PhD Thesis Title: Development of a Robust LINAC-based Radiosurgery Program for Multiple Brain Metastases and Estimation of Radiobiological Response of Indirect Cell Kill

Author: Allison Palmiero, PhD
Emails: allison.palmiero@uky.edu
    ANPalmiero@mdanderson.org
Institution: University of Kentucky, Department of Radiation Medicine
    Medical Physics Graduate Program, Lexington, KY
Supervisor: Damodar Pokhrel, PhD
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ABSTRACT:

Accurate and precise delivery of Stereotactic Radiosurgery (SRS) using Leksell Gamma Knife (GK) unit 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 method 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 the daily cone beam CT imaging during patient set up and verification. These simulations resulted in dosimetric discrepancies of 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 $\pm 1^{o}/1$ mm set up errors in all 6-directions, demonstrated a 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 the required target coverage and spatial uncertainty. For a 20 Gy prescription, it was found that the 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 rate. This provides guidance to treating physicians for clinically acceptable patient setup errors and perhaps resulting in acceptable treatment outcomes. A prospective clinical trial is necessary to further validate this radiobiological model, thus incorporating the secondary cell death with a direct cell kill using a single-isocenter VMAT plan for multiple brain lesions.

References to author publications that relate specifically to the dissertation:

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2. Pokhrel D, **Palmiero A**, Bernard M, and St. Clair W. Dynamic Conformal Arcs-based Single-Isocenter VMAT Planning Technique for Radiosurgery of Multiple Brain Metastases. Medical Dosimetry, 2021. 46(2): 095-200. https://doi.org/10.1016/j.meddos.2020.11.005

3. **Palmiero A**, Fabian D, St. Clair W, Randall M and Pokhrel D. Management of Multiple Brain Metastases via Dual-Isocenter VMAT Stereotactic Radiosurgery. Medical Dosimetry, 2021. 46(3): 240-246. https://doi.org/10.1016/j.meddos.2021.01.002

4. **Allison N Palmiero**, Denise Fabian, Marcus E Randall, William St. Clair, and Damodar Pokhrel. 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.2021;22(10):94–103. https://doi.org/10.1002/acm2.13400