunity is

advantageous to the patients who struggle with longer treatment times, benefiting overall patient compliance and potentially minimizing the brain toxicity. This study uses standard millennium MLC (5 mm), though it is recommended to use micro MLC for Linac-based SRS for more conformal dose distribution.[32] Utilizing micro-MLCs in this dual isocenter plan would create highly conformal dose distributions along with further reducing intermediate dose bridging and spare adjacent OAR.

5.5 Conclusion

The results of this study clearly indicate the advantages of using the dual isocenter VMAT approach for managing multiple brain metastases patients that can minimize low and intermediate dose spills in the brain. With a dual isocenter method, complex patients with many brain metastases can be treated with similar plan quality with more accurate treatment delivery accuracy while limiting dose to normal brain and adjacent OAR and improving patient comfort compared to multiple isocenter treatments. Incorporating dual isocenter VMAT-SRS is recommended for managing difficult patients with large number of brain lesions on the palliative setting.

CHAPTER 6. PREDICTING THE EFFECT OF INDIRECT CELL KILL IN THE TREATMENT OF MULTIPLE BRAIN METASTASES VIA SINGLE ISOCENTER/MULTI-TARGET VOLUMETRIC MODULATED ARC THERAPY STEREOTACTIC RADIOSURGERY

With peaking interest of the fast delivery of SIMT VMAT SRS of multiple brain lesions resulting in improved patient compliance and clinic workflow, a few clinical outcome studies have recently shown positive results of tumor local control rates. This positive feedback is present even with residual patient set up errors reported in Chapters 1 and 2. To further understand the results, an investigation of the radiobiological mechanisms, such as secondary cell death as a function of patient setup error was explored. In addition to direct cell death, indirect cell kill could have played a major role in providing clinically acceptable outcomes in these treatment types. The results of this chapter provide a better understanding for the importance of patient setup uncertainty when considering secondary cell kill effects in SIMT setting. Physicians can have the opportunity to consider these radiobiological effects, understand the limitations of patient setup errors and have more confidence in their SIMT VMAT plans for treating complex patients with multiple brain metastases. This chapter has been adopted by the recently revised manuscript by: Palmiero A, Fabian D, Randall M, St. Clair W and Pokhrel D. "Predicting the Effect of Indirect Cell Kill in the Treatment of Multiple Brain Metastases via Single Isocenter/Multitarget Volumetric Modulated Arc Therapy Stereotactic Radiosurgery. *J Appl Clin Med Phys*. (Under Review, submitted February 2021).

Abstract

Purpose: Due to spatial uncertainty, patient setup errors are of major concern for radiosurgery of multiple brain metastases (m-bm) when using single-isocenter/multi-target (SIMT) volumetric modulated arc therapy (VMAT) techniques. However, recent clinical

outcome studies show high rates of tumor local control for SIMT-VMAT. In addition to direct cell kill (DCK), another possible explanation includes the effects of indirect cell kill (ICK) via devascularization for a single-dose of 15 Gy or more. This study quantifies the role of indirect cell death in dosimetric errors as a function of patient setup uncertainty.

Material/Methods: Nine complex patients with 61 total tumors (2-16 tumors/patient) were planned using SIMT-VMAT with geometry similar to HyperArc with a 10MV-FFF beam (2400 MU/min). Isocenter was placed at the geometric center of all tumors. Average gross tumor volume (GTV) and planning target volume (PTV) were 1.1 cc (0.02–11.5 cc) and 1.9 cc (0.11–18.8 cc) with an average distance to isocenter of 5.5 cm (1.6–10.1 cm). Prescription was 20 Gy to each GTV. Plans were recalculated with induced clinically observable patient setup errors [± 2 mm, ± 2º] in all 6 directions. Boolean structures were generated to calculate the effect of DCK via 20 Gy isodose volume (IDV) and ICK via 15 Gy IDV minus the 20 Gy IDV. Contributions of each IDV to the PTV coverage were analyzed along with normal brain toxicity due to the patient set up uncertainty. Induced uncertainty and minimum dose covering the entire PTV were analyzed to determine the maximum tolerable patient setup errors to utilize ICK for radiosurgery of m-bm via SIMT-VMAT.

Results: Patient set up errors of 1.3 mm/1.3°in all 6 directions must be maintained in order to achieve PTV coverage of the15 Gy IDV for ICK. Setup errors of 2 mm/2° showed clinically unacceptable loss of PTV coverage of 29.4 ±14.6% even accounting the ICK effect. However, no significant effect on normal brain dosimetry was observed.

Conclusion: Radiosurgery of m-bm using SIMT-VMAT treatments have shown positive clinical outcomes even with small residual patient set up errors. These clinical outcomes,

while largely due to DCK, may also potentially be due to ICK. Potential mechanisms, such as devascularization, should be explored to provide a better understanding of the radiobiology of stereotactic radiosurgery of m-bm using a SIMT-VMAT plan.

6.1 Introduction

Due to fast treatment delivery, single-isocenter/multi-target (SIMT) volumetric modulated arc therapy (VMAT) stereotactic radiosurgery (SRS) has become an increasingly popular treatment modality in the management of multiple brain metastases (m-bm).[1-3] Recently, this approach has been adopted and automated by Varian (Varian Medical Systems, Palo Alto, CA) in the Eclipse treatment planning system (TPS, version 15.6) as the HyperArc module, which has generated global clinical interest.[4-9] SIMT-VMAT reduces treatment times while improving patient comfort and clinic workflow; however, there are concerns with patient set up uncertainty when treating multiple targets simultaneously. It has been previously demonstrated that clinically unacceptable dosimetric discrepancies due to rotational set up errors were present compared to treating each lesion individually.[10-19] The most recent simulation study demonstrated that there was a large loss of target(s) coverage, (30% average, but up to 70% for small lesions) due to both rotational and translational set up errors while using SIMT-VMAT SRS for m-bm.[20] This is a challenge in lining up all tumors correctly using a single daily conebeam CT, especially since skull-based rigid alignment is required. In addition, visibility is low inside the brain on low quality CBCT. Targets may slightly move if there is intracranial edema. Nevertheless, a recent clinical study by Palmer et al. demonstrated positive outcomes of SIMT treatments.[21] They reviewed 173 patients treated with 1 to 5 brain lesions that underwent single-isocenter SRS treatments. After an average of 12 months following up,

very promising 1 year and 2 year tumor local-control rates of 99% and 95% was observed. Other clinical studies have observed similar patient outcomes demonstrating SIMT-VMAT SRS for m-bm to be both safe and effective with high rates of tumor response.[22-25]

However, the presence of positive clinical outcomes cannot be fully explained knowing the effects of patient positioning uncertainties in SIMT-VMAT treatments. Biological modeling, specifically with the linear-quadratic (LQ) model, overestimates tumor control rate with SRS techniques due to the LQ cell survival curve bends continuously downward with increases in radiation dose due to quadratic component in the model.[26] This suggests that mechanisms in addition to tumor DNA double strand breaks and/or chromosomal aberrations must be involved. It is hypothesized that in addition to direct cell kill (DCK), the effect of indirect cell kills (ICK) could be playing a major role in SRS treatments. There are three types of indirect cell death to consider: strand breaks by free radicals, antitumor immunologic rejection, and devascularization.[27] A majority of literature suggests that cell death happened soon after irradiation, pointing toward devascularization as the mode of ICK.[26-29] For instance, Song et al. performed a study to connect the effects of radiobiological response on SBRT and SRS treatments.[29] They concluded that irradiation of tumors with doses higher than 15 Gy per fraction causes major vascular damage accompanied by deterioration of intratumor microenvironment resulting in secondary tumor cell death. Other studies had comparable findings.[30-33] Tumor vasculature is disorganized with weak and fragile cellular walls. Subjecting tumor vascular to radiation damage when exposed to a single high-dose (15 Gy or higher) results in the inverted “hockey-stick” phenomena.[32] With this theoretical phenomenon, the bend of the cell survival curve increases, where cell death is increasing at higher doses of radiation.

When considering the effects of ICK, the local tumor control rates with the presence of dosimetric discrepancies due to patient setup errors in SIMT-VMAT treatments has yet to be explored.

Therefore, to provide dosimetric support for the potential contribution of secondary cell death in the treatment of m-bm with SIMT-VMAT, a model has been created to define the relationship between spatial uncertainty and the delivered dose. Given the previous studies suggesting high levels of vascular damage at 15 Gy, the 15 Gy isodose volume (IDV) around the tumor was chosen as a threshold dose that best utilizes the effects of ICK in addition to DCK. As long as the target receives a minimum dose of 15 Gy or higher, vascular damage could theoretically influence indirect tumor cell death. This study attempts to characterize the patient set up errors that should be maintained in the treatment of m-bm via SIMT-VMAT to account for both effects of direct and indirect cell kill. Therefore, the relationship between indirect cell kill and patient setup errors was used to define an uncertainty cutoff. This model can give suggestions for limits on patient setup uncertainty that physicians can consider, giving them confidence in their SIMT-VMAT plans for treating multiple brain metastases.

6.2 Materials and Methods

6.2.1 Patient information

Nine complex patients with 2-16 (61 total) brain metastases (all lung primary) were included in this study approved by our institutional review board. These patients were previously treated through single fraction SRS. High resolution double contrast MPRAGE MRI images (Siemens MAGNETOM, 1.5T MRI System, Ferndale, MI) were used for

tumor and organs at risk (OAR) delineation and were co-registered to planning CT images in the Varian Eclipse TPS. The MPRAGE MRI images were 512 × 512 pixels with 1 mm slice thickness and no gap in between slices. The target volumes were delineated by a radiation oncologist on the MRI with the gross tumor volumes (GTVs) defined by the visible tumor. The planning target volumes (PTVs) were created using a uniform 1.0 mm margin around each GTV using departmental SRS protocol. The tumor characteristics are summarized in Table 6.1. The normal brain was considered all tissue with the GTVs included. Additionally, nearby OAR (hippocampi, brainstem and optics apparatus) were contoured for dose reporting. Distance to isocenter was calculated as the 3D Euclidian distance from the isocenter and the lesion. The average distance to isocenter was 5.5 cm (range: 1.6–10.2 cm) as shown in table 6.1.

Table 6.1 Tumor characteristics of the patients included in the study

Patient no.	No. of lesions	Avg. distance to isocenter (cm)	Total GTV (cc)	Total PTV (cc)	Adjacent OAR
I	2	2.2	2.2 ± 0.78	3.7 ± 1.1	Hippocampi
II	3	5.7	0.43 ± 0.78	0.93 ± 0.78	Hippocampi
III	4	6.5	3.9 ± 5.2	6.5 ± 8.3	Hippocampi, Optics
IV	5	8.9	3.3 ± 3.3	4.9 ± 4.3	Hippocampi
V	6	5.4	1.3 ± 0.72	2.1 ± 1.1	Hippocampi

Table 6.1 (Continued)

VI	**7**	**5.0**	**0.75 ± 0.81**	**1.4 ± 1.2**	**Brainstem, Hippocampi**
VII	8	4.3	0.51 ± 0.58	1.0 ± 0.93	Brainstem, Hippocampi
VIII	10	5.5	0.39 ± 0.46	0.86 ± 0.46	Hippocampi
IX	16	5.4	0.43 ± 0.63	0.83 ± 1.0	Optic apparatus, Hippocampi, Brainstem

6.2.2 SIMT-VMAT plans

SIMT-VMAT SRS plans were generated in the Eclipse TPS for the TrueBeam LINAC (Varian Medical Systems, Palo Alto, CA) with a 10 MV flattening filter free (FFF) beam (2400 MU/min). A HyperArc style, fixed-geometry was mimicked with 3 noncoplanar partial arcs and one full arc with couch positions at 0º, 45º, 315º, and 270º. The isocenter position was chosen at the approximate geometric center of all targets. Patient specific collimator angles were manually assigned to best minimize island blocking and dose spill outside of the target(s). The prescription was 20 Gy to each lesion to the 70-80% isodose line and optimized so that 95% of the target volume receives 100% of the prescription dose. The dose was calculated using Anisotropic Analytic Algorithm (AAA) (Eclipse, version 15.5) with the smallest calculation grid size of 1.25 mm. Ring structures to each target, jaw tracking and normal tissue objective were used during inverse optimization for dose steering and to maintain dose fall-off outside the target(s). Hippocampi were spared following RTOG-0933 along with the optics apparatus and brainstem meeting QUANTEC guidelines.[34-36]

6.2.3 Simulated SIMT-VMAT plans

Clinically observable patient setup uncertainties of ±0.5 mm/0.5°, ±1 mm/1° and ±2 mm/2° in all 6 degrees-of- freedom (6DOF) were systematically simulated by using an in-house registration method. Rotational errors were defined as the pitch (y-z plane), roll (x-z plane) and yaw (x-y plane) relative to the isocenter position. After the SIMT-VMAT plans were generated, the image set was duplicated and re-registered to the original MRI images. This registration was exported from the Eclipse TPS as a DICOM file and imported into a MATLAB script (Mathworks Inc., WA, USA). The script generated a matrix with rotational ($\Delta\alpha$, $\Delta\beta$, $\Delta\gamma$) and translational (Δx, Δy, Δz) values and was applied to the reference frame. A new image registration DICOM file was generated and then imported back into the Eclipse TPS with a new transformation matrix applied. The original plan was then overlaid on to the new transformation and the dose was recalculated with the only difference being the isocenter shift.

6.2.4 Modeling direct vs. indirect cell kill

This work attempts to model the effects of cell killing due to both direct and indirect cell kill methods. An assumption is made that for areas of the target receiving the prescription dose, 20 Gy or higher, tumor death is due to primarily direct cell killing methods, or DNA double strand breaks. Alternatively, for areas of the target receiving 15 Gy or higher, it is hypothesized that the tumor cell death is largely due to ICK method via devascularization of the tumor and deteriorating the intratumor microenvironment. This threshold for ICK comes from the literature, as mentioned previously. Doses above 15 Gy could result in vasculature damage and, therefore, indirectly killing the tumor.[26-33] These

assumptions are made to simplify the model, though, realistically, combinations of both direct and indirect cell kill are present.

Both DCK and ICK methods were modeled using Boolean operators in the contouring module of the Eclipse TPS. For each PTV, the 20 Gy and 15 Gy IDV were exported from the original SIMT-VMAT plan and each of the simulated plan for the corresponding set up errors. Boolean operators were used to determine the overlap of the 20 Gy IDV and each PTV. This volume was denoted as the volume of the PTV receiving DCK. Another Boolean operator was used to find the overlap of the 15 Gy IDV and each PTV minus the 20 Gy IDV overlap with the target. This volume was signified as the volume of the tumor that was receiving primarily ICK effects. The concepts are further illustrated in figure 6/1. This is an example patient with 16 lesions. The orange contour is the PTVs, the green isodose line is the prescription dose (20 Gy) and the yellow isodose line is the 15 Gy. For the original plan, the PTV is well covered by the prescription dose, therefore should receive the greatest effects of DCK. However, the simulated plan with the set-up errors of 1 mm and 1° shows slight deviation of the 20 Gy isodose line, but the tumor is still covered entirely by the 15 Gy line (see figure 6.1). This should result in a combination of both direct and indirect cell kill in this patient's treatment, which could result in positive local tumor control rate. Furthermore, the simulated plan with 2 mm/ 2° set up errors has shown the significant loss of target coverage by the 20 Gy isodose line, but still displays a majority of the PTV coverage by the 15 Gy isodose line. With these large set up errors, the lesions will have a decreased target coverage, therefore lower rate of tumor local control, even when considering the effects of ICK.

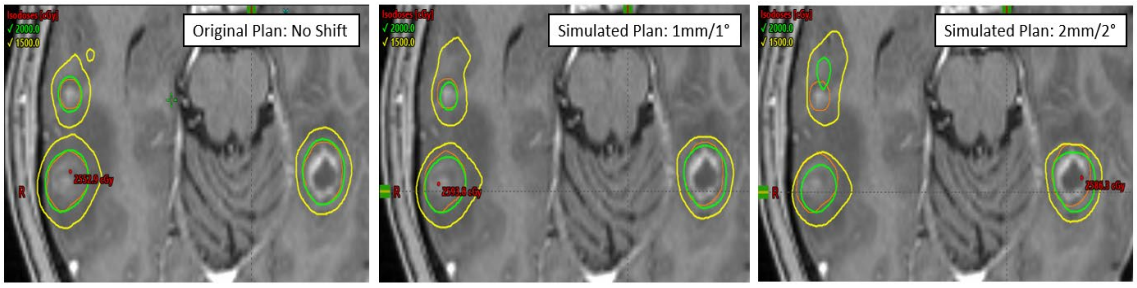


Figure 6.1 Example patient with 16 lesions.
Example patient's SIMT-VMAT plan with 16 lesions and a prescription of 20 Gy to each lesion. The left panel shows the original plan with no induced setup uncertainties, the middle panel shows a simulated plan with 1 mm/ 1° setup errors and the right panel shows another simulated plan with 2 mm/ 2° setup uncertainty in all 6 DOF. The orange contour is the PTV(s), the green isodose line is the prescription dose (20 Gy) and the yellow isodose line is 15 Gy. The simulation plans show decreasingly less coverage by the 20 Gy isodose line compared to the original plan, demonstrating the dosimetric effects of set up errors and the contribution of ICK.

6.2.5 Data Analysis

None of these SRS patients were treated with the SIMT-VMAT plans. This simulation study sought to find the maximum tolerable set up errors to fully utilize the effects of both direct and indirect cell kill to achieve acceptable local tumor control in the SIMT setting. Boolean structures of IDV were created iteratively until a dose was found to just fully cover the target. This process was repeated for the original SIMT-VMAT plans and each of the corresponding simulated VMAT plan. Doses found to cover the target with 15 Gy IDV and above were deemed acceptable and assumed to generate positive local tumor control rate via ICK. The roles of direct vs. indirect cell killing were also compared for each tumor. These were defined by creating Boolean structures for both the 15 Gy and 20 Gy IDV as further described in the previous section. The volumes of these structures were taken and compared as a percentage of the PTV volume receiving that dose. These

values were compared for the original SIMT-VMAT plans and each of the corresponding simulated VMAT plans with the clinically realistic setup errors.

It is also of clinical interest to compare the effect that patient setup uncertainties have on normal brain dose and the role it could play in radionecrosis. For this reason, the normal tissue (brain) complication probability (NTCP) was modeled based on a study by Milano et al.[37] This group pooled published reports of clinical data of radiation induced brain toxicity after receiving brain SRS treatments (single and multiple fractions). The data was fitted and a logistic model was used to create a usable NTCP function given by the following relation:

$$NTCP = \frac{1}{1 + (\frac{V_{x50}}{Vx})^{4\gamma_{50}}}$$

Where, Vx is considered the volume receiving greater than or equal to a dose of x Gy and V_{x50} is the volume corresponding to 50% risk of radionecrosis with γ_{50} as a slope parameter. The values of V_{x50} and γ_{50} were taken from their NTCP model for brain metastases.[37] In addition to doses to normal brain, changes in the maximum dose to OAR due to setup errors were also reported.

6.3 Results

Figure 6.2 demonstrates the setup uncertainty limitations for the target (PTV) to be fully covered by at least 15 Gy or higher and, therefore, best utilize the effects of ICK in addition to DCK. The dose covering the target was taken for the original SIMT-VMAT plans and all the corresponding simulated VMAT plans. The original SIMT-VMAT plans were found to be fully covered the target by an average of 19.2 ± 0.3 Gy. As expected, the

corresponding simulated plans with an induced setup errors of 0.5 mm/ 0.5°, 1 mm/ 1° and 2 mm/ 2° were found to have the corresponding lower doses by 17.8 ± 0.8 Gy, 15.9 ± 0.9 Gy and 12.6 ± 1.5 Gy, respectively. This data was evaluated with a threshold of ICK by 15 Gy or higher in figure 6.2. To fully utilize indirect cell killing methods, patient set up errors of at least 1.3 mm/1.3° in all 6 DOF must be maintained as shown by the background change of blue to red. Above this threshold of 1.3 mm/1.3° in all 6DOF, indirect cell kill could potentially contribute to the tumor cells death.

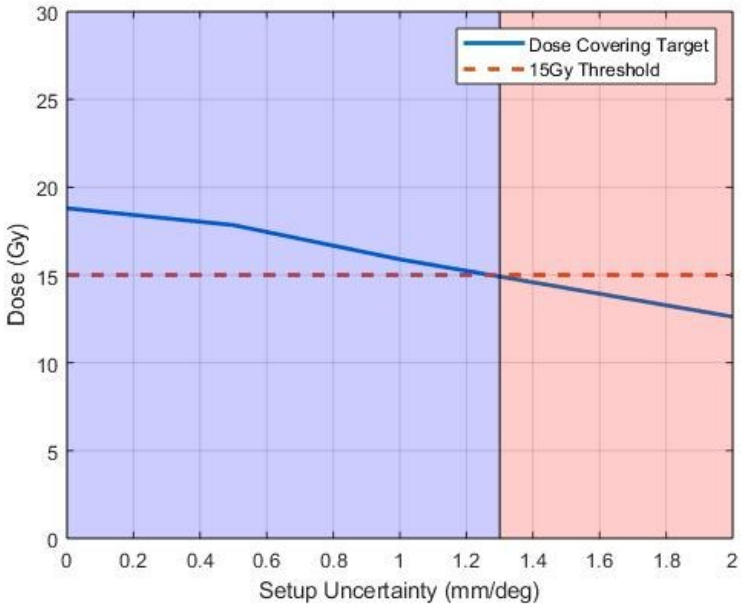


Figure 6.2 Illustration of dose to targets for original and simulated VMAT plans
Illustration of the dose to target(s) for the original SIMT-VMAT plans and the corresponding simulated VMAT plans with 0.5 mm/ 0.5°, 1 mm/ 1° and 2 mm/ 2° setup errors. The blue line represents the dose that fully covers the target and the dotted red line represents the 15 Gy ICK threshold. The section of the plot covered in blue represents the target(s) coverage that is above the 15 Gy threshold, and the orange is below 15 Gy. Patient set up errors must be limited to those defined by the blue area.

The contributions of the direct vs indirect cell kill methods are explained in figure 6.3. The Boolean structure of the 20 Gy IDV and PTV is considered primarily DCK

contributions, whereas the Boolean structure of the 15 Gy IDV and PTV minus the 20 Gy IDV is considered contributions from primarily ICK. For the original plans, the PTV was covered almost completely by the 20 Gy IDV for 97.97 ± 3.52 % and no coverage by the 15 Gy IDV. For the corresponding simulated VMAT plans of 0.5 mm/ 0.5°, 1 mm/ 1° and 2 mm/ 2° of setup errors the 20 Gy IDV coverage was 80.0 ± 28.5%, 67.9 ± 21.6% and 47.6 ± 23.6% and the 15 Gy IDV coverage was 4.2 ± 13.1%, 15.4 ± 10.8% and 29.4 ± 14.6%, respectively. The contribution of DCK decreases as that of ICK increases, with 2 mm/ 2° having the worst overall target coverage, but most importantly adding some ICK contributions. The DCK is somehow compensating for much of the dosimetric discrepancy up to 1.0 mm/1.0°. There is acceptable target coverage (> 15 Gy), providing a better combined coverage, and therefore potentially positive outcomes.

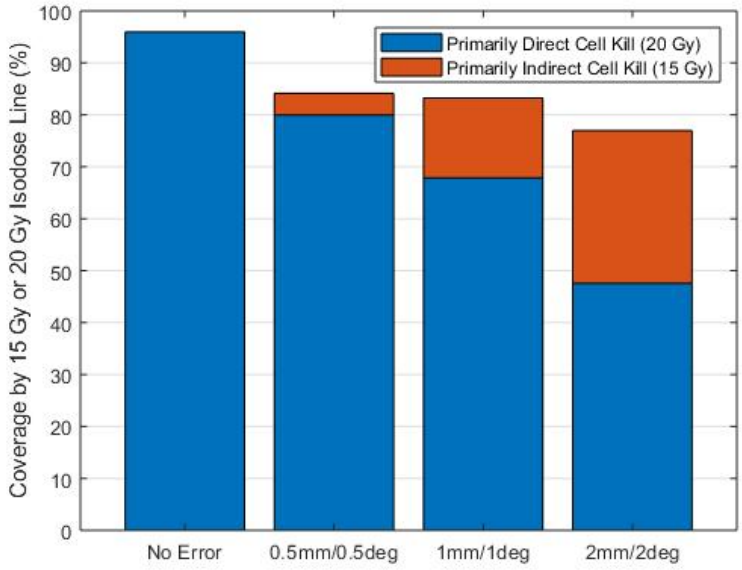


Figure 6.3 Illustration of the target coverage by direct and indirect cell kill.
Illustration of the target coverage by the 15 Gy and 20 Gy isodose lines. The blue represents the coverage obtained by 20 Gy isodose line, which is assumed to be primarily responsible for DCK. The red represents the 15 Gy isodose line or more, which is assumed to be primarily inducing ICK in addition to DCK. Without considering setup uncertainty, the

target is nearly fully covered by the prescription isodose line (20 Gy) and could receive full effects of DCK. With induced setup errors, the coverage of the target by the prescription decreases, but is somewhat counterbalanced by the effects of ICK by 15 Gy or higher.

It has been observed that patient misalignment errors have minimal or no effect on NTCP of brain as shown in figure 6.4. For each of the patients, the NTCP was calculated and compared with the whole brain receiving V14 Gy. For a majority of patients, there is not much of an increase in values of NTCP with any setup uncertainties up to 2 mm and 2°. For instance, the increase of NTCP of normal brain toxicity at set up errors of 2 mm and 2°in each direction had an absolute difference of < 0.4 compared to the original plan with no set up errors, suggesting minimal brain toxicity risk while still resulting in clinical local tumor control. Based on percent differences in NTCP, it was determined that brain toxicity was 1.3%, 1.5% and 1.7% more likely for 0.5 mm/ 0.5°, 1 mm/ 1° and 2 mm/ 2° simulated plans. However, it is apparent that NTCP does increase with whole brain V14Gy, but the increase due to setup errors is not clinically significant for lower brain V14 Gy (see figure 6.4).

The dose to OAR fluctuated depending on the distribution and orientation of the lesions to the immediately adjacent organs. Many cases resulted in substantial increases in dose to OAR with increased dose to hippocampi, brainstem and optic apparatus up to 3 Gy, 2 Gy and 1 Gy, respectively, due to patient set up errors using SIMT-VMAT.

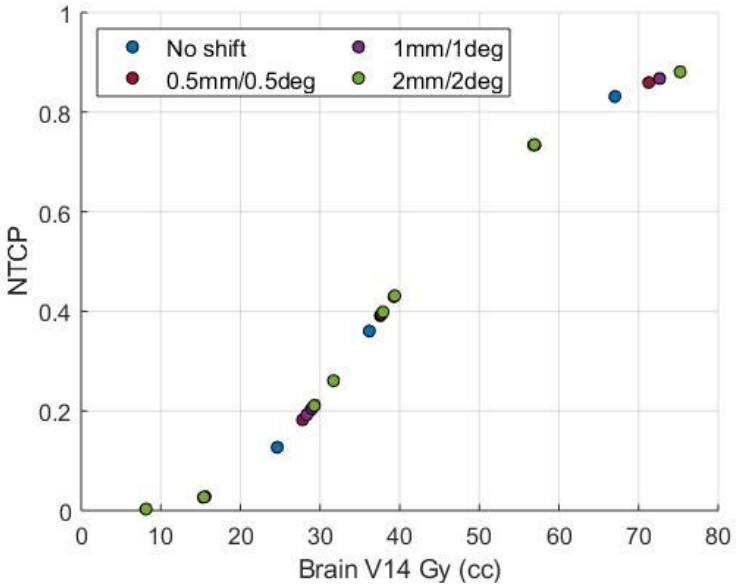


Figure 6.4 Comparison of NTCP with brain V14 for all plans
Comparison of NTCP of whole brain V14Gy for original SIMT-VMAT plans and the corresponding simulated VMAT plans with induced setup uncertainties of 0.5 mm/ 0.5°, 1 mm/ 1° and 2 mm/ 2° in all 6DOF. Values of Vx50 and γ50 were obtained from literature as 45.8 cc and 0.88, respectively. [37] The blue points represent NTCP with no setup uncertainty, the red ±0.5 mm/ 0.5°, the purple ±1 mm/ 1 and the green ±2 mm/ 2° as a function whole brain V14Gy. There is no clinically significant increase in NTCP due to patient set up errors, however NTCP of normal brain increases significantly as a function of V14Gy for those patients with increasing V14Gy above 30 cc.

6.4 Discussion

In addition to DCK, the effects of ICK responsible for providing better local tumor control rates for SIMT-VMAT plan are explored with consideration of dosimetric discrepancies due to patient setup errors. This model determines the setup uncertainty limits for physicians that fully utilizes ICK to maintain acceptable tumor coverage. This was done by determining the dose levels that fully cover the target for SIMT-VMAT plans with no setup uncertainty compared to clinically observable patient set up errors of 0.5 mm/ 0.5°, 1 mm/ 1° and 2 mm/ 2° in all 6 DOF. Setup limits of at least 1.3 mm and 1.3° or better in all 6DOF was found as the threshold to maintain acceptable target dose while

including the effects of ICK. The amount of contribution of both direct and indirect cell kill was also modeled using Boolean structures, so that 20 Gy IDV was assumed to be primarily responsible for DCK, while the 15 Gy to 20 Gy IDV was assumed to be primarily contributing due to ICK. As set up uncertainty increases, the contribution of ICK increases and, therefore, tumor cell death by devascularization. The apparent dosimetric disparity from losing target coverage of the prescription dose is partially mitigated by incorporating the concept of secondary cell kill. In addition, the effects of setup uncertainty on the normal brain were modeled using NTCP. No clinically significant increase of NTCP of the brain due to set up errors was observed, while clinically significant increases in OAR are possible for these set up uncertainties due to the proximity of the organs.

Treating m-bm with a single-isocenter plan comes with many challenges including dosimetric disparities due to patient positioning errors.[14-20] This presents concerns in terms of local tumor control and unexpected dosing to the normal brain and other adjacent critical structures in the brain. The QUANTEC guidelines for normal brain tissue cite a study relating V12Gy to radiation induced necrosis, where the risk of NTCP increases from 23% for V12Gy between 0 and 5 cc and 54% for V12Gy at 10 to 15 cc.[38-39] It should be noted that dose to whole brain to a certain dose level is primarily on treated volume rather than number, shape, or location of lesions.[40] Several clinical outcome studies have reported positive results of higher tumor local control rates of SIMT-VMAT treatment that do not align with the presence of these dosimetric disparities.[21-25] For instance Alongi et al. used Varian single-isocenter VMAT in the treatment of 43 patients with m-bm and performed a clinical follow up study within 6 months. They observed that 60% of the patients with partial or complete responses and 40% with stable disease control, though the medial

overall survival had not yet been reported.[22] Other studies have found similar tumor local control rates for linac based brain SRS using single-isocenter plans.[21,23-24] These clinical observations lead to the consideration of how the radiobiology of single fraction, high dose SRS could play an important role in SIMT-VMAT for treating m-bm.

Recently, Sperduto et al. discussed the high control rates of stereotactic body radiation therapy (SBRT) and SRS and suggested the concept of ICK.[32] They discuss the roles biological models play in the evaluation of outcomes in SRS treatments. Their results suggest that a single dose of 15 Gy or higher correlates with indirect death of hypoxic cells by modes of devascularization and potentially radiation induced immune enhancement. The authors conclude that in addition to DCK, the secondary cell death by modes of devascularization may be the mechanism of interest that providing success for SRS/SBRT. This must be considered when evaluating dosimetric uncertainties due to set up errors for SIMT-VMAT treatments. Both direct and indirect cell kill could be playing roles in tumor cells death, resulting in the higher local control rates reported by the mentioned clinical observations. This simulation study demonstrated that acceptable target dose could be maintained when small setup uncertainties exist because the target coverage by a dose of 15 Gy or higher is still maintained and there for cell death by devascularization. It is therefore suggested that if setup errors cannot be maintained between 1.3 mm/1.3° in all 6 DOF, alternative treatment methods to m-bm should be used. It is recommended to use either a dual-isocenter approach or traditional individual isocenter to each tumor methods instead.[41]

Though this study brings perspective to radiobiological effects that exist when treating m-bm via SIMT-VMAT plan, some limitations must be considered. Though

positive outcomes were evident, there were still discrepancies between the literature for local controle rates. This study is describing single fraction treatments, while the literature supporting positive local control range from single to 5 fractions with a variable number of patients receiving WBRT or surgical resection in addition to SRS treatments. They also use larger margins of 2-3 mm, which could be accounting for some levels of uncertainty, though the effect on normal brain is not mentioned.[21-22] These high local control rates are still useful in describing the indirect cell kill effects that could be taking place with high dose per fraction treatments, even with patient setup errors, although cannot be predictive for all patient cohorts. As mentioned previously, an assumption is made in this study that the 15 Gy or higher IDV is a parameter of choice to describe the effect of ICK. However, there are some studies suggesting a single dose of 10-12 Gy as a threshold for ICK.[28-30] Moreover, it is actually a combination of both indirect and direct killing methods that take place between 15 Gy and 20 Gy, though for simplification, just ICK is considered. This study is also limited by the TPS resolution limits when considering the tumor size of this patient cohort. These in combination will cause rounding of IDV and Boolean structures, meaning some results for very small tumors will not be as accurate as those of larger tumors. Lastly, the LQ model is not an adequate representation of a dose response relationship for single fraction SRS treatments, and though work has been done to create a relevant model, there is not currently a definite solution.[42] Though 15 Gy is a potential parameter to consider, it may be difficult to directly apply this value. The studies mentioned were done with human fibrosarcoma xenografts that grew in the legs of mice up to 6-7 mm in diameter and irradiated with single fractions, where some brain mets are larger in size.[25-31] Therefore, it must be recognized that this is a simulation study, therefore the results

reported are not predictive of current patient treatment. Further clinical studies are warranted.

However, future research includes incorporating this ICK approach for SIMT-VMAT plans in the treatment of m-bm for reporting and clinical follow up of the patient's tumor local control and treatment related toxicity. It is also important to further investigate the radiobiological models of single fraction SRS treatments in terms of tumor control probability (TCP) and how residual patient setup errors could affect the predicted treatment outcomes. Efforts have been made to model the TCP for single fraction treatments, but many still present with problems associated with unreliability of the LQ model that was historically generated for fractionated radiotherapy.[43] Therefore, TCP depends on clinical observations rather than predicting local control rates. It will also be useful to use cellular modeling to further understand the magnitude of the damage made by DCK vs. ICK with respect to reduced tumor cell kill for some given dose levels as seen by tumor recurrences.

6.5 Conclusion

SRS treatment of m-bm using a SIMT-VMAT plan will result in dosimetric discrepancies due to immitigable residual patient positioning uncertainties. In addition to DCK, vascular damage as a form of ICK due to single-dose of 15 Gy or higher could potentially compensate for these dosimetric errors and still presenting positive outcomes for the tumor local control along with no significant increases in normal brain toxicity. Clinical follow up results of the m-bm patients treated via a SIMT-VMAT SRS plan that incorporates ICK in addition to DCK is warranted.

CHAPTER 7. SUMMARY AND CONCLUSIONS

7.1 Study Summary

This dissertation has described the development and clinical exploration of stereotactic radiosurgery to treat multiple brain metastases efficiently and accurately using a single isocenter VMAT. **Chapter 1** of this dissertation gave a brief overview of how brain metastases are diagnosed and a discussion of treatment options with clinical limitations. Chapter 1 then concluded with an outline of the dissertation and the clinical innovations of each aim of the study. It outlines the overall clinical rationale and purpose to further develop single isocenter VMAT techniques to further develop SIMT-VMAT to be a more accurate and efficient treatment modality.

Chapter 2 presented a study that investigates the effect rotational and translational patient set up errors have on target coverage and dose to OAR. SIMT VMAT is an efficient form of SRS to multiple brain metastases. However, in current clinical practice, this treatment technique does not account for residual patient setup uncertainty, which would degrade treatment delivery accuracy. In the study presented in Chapter 2, loss of target coverage is quantified along with the potential collateral damage to adjacent normal tissue (including normal brain) due to isocenter misalignment. During single isocenter VMAT planning, the isocenter was placed at the geometric center of all the tumors. A MATLAB script was developed and used to induce clinically realistic, random setup uncertainties in all 6 DOF. This script used image registration files to shift the isocenter with the clinically observable patient setup shifts, inducing translational and rotational errors on the original planning images. The dose was then recalculated on the rotated and translated images and the new target coverage and dose to nearby critical structures was compared to that of the

original, unshifted plan. It was hypothesized that small setup uncertainties would lead to a large, clinically unacceptable, loss of target coverage in this setting. The loss of target coverage was found to be 22% on average with losses up to 94% with severity increasing for smaller tumor volumes. However, in these complex clinical cases the clear relationship for loss of target coverage as a function of distance to isocenter could not be concluded, suggesting that there could be other multiple factors (such as slight change in source to surface distance (SSD), or steep dose gradients) contributing the loss of target coverage as well.

Chapter 3 describes and compares a novel DCA-based VMAT planning approach with a standard single isocenter VMAT for SRS of multiple brain lesions. For small brain lesions, in addition to patient set up uncertainty, the small field dosimetry errors are a major concern when using small beamlets in the delivery of highly modulated single isocenter VMAT plans. Chapter 3 investigates new planning features in order to provide the highest quality plan and the most efficient and accurate treatment delivery. The study in this chapter evaluates a new MLC aperture controller feature in the Varian Eclipse TPS. SIMT VMAT plans were re-optimized using DCA-based VMAT planning approach with identical beam geometry, dose calculation algorithm, dose calculation grid size, planning objectives and parameters. The DCA-VMAT plans utilized a DCA base dose with high strength field aperture shaper control priority before VMAT optimization. It was hypothesized that less beam modulation through multiple targets would be expected. DCA-VMAT plans resulted in similar tumor dose, target coverage and conformity with lower dose to normal brain and other adjacent OAR. It also had a lower number of monitor units and less beam modulation, resulting in a significantly reduced treatment time with higher

QA pass rates. This approach provided excellent plan quality and also minimized small field dosimetry errors, suggesting that incorporating DCA-based VMAT optimization for multiple brain lesions in single isocenter VMAT approach, similar to HyperArc VMAT module merits future investigation.

In effort to create a more accurate treatment technique when using single isocenter VMAT, a risk adapted approach was presented in **Chapter 4**. Thus far, this issue has been addressed by adding an additional margin around the tumors, providing added risk by increasing the dose to OAR and the normal brain tissue. The risk adapted approach is an alternative treatment planning approach that escalates dose to tumors away from isocenter, compensating for residual setup errors. In the original single isocenter VMAT plans, 20 Gy was prescribed to each lesion. These plans were replanned using the risk adapted approach utilizing 3 different potential prescriptions based on distance to isocenter, tumor size and proximity to the OAR. Where tumors at a greater distance to isocenter prone to uncertainty have an escalated prescription dose of 24 Gy; whereas larger targets in close proximity to OAR have a decreased prescription of 18 Gy. With this technique, the hypothesis is the lesions at a large distance from the isocenter could still receive a nominal dose of 20 Gy to each lesion with an escalated prescription. These plans also provided less spread of intermediate dose to the normal brain with similar treatment delivery parameters. The risk adapted SIMT VMAT plan demonstrated promising plan quality and treatment delivery accuracy for uncertainties up to ±1°/1 mm for patients with multiple brain lesions.

Another novel technique was introduced in **Chapter 5** to manage the complexity of treating large number of brain metastases. With a large number of lesions and a single isocenter VMAT plan, it is unavoidable for some lesions to share the same MLC pair during

delivery. This is known as island blocking, causing higher volume of low and intermediate dose spill in the brain and an increased dose to OAR. The study in Chapter 5 proposed a dual isocenter VMAT planning strategy that groups lesions based on hemisphere location in the brain tissue, potentially providing less distance for MLC travel and reducing the effect of island blocking, which then minimizes dose spill and improves overall plan quality. This technique simplifies planning while increasing patient compliance by allowing for the large number of lesions to be treated in groups. For the SIMT VMAT plan, the isocenter was placed in the geometric center of all tumors, just as mentioned in previous chapters. These patients were replanned with the dual isocenter approach where two separate plans were generated with each isocenter at the geometric center of each group of lesions. The dual isocenter VMAT plans had similar target coverage and dose conformity with less spread of intermediate dose to the normal brain and reduced dose to OAR. It is a simplified planning approach that comes with a tradeoff of slightly increased overall treatment time, though it is still less than treatment times of GK SRS and traditional multiple isocenters techniques (1 isocenter per target). Dual isocenter VMAT has potential to improve targeting accuracy by limiting the region of interest necessary for localization. Rather than matching the entire patient's skull on a daily CBCT image and applying shifts, half of the skull is matched on either side of the brain by reducing the region of interest on the daily CBCT scan. This method is recommended for managing difficult patients with a large number of multiple brain lesions in a palliative setting.

Due to spatial uncertainty, patient setup errors are of major concern for radiosurgery of multiple brain metastases when using a single isocenter VMAT, as discussed in Chapter 2. However, recent clinical outcome studies showed high rates of tumor local control for

multiple brain metastases using a single isocenter treatments.[1, 2] These promising clinical outcomes cannot be fully explained when considering patient positioning uncertainties discussed in Chapters 1 and 2. Radiobiological response with the LQ model overestimates the tumor control rates with SRS treatments as the survival curve bends downward with increasing dose due to increased contribution of the quadratic component of the model. [3, 4] It is hypothesized that in addition to direct cell kill, indirect cell killing could be playing a role in SIMT VMAT SRS, specifically devascularization of the weak, fragile intratumor microenvironment. Recent literature suggests that tumors with doses higher than 15 Gy per fraction cause major vascular damage resulting in secondary cell death.[4] **Chapter 6** works to further quantify the role of secondary cells death in the treatment of multiple brain metastases using single isocenter VMAT. Contributions of both direct cell kill (20 Gy prescription isodose volume) and indirect cell kill (15 Gy minus 20 Gy isodose volume) were investigated. Minimum dose covering the entire tumor was analyzed to determine the maximum tolerable patient setup errors to utilize the potential radiobiologic effect of indirect cell kill. It was found that patient setup errors of ±1.3 mm/1.3°in all 6 directions must be maintained to achieve the acceptable target coverage of the 15 Gy isodose volume or higher to account for the effect of indirect cell death. Setup errors above this threshold showed unacceptable loss of target coverage, even when considering indirect cell kill, although no significant changes in normal brain dose was observed. Positive clinical outcomes for single isocenter VMAT could be largely due to the effect of secondary cells death via devascularization, providing a better understanding of the radiobiological response of SRS of multiple brain metastases in this setting.

7.2 Study Limitations

This study aimed to ensure SIMT VMAT to be a safe, effective and accurate treatment modality for multiple brain lesions. Though great improvements were made, there are still some limitations that must be mentioned. The patient number among every study performed in this dissertation was limited. The patient number used was based on the availability of the patient data at the University of Kentucky Medical Center. This lack of data likely impacted the statistical analysis of these studies and larger studies with a larger patient cohort is warranted. Many of the patient images were taken from those with previous GK radiosurgery treatments. That means the patient images were using high resolution MRI images; therefore, for some patients, we did not have appropriate planning CT imaging for heterogeneity corrections. For these patients, a homogeneous dose distribution to the brain was calculated by assigning a CT value equal to water to the brain. However, Pokhrel et al. performed a Monte Carlo study with homogenous pencil beam algorithms concluding that only less than 2% discrepancy within the brain dose distribution was found even with the cavernous sinus tumors.[5] We do acknowledge that there might be slight dosimetric errors by not accounting for heterogeneities in the brain, specifically the skin dose. However, in the future, heterogenous dose distribution will be calculated on the planning CT images (co-registering high-resolution MRI for tumor and OAR delineation) for actual patient's treatment via single isocenter VMAT plan.

Another caveat is all treatment planning in this dissertation was done with standard MLC with 5 mm width due to availability at the University of Kentucky Medical Center. The manufacture suggests that single isocenter VMAT for multiple brain lesions be limited to linear accelerators utilizing 2.5 mm high definition MLC. However, a study from Duke

University Medical Center demonstrated that for radiosurgery of multiple brain metastases using single isocenter VMAT plans, 5 mm MLC can produce similar target conformity with slightly increased 30-50% dose spillage, but can be minimized by adding more VMAT arcs.[6] We acknowledge that, by incorporating micro-MLC in the planning methods suggested in this dissertation, even higher quality SRS treatment plans can be generated.

In **Chapter 2**, was hypothesized that the loss of target coverage would increase with distance from isocenter as well as for small tumor sizes. Loss of target coverage as function of rotational patient's set up errors were studied by a few investigators.[7-9] For instance, Roper et al. performed a dosimetric study by systematically inducing rotational errors of 0.5º, 1.0º, and 2.0º using Velocity AI (Velocity Medical, Atlanta GA) for patients with 2 lesions, showing a linear relationship between diminishing PTV coverage and distance to isocenter.[7] This linear relationship was not evident in this dissertation for the complex patient cohort with large numbers of brain lesions with some of irregular shape. There are several other factors that could have contributed to this result. In addition to the steep dose gradient, the small translations and rotational errors lead to changes in SSD affecting in dose calculation algorithm resulting different dose distribution when it is recalculated. Finally, the complexities of the many body problem presented here must be considered, with a larger number of lesions with irregular tumor shapes, the complication of the problem increases and might deviate the expected results based on a simple geometry with two spherical lesions demonstrated by Roper et al.[7] Compared to the above mentioned studies, who used third party dose calculation algorithms, our dose recalculation in the same planning system with identical algorithm (only accounting for the residual patient

setup errors) would be accurate representation of a real time clinical scenarios. Although, future investigation of this trend is required.

In **Chapter 6**, the radiobiological responses of single isocenter VMAT treatment to multiple brain lesions was investigated as a function of residual patient setup uncertainty. It must be noted that the LQ model begins to break down when used for single fraction treatments, although it is controversial.[10] It has been questioned whether the LQ model is applicable to a single high dose treatment. The LQ model assumes that radiation damage and cellular death is to DNA double strand breaks only.[10] Other mechanism of cells death, as mentioned in Chapter 6, such as devascularization could causing a delayed tumor cells death. The LQ model is not an adequate representation of a dose response relationship for single fraction treatments, though it is still a trusted and useful model for fractionated SRS treatments. Though some work has been done to create a better model by accounting secondary cells death, there is not currently a definite solution in this regard and is an active area of ongoing research.[3,4,11] It must then be recognized that the work in Chapter 6 is a retrospective simulation study and the results reported is not predictive of current patients' treatment.

Clinically promising tumor local control rates for SRS of multiple brain lesions using a single isocenter treatments were reported in recent literatures as discussed in Chapter 6. Though positive outcomes were evident, there were still discrepancies between the literature for local control rates. This dissertation is describing single fraction treatments, while the literature supporting positive local control was achieved from single fraction to 5 fraction treatments with a variable number of patients receiving WBRT or surgical resection in addition to single and multiple isocenter SRS treatments.[1,2] These high

local control rates are still useful in describing the indirect cells kill effects that could be taking place with high dose per fraction treatments, even though with residual patient set up errors. Although these results should not be predictive among all patient cohorts. These studies also have no documentation of normal tissue toxicities. It must also be noted that the normal tissue complication probability (NTCP) described in Chapter 6 should also not be used as a predictive measure. There is controversy on which parameter is best to be used to predict normal brain toxicity. Whole brain V12 Gy is the most popular in the SRS community, though V8 Gy, V14 Gy and mean brain dose (MBD) are still worthwhile to considered. In Chapter 6, V14 Gy was used as a predictive measure of NTCP based on the most recent research. Milano et al. generated a NTCP model based on the V14 Gy and the volume corresponding to 50% risk of radionecrosis due to SRS to brain lesions.[11] For consistency with this model, we used the same parameters that this research chose, though it should be considered that other parameters might have the possibility to better predict the brain toxicity.

7.3 Future Research Directions

There are several directions this dissertation can be further expanded. There is much more work to be done on the investigation of the radiobiological response of single fraction SRS via SIMT VMAT, specifically in terms of indirect cell killing. It would be useful to report the absolute magnitude of indirect cell death for single isocenter VMAT treatments in conjunction with clinical follow-up results of patient's tumor local control and treatment related toxicity. This has potential to expand and better predict the role that indirect cells kill could plays in single fraction, high dose treatments, potentially guiding treating physicians prescribing the most appropriate dose to the lesion. A simplified radiobiological

model was discussed in Chapter 6 for describing the effects of direct and indirect cell kill. In reality, they both play a role in different magnitudes for any given doses. Cellular modeling with SRS could be used to further understand this magnitude of contribution for both direct and indirect cell death. These contributions can be used to improve the biological model's performance in the future for predicting and understanding the role of indirect cell kill in SRS treatment of multiple brain metastases. This can all be further expanded by generating a novel model for accurately predicting tumor local control rates for single fraction treatments of multiple brain metastases. This can then be used to investigate how residual setup errors affect patient outcomes and potentially be used as a predictive model for future patient's treatments.

There is also room to expand the usability of SIMT VMAT treatments in the clinic by examining the potential for fractionated single isocenter treatments that were traditionally treated on GK radiosurgery unit. For example, a large tumor bed or larger brain metastases could be treated in a fractionated treatment scheme with 24 to 30 Gy in 3 to5 fractions, while managing brain toxicity. There is also potential for larger acoustic neuromas or meningiomas to be given a fractionated treatment with 25 Gy in 5 fractions and maintaining brainstem toxicity. This gives potential to reduce side effects on the normal brain and other immediately adjacent OAR and potentially improve patient outcomes.

As mentioned in Chapters 2 to 4, in the multi-lesions setting, there is a major issue of higher dose spill to the normal brain due to island blocking between/among the tumors. This was addressed in Chapter 4 with the dual isocenter approach by reducing the amount of island blocking, lessening the dose spill between tumors. This can be further moderated by introducing a new degree of freedom via collimator optimization during gantry

rotations. In addition to a variable dose rate and gantry speed with continuous gantry rotation as in standard SIMT VMAT plan, the collimator angle could also vary in an optimized fashion. This extra degree of freedom could potentially limit the amount of island blocking and therefore reducing dose to the normal brain.

Recently, Varian HyperArc VMAT has been a major development in Linac-based SRS programs to treat multiple brain lesions simultaneously. With the results mentioned in Chapter 3, the novel DCA-based VMAT approach can be adopted and fully automated into the current geometry that HyperArc VMAT uses. This could further reduce dose to normal brain and spare other OAR while reducing the total monitor units and ultimately further improving the beam on time as demonstrated in Chapter 3. It also has less MLC modulation to minimize the presence of leakage and transmission and improving small field dosimetry errors.

Finally, there is a potential to further automate the entire course of treatment planning and delivery for SIMT VMAT SRS for multiple brain metastases. As mentioned above, Varian Medical Systems developed a prescription-based planning module for single isocenter VMAT known as HyperArc in the Eclipse TPS (Varian Medical Systems, v 15.6, Palo Alto, CA). From placement of isocenter and the application of beam geometry to the virtual "dry run" it is nearly all automated. However, in order to fully automate the planning process, a knowledge-based planning (KBP) model, such as RapidPlan (Varian Medical Systems, v 15.6, Palo Alto, CA), could be used to further automate the treatment plan optimization process.[12,13] Full automation of the treatment planning process via KBP model could further simplify these complex patient's single isocenter VMAT treatments, potentially increasing clinic workflow, patient safety and decreasing intraplanar variability.

7.4 Closing Remarks

This research develops a Linac-based SRS protocol for the fast, safe, effective and accurate treatment delivery for multiple brain metastases using SIMT VMAT, improving patient comfort and clinic efficiency. Utilizing these novel patient setup correction strategies, more accurate SRS treatments could be delivered to multiple brain lesions. It will open an avenue for patients who cannot tolerate traditionally longer treatment times or frame-based treatments. It provides treatment availability to those who do not qualify for GK SRS due to large tumor sizes and critical locations, those who deny WBRT or patients without access to other SRS treatment options. The findings in this dissertation provide clear instructions for optimal treatment planning strategies for the treating physicians and physicists along with simplified patient's setup instructions for the therapists. These guidelines can be provided to support other radiotherapy clinics including community centers who have less or no experience in treating multiple brain metastases. This dissertation fully explores the clinical usefulness and limitations of SIMT VMAT as an SRS treatment alternative for multiple brain metastases patients.

APPENDICES

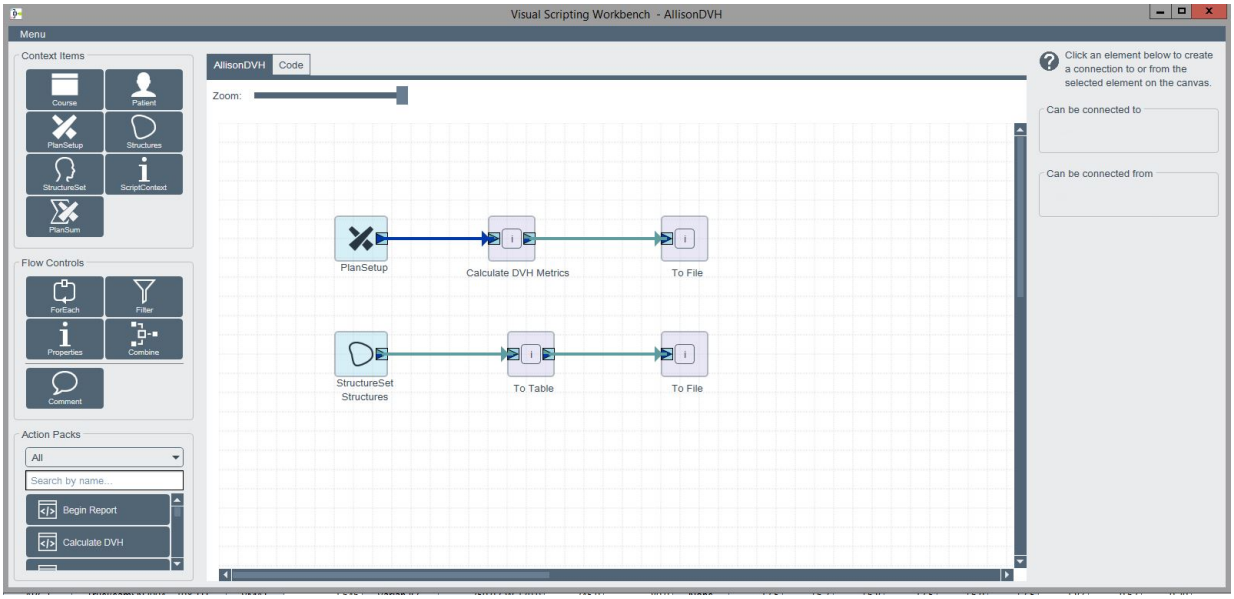
APPENDIX 1. GLOSSARY

6DOF	Six Degrees of Freedom
AAA	Anisotropic Analytic Algorithm
BED	Biological effective dose
BEV	Beam's Eye View
BOT	Beam On Time
CBCT	Cone Beam Computed Tomography
CGS	Calculation Grid Size
CI	Conformity Index
CN	Conformity Number
DCA	Dynamic conformal arcs
DCK	Direct Cell Kill
DVH	Dose Volume Histogram
EPID	Electronic Portal Imaging Device
FFF	Flattening Filter Free
GK	Gamma Knife
GTV	Gross Tumor Volume
HA	HyperArc
HI	Heterogeneity Index
ICK	Indirect Cell Kill
IDV	Isodose Volume
IMRT	Intensity Modulated Arc Therapy
KBP	Knowledge Based Planning
KPS	Karnofsky performance status
Linac	Linear Accelerator
LQ	Linear Quadratic
MBD	Mean Brain Dose
m-bm	Multiple Brain Metastases
MBD	Mean Brain Dose
MF	Modulation Factor
MLC	Multi-leaf collimator
MME	Multiple Metastases Element
MRI	Magnetic Resonance Imaging
MF	Modulation Factor
MU	Monitor Units
NTCP	Normal Tissue Control Probability
NTO	Normal Tissue Objective
OAR	Organs at Risk
PD	Portal Dosimetry
PO	Photon Optimizer

PTV	Planning Target Volume
QA	Quality Assurance
RPS	Recursive Partitioning Analysis
RTOG	Radiation Therapy Oncology Group
SIDCA	Single Isocenter Dynamic Conformal Arc
SIMT	Single Isocenter Multitarget
SRS	Stereotactic Radiosurgery
SSD	Source to Surface Distance
STD	Standard Deviation
TCP	Tumor Control Probability
TPS	Treatment Planning System
TV	Target Volume
UR	Undertreatment Ratio
VMAT	Volumetric Modulated Arc Therapy
WBRT	Whole Brain Radiotherapy

APPENDIX 2. VISUAL SCRIPT FOR PLAN DATA EXTRACTION

This visual script is useful as a data taking tool from information that can be found in the dose volume histogram (DVH). The first line of the visual script calculates the DVH and puts the metrics into a file. The second line allows you to pick which structure sets and metrics that you want exported. For this dissertation, the PTV and GTV maximum doses along with hippocampi, brainstem and optic apparatus maximum doses. The normal brain V8 Gy, V12 Gy and MBD were also exported. The exported files were placed in a word document that could then be further used in the data analysis process.



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Chapter 7

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VITA

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University of Kentucky, Lexington, KY
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Professional Experience

Physics Assistant
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Teaching Assistant
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Peer-Reviewed Journal Publications Relevant to Thesis (3)

1. **Palmiero A**, Critchfield L, St. Clair W, Randall M and Pokhrel D. Single-Isocenter VMAT Radiosurgery for Multiple Brain Metastases: Potential Loss of Target(s) Coverage due to Isocenter Misalignment. Cureus, 2020. 12(10): e11267.

2. Pokhrel D, **Palmiero A**, Bernard M, and St Clair W. A Novel Dynamic Conformal Arcs-based Single Isocenter VMAT Planning for Radiosurgery of Multiple Brain Metastases. Med Dosim, 2020; 1-6 (Article in Press) Elsevier

3. **Palmiero A**, Fabian D, St. Clair W, Randall M and Pokhrel D. Management of Multiple Brain Metastases via Dual Isocenter VMAT Stereotactic Radiosurgery. Med Dosim, 2020; 1-7 (Article in Press) Elsevier

Submitted Manuscripts Relevant to Thesis (2)

1. **Palmiero A**, St. Clair W, Randall M and Pokhrel D. A Novel Risk Adapted Single Isocenter VMAT Planning Technique for Radiosurgery of Multiple Brain Lesions to

Minimize Spatial Setup Uncertainties. J Appl Clin Med Phys (Under Review, Submitted on November 2020)

2. **Palmiero A**, Fabian D, Randall M, St. Clair W and Pokhrel D. Predicting the Effect of Indirect Cell Kill in the Treatment of Multiple Brain Metastases via Single Isocenter/Multitarget Volumetric Modulated Arc Therapy Stereotactic Radiosurgery. J Appl Clin Med Phys (Under Review, Submitted February 2021).

Abstract Presentations Relevant to Thesis

1. **Palmiero A**, St. Clair W, Randall M and Pokhrel D. A Novel Restricted Single Isocenter Stereotactic Radiosurgery Technique for Treating Multiple Brain Metastases. [Abstract] Submitted to AAPM Annual Meeting, February 2021
2. **Palmiero A**, Fabian D, Randall M, St. Clair W and Pokhrel D. Predicting the Effect of Indirect Cell Kill for Radiosurgery of Multiple Brain Metastases via SIMT-VMAT. [Abstract] Submitted to AAPM Annual Meeting, February 2021
3. Land S, **Palmiero A**, Bernard M and Pokhrel D. Single-Isocenter/Multi-Target (SIMT) SRS to Multiple Brain Lesions via Dynamic Conformal Arcs (DCA)-based VMAT with MLC Aperture Shape Controller. [Abstract] Submitted to AAPM Annual Meeting, February 2021
4. **Palmiero A** and Pokhrel D. Management of Multiple Brain Metastases Patients via Dual-Isocenter VMAT SRS. ORVC Oral Presentation, (Virtual Meeting) October 2020
5. **Palmiero A**, Randall M, St. Clair W and Pokhrel D. Hippocampal Sparing HyperArc VMAT Radiosurgery for Multiple Brain Metastases Patients in 15 Minutes Treatment Slot. [Abstract] Med Phys. July 2020 [ePoster]
6. **Palmiero A**, Molloy J, Randall M, St. Clair W and Pokhrel D. Single-isocenter VMAT-based stereotactic radiosurgery (SRS) for multiple brain metastases: Potential loss of target coverage due to isocenter misalignment. [Abstract] Med Phys, July 2019 [Short Oral Presentation]
7. **Palmiero A**, Molloy J, Randall M, St. Clair W and Pokhrel D. Single-isocenter VMAT-based stereotactic radiosurgery (SRS) for multiple brain metastases patients: Potential loss of target coverage due to isocenter misalignment. Varian Medical Systems Research Symposium, Chicago, IL [Abstract, ePoster], May 13-15, 2019
8. **Palmiero A** and Pokhrel D. Single-isocenter VMAT-based stereotactic radiosurgery for multiple brain metastases patients: Loss of target coverage from isocenter misalignment. ORVC, SLAM Oral Presentation, Liouville, KY, March 2019