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DEVELOPMENT OF A ROBUST TREATMENT DELIVERY FRAMEWORK FOR STEREOTACTIC BODY RADIOTHERAPY (SBRT) OF SYNCHRONOUS MULTIPLE LUNG LESIONS

Lana Catherine Critchfield
University of Kentucky, lanacritch@gmail.com
Author ORCID Identifier:
 https://orcid.org/0000-0002-9010-5871
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DEVELOPMENT OF A ROBUST TREATMENT DELIVERY FRAMEWORK
FOR STEREOTACTIC BODY RADIOTHERAPY (SBRT) OF SYNCHRONOUS
MULTIPLE LUNG LESIONS

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DISSERTATION
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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

By
Lana Catherine Critchfield
Lexington, Kentucky
Director: Dr. Damodar Pokhrel, Associate Professor of Medical Physics
Lexington, Kentucky
2020

ABSTRACT OF DISSERTATION

DEVELOPMENT OF A ROBUST TREATMENT DELIVERY FRAMEWORK FOR
STEREOTACTIC BODY RADIOTHERAPY (SBRT) OF SYNCHRONOUS
MULTIPLE LUNG LESIONS

Stereotactic body radiation therapy (SBRT) of lung tumors uses high doses of radiation to deliver high biological effective doses (BED) in very few fractions (1-5). With the use of highly conformal fields to cover the tumor without depositing large doses to non-cancerous structures, this technique has proven time and again to be successful at achieving high local control. However, frequently patients receiving SBRT are elderly with multiple medical comorbidities who may not tolerate long treatment times. Furthermore, many patients present with oligometastatic or multiple primary lung tumors. The success of SBRT on oligometastatic lung disease relies on physician experience with precise patient positioning and immobilization, not available in all clinics. Likewise, there is no standard framework to guide radiation oncology clinics experienced in SBRT with planning and treating multiple lung tumors synchronously. This dissertation explores the treatment planning methods available for the SBRT of multiple lung lesions and presents innovative solutions to the challenges in current practice.

To begin, two treatment planning methods for multiple lesion SBRT are compared: treating each lesion individually with separate isocenters and treating all lesions at the same time with a single isocenter. Treating multiple lesions with multiple isocenters will increase the patient's imaging and treatment time and the number of instances a radiation therapist must enter the treatment room, thus increasing the chances a patient will move from the setup position. Using an individual isocenter placed between the tumors and volumetric arc therapy (VMAT) to treat all tumors at the same time can reduce the treatment time, increasing patient comfort and decreasing the chance of movement from the treatment position. However, there is a chance of decreased target coverage and reduced BED due to small setup errors in the SBRT of synchronous lesions using a single-isocenter. The dissertation continues by quantifying this loss in target coverage using a novel simulation method. Simulations yielded average deviations of 27.4% (up to 72% loss) (p < 0.001) from planned target coverage. The largest deviations from planned coverage and desired BED were seen for the smallest targets (<10 cc), some of which received <100 Gy BED, which is suboptimal for SBRT. Patient misalignment resulted in a substantial decrease in conformity and increase in the gradient index, violating major characteristics of SBRT. To minimize coverage loss due to small setup errors, a novel Restricted Single-Isocenter Stereotactic Body Radiotherapy

(RESIST) treatment method was developed to provide efficient and effective treatments without substantially increasing treatment time. Lastly, RESIST was automated in the treatment planning system to allow for efficient and accurate treatment planning for two lung lesion SBRT. Automation includes beam geometry, algorithm selection, and an in-house trained dose volume histogram estimation model to improve plan quality. Automated planning significantly improves treatment planning time and decreases the chance of planning errors. This treatment delivery framework allows all patients who are to be treated with SBRT to multiple lung lesions to be treated efficiently and effectively. Further development of RESIST for >2 lesions and multi-site SBRT merits further investigation.

KEYWORDS: Lung SBRT, VMAT, Synchronous Multiple Lesions, Setup Errors, RESIST, Automation

Lana Catherine Critchfield
(Name of Student)

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Date

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By
Lana Catherine Critchfield

Damodar Pokhrel, PhD, DABR
Director of Dissertation

Lee Johnson, PhD, DABR
Director of Graduate Studies

11/11/2020
Date

DEDICATION

To my husband, Corey, for his endless love and support and to our dog, Nala, for being the best pandemic support partner.

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physics, for guiding me through the graduate school processes, and for taking time to help

me solve virtually any problem.

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CHAPTER 1. INTRODUCTION

1.1   A Brief History of Lung SBRT

The eventual concept of stereotactic body radiation therapy (SBRT) originated with Lax, Blomgren, and colleagues in 1994 at the Karolinska Hospital in Sweden.[1] Their goal was to create very precise and accurate treatments for lesions that could not be resected and did not respond well to low doses of radiation. Although they focused on abdominal malignancies, the technique was inspired by radiosurgery of intracranial targets using a Gamma Knife (Elekta, Stockholm, Sweden). Gamma Knife radiosurgery uses a rigid stereotactic system attached to the skull for target localization and patient setup. The technique uses a high dose with a heterogeneous distribution and is typically delivered in a single fraction. Tumor dose is prescribed to the tumor margin (i.e. tumor periphery), typically the 50% isodose line. For example, if the dose at the margin is 20 Gy to the 50% line, then the maximum dose in the tumor is 40 Gy. Conformation of dose to the target and rapid fall-off of dose is required for stereotactic procedures to limit doses to non-cancerous structures. The authors took these ideas to create a treatment regimen for extracranial lesions. They began with the creation of a stereotactic body frame. The frame consisted of a box-like structure with rigid walls on either side of the patient attached to a flat base. The walls had position indicators that can be visualized on a CT scan in order to localize the tumor. The patient was immobilized on a vacuum pillow and diaphragmatic movements were reduced with the use of abdominal compression. Their stereotactic treatments were prescribed to a high dose ($\geq$6 Gy/fraction) and delivered in a few fractions, compared to conventional fractionation at a dose of 1.8-2 Gy per day for multiple weeks. These plans consisted of 6 or 21 MV photons utilizing 4-8 non-coplanar static beams all focused at an

isocenter located in the tumor. These planning parameters were dramatically different from Gamma Knife planning which used 201 Co-60 beams of 1.25 MV photons. In 1995, the same group published the results from the first trial of 31 patients treated with the technique.[2] This trial included intrahepatic tumors, liver metastases, metastases to the thoracic cavity and retroperitoneal and skeletal metastases. The dose was prescribed to the margin and planned such that the maximum dose in the target was 50% higher than the margin. The maximum doses in the target varied from 9-82 Gy, delivered in 1-4 fractions. Observed with patient follow-up, 50% of the irradiated tumors decreased in size and 80% had local rate of no progressive disease. Based on these findings, they determined that their stereotactic radiotherapy technique was convenient for patients and may be of clinical value for extracranial lesions.

Focusing on the American progression of SBRT, in 2002 surgery was still considered standard primary care for stage 1 non-small cell lung cancer (NSCLC). At the VA Medical Center in Indianapolis, Indiana, McGarry and colleagues identified a cohort of patients from the institutional tumor registry with NSCLC who were ineligible for surgery and thus were left under observation.[3] They determined that more than 50% of these observation-only patients would die of their lung cancer. Looking to find an acceptable treatment option for these patients, they began the first dose escalation trial to treat surgically ineligible patients with high doses of radiation in a few fractions. Thus, in 2003, the institution reported the results from a dose escalation trial utilizing stereotactic radiosurgery, called Extracranial Stereotactic Radioablation (ESR), for medically inoperable stage 1 NSCLC.[4] Prescribed doses escalated from 8 Gy per fraction to 20 Gy per fraction in 2 Gy increments. Heterogeneous dose distributions were calculated to water,

prescribed such that the tumor margin was covered by the 80% isodose line and delivered in 3 fractions over 2 weeks. 87% of tumors responded to the treatment. In all cases of local failure, the patient received less than 18 Gy per fraction. This study was just the beginning of many to determine the roll of SBRT in the treatment of lung cancer between 2003 and 2009.[5-7] These studies included the first Radiation Therapy Oncology Group (RTOG) studies for lung SBRT, RTOG 0236 to study the role of SBRT for patients with medically *inoperable* early stage NSCLC and RTOG 0618 for patients with *operable* early stage NSCLC.[8,9] Both studies employed the dosing scheme of 20 Gy per fraction for 3 fractions. Similar to the Indiana dose escalation trial, tissue heterogeneities in the lung were not considered in the dose calculation. It was observed that 20 Gy without heterogeneity correction is roughly equivalent to 18 Gy with corrections. Findings from the studies revealed that SBRT to early stage NSCLC resulted in a high rate of tumor control and low rates of radiation induced toxicity for both medically operable and inoperable patients.

In 2009, the RTOG began two trials using SBRT for early stage NSCLC, RTOG-0813 for centrally located lesions and RTOG-0915 for peripherally located lesions.[10,11] These studies are frequently referred to in practice today, providing guidelines for treating single lesions. Both studies considered lung heterogeneities in the dose calculations. Shortly after, the American Society for Therapeutic Radiology and Oncology (ASTRO) and the American College of Radiology (ACR), as well as the American Association of Physicists in Medicine, published practice guidelines for SBRT.[12,13] Results from these studies and using the practice guidelines further encouraged clinicians that using SBRT for either NSCLC or any localized lung cancer could result in local control rates comparable to surgery.[14,15] Excellent outcomes were associated with high biological effective doses

(BED) of at least 100 Gy, using an α/β ratio of 10 Gy for lung tumors.[16] BED aims to quantitate the biological effect of radiation therapy, considering the type of tumor and the dose delivered.[17] By 2013, the radiation community generally agreed that a BED of at least 100 Gy was necessary for successful lung SBRT.[18] Most common lung SBRT prescriptions are 50 Gy in 5 fractions (100 Gy BED), 48 Gy in 4 fractions (105.6 Gy BED) and 54 Gy in 3 fractions (151.2 Gy BED). SBRT to lung lesions is typically utilized for small volumes (3-5 cm), with treatment to larger volumes (>7.0 cm) resulting in higher dose spread and chance of radiation induced pneumonitis. Physicians may choose differing prescriptions depending on lesions size and proximity to normal structures, such as the ribs or bronchial tree.

In current practice, it is acknowledged that the success of SBRT relies on accuracy and confidence throughout the entire process, from patient imaging to treatment planning and delivery. Clinics must adapt to continuing improvements in technology, however the success of lung SBRT treatments is more likely attributed to the experience of a clinic rather than technological advances.[19] The external stereotactic body frame with abdominal compression maintains a presence in clinics practicing SBRT, however most frames are now made without walls and with more robust materials, such as Kevlar. Patients are positioned on a vacuum bag with arms up and abdominal compression to minimize tumor motion, when possible. If the patient cannot tolerate compression, alternative forms of motion evaluation and management are used such as 4DCT, slow CT, breath holds, or optical tracking techniques.[20-23] Further adapting to improvements in technology, many clinics now treat lung SBRT patients with volumetric modulated arc therapy (VMAT).[24,25] VMAT modulates dose rate and multileaf collimator (MLC) position as the gantry rotates.

VMAT provides lower dose to non-cancerous structures compared to more traditional treatment methods such as static 3D fields, static intensity modulated radiation therapy (IMRT) or coplanar dynamic conformal arcs (DCA). Helical Tomotherapy and robotic CyberKnife are two alternatives to the traditional C-arm linear accelerator that are used for SBRT treatments. However, both Tomotherapy and CyberKnife lung SBRT treatments are considerably longer than VMAT on a C-arm linear accelerator.[26,27] Even more recently, the technique of flattening filter free (FFF) beams (removal of the flattening filter that traditionally provides a uniform beam of radiation) has been shown to have considerable benefit for lung SBRT by both decreasing treatment time and improving dose coverage at the tumor-lung interface.[28]

1.2   Multiple Lesion Lung SBRT

There is a large cohort of patients who present with multiple primary or metastatic disease in the lung. Lungs are one of the most common sites of metastasis from many cancers including colorectal cancer, renal cancer and hepatocellular carcinoma, which can all be treated with SBRT.[29] In 2006, the first study for bilateral multiple primary lung cancers concluded that SBRT is a possible safe and effective treatment option for these patients.[30] This study was followed by others that reported SBRT as a treatment to successfully manage multiple primary lung tumors or oligometastatic disease.[31-34] NRG Oncology began a study in 2014, *NRG-BR001 A Phase 1 Study of Stereotactic Body Radiotherapy (SBRT) for the Treatment of Multiple Metastases*. This study was intended for oligometastases arising from the breast, lung or prostate to determine the tolerability of SBRT to multiple lesions. This study was closed in March 2018 with outcomes continuing to be reported. Preliminary results from the study indicate that SBRT is safe for 2 lesions

in close proximity and up to 4 lesions irrespective of proximity.[35] However, the study allowed for virtually any treatment planning parameters including either flattened or FFF beams as well as 3D conformal radiation therapy or IMRT/VMAT. It is important to acknowledge that, contrary to conventional radiation therapy, SBRT treatments are long. The increased time can be attributed to the higher accuracy needed in patient setup, the high dose being delivered, the complexity of the plans and the need for pre-treatment imaging, typically a cone beam CT scan (CBCT). Hoogeman, Nuyttens, and colleagues determined for a subset of immobilized patients intrafraction motion increased linearly with time.[36] This gives incentive to create treatment plans that can be delivered as quickly and accurately as possible. Likewise, most SBRT studies report participants of greater than 75 years of age. These patients may have a difficult time remaining still and comfortable in the treatment position due to associated medical comorbidities. Furthermore, treating multiple lesions with SBRT will increase the treatment time.

To reduce the delivery time for multiple lesion lung SBRT treatments, all lesions can be treated at the same time using a single isocenter. Due to the long SBRT times reported for both Tomotherapy and CyberKnife, a C-arm linear accelerator using VMAT is the most reasonable modality for decreasing treatment times for these patients. Likewise, the high dose rate associated with FFF beams can provide highly conformal and faster treatments.[37] However, there is currently no protocol in place to guide radiation therapy clinics in the efficient and accurate treatment of synchronous multiple lung lesions using SBRT. Likewise, if the success of SBRT relies on the clinic experience with SBRT, how do clinics gain experience without risking patient care? Thus, when a clinic must treat a patient with multiple lesions there are questions left unanswered: How should multiple

lesions be planned? If to be treated at the same time, what happens if the targets don't line up on the single pre-treatment CBCT? What is the result of slight patient misalignments in terms of target dose and dose to critical structures? How can these treatments become more efficient? How can we ensure these treatments are safe, effective, and accurate?

1.3   Purpose of Dissertation

There are no standard guidelines for radiation therapy clinics planning to treat synchronous multiple lung lesions with VMAT SBRT. **This dissertation aims to create a protocol for the fast, safe, effective and accurate treatment delivery of synchronous multiple lung lesions using single-isocenter VMAT SBRT.** The proposed protocol described in this dissertation will simplify the treatment planning and delivery, shorten the patient treatment course, improve patient compliance, reduce setup uncertainties and support the community with minimal experience treating multiple lung lesions with SBRT.

1.4   Thesis Organization and Clinical Innovations

Chapter 2 is a dosimetric comparison of two treatment planning techniques frequently used in our clinic for two lesion lung SBRT. The first technique consists of two plans and two different isocenters, one for each lesion. The second technique plans for both lesions to be treated at the same time using a single-isocenter VMAT SBRT plan. The isocenter is placed approximately between the two lesions. **We hypothesized that the single-isocenter plans would be dosimetrically equivalent to multi-isocenter plans, but will improve treatment delivery efficiency**. It was found that although the two techniques provided dosimetrically equivalent plans, treating both lesions with a single isocenter reduced the beam-on time by a factor of 1.5. Efficiency of the treatment can improve both

patient compliance and clinic workflow. However, lining up both lesions on a single CBCT can be difficult and there is no evidence that the single isocenter plans were more accurate upon patient setup and delivery. Upon visualization of the setup of previous patient treatments, it was observed that small setup errors were possible due to the complications of aligning multiple lesions on a pre-treatment CBCT.

Clinical Innovation #1: Creation of a novel method for simulating patient setup errors in six dimensions.

Our current treatment planning system (TPS) is limited to simulate four dimensions (3 translational and 1 rotational), providing disparities with actual treatment delivery. Therefore, to account for all six dimensions of patient setup uncertainties, we have developed a novel registration approach utilizing transformation matrices created with image registrations. Studies that have demonstrated dosimetric effects of patient setup errors have relied on external programs created by the user or "third-party" programs that are bought by the department. A script was written in MATLAB (Appendix 2) which allows for patient images to be transformed which can then be brought into the TPS for dose calculation while preserving all treatment planning parameters, including beam geometry, MLC positions, and algorithms. This method allows for quick, easy, and accurate quantification of the dosimetric effects of patient misalignment. This method has already been implemented by other users in clinical research for treatment sites including multi-lesion brain stereotactic radiosurgery (SRS) and prostate SBRT.

Thus, using this novel simulation method (**Clinical Innovation #1**), **Chapter 3** aims to quantify the loss of target coverage due to patient set up uncertainties in the treatment of synchronous multiple lung lesions using single-isocenter VMAT SBRT. **We**

hypothesized that small patient setup uncertainties could lead to clinically unacceptable target coverage loss. Using this clinically realistic approach, it was determined that target coverage loss is possible due to the setup errors resulting from misalignment of multiple lesions on a pre-treatment CBCT. This method was tested on 26 previously treated patients with two lung lesions each. This deviation from planned target coverage was found to be 27.4% on average, but as much as 72% for smaller lesions. Consequently, the largest deviations from planned coverage and desired BED were seen for the smallest targets (<10 cc), some of which received <100 Gy BED, delivering suboptimal SBRT dose. In order to minimize the consequences of these setup errors and to provide more accurate and flexible patient treatments, a novel treatment method was created.

Clinical Innovation #2: Creation of Restricted Single-Isocenter Stereotactic Body Radiotherapy (RESIST) treatment planning method to minimize setup uncertainties.

Chapter 4 presents a novel treatment technique, RESIST (**Clinical Innovation #2**). **We hypothesized that RESIST could be used to minimize the patient setup errors possible in the treatment of multiple lesions using a single isocenter while providing efficient treatments**. RESIST utilizes a single isocenter placed at the mediastinum. This allows a plan to be created for each tumor, while allowing both tumors to be treated sequentially during the same session. It uses novel features in Eclipse TPS with dynamic conformal arc (DCA)-based dose and user-controlled field aperture shape before VMAT optimization. This method can be followed by treatment planners to produce consistent plans and more flexible treatment delivery. RESIST was tested using 21 patients with two lesions each. This is the first step-by-step protocol for treatment of multiple lung lesions

with VMAT SBRT. RESIST increases the accuracy of single-isocenter treatments and the subsequent patient setup. This technique is fully supported by our clinical Radiation Oncologists and has been clinically implemented.

Clinical Innovation #3: Automation of the RESIST methodology (*a*-RESIST), the first adaptable automated treatment planning strategy for synchronous multiple lung lesion SBRT. This automated RESIST method is clinic specific and can be adapted to fit the planning and delivery preferences of the clinic. The *a*-RESIST method reduces treatment planning time, reduces inter-planner variability, and standardizes multi-lesion lung SBRT treatments.

In **Chapter 5**, RESIST was scripted and automated in Eclipse TPS (Appendix 3) to allow for efficient and accurate treatment planning (**Clinical Innovation #3**). **We hypothesized that *a*-RESIST could quickly produce acceptable and consistent treatment plans for two lung lesion VMAT SBRT.** Automation includes beam geometry, algorithms selection, and integration of an in-house trained dose volume histogram estimation model to increase the quality and consistency of the plans. The *a*-RESIST method provides guidance for inexperienced planners by standardizing beam geometry and plan optimization. To demonstrate feasibility of *a*-RESIST, 10 patient plans with two lung lesions, previously treated with single-isocenter VMAT, were compared. *a*-RESIST not only exhibited similar plan quality to the clinical plans, it significantly reduced the treatment planning time to less than 20 minutes and provided a higher dose to the lung tumors. This treatment delivery framework allows all patients who are to be treated with SBRT to multiple lung lesions to be treated efficiently and effectively. Automated planning

is only recently available and this is the first proof of concept for lung SBRT automated planning.

Finally, **Chapter 6** discusses the limitations of this study and future research directions utilizing the innovative techniques and tools created in this study.

CHAPTER 2. EVALUATION OF PLAN QUALITY AND TREATMENT EFFICIENCY FOR SINGLE-ISOCENTER/TWO-LESIONS LUNG STEREOTACTIC BODY RADIATION THERAPY

Abstract

Our goal is to evaluate the plan quality and treatment delivery efficiency of single-isocenter/two-lesions volumetric-modulated arc therapy (VMAT) lung stereotactic body radiation therapy (SBRT). Eight patients with two peripherally located early-stage non-small-cell-lung cancer (NSCLC) lung lesions underwent single-isocenter highly-conformal non-coplanar VMAT SBRT treatment in our institution. A single-isocenter was placed between the two lesions. Doses were 54 Gy or 50 Gy in 3 and 5 fractions, respectively. Patients were treated every other day. Plans were calculated in Eclipse with AcurosXB algorithm and normalized to at least 95% of the planning target volume (PTV) receiving 100% of the prescribed dose. For comparison, two-isocenter plans (isocenter placed centrally in each target) were created. Conformity indices (CIs), heterogeneity index (HI), gradient index (GI), gradient distance (GD), and D_{2cm} were calculated. The normal lung V5, V10, V20, mean lung dose (MLD) and other organs at risk (OARs) doses were evaluated. Total number of monitor units (MUs), beam-on time and patient-specific quality assurance (QA) results were recorded. The mean isocenter to tumor distance was 6.7±2.3 cm. The mean combined PTV was 44.0±23.4 cc. There was no clinically significant

difference in CI, HI, GD, GI, D_{2cm} and V20 including most of the OARs between single-isocenter and two-isocenter lung SBRT plans, evaluated per RTOG guidelines. However, for single-isocenter plans as the distance between the lesions increased, the V5, V10 and MLD increased, marginally. The total number of MUs and beam-on time was reduced by a factor of 1.5 for a single-isocenter plan compared to a two-isocenter plan. The single-isocenter/two-lesions VMAT lung SBRT QA plans demonstrated an accurate dose delivery of 98.1±3.2% for clinical gamma passing rate of 3%/3 mm. The SBRT treatment of two peripherally located lung lesions with a centrally placed single-isocenter was dosimetrically equivalent to two-isocenter plans. Faster treatment delivery for single-isocenter treatment can improve patient compliance and reduce the amount of intra-fraction motion errors for well-suited patients.

2.1   Introduction

For medically inoperable stage I/II non-small-cell lung cancer (NSCLC) patients, several Phase I/II trials have shown that the use of SBRT treatment for solitary lung lesions representing the primary tumor mass is safe, effective and has a high cure rate comparable to surgery.[1-7] In these studies, medically inoperable patients with early-stage NSCLC who underwent stereotactic body radiotherapy (SBRT) had 3-year primary tumor local control rates of up to 98% and a low risk of treatment-related toxicity.

In the setting of either multiple primary lung cancers or limited metastatic lesions to the lungs (oligometastastic), SBRT presents a relatively new treatment opportunity. Optimal treatment planning must consider microscopic disease extension around the visible mass and allow for tumor movement, primarily due to respiration. Multiple metachronous or synchronous lung cancers are relatively common and have been managed

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by SBRT.[8] Based on Phase I/II trials of SBRT in the management of oligometastatic lung lesions, for patients with one to three tumors, up to five tumors (with curative intent) and more than five tumors with palliative treatment have been reported.[9,10] Rusthoven and colleagues treated thirty-eight patients, 63 total tumors, with lung SBRT of total dose of 48-60 Gy in 3 fractions. Actuarial local control rates at 1- and 2-year after SBRT was 100% and 96%, respectively.[10]

SBRT to multiple lung lesions presents with technical challenges and can be treated either sequentially with separate treatment plans or synchronously to all lesions. However, the location and geometry of synchronous plans can be challenging since minor inaccuracies of patient setup can result in geometric misses. Attention must be paid to overlapping doses to organs at risk (OARs) and respiratory control is critical since different parts of the lung can move independently. Sequential treatment plans for each individual tumor, using a multi-isocentric technique, requires relatively longer planning and treatment delivery time. Safe and effective delivery of SBRT to the lung requires precise, highly conformal treatment planning and delivery techniques.[11-15] In the past decades, treatment techniques for lung SBRT included Linear accelerator-based 3D-conformal radiation therapy, intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT) (RapidArc,Varian Inc.), CyberKnife and helical Tomotherapy (Accuray Inc.). However, as the complexity of the technology has evolved, treatment has required very high total monitor units (MU) and relatively long treatment times to deliver a highly conformal plan and spare OARs.[16-18]

With the recent technological advances, VMAT may provide highly-conformal radiation dose delivery with faster delivery times.[19-22] VMAT lung SBRT simultaneously

optimizes gantry speed, multi-leaf collimator (MLC) position and high dose-rate (FFF, flattening filter free mode) to provide highly-conformal dose distributions to the planning target volume (PTV) while minimizing dose to adjacent OARs. Reducing treatment time would improve patient compliance which helps reduce error due to motion, and promote more efficient clinic flow. For multiple brain metastases, recent studies have shown that single-isocenter VMAT can provide highly conformal radiosurgical dose distributions, excellent plan quality and safe and faster treatment delivery compared to conventional multi-isocenter technique.[23-25] However, there is little literature in the medical physics community on the treatment of multiple lung lesions using single-isocenter VMAT-SBRT technique.

A few studies have examined the use of single-isocenter SBRT for multiple lung lesions. A study by Trager *et al* discusses the use of a technique that utilizes a single-isocenter with distinct optimizations for extracranial radiosurgery.[26] Gulam *et al* examined six patients and found that the criteria set forth by Radiation Therapy Oncology Group (RTOG) study 0915 protocol was met with regard to CI, but not for some other critical dosimetric parameters.[27] A retrospective study of eleven patients by Quan *et al* showed no difference in multiple dosimetric parameters between single-isocenter VMAT plans (four single-isocenter VMAT plans were compared) and multi-isocenter intensity-modulated SBRT to the lung.[28] Still, the ability of a single-isocenter treatment to two or more lung lesions to deliver curative treatment plans in adherence with RTOG dosimetric compliance criteria has not been fully explored. In this report we present our recently adopted treatment method utilizing single-isocenter VMAT plan for SBRT of two lung lesions evaluated per RTOG protocols.[12-14] For completeness, the original single-isocenter lung SBRT plans and

retrospectively generated conventional two-isocenter lung SBRT plans were compared via their protocol compliance, plan quality, dose to critical structures, treatment delivery efficiency and accuracy.

2.2 Materials and Methods

2.2.1 Patient setup and Target Delineation

A total of eight patients were included in this retrospective study, all of whom had two peripherally-located Stage I NSCLC lesions. The patients were immobilized using Body Pro-Lok^{TM} platform (CIVCO system, Orange City, IA) in the supine position with their arms above their head with abdominal compression when possible, potentially reducing diaphragmatic motion to less than or equal to 1.0 cm. Conventional 3D CT scans and for patients unable to tolerated the compression, respiration-correlated 4D CT scans, were acquired on a GE Lightspeed 16 slice CT scanner (General Electric Medical Systems, Waukesha, WI) with 512×512 pixels at 2.5 mm slice thickness. Varian's Real Time Position Management Respiratory Gating System (version 1.7) was used for collection of 4D CT data. All 10 phases of 4D CT slices and respiratory motion signal were transferred to an Advantage 4D Workstation (General Electric Medical Systems, San Francisco, CA), where the maximum intensity projection (MIP) images were generated after a phase binning of the 4D CT images. In addition to the MIP images, the motion of both tumors was evaluated by an experienced physicist to affirm synchronous tumor motion that was less than 1 cm. The regular 3D CT scan and the MIP images were imported into the Eclipse treatment planning system (TPS) (version 13.0, Varian Medical Systems, Palo Alto, CA) and co-registered for target contouring. Gross tumor volumes (GTV) were delineated on

the 3D CT images and, for 4D CT patients, internal tumor volumes (ITV) were delineated on the 3D CT images with references to the MIP images. Planning target volumes (PTV) were generated by adding non-uniform 5-10 mm margins to the GTV or uniform 5 mm margin to the ITV to accommodate the patient setup uncertainties based on tumor size, location and synchronous tumor motion. The critical structures, such as bilateral lungs excluding the GTV/ITV (normal lung), spinal cord, ribs, heart, great vessels, esophagus, and skin were delineated on the 3D CT images.

2.2.2 Treatment Planning

2.2.2.1 Clinical Single-Isocenter VMAT Plan

Highly conformal, clinically optimal VMAT treatment plans were generated using 3-4 non-coplanar partial arcs (5-10º, couch kicks were used for arcs) for the Truebeam linear accelerator (Varian, Palo Alto, CA) with millennium MLC and a 6MV-FFF (1400MU/min) beam. A single-isocenter was placed approximately between the two lesions. As the isocenter location does not need to be exactly in the middle of the lesions, an offset allowing for the gantry to rotate in a partial arc can be made. For those arcs, collimator angles were chosen in such a way that the opening of the MLC between tumors was minimized while the gantry rotates around the patient. Additionally, jaw tracking was used to further minimize the out of field leakage dose. The isocenter to tumors distance was the maximum 3D-linear distance from the single-isocenter location to the geometric center of the individual tumor/isocenter. This distance was calculated in the TPS using the x-, y-, and z- primary coordinates of the tumor centers. This distance was estimated to evaluate the normal lung doses as a function of isocenter distance from the targets. A dose

of 54 Gy or 50 Gy in 3 and 5 fractions, respectively, was prescribed to the PTV D95% and planned such that the maximum dose in the GTV was about 120%. All clinical treatment plans were calculated using the Eclipse TPS with Acuros-XB (version 13.6.0, Varian Medical Systems, Palo Alto, CA) algorithm on the 3D CT images for heterogeneity corrections with a $2.0 \times 2.0 \times 2.0$ mm^3 dose calculation grid-size. Dose to medium reporting mode was selected. All clinical plans were inversely optimized using variation of gantry rotation speed, dose rate and MLC positions. The generalized normal tissue objective (NTO) parameters were used to control the gradients for single-isocenter clinical plan. As recommended by Varian, in our department, we used the following NTO parameters for lung SBRT plans: NTO with high priority of 150 with distance to target border of 0.1 cm. Start dose of 100.0% and fall dose of 40% was used with 0.5 fall factor. Moreover, the ring structures of 5 mm, 10 mm and 20 mm annulus from each lesion with 5 mm gaps were generated to enforce the high dose regions (typically enforcing maximum 120% hotspot inside each ITV) and minimize the intermediate dose spillage. All the planning objectives were per RTOG 0915, RTOG 0813 or RTOG 1021 guidelines. The patients were treated every other day per lung SBRT protocol.

2.2.2.2 Two-Isocenter VMAT Plan

For comparison, the SBRT treatment plans for all patients were retrospectively re-planned with a conventional two-isocenter approach. Individual isocenters were placed in the geometric center of each tumor. For each target, the plans were generated using 3-4 non-coplanar partial arcs, similar to single-isocenter plan. Collimator rotations and jaw tracking were applied. The plan for the first tumor (PTV1) was first computed using same

RTOG guidelines as described before. The plan for PTV1 was then used as the base-plan for generating the plan for the second tumor (PTV2) in order to allow full scatter contributions from both plans. All the planning objectives used were the same as the single-isocenter plan including the NTO parameters and ring structures. Dosimetric parameters for the target coverage and the adjacent OARs, including normal lung, were evaluated.

2.2.3 Plan Evaluation

Each plan was evaluated for the target coverage and the dose to OARs. For example, using the percentage prescribed isodose volume and target size, the RTOG conformity index (CI) was calculated as follows:[29]

$$RTOG\ CI = \frac{Rx\ Isodose\ Volume}{PTV\ volume} \tag{2.1}$$

Ideally, CI = 1.0, implying a perfectly conformal plan. The RTOG recommendation for the CI is < 1.2 with 1.2-1.5 being acceptable with minor deviations. In addition, the Paddick conformation number (CN) was calculated by:[30]

$$Paddick\ CN = \frac{(TV_{PIV})^2}{(TV*PIV)} \tag{2.2}$$

Where TV_{PIV} is the target volume covered by the prescription isodose volume, TV is the target volume and PIV is the prescription isodose volume. CN = 1.0 would be ideal. The heterogeneity index (HI) was determined by;

$$HI = \frac{D10\%}{D95\%} \tag{2.3}$$

Where D10% is the dose to the hottest 10% of the PTV and D95% is the dose to the 95% of the PTV coverage. The intermediate dose spillage was evaluated by using, gradient index (GI), D_{2cm} and gradient distance (GD). The GI was given by;

$$GI = \frac{R50\%}{R100\%} \qquad \qquad (2.4)$$

Where R50% is the ratio of 50% prescription isodose volume to the PTV and R100% is the ratio of 100% prescription isodose volume to the PTV. Per RTOG, depending on the target size, a GI of 3.0-6.0 is desirable. Similarly, D_{2cm} is the maximum dose, in percent of dose prescribed, at 2 cm from the PTV in any direction; and the GD, is the average distance from 100% prescription dose to 50% of the prescription dose. Although, RTOG only recommended normal lung, V20 < 10% (10-15% was acceptable with minor deviations), we have evaluated V5, V10 and mean lung dose (MLD) for normal lung for all plans.

2.2.4 Dose to Other OARs

In addition to the lung dose, all the clinical single-isocenter plans were evaluated for dose to spinal cord, heart, esophagus, trachea, ribs and skin per RTOG guidelines. The dose volume histogram parameters were compared between the single-isocenter and the two-isocenter plans. Data was assessed for normality, then the mean and standard deviation values for each of the dose metrics were compared using Student's t-tests (Microsoft Excel, Microsoft Corp., Redmond, WA) or Mann-Whitney test (Minitab, Minitab LLC, Chicago, IL) for single-isocenter vs two-isocenter computed dosimetric parameters for the OARs dose tolerances using an upper bound of p-value < 0.05.

2.2.5 Delivery Efficiency and Accuracy

The dose delivery efficiency of each lung SBRT plan was evaluated based on total number of MU and actual beam-on time. For the single-isocenter plan, actual beam on time

was recorded at the treatment machine while delivering the VMAT-SBRT QA plan. Delivery accuracy of the VMAT-SBRT QA plan was evaluated by physically measuring the 2D dose distribution of each plan using an Octavius phantom (PTW, Freiburg, Germany). All QA plans were delivered at the machine the day before the patient's 1st treatment. The measured cumulative 2D dose plan was compared with the computed dose distributions calculated on the Octavius QA phantom plan by the TPS. Upon completion of delivered dose, data were analyzed with Octavius MEPHYSTO Navigator (VeriSoft Patient Plan Verification, Version 6.3, PTW) using the standard clinical gamma passing rate criteria of 3%/3mm maximum dose difference and distance-to-agreement (DTA) with 10% threshold as well as point dose. Since the two-isocenter plans were not used for patient treatment, no VMAT QA was done. The beam on time was estimated by using dose rates of 1400MU/min for these plans.

2.3   Results

2.3.1   Target Coverage and Normal Lung Dose

All patients were treated with a single-isocenter VMAT plan in our clinic, which utilized 2-4 non-coplanar partial arcs. The prescription dose was 50-54 Gy in 3-5 fractions for at least 95% of the PTV receiving 100% of the prescribed dose. The single-isocenter to tumors distance was calculated in the TPS using the x-, y-, and z- primary coordinates of the tumor centers, as described above. The isocenter to tumor distance was approximately 3.7 to 9.6 cm (mean, 6.7 ± 2.3 cm). The mean combined PTV was 44.0 ± 23.4 cc (range, 20.5-91.8 cc). The DVHs for both single-isocenter and two-isocenter treatment plans are shown in **Figure 2.1** for patient #8. In this case, both planning approaches produced

dosimetrically equivalent plans. However, the treatment delivery time for the single-isocenter technique is less than the two-isocenter technique by a factor of 1.5. That was just a reported treatment delivery time, the actual patient set up and verification for the second isocenter with two-isocenter plan would take extra-time, prolonging the treatment delivery. The estimated time for initial patient setup on the machine is about 10 minutes and the estimated time to complete one CBCT is 1 minute followed by another about 3 minutes for tumor matching and applying shifts. Setup and imaging for the second isocenter plan is estimated at an additional 8 minutes.
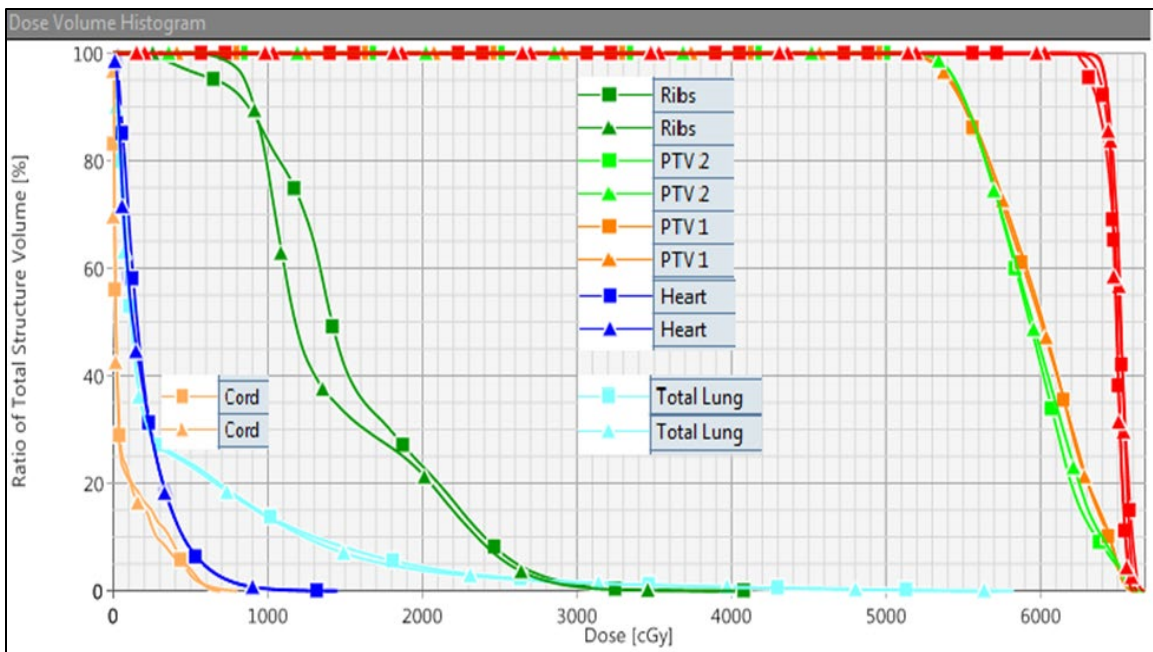
Figure 2.1: The dose volume histogram comparison for the target coverage of Patient #8 (for both PTV1 and PTV2).
The ITVs (red) and a few OAR such as total normal lung (light blue), heart (dark blue), ribs (green) and spinal cord (orange) are shown in **Figure 2.1** for patient #8. Prescription dose was 54 Gy in 3 fractions. The square symbols representing the single-isocenter plan and the triangle symbols representing the two-isocenter plan. Both plans were normalized to at least 95% of PTV received 100% of the prescribed dose. In this case, the isocenter to tumors distance was about 4 cm; the dosimetrically equivalent plans were generated using single-isocenter technique, as demonstrated, with similar target coverage and dose to the OARs.

Figure 2.2 displays a sagittal view of both single-isocenter and two-isocenter treatment plans for the same patient (#8). In this case, the normal lung V5 and V10 were similar; V20 was slightly higher with single-isocenter plan compared to two-isocenter plan. However, both plans met the RTOG compliance criteria for the target coverage (see **Table 2.1**), normal lung and the other OARs dose tolerances.
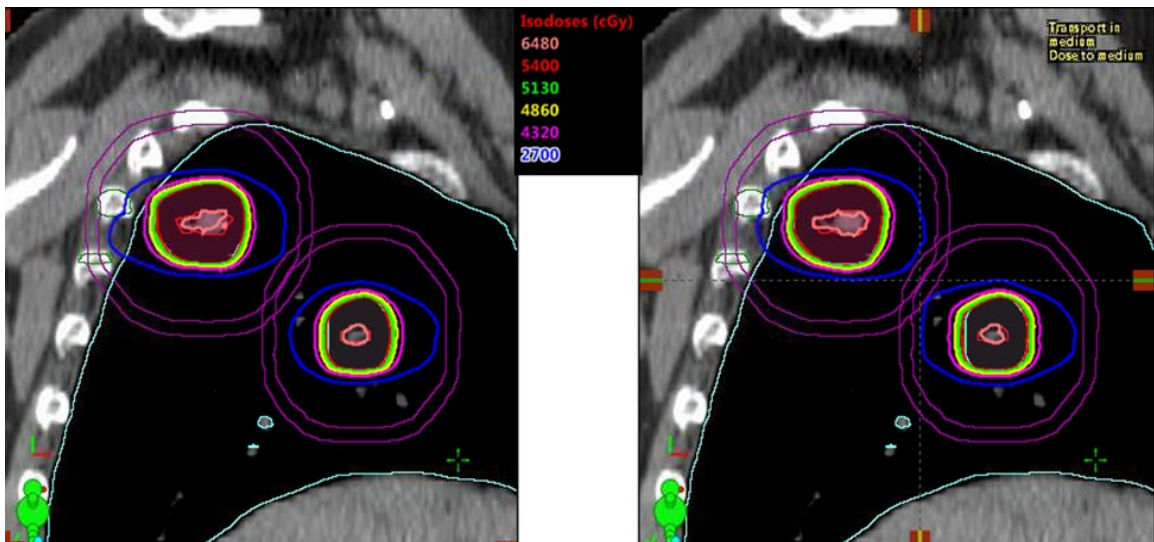
Figure 2.2: Comparison of isodose distributions in sagittal view for patient #8 generated via single-isocenter and two-isocenter plans.
In the right panel a single-isocenter location is shown by the intersection of the cross-hair; in the left panel two-isocenter plan sum is shown for the both targets (PTV1 and PTV2). Target volumes contoured include both ITVs (red, innermost) followed by PTVs (orange and green, outermost). Higher isodose lines, such as 54 Gy (100%), 51.3 Gy (95%), 48.6 Gy (90%), 43.2 Gy (80%), exhibit sharp dose fall off for the both plans, including 27.0 Gy (50%) isodose line (blue). In both plans, the hotspot, 120% isodose line (thick-orange) was shown in the middle of the ITV. Other OARs such as ribs and lung contours are shown. Purple color rings were contoured to calculate D_{2cm} (%) for each target.

Detail of the plan comparison for target coverage including tumor location and the tumors distance from the isocenter are shown in **Table 2.1**.

Table 2.1: Comparison of plan evaluation parameters for single-isocenter vs two-isocenter treatment plans of all eight lung SBRT patients.

Patient no.	Plan type and Tumor location	Combined PTV (cc)	RTOG CI	Paddick CN	HI	GI	D_{2cm} (%)	GD (cm)	Isocenter to tumors distance (cm)
1	Lesion 1, LUL	5.0	1.08	0.75	1.16	6.6	47.9	0.90	5.2
	Lesion 2, LLL	16.1	1.01	0.84	1.17	4.1	41.4	0.95	
	Two-iso (plan sum)	21.1	1.05	0.81	1.18	4.8	47.6	0.97	
	Single-isocenter		1.05	0.79	1.16	5.0	56.5	1.20	
2	Lesion 1, LUL	30.7	1.01	0.83	1.11	4.2	57.3	1.21	9.5
	Lesion 2, RUL	43.6	0.99	0.84	1.22	3.6	55.2	1.18	
	two-iso (plan sum)	74.3	1.02	0.80	1.23	4.2	60.2	1.24	
	single-isocenter		1.02	0.82	1.21	4.6	62.8	1.75	

Table 2.1 (Continued)

3	Lesion 1, LLL	16.2	1.05	0.76	1.17	4.8	50.8	1.05	9.6
	Lesion 2, RUL	34.9	1.19	0.68	1.08	5.5	69.2	1.43	
	Two-iso (plan sum)	51.1	1.26	0.70	1.26	5.4	76.3	1.49	
	Single-isocenter		1.29	0.67	1.39	6.4	80.5	1.78	
4	Lesion 1, LLL	8.6	1.03	0.80	1.17	4.8	43.2	0.87	4.6
	Lesion 2, RUL	26.6	1.01	0.84	1.20	4.1	51.8	1.11	
	Two-iso (plan sum)	35.2	1.07	0.76	1.22	4.9	55.9	1.21	
	Single-isocenter		1.16	0.74	1.18	5.5	53.6	1.45	
5	Lesion 1, LUL	80.9	0.99	0.83	1.15	3.3	56.1	1.34	8.4
	Lesion 2, RLL	10.9	1.02	0.72	1.21	5.0	48.7	0.97	

Table 2.1 (Continued)

	Two-iso (plan sum)	**91.8**	**1.01**	**0.81**	**1.17**	**3.9**	**57.6**	**1.38**	
	Single-isocenter		1.02	0.81	1.16	4.1	56.4	1.68	
6	Lesion 1, Ant. LLL	19.6	1.04	0.77	1.16	4.3	49.3	1.02	4.8
	Lesion 2, Post. LLL	7.7	1.20	0.63	1.20	6.7	44.8	1.00	
	Two-iso (plan sum)	27.3	1.09	0.72	1.19	5.6	50.3	1.11	
	Single-isocenter		1.03	0.76	1.17	5.3	48.7	1.38	
7	Lesion 1, RUL	13.6	1.04	0.67	1.10	5.3	48.0	1.04	4.9
	Lesion 2, LUL	17.2	1.02	0.78	1.05	4.5	48.6	1.03	
	Two-iso (plan sum)	30.8	1.05	0.62	1.11	5.6	51.4	1.09	

Table 2.1 (Continued)

	Single-isocenter		**1.04**	**0.70**	**1.16**	**5.2**	**48.6**	**1.43**	
8	Lesion 1, Post. RUL	13.5	0.99	0.83	1.19	4.3	46.5	0.94	3.7
	Lesion 2, Ant. RUL	8.0	1.00	0.80	1.18	5.1	45.4	0.90	
	Two-iso (plan sum)	21.5	1.04	0.81	1.19	4.8	47.0	1.13	
	Single-isocenter		1.03	0.81	1.19	5.1	48.9	1.23	

All lung SBRT plans were acceptable per RTOG guidelines for the high (CI, HI) and intermediate dose spillage (GI and D_{2cm}). In addition, similar results were shown for the Paddick CN between the two plans. No clinically significant difference was observed in CI, HI, GD, GI and D_{2cm} between single-isocenter and two-isocenter lung SBRT plans evaluated per RTOG guidelines by the treating physician. However, the GD values were slightly higher with single-isocenter plan of about 3-5 mm, especially for the larger tumor distance from the isocenter compared to two-isocenter plan. Clinical significance of higher GD values, compared to relatively faster delivery of single-isocenter plan, may need to be explored.

The absolute differences between single-isocenter and two-isocenter plans for normal lung V20, V10, V5 and MLD were listed in the **Table 2.2**. All patients had V20 <10-15 % for both treatment plans. A statistically insignificant difference (p = 0.09) was found for the normal lung V20 between two plans. However, V10, V5 and MLD increases slightly with single-isocenter plan compared to two-isocenter plan, giving statistically significant differences (p = 0.03, 0.01 and 0.03, respectively). Statistically significant p-values are highlighted in bold (see **Table 2.2**). Although, V10, V5 and MLD shown statistically significant differences, the absolute differences were on the order of less than 0.8% for V20, 2.8% for V10 and 6.5% for V5) and less than 60 cGy for MLD, on average, therefore, we do not expect the differences would be clinically significant.

Table 2.2: Normal lung doses statistics between single-isocenter and two-isocenter plans for all 8 lung SBRT patients. Data is presented as mean ± standard deviation (range) and p-values.

Plan type	V20 (%)	V10 (%)	V5 (%)	MLD (Gy)
two-isocenter	6.7 ± 2.7 (2.9 to 12.2)	18.2 ± 6.7 (7.2 to 29.9)	29.7 ± 10.4 (21.1 to 46.5)	5.4 ± 1.4 (3.3 to 8.2)
single-isocenter	7.5 ± 13.4 (3.2 to 13.5)	21.0 ± 8.9 (7.5 to 36.8)	36.1 ± 13.8 (18.2 to 61.7)	6.0 ± 1.8 (3.7 to 9.2)
p-value	*p* = 0.09	*p* = **0.03**	*p* = **0.01**	*p* = **0.03**

The ratios between single-isocenter and two-isocenter plans for the V20, V10 and V5 as a function of isocenter to tumors distance can be seen in **Figure 2.3**. When the isocenter to tumor distance increased, the low dose volume to the normal lung, such as V5 and V10, was slightly increased. However, 2 of 8 patients had lower values of V20 with single-isocenter plan.
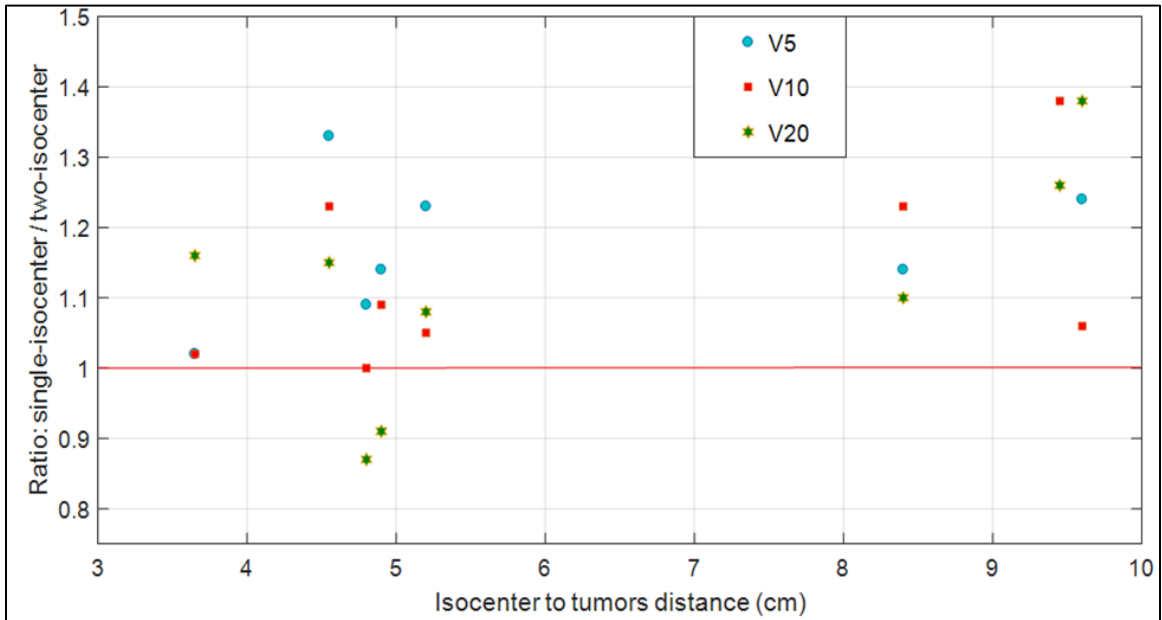
Figure 2.3: For all 8 lung SBRT patients, the ratios of V5, V10 and V20 of normal lung doses calculated by single-isocenter and two-isocenter plans as a function of isocenter to tumors distance.
For the identical planning objectives, the single-isocenter plan gave slightly higher values of V5, V10 and V20 by a factor of 1.2, 1.1 and 1.1, on average, respectively, compared to two-isocenter plan. This suggests that comparable dosimetric parameters can be obtained for the normal lung. However, single-isocenter plan would have considerably faster treatment delivery by an almost a factor of 2, eliminating the setup and verification time for the 2nd isocenter plan.

2.3.2   Dose to Other OARs

A comparison of other OARs dosimetric parameters for single-isocenter and two-isocenter plans for all 8 lung SBRT patients is presented in **Table 2.3**. Critical organs such as spinal cord (D_{max}, and $D_{0.35cc}$), heart (D_{max} and D_{15cc}), esophagus (D_{max} and D_{5cc}), trachea (D_{max} and D_{4cc}), ribs (D_{max} and D_{1cc}) and skin (D_{max} and D_{10cc}) were evaluated per SBRT protocol guidelines.

Table 2.3: Average values of absolute dose differences between single-isocenter and two-isocenter plans for parameters of the OARs for all 8 lung SBRT patients. Ratio=single-isocenter/two-isocenter.

OARs	Parameters	Mean ± SD (Gy)	Range (Gy)	Ratio*	*p*-value
Spinal cord	D_{max}	0.5 ± 1.1	-0.9 to 2.9	1.05 ± 0.13	*p* = 0.25
	$D_{0.35cc}$	0.5 ± 1.1	-0.7 to 2.7	1.03 ± 0.13	*p* = 0.62
Heart	D_{max}	0.9 ± 3.0	-5.4 to 5.0	1.07 ± 0.14	*p* = 0.42
	D_{15cc}	2.0 ± 1.2	0.0 to 3.9	1.15 ± 0.09	***p* = 0.002**
Esophagus	D_{max}	2.1 ± 3.9	-4.5 to 3.5	1.13 ± 0.23	*p* = 0.18
	D_{5cc}	1.9 ± 3.3	-3.3 to 4.6	1.18 ± 0.31	*p* = 0.15
Trachea	D_{max}	0.7 ± 1.8	-5.0 to 5.9	1.13 ± 0.27	*p* = 0.55
	D_{4cc}	-0.8 ± 1.8	-4.5 to 1.0	0.96 ± 0.27	*p* = 0.27
Ribs	D_{max}	0.0 ± 3.9	-5.1 to 7.4	0.99 ± 0.08	*p* = 0.98
	D_{1cc}	-0.1 ± 2.2	-4.5 to 2.4	0.99 ± 0.07	*p* = 0.91
Skin	D_{max}	-0.6 ± 1.5	-3.9 to 0.6	0.97 ± 0.07	*p* = 0.28
	D_{10cc}	1.2 ± 1.1	-0.4 to 2.8	1.11 ± 0.08	***p* = 0.02**

Absolute dose differences = single-isocenter–two-isocenter. The negative sign indicates that the results of the two-isocenter plans were larger than those of single-isocenter plans. Statistically significant p-values are highlighted in bold.

The average values of maximum doses to spinal cord, ribs and skin were similar (see the average of the ratios in **Table 2.3**) between the two planning methods. Although, the average values of the absolute dose differences and ratios for heart, esophagus and

trachea were slightly higher with single-isocenter plan, the average absolute dose differences were up to 1-2 Gy. While evaluating those plans per SBRT protocol guidelines, those values met the protocol criteria and, therefore, the differences were not deemed clinically significant. Almost all p-values were insignificant, except for dose to 15 cc of heart (p = 0.002) and dose to 10 cc of ribs (p = 0.02). Both the single-isocenter and two-isocenter plans were within clinically acceptable limits per RTOG.

2.3.3   Delivery Efficiency and Accuracy

For single-isocenter plans, the mean values of the total number of MUs and beam on time were 6014 (4013 to 10727) and 4.3 minutes (2.9 to 7.7 minutes). Compared to two-isocenter plans, the total number of MUs and beam on time were reduced by a factor of 1.5. Furthermore, with two-isocenter plans, the actual patient set up and verification for the second isocenter plan would take extra-time, prolonging the treatment delivery. The estimated time for initial patient setup on the machine for both techniques is about 10 minutes and the estimated time to complete one CBCT is 1 minute followed by another about 3 minutes for tumor matching and applying shifts. Setup and imaging for the second isocenter plan is estimated at an additional 8 minutes. In addition, lower total MUs could potentially deliver lower leakage dose. The complete details regarding number of MUs, beam-on time, VMAT QA gamma pass rates, and the measured point dose percent difference are found in **Table 2.4**. Since the isocenter location for single-isocenter is blocked by the MLC, the maximum point dose was measured in the middle of the targets where the maximum fluence was delivered off axis to the two targets and compared to the computed VMAT QA plan on Octavius phantom.

Table 2.4: The detailed information on total number of MUs and beam-on time for the both single-isocenter and two-isocenter plans for all 8 lung SBRT patients. The Octavius VMAT-SBRT QA pass rates and point dose measurements for single-isocenter plans were also shown.

Patient no.	Plan type	Total no. of MUs	Beam-on time (min)	Gamma pass rates 3%/3mm (%)	Point dose % diff. (%)
1	two-isocenter	10069	7.19	---	---
	single-isocenter	5777	4.13	99.3	0.9
2	two-isocenter	13198	9.43	---	---
	single-isocenter	10727	7.66	91.7	1.8
3	two-isocenter	9095	6.50	---	---
	single-isocenter	6607	4.72	100.0	1.5
4	two-isocenter	7185	5.13	---	---
	single-isocenter	6029	4.31	100.0	2.3
5	two-isocenter	6219	4.44	---	---
	single-isocenter	4093	2.92	99.4	0.3
6	two-isocenter	9047	6.46	---	---
	single-isocenter	5047	3.61	94.3	0.4
7	two-isocenter	5608	4.01	---	---
	single-isocenter	4149	2.96	100.0	0.4
8	two-isocenter	10500	7.50	---	---
	single-isocenter	5680	4.06	100.0	0.7
Mean ± SD	two-isocenter	8865 ± 2330	6.3 ± 1.7	---	---
	single-isocenter	6014 ± 1963	4.3 ± 1.4	98.1 ± 3.0	1.04 ± 0.7

The Octavius QA pass rates for the single-isocenter plan was 98.1 ± 3.0%, on average, for 3%/3mm clinical gamma pass rate criteria and the point dose measurement were within 1%, on average, suggesting accurate delivery of the lung SBRT plan. However, for patient #2, the gamma pass rates were around 92% for 3%/3mm criteria. In this case, both tumors were relatively large, and the tumor to isocenter distance was relatively large, around 9.5 cm. In addition, the tumors were located in bilateral lungs. Therefore, the MLCs have to travel a longer distance, providing sub-optimal VMAT QA pass rates. This suggests that exceeding 10 cm (isocenter to tumors distance) many not provide a clinically optimal

plan with single-isocenter. Since the two-isocenter plans were not used for actual patient's treatment we did not run VMAT QA for those plans.

2.4   Discussion

In this study, we have presented our initial clinical experiences of a fast treatment planning and delivery technique using single-isocenter VMAT plans for SBRT of two lung lesions following RTOG protocol guidelines.[12-14] Our single-isocenter VMAT plan for SBRT of two lung lesions uses 3-4 non-coplanar partial arcs. Transmission between individual MLC leaf ends travelling between the two tumors is estimated to be between 12-28%, which increases the low dose volume of the lung in between the tumors. Our technique reduces this dose with the use of jaw tracking and patient specific collimator angles. Single-isocenter VMAT-SBRT plans were highly-conformal and achieved adequate target coverage (see **Table 2.1** for CI, HI, Paddick CN, GI, D_{2cm} and GD) compared to conventional two-isocenter plans. For all patients, the single-isocenter plans met RTOG guidelines including normal lung V20 and were similar compared to two-isocenter plans. However, when the isocenter to tumor distance increased, the low dose volume to the normal lung, such as V5 and V10, was slightly increased as shown in **Figure 2.3**. In addition, the other OARs such as spinal cord, heart, esophagus, trachea, ribs and skin dose tolerances were also within protocol. The single-isocenter treatment was well tolerated with all patients. The beam on time was 4.3 minutes and VMAT-SBRT QA gamma passing rates were 98.1% (3%/3mm clinical gamma passing criteria), on average, demonstrating an excellent potential for a fast, reliable and accurate delivery of single-isocenter VMAT lung SBRT treatment for two lung lesions.

The single-isocenter plan for treating multiple lung tumors has been reported by a few investigators.[31,32] For instance, using both coplanar and non-coplanar 9 field IMRT (in Pinnacle TPS), Zhang *et al* compared those IMRT plans with helical Tomotherapy for single-isocenter/multi-target lung SBRT treatment.[31] The prescription was 60 Gy in 3 fractions. In their study, it was concluded that compared to IMRT, helical Tomotherapy gave better target coverage at the cost of overall 73.0 ± 20.6 minutes treatment time. However, IMRT treatment time was not reported. It was also highlighted that compared to IMRT plans, Tomotherapy plan also gave a relatively higher normal lung V5. Another study by Li *et al* reported that they treated two patients with single-isocenter lung SBRT plan for more than 5 lung metastases.[30] Their prescription doses were 48 Gy/8 fractions for Patient A (5 tumors) and 42 Gy/7 fractions for patient B (7 tumors). Plans were generated in Monaco TPS (CMS Software Inc., St Louis, MO) using a few partial-arcs and delivered with Elekta Axesse linear accelerator with 6MV beam (660MU/min). The beam on time for each treatment was about 10 minutes. Both patients were followed up, and the treatment was well tolerated by the patients with a minimal toxicity. In contrast, utilizing 6MV-FFF beam (in Eclipse) for a Truebeam Linac, our single-isocenter VMAT planning technique delivered a fast (average beam on time 4.3 min) and potentially effective treatment (curative high biological effective dose of >100-150 Gy for each lesion).

One potential concern for single-isocenter VMAT-SBRT plan for two lung lesions was low dose spill in the normal lung, such as V20, V10 and V5. Per RTOG recommendation, all our single-isocenter/two-lesions VMAT lung SBRT plans had V20 <10-15%. Moreover, normal lung V5 was maintained less than 40%, on average.[33-35] Although, in our experience when the isocenter to tumor distance increased, the normal

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lung V10 and V5 slightly increased, as expected, when compared to two-isocenter plan. Our treatment planning strategy favored minimizing normal lung dose during single-isocenter VMAT planning by optimizing patient specific collimator angles in conjunction with jaw tracking such that the leakage dose due to the leaf travel in between two tumors could be minimized. This could potentially help reduce severe lung toxicity with careful attention to V5 and V10 during plan optimization.

Another potential concern for single-isocenter VMAT plan was the patient set up errors, for example tumor motion and rotational errors. This may result in geographic miss and compromise the local tumor control rates. The single-isocenter/two-lesion VMAT plan isocenter was generally chosen at the midpoint of the two lesions, therefore, the isocenter distance between two lesions was evenly distributed. However, it would be difficult to find a perfect midpoint for non-coplanar lesions. The variability of respiratory patterns between the CT simulation and the time of treatment was studied by many researchers.[36-39] It has been reported in the literature that there were only small changes (within ±3 mm) due to intrafractional and interfractional motion while using conventional multi-isocenter lung SBRT treatment. Their mean patient set up time from tumor localization to the end of treatment CBCT scan was about 40 min.[38, 39] It was recommended that a 5 mm PTV margin was sufficient to address those motion errors. Furthermore, the spatial uncertainties for this kind of beam arrangement was discussed by Gary A. Ezzell for single-isocenter/multitarget cranial radiosurgery.[40] It was demonstrated that with a Truebeam CBCT the maximum spatial uncertainties were less than 1.5 mm at 10 cm distance from the isocenter tested using 12 target BBs in a phantom. Before delivering each SBRT treatment, a daily QA check on kilovoltage to megavoltage imaging isocenter coincidence was performed,

including IsoCalc test for precise and accurate target localization. Our IsoCalc localization accuracy for Truebeam was < 0.5 mm at isocenter. All the quality assurance procedures complied for SBRT treatment delivery. Our image guidance CBCT matching parameters (at Truebeam) were consistent with previous findings. Our average beam on time of about 4.3 minutes per treatment could potentially decrease the possibility of breathing changes from coughing or pain and making geographic miss unlikely, potentially improving patient stability.

In addition, due to rotational errors, for small targets and those away from the single-isocenter could potentially alter the dose distributions. For those highly conformal VMAT plans, the small deviation of motion error could potentially irradiate normal tissues, and it may increase the chance of radiation-induced toxicity or miss the target. Our attending physician has addressed this issue by individually reviewing these target volumes and the associated tumor motion pattern and by assigning appropriate ITV to PTV margins (usually 5 mm in the medio-lateral and anterior-posterior directions and 8 to 10 mm in superior-inferior direction) to accommodate potential tumor deformation. Moreover, great care has been taken by our treating physician and the physicist to address some of the above-mentioned issues, for example, being available for the patient set up (in the 3D, 4D CT simulation and each treatment), image guidance and CBCT matching and physically authorizing each treatment fraction for all patients.

In summary, each plan was rigorously evaluated using the dosimetric parameters listed in **Tables 1**, **2**, and **3**. All parameters were deemed acceptable for both single-isocenter and two-isocenter plans per SBRT protocol, suggesting that single-isocenter plans could be dosimetrically equivalent to two-isocenter plan with a faster and equally

effective treatment delivery which can be offered to well suited patients. In the future, these patients will be followed up clinically and evaluated for local control rates and treatment related toxicity such as the effect of normal lung dose as a function of isocenter to tumors distance. Moreover, single-isocenter VMAT plan for SBRT of lung for more than two lesions will be investigated.

2.5   Conclusion

This report presents our initial clinical experience with a single-isocenter for two-lesion SBRT procedure for lung tumors compared with conventional two-isocenter plans. Treatment of peripherally located two lung lesions with a centrally assigned single-isocenter was dosimetrically equivalent to two-isocenter plans. For single-isocenter plans, it was observed that as the distance between the lesions increased the normal lung V5, V10 and MLD somewhat increased. The single-isocenter technique was fast, accurate and well tolerated by all the patients, improving patient comfort and potentially reducing the amount of intra-fraction motion errors for well-suited patients. Clinical follow up of these patients is warranted to determine the tumor local control rates and treatment related toxicity.

CHAPTER 3. RISK OF TARGET COVERAGE LOSS FOR STEREOTACTIC BODY
RADIOTHERAPY TREATMENT OF SYNCHRONOUS MULTIPLE LUNG
LESIONS VIA SINGLE-ISOCENTER VOLUMETRIC MODULATED ARC
THERAPY

The following chapter has been adapted from a manuscript revised and under review for publication: Lana Sanford Critchfield, Mark Bernard, Marcus Randall, Ronald McGarry, Damodar Pokhrel, "Risk of Target Coverage Loss for Stereotactic Body Radiotherapy Treatment of Synchronous Lung Lesions via Single-Isocenter Volumetric Modulated Arc Therapy", *J Appl Clin Med Phys,* August 22, 2020.

Abstract

Treating multiple lung lesions synchronously via single-isocenter volumetric modulated arc (VMAT) stereotactic body radiation therapy (SBRT) improves treatment efficiency and patient compliance. However, aligning multiple lung tumors accurately on one single pre-treatment cone beam CT (CBCT) can be problematic. Tumors not correctly aligned could lead to target coverage loss. To quantify this potential target coverage loss due to small, clinically realistic setup errors, a novel simulation method was developed. This tool was used on twenty-six previously treated patients with two metastatic lung lesions. Patients were treated with 4D-CT based, highly conformal non-coplanar VMAT plans (clinical VMAT) with 6MV-flattening filter free (FFF) beam using AcurosXB dose calculation algorithm with heterogeneity corrections. A single isocenter was placed approximately between the lesions to improve patient convenience and clinic workflow. Average isocenter to tumor distance was 5.9 cm. Prescription dose was 54Gy/50Gy in 3/5 fractions. For comparison, a plan summation (simulated VMAT) was executed utilizing randomly simulated, clinically relevant setup errors, obtained from pre-treatment set up,

per treatment fraction, in Eclipse treatment planning system for each of the six-degrees of freedom within ± 5.0 mm and ± 2º. Simulations yielded average deviations of 27.4% (up to 72% loss) (p < 0.001) from planned target coverage when treating multiple lung lesions synchronously using a single-isocenter plan. The largest deviations from planned coverage and desired biological effective dose (BED10) were seen for the smallest targets (<10 cc), some of which received <100 Gy BED10. Patient misalignment resulted in substantial decrease in conformity and increase in the gradient index, violating major characteristics of SBRT. Statistically insignificant differences were seen for dose to normal tissues. The authors recommend alternative treatment planning strategies to minimize the probability of a geometric miss when treating small lung lesions synchronously with single-isocenter VMAT SBRT plans.

3.1   Introduction

Stereotactic body radiation therapy (SBRT) has become a standard of care for selected early stage non-small-cell lung cancer (NSCLC) patients.[1-4] Furthermore, SBRT of solitary primary or metastatic lung lesions is a fast, safe and effective treatment option with a high control rate comparable to surgery.[4] For elderly medically inoperable patients, SBRT treatment has been shown to be effective.[5] However, elderly patients or those with poor pulmonary function and multiple oligometastastic (< 5 lesions) lung lesions may not retain their treatment position for long SBRT treatment times. Traditional SBRT treatment to lung lesions requires an individual plan for each lesion with a separate isocenter placed in each, prolonging patient set up and treatment time. Treating multiple lung lesions synchronously with a single-isocenter plan, either using intensity modulated radiation therapy (IMRT) or volumetric arc therapy (VMAT), has been studied.[6-9] Single-

isocenter/multi-lesion VMAT lung SBRT treatments have been shown to be fast and efficient improving patient comfort[14-18] Additionally, treatment efficiency and dose build-up at the tumor-interface is improved with use of a flattening filter free (FFF) beam.[10-13] This faster treatment option could potentially reduce intrafraction motion errors and improve patient compliance.[14]

Despite the growing interest in single-isocenter/multi-lesion VMAT lung SBRT treatments, there is a decrement in accuracy when treating multiple lesions synchronously compared to treating the lesions individually. When each lesion is treated separately, the treatment plan has an isocenter in the center of the lesion, and daily conebeam CT alignment corrections can be made focusing on that lesion. Single-isocenter/multi-lesion VMAT plans are not robust against set up errors because one or all lesions could be offset from the single-isocenter location, potentially resulting in less accuracy. Moreover, in many treatment planning systems (TPS) including Eclipse TPS (Varian Medical Systems, Palo Alto, CA), there is no way to simulate residual set up errors in all six-degrees of freedom (6DoF) without using "third party" software. Herein is described a simple and clinically useful method for demonstrating the dosimetric effects of setup errors in Eclipse TPS. To simulate and quantify possible treatment inaccuracy, this tool uses simulation CT images for generating a lung SBRT treatment plan, identical beam data and original clinical treatment plan including dose calculation algorithm, without introducing additional sources of errors, thus only simulating the dosimetric effects of patient set up uncertainties. Utilizing this method, it is demonstrated that when treating multiple lung lesions with a single-isocenter VMAT-SBRT plan, small but clinically representative setup errors may result in unacceptable loss of target coverage and unintended dose to normal tissues.

This comparison was undertaken to quantify the dosimetric impact of residual set up errors on target coverage and collateral dose to adjacent organs-at-risk (OAR) in the context of single-isocenter VMAT SBRT treatment of multiple lung lesions. Lung SBRT literature suggests that a biological effective dose (BED10) of $\geq$ 100 Gy (α/β = 10 Gy) to each lesion is required for optimal tumor local control (LC) and overall survival.[19, 20] Olsen and colleagues reported clinical outcomes of 130 lung SBRT patients treated with 3 different dosing schemes. They demonstrated that lung SBRT treatments to 45 Gy in 5 fractions (85.5 Gy BED10) provided inferior tumor LC rate (50% LC at 2 years) compared to 50 Gy in 5 fractions (100% LC at 2 years) and 54 Gy in 3 fractions (91% LC at 2 years), suggesting that at least 100 Gy BED10 is necessary. Thus, in addition to evaluating the loss of target coverage, this simulation study compared planned versus simulated BED10 to each lesion.

3.2   Materials and Methods

After obtaining Institutional Review Board approval, 26 patients with two synchronous lung tumors who underwent single-isocenter VMAT lung SBRT treatment of 54 Gy in 3 fractions or 50 Gy in 5 fractions were included in this study.

3.2.1   Patient Setup and Contouring

Patients were immobilized using the Body Pro-Lok™ SBRT system (CIVCO, Orange City, IA) in the supine position with arms up. A free-breathing CT was obtained on a GE Lightspeed 16 slice CT scanner (General Electric Medical Systems, Waukesha, WI) with 512 × 512 pixel image size and 2.5 mm slice thickness in the axial helical mode.

Respiratory assessment and motion management included abdominal compression (n=21) or 4D-CT scan (n=5) utilizing Varian RPM system (version 1.7). The 3D-CT scan was brought into Eclipse Treatment Planning System (Version 15.6, Varian Medical Systems, Palo Alto, CA). Both gross tumor volumes (GTV's) were contoured on the 3D-CT. If a 4D-CT was obtained, an internal target volume (ITV=GTV) was contoured based on the registered 4D-CT reconstructed maximum intensity projection (MIP). The planning target volumes (PTV's) were created either by expanding a uniform margin of 5 mm from the ITV or in the case of no 4D-CT, 5 mm expansion of the GTV in the lateral direction and 10 mm expansion in the superior-to-inferior direction. The names of the PTVs (PTV 1 or PTV 2) were arbitrarily chosen by the treating physician. All planning was done on the free-breathing CT and Houndsfield units (HU) within the PTV were maintained per the CT dataset. Average PTV size was 20.4 ± 16.2 cc (4.7–80.9 cc). Distance to isocenter was determined by finding the coordinates of the PTV geometric center and calculating Euclidian distance in 3D geometry with the isocenter coordinates. Critical structures were contoured including lungs (right, left and combined), cord, heart, bronchus, trachea, esophagus, skin and ribs (right, left and combined). Tumor characteristics for the cohort are summarized in **Table 3.1**.

Table 3.1: Main tumor characteristics of the 26 lung SBRT patients included in this study. Each patient had 2 tumors. STD = standard deviation.

Parameters	Mean ± STD (range or n = no. of patients)
Tumor 1, PTV1 (cc)	22.0 ± 19.7 (5.0 – 80.9)
Tumor 2, PTV2 (cc)	17.5 ± 11.6 (4.7 – 43.6)
Prescribed dose to each lesion	54 Gy in 3 fractions (n = 7)
	50 Gy in 5 fractions (n = 19)
Isocenter to tumors distance (cm)	5.9 ± 2.5 (range: 2.1–11.5)
Tumor location (left/right/bilateral)	(n = 7 / 7 / 12)
Uninvolved lung (cc) = lungs minus both PTV	3696.4 ± 1059.7 (1921.6 – 6785.6)

3.2.2 Clinical Single-Isocenter VMAT Plans

For all 26 patients, single-isocenter VMAT lung SBRT plans were generated in Eclipse TPS for treatment on a Truebeam Linac (Varian Medical Systems, Palo Alto, CA) consisting of standard millennium 120 MLC and 6 MV-FFF (1400 MU/min) beam. A single isocenter was placed approximately midway between the two tumors. Doses were 54 Gy or 50 Gy in 3 or 5 fractions, respectively. Both PTVs (PTV 1 and PTV 2) were planned with dose prescribed to the 80% isodose line and optimized such that 95% of each PTV received 100% of the prescription dose. The maximum dose to the PTV fell inside the GTV. Full arcs (co-planar) were utilized for bilateral lung tumors and partial non-coplanar arcs utilized for uni-lateral lung tumors, with ± 5-10° couch rotations. Optimal collimator angles and jaw-tracking was chosen to reduce MLC leakage between each arc. Dose was calculated using Boltzmann transport based AcurosXB algorithm for heterogeneity corrections with dose to medium reporting mode.[21-23] Planning objectives followed RTOG guidelines.[24, 25] Each of the clinical VMAT plans was delivered to the patient in the clinic.

3.2.3 Simulated Single-Isocenter VMAT Plans

To evaluate patient setup uncertainties, clinically observable setup errors in all 6DoF were simulated in Eclipse TPS. Evaluation of pre-treatment cone beam CT scans for single-isocenter VMAT treatments allowed for determination of clinically representative random setup errors to be within ± 5 mm in the x-, y-, and z-direction and within ± 2° for pitch, yaw and roll. The 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. Since demonstrating the loss of target coverage due to setup errors in current Eclipse TPS in all 6DoF was not readily accessible, an in-house MATLAB (Math Works, MA USA) script (Appendix 2) and simulation method was developed in order to achieve the desired transformations and re-compute the simulated VMAT plan. The in-house script utilizes a RE DICOM file that is created with an image registration module in Eclipse. This RE DICOM file consists of the patient CT registered to itself, thus the transformation matrix between the two images will be null. The MATLAB script utilizes a random number generator to re-write the transformation matrix of one of the identical patient CT datasets to apply translations and rotations within the determined range of possible shifts. The random number generator utilized creates uniformly distributed random number, thus the transformation likely simulates the worst-case scenario for patient setup errors. The image registration workspace in Eclipse TPS allows for visualization of these rigid transformations in all 6DoF. This is repeated for the number of fractions, with the original plan copied to the transformed image. The result of the simulation process is a plan summation of all 3 or 5 randomly transformed treatment fractions that mimics day-to-day clinical scenarios, allowing for evaluation of a clinically representative single-isocenter/multi-tumor VMAT lung SBRT treatment. **Figure 3.1** below demonstrates the steps taken to achieve a complete simulated VMAT plan. **Figure 3.2** demonstrates randomly transformed CT images, used for one treatment (out of 5 fractions) of a representative plan.
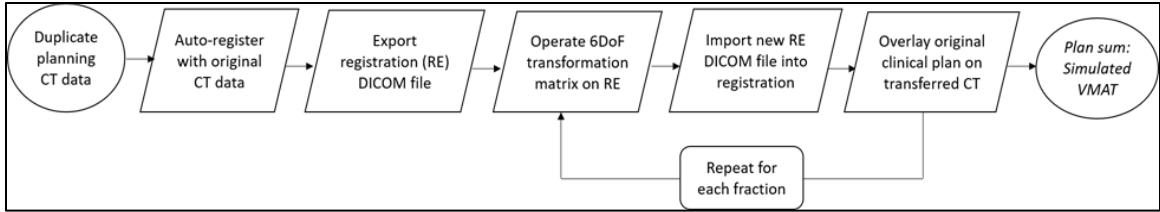
Figure 3.1: The workflow describes the steps required to complete simulation of isocenter misalignment in Eclipse TPS in all six dimensions.
It utilizes image registration and the external beam treatment planning modules in Eclipse. The result is a plan summation of all treatment fractions that have been individually and randomly transformed, representing a clinically realistic treatment scenario.

Figure 3.2: A demonstration of randomly rotated (within, ± 2°) and translated (within, ± 5 mm) CT data set (see bottom right inset) around the plan isocenter location (cross-hair) for a representative patient (one fraction).
The PTVs are shown in orange and pink and the GTVs are in red in both lungs. Normal tissue structures are shown: lungs (light blue and green), skin (purple), cord (yellow), and ribs (blue). This patient was treated for 50 Gy in 5 fractions to both tumors, thus the random transformation process was repeated for a total of 5 treatments (see top left inset).

3.2.4 Plan Comparison

All plans were compared per RTOG guidelines for target coverage along with maximum and volumetric dose to the adjacent OAR. Normal tissues that were evaluated included maximum dose to 0.03 cc of ribs, spinal cord, heart, bronchial tree, esophagus and skin. Lung doses were evaluated using the mean lung dose (MLD), percentage of lung receiving 10 Gy (V10Gy) and 20 Gy (V20Gy) or more. Distance to isocenter was determined by utilizing the coordinates of the geometric center of each PTV as described above. In addition to the OAR doses, both plans were rigorously evaluated using the following metrics:

- Plan maximal dose: Maximum dose in the target

- Conformality Index (CI): Ratio of prescription isodose volume to the PTV volume. Values between 1.0–1.2 are desirable, but values between 1.2–1.5 would be acceptable per protocol with minor deviations. Therefore, for prescription isodose volume (V_{RI}),

$$CI_{RTOG} = \frac{V_{RI}}{PTV} \tag{3.1}$$

- Paddick Conformation Number (PCN): Determines the overlap of the prescription isodose volume and the PTV volume. Ideally, PCN = 1.0. For target volume covered by the prescription dose (*PIV*), and total volume covered by the prescription dose (V_{RI}),

$$PCN_{Paddick} = \frac{PTV_{PIV}^2}{(PTV \times V_{RI})} \tag{3.2}$$

- Heterogeneity Index (HI): Evaluates the dose heterogeneity inside the PTV,

$$HI = \frac{D_{Max}}{Rx} \qquad (3.3)$$

- Gradient Index (GI): Used to evaluate the intermediate dose fall off,

$$GI = \frac{50\% IsodoseVolume}{PIV} \qquad (3.4)$$

- Maximum dose at 2 cm away from the PTV in any direction (D2cm): Acceptable values depend on PTV size.

- Biological Effective Dose (BED10): For each PTV, BED10 was calculated using the prescribed dose to PTV D95% (Gy). For each GTV, BED10 was determined using the minimum dose (d) per fraction to the GTV. An α/β ratio of 10 Gy was used for the pulmonary tumor and for n = number of treatments, the BED10 was calculated using the following formula:

$$BED10 = n \times d \left[1 + \frac{d}{\alpha/\beta}\right] \qquad (3.5)$$

3.2.5 Statistical Analysis

Data was assessed for normality, then either a paired two-tail Student's t-test (Microsoft Excel, Microsoft Corp., Redmond, WA) or a Mann-Whitney test (Minitab, Minitab LLC, Chicago, IL) was used to compare the data for the clinical VMAT versus simulated VMAT plans for all parameters of target coverage and dose tolerances to OAR. A value of $p < 0.05$ was considered statistically significant.

3.3 Results

After simulation of setup errors, all PTVs had loss of dose coverage as well as some ITVs and GTVs. Simulated VMAT plans demonstrated an average PTV coverage loss of

$27.4 \pm 14.6\%$, with a maximum loss of 71.7% compared to the original clinical plans. **Table 3.2** shows the analysis of target coverage for all 52 lesions. After the random transformations were applied, statistically significant decreases in PTV dose coverage, CI, PCN, and HI were observed. The drastic decrease in average CI and PCN for the simulated plans suggests that the prescription isodose volume was not covering the PTV as originally intended. It is important to note that for one patient the proximity of the lesions resulted in dose bridging between the lesions and thus a large CI of 2.69 was evaluated for one PTV, which was reduced to 1.33 for the simulated plan. The GI increased from 5.24 ± 1.21 (3.66–8.31) for the original plans to 8.38 ± 3.78 (3.89–23.76) for the simulated plans. This suggests that due to small rotational and translational set up errors, there was significantly higher intermediate dose spillage, and the sharp dose fall off indicative of lung SBRT treatments no longer existed. For the smaller (<10 cc) target sizes, clinically unacceptable GI up to 23.76 was observed (see **Table 3.2**).

Table 3.2: Analysis of the dosimetric and delivery parameters for 26 lung SBRT patients treated with a single-isocenter/multiple-target VMAT plan. Mean ± STD (range) and p-values were reported for clinical VMAT and simulated plans. n. s. = not significant. Significant values are highlighted in bold. STD = standard deviation. PCN = Paddick Conformation Number.

Target	Parameter	Clinical VMAT	Simulated VMAT	*p*-value
PTV (n = 52)	Max target dose (%)	122.5 ± 3.8 (115.4–131.1)	121.6 ± 3.1 (115.3–128.6)	*n. s.*
	% Volume covered by Rx dose (%)	96.1 ± 1.2 (95.0–98.8)	68.7 ± 14.7 (25.6–95.2)	***p < 0.001***
	CI	1.08 ± 0.25 (0.95 – 2.69)	0.75 ± 0.19 (0.26 – 1.33)	***p < 0.001***
	PCN	0.89 ± 0.03 (0.81 – 0.98)	0.64 ± 0.13 (0.26 – 0.85)	***p < 0.001***
	HI	1.21 ± 0.04 (1.13 – 1.31)	1.20 ± .04 (1.12 – 1.29)	***p = 0.03***
	GI	5.37 ± 0.94 (3.66 – 7.2)	8.36 ± 3.7 (3.89 – 23.76)	***p < 0.001***
	D2cm (%)	51.7 ± 5.6 (38.8 – 67.0)	51.7 ± 5.1 (42.4 – 62.3)	*n. s.*
GTV (n = 52)	% Volume covered by Rx dose (%)	100 ± 0	99.4 ± 2.2 (87.7 – 100.0)	***p = 0.02***
ITV (n=10)	% Volume covered by Rx dose (%)	100 ± 0	99.3 ± 1.3 (95.7-100)	*n.s.*

For all 52 lesions, the average GTV coverage loss following the random transformations was 0.6%. However, for PTV volumes less than 10 cc, the GTV coverage loss was the greatest at an average of 1.6%, with a maximum loss of up to 12.3% in some cases. For the subset of patients with an ITV (n=5), statistically insignificant coverage loss following the random transformation was 0.7%.

The greatest target coverage loss was seen with the smallest PTV sizes. For PTV volumes less than 10 cc (n = 14), the relative dose error for the simulated VMAT plans was -39.8 ± 18.3% with respect to the clinical VMAT plans. For PTV volumes greater than 10

cc (n = 38), the average relative dose error was -19.8 ± 6.1%. **Figure 3.3** demonstrates the trend in relative dose error with respect to PTV sizes while the relative dose error binned by PTV volume is shown in **Figure 3.4**. However, no obvious correlation between the PTV coverage loss and distance to isocenter was observed, as shown in **Figure 3.5**. It indicates that random translational shifts dominated the loss of target coverage in these clinically descriptive simulations. However, the largest coverage loss with greater than 50% was observed for those lesions with the smallest target size of about 5.0 cc. **Figure 3.6** demonstrates BED calculated utilizing the minimum dose received by the GTV, whereas the BED10 for the PTV was calculated using the dose covering 95% of the PTV volume as described above.
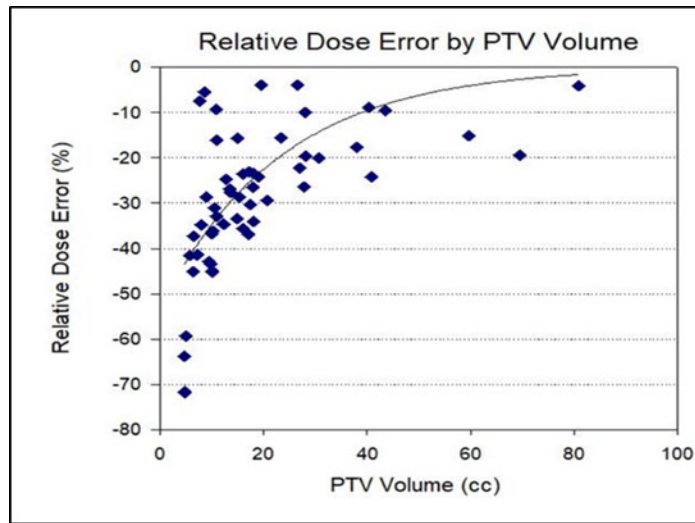
Figure 3.3: Loss of target coverage for all 52 lesions plotted as a function of PTV size. The curve fit (R^2 = 0.43) indicates a probable correlation between the target size and coverage loss, suggesting that setup errors will result in a larger coverage loss for small PTV sizes.
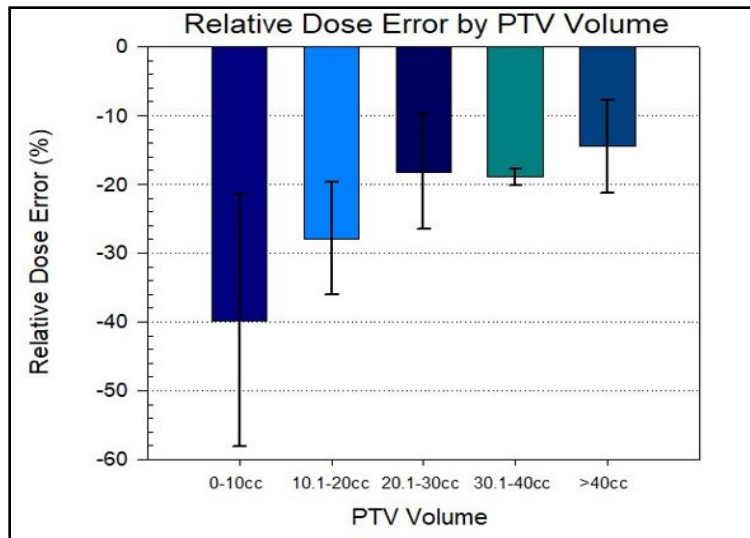
Figure 3.4: Loss of target coverage for all 52 lesions as a function of binned PTV sizes.
The largest coverage loss was seen for lesions less than 10 cc. Target sizes ≤ 10 cc exhibited average coverage losses of 40%, up to 70% in some cases. The corresponding GTV loss for this subset was an average of 1.6%, up to 12.3% in some cases.
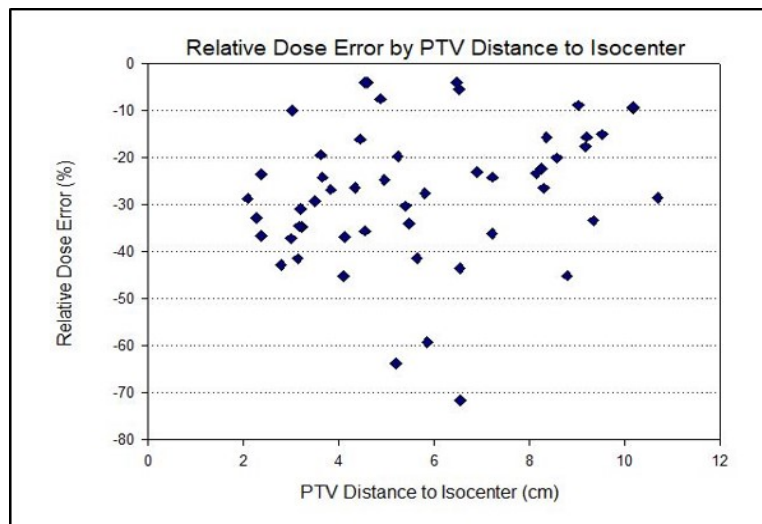
Figure 3.5: Scatter plot of relative dose error for all 52 lesions as a function of distance to isocenter.
For randomly assigned rotational [± 2°] and translations [± 5 mm] errors in each direction, no clear relationship between the loss of target coverage and distance to isocenter was observed suggesting that random translational shifts dominated the loss of target coverage. However, the largest coverage loss (>50%) was seen for those lesions with the smallest PTV of about 5 cc.
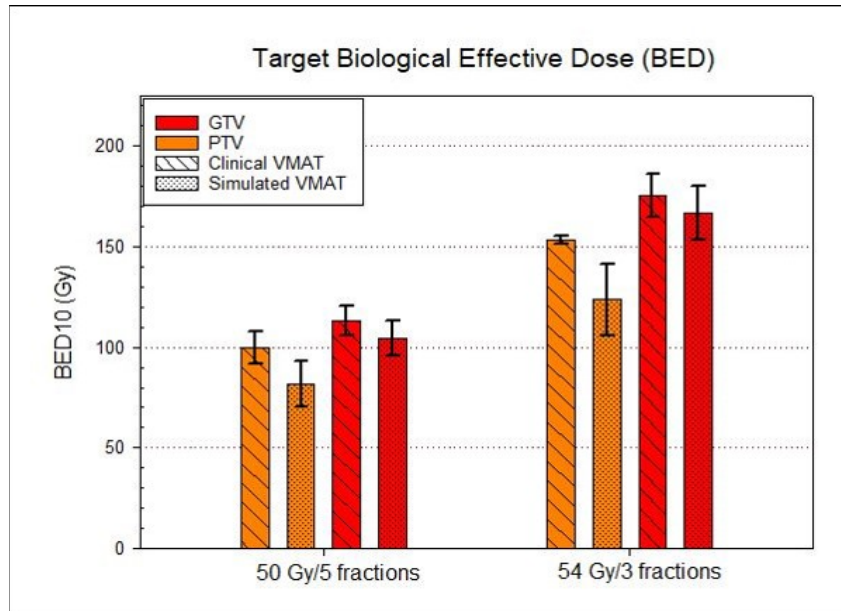
Figure 3.6: Comparison of calculated BED10 for both PTV and GTV for all 52 targets is shown for both plans.
For patients treated with 54 Gy in 3 fractions, >100 Gy BED10 was always preserved for each PTV and GTV even with residual set up errors. However, for patients treated with 50 Gy in 5 fractions (see left panel), the average BED10 for PTV and GTV were 81.5 Gy and 104.4 Gy, respectively, with simulated VMAT plans compared to 100.0 Gy and 113.0 Gy BED10 with original VMAT plans, suggesting that there is a risk of underdosing targets due to set up errors. However, on average, the greatest is PTV coverage with less change in the GTV BED10.

Table 3.3 shows the comparisons of maximal doses to normal tissue structures. In contrast, the maximum dose to the skin, ribs, and esophagus were all lower for the simulated VMAT plans and were statistically significant, however likely not clinically significant. The largest decrease in maximal ribs dose for one patient was 10.9 Gy in which case both lesions (PTV1, 5.0 cc and PTV2, 16.1 cc) were proximal to the chest wall. Despite the loss of target coverage for the PTVs demonstrated in Table 3.2, the normal lung V20Gy, V10Gy, and MLD did not change significantly suggesting that the doses intended for the PTVs were not subsequently deposited in the uninvolved lungs.

Table 3.3: Analysis of the maximal dose to OAR for 26 lung SBRT patients. Mean ± STD (range) and p-values were reported for clinical VMAT and simulated VMAT plans. n. s. = not significant. Significant values are highlighted in bold. STD = standard deviation.

Maximal dose to OAR & uninvolved lung	Parameter	Clinical VMAT	Simulated VMAT	p-value
	Skin (Gy)	17.7 ± 3.6 ($11.0 - 26.6$)	16.8 ± 3.5 ($10.4 - 25.8$)	*p < 0.001*
	Ribs (Gy)	45.2 ± 11.2 ($22.5 - 59.0$)	42.8 ± 9.2 ($24.7 - 59.1$)	*p = 0.003*
	Spinal cord (Gy)	10.5 ± 3.3 ($4.7 - 15.5$)	10.6 ± 3.5 ($4.5 - 16.1$)	*n. s.*
	Heart/Pericardium (Gy)	21.1 ± 11.5 ($0.9 - 52.0$)	20.5 ± 11.8 ($0.9 - 54.2$)	*n. s.*
	Bronchus (Gy)	18.2 ± 11.9 ($0.8 - 50.4$)	17.9 ± 12.4 ($0.7 - 51.1$)	*n. s.*
	Esophagus (Gy)	16.2 ± 8.2 ($5.7 - 43.5$)	15.8 ± 8.1 ($5.6 - 41.9$)	*p = 0.005*
	V20Gy (%)	6.8 ± 4.1 ($2.1 - 17.0$)	6.9 ± 4.1 ($2.0 - 17.5$)	*n. s.*
	V10Gy (%)	18.3 ± 10.1 ($6.8 - 43.6$)	18.5 ± 10.2 ($6.8 - 44.0$)	*n. s.*
	MLD (Gy)	5.6 ± 2.5 ($2.4 - 10.9$)	5.5 ± 2.5 ($2.3 - 10.9$)	*n. s.*

Dose to the bronchus did not change significantly between clinical VMAT and simulated VMAT plans. However, the largest increase in maximal dose to bronchus was 3.7 Gy for the example patient shown in **Figure 3.7**, although still acceptable per RTOG-0813 protocol.[25] **Figure 3.8** shows the DVH associated with this patient.
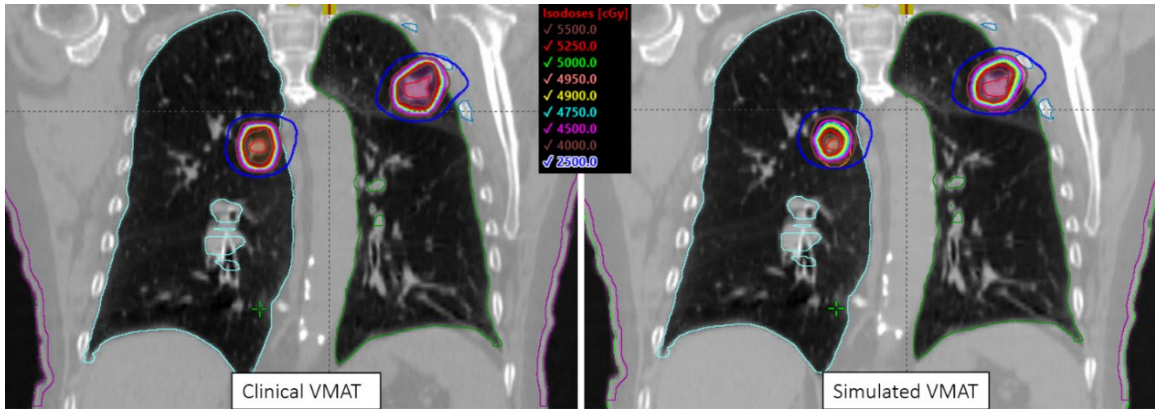
Figure 3.7: Example dose distribution for Clinical VMAT vs. Simulated VMAT.
Coronal view of the isodose distribution is shown for the clinical VMAT plan (left panel) and the simulated VMAT plan (right panel), showing the significant loss of target coverage (see higher isodose lines with respect to both PTVs). The single-isocenter location is shown by the cross-hair. For this patient, the bronchus dose increased by 3.7 Gy with simulated VMAT whereas the maximal rib dose was decreased by 5.8 Gy.
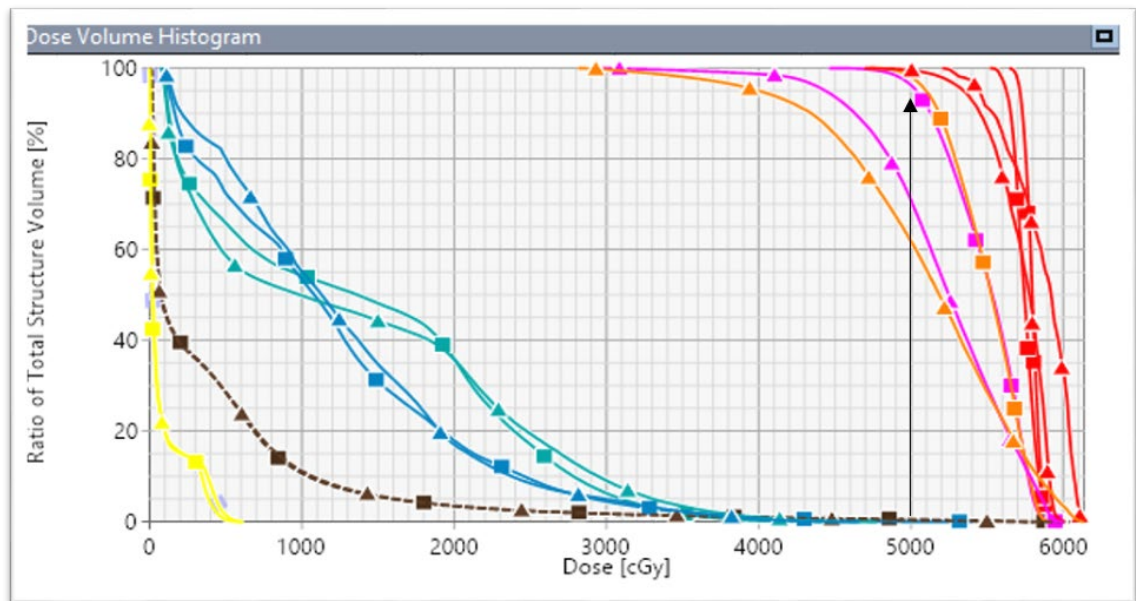
Figure 3.8: Dose volume histogram for the example patient.
The vertical black arrow shows the original planned coverage for both PTV1 (orange) and PTV2 (pink). Squares represent the clinical VMAT plan and triangles represent the simulated VMAT plan. Shown are the GTVs (red), total lung (brown), ribs (light blue), bronchus (cyan), and spinal cord (yellow). The right PTV1 (6.5 cc) and the left PTV2 (18.0 cc) lost 37.2% and 26.5% coverage, respectively, compared to the original clinical 95% PTV coverage of both targets. A small loss of GTV coverage was seen with the simulated VMAT plan.

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3.4   Discussion

A novel and clinically useful tool was developed to simulate and quantify the dosimetric effects of interfraction set up errors in the case of synchronous multiple lesions treated via a single-isocenter VMAT lung SBRT. After applying clinically observable pre-treatment cone beam CT random translational shifts of $\pm$ 5 mm and rotational errors of $\pm$ 2° in each direction, dramatic loss of PTV coverage was observed with an average relative dose error of 27.4 $\pm$ 14.6% (up to 71.7% in some cases) ($p < 0.001$). Smaller tumors (< 10 cc) exhibited the greatest PTV coverage loss with random rotations and translations at 39.8 $\pm$ 18.3% and 19.8 $\pm$ 6.1% for < 10 cc and $\geq$ 10 cc, respectively. Overall, the GTV dose error was less than 1%, on average, but for smaller target sizes was up to -12.3% ($p = 0.02$). Major dosimetric differences were observed in loss of target conformity ($p < 0.001$) and gradient index ($p < 0.001$), negatively affecting the steep dose gradient desired in SBRT treatments. The change in dose to most normal tissues was statistically insignificant and probably clinically unimportant, unless critical structures are abutting the target or if re-irradiation is being considered. In this 6DoF simulation, there was no clear trend of PTV coverage loss as a function of distance to isocenter. This is likely due to changing depths and SSD affecting the dose calculation rather than the dose just being shifted in the patient's heterogeneous anatomy. Also effecting this trend are randomly generated clinically realistic translational errors of $\pm$5mm (in each direction) dominating the small but clinically observed rotational error of $\pm$2° (in each direction) or could be due to the vast array of PTV sizes obscuring the coverage loss. This is consistent with previously published spine SBRT treatment data.[32] For instance, Wang et al from MD Anderson Cancer Center demonstrated that dosimetric effects from isocenter translational displacement of 1-3 mm were more severe than that from patient rotations of 1-3°.

Although their study has shown the results of setup uncertainties in the case of a single spine lesion treated with an isocenter at the center of the target, a 2-mm translational set up error resulted in clinically significant loss of target coverage.

Using a total of 124 patients with 159 pulmonary lesions treated with variable fractionation schemes of SBRT, Guckenberger *et al* demonstrated that doses of greater than 100 Gy BED10 to the CTV based on 4D-CT dose calculation resulted in excellent tumor local control rates (90% at 3 years).[19] Their CTV was generated in the CT pulmonary window and the ITV was the sum of the CTV positions in inhalation and exhalation, similar to our GTV volume. In this study, the BED10 for the GTV was calculated utilizing the minimum dose received by the GTV, whereas the BED10 for the PTV was calculated using the dose covering 95% of the PTV volume as described above. We have demonstrated that due to residual set up errors, for all patients receiving 50 Gy in 5 fractions, any loss in PTV coverage resulted in a BED10 < 100 Gy ($p < 0.001$) (see **Figure 3.6**, left panel). For one patient, the BED10 for a GTV was only 83.0 Gy. However, for the majority of cases the GTV BED10 was still > 100 Gy, suggesting that acceptable tumor local-control is likely. For the five patients who had an ITV, all received a prescription dose of 50Gy in 5 fractions. For these patient's, three had ITV which received a minimum dose less than 50Gy and thus did not achieve a BED10 of >100Gy. In the case of the low BED10, whether 5 mm margin around the GTV is sufficient or not to achieve > 100 Gy BED10 to the GTV in this setting merits further investigation. On the other hand, these results suggest that the dosing scheme of 54 Gy in 3 fractions always maintains a high BED10 (> 100 Gy) to the both PTV and GTV even with simulated set up errors for a single-isocenter/multiple lesions VMAT. Therefore, while there was under dosing of the PTV and GTV, it still resulted in a

BED >100Gy, implying that this dose and fractionation regimen is the regimen of choice. However, if the tumor is near critical structures and warrants 5 treatments, a higher dose per day (such as 11-12 Gy for 5 fractions as seen in the RTOG 0813 trial) can be considered.

For many patients, remaining in the treatment position for long periods may be uncomfortable and result in intrafraction motion, causing the desire for faster yet effective treatment plans. Bissonnette *et al* demonstrated that spatial errors, although typically small in lung SBRT, could be larger with longer treatment times.[26] A study by Hoogeman *et al* reported that intrafraction setup errors will increase linearly with treatment time, giving incentive to decrease the treatment time for single-isocenter multi/lesions VMAT.[27] Although this simulation study does not account for intrafraction set up errors, this consideration would increase uncertainty. Treating patients faster with a single-isocenter VMAT plan could minimize intrafraction patient motion errors and improve patient comfort.

Despite growing interest in single-isocenter/multiple-lesion VMAT lung SBRT treatments, difficulties due to daily patient set up errors have been described. When treating multiple lesions with a single-isocenter VMAT plan, a physician has the task of lining up all the lesions on a daily cone beam CT (CBCT) images. It has been reported that boney anatomy cannot be used as a surrogate for soft tissue matching for lung SBRT treatment.[28] A clinical study by Trager *et al* demonstrated that when two lesions share a same isocenter, approximately 30% of the time both lesions do not line up correctly in a single CBCT images.[29] Thus, the physician is faced with a dilemma: what to do if the lesions do not line up correctly? The first option would be to align the lesions as best as possible, potentially

"splitting-the-difference" if the differences are small and clinically acceptable. The second option would be to reposition the patient, repeat the CBCT scan and realign the lesions again. If, once again, the lesions do not line up properly the treating physician may need to abandon the treatment and either re-plan or try again. This can lead to delays in providing appropriate treatment, in addition to adding stress to the SBRT team and slowing down the clinic workflow. Quan *et al* described the feasibility of treating ≥ 2 lesions with VMAT or intensity-modulated radiosurgery (IMRS) and suggested that if all the lesions do not match up correctly on the daily pre-treatment CBCT the only option is to abandon the SBRT treatment.[30] Although aforementioned studies have shown the results of setup uncertainties in the case of a single-lesion SBRT treated with an isocenter at the center of the target, the authors believe that this is the first study to report the results of patient misalignment for extracranial single-isocenter/multi-lesion lung SBRT. Similarly, Clark *et al* demonstrated the dosimetric impact of rotational setup errors for single-isocenter/multi-target VMAT SRS to multiple brain metastases using a "third party" software.[31] It was reported that minimizing rotational setup errors was essential for adequate target coverage, even more so for small lesions in the brain and lesions far from the isocenter location. This study found that with even 2° rotations in all directions could result in an inadequate PTV target coverage with an average of $89.4 \pm 10.6\%$, up to 100% in some cases, however the study did not consider the translational set up errors. This current study does not use a "third party" software but rather a novel tool to preserve all treatment planning parameters including planning CT images and structure contours in Eclipse TPS, therefore introducing no additional sources of errors. This tool can be used for both extracranial multi-lesion and

single-lesion SBRT or intracranial SRS for multiple or single-lesion treatment, as needed. As demonstrated, imperfect patient setup resulted in an unacceptable target coverage loss.

To minimize this potential loss of target coverage due to set up errors and still allowing for a fast SBRT treatment of multiple lung lesions, ongoing research includes developing a novel method utilizing a single-isocenter placed at patient's midline and allowing for partial arcs to deliver dose to individual tumors. To minimize setup uncertainties, each plan can be re-optimized separately while sharing the same isocenter. This allows a SBRT plan to be created for each tumor, while allowing both tumors to be treated sequentially during the same session with soft tissue alinement one at a time while reducing chance of a geometric miss due to residual setup uncertainties. Placement of a single-isocenter at patient's mediastinum will avoid potential patient collisions and provide greater degree of non-coplanar arcs geometry. It will eliminate the need of additional couch moments during CBCT imaging (couch centering is required for Varian Linac for lateral offsets of > 5 cm, potentially introducing an additional source of error) and minimize the need for therapists to enter the treatment room for multiple couch positions.

3.5   Conclusion

A novel and simple method for demonstrating isocenter misalignment in six dimensions and the resulting dosimetric impact for single-isocenter VMAT lung SBRT plans for two lesions has been presented. Clinically representative patient setup errors may result in large deviations (up to 72% loss) from planned target coverage. Smaller targets show the largest deviation from planned coverage including delivering < 100 Gy BED10 to some targets. Small misalignments can result in substantial decrement in dose gradient indicative of SBRT and significantly increase the intermediate dose-spillage. When

treating small lesions synchronously with a single-isocenter VMAT lung SBRT plan, alternative treatment planning strategies should be explored to minimize the likelihood of a geometric miss.

CHAPTER 4. A NOVEL RESTRICTED SINGLE-ISOCENTER STEREOTACTIC BODY RADIOTHERAPY (RESIST) METHOD FOR SYNCHRONOUS MULTIPLE LUNG LESIONS TO MINIMIZE SETUP UNCERTAINTIES

The following chapter has been adapted from a manuscript currently under review for publication: Lana Sanford Critchfield, Mark Bernard, Marcus Randall, Ronald McGarry, Damodar Pokhrel, "A Novel Restricted Single-Isocenter Stereotactic Body Radiotherapy (RESIST) Method for Synchronous Multiple Lung Lesions to Minimize Setup Uncertainties", *J Appl Clin Med Phys,* August 8, 2020.

Abstract

Treating multiple lung lesions synchronously using a single-isocenter volumetric modulated arc therapy (VMAT) stereotactic body radiation therapy (SBRT) plan can improve treatment efficiency and patient compliance. However, due to set up uncertainty, aligning multiple lung tumors on a single daily cone beam CT (CBCT) image has shown clinically unacceptable loss of target(s) coverage. Herein, we propose RESIST, an alternative treatment that mitigates setup uncertainties. Twenty-one patients with two lung lesions were treated with single-isocenter VMAT-SBRT using a 6MV-FFF beam to 54 Gy in 3 fractions (n=7) or 50 Gy in 5 fractions (n=14) prescribed to 70-80% isodose line. To minimize setup uncertainties, each plan was re-planned using a Restricted Single-Isocenter Stereotactic Body Radiotherapy (RESIST) method, utilizing a single-isocenter placed at the mediastinum. It allows for an individual plan to be created for each tumor, using the first plan as the base-dose for the second plan, while still allowing both tumors to be treated in the same session. The technique uses novel features in Eclipse, including dynamic conformal arc (DCA)-based dose and aperture shape controller before each VMAT optimization. RESIST plans provided better target dose conformity and gradient indices

and lower dose to adjacent critical organs. Using RESIST to treat synchronous lung lesions with VMAT-SBRT significantly reduces plan complexity, as demonstrated by smaller beam modulation factors, without unreasonably increasing treatment time. RESIST reduces the chance of a geometric miss by allowing CBCT matching of one tumor at a time. Placement of isocenter at the mediastinum avoids potential patient/gantry collisions, provides greater flexibility of non-coplanar arcs and eliminates the need for multiple couch movements during CBCT imaging. Efficacy of RESIST has been demonstrated for two lesions and can potentially be used for more. Clinical implementation of this technique is ongoing.

4.1   Introduction

The high doses per fraction and complexity associated with lung SBRT leads to long treatment times that are further magnified for patients with multiple synchronous lung lesions.[1] Patients may be uncomfortable in the treatment position and not able to maintain it for long treatment times, especially elderly patients and those with multiple comorbidities.[2] Furthermore, longer SBRT times have been associated with greater intrafraction motion errors thus degrading the treatment accuracy.[3] The desire to treat multiple lung lesions quickly and efficiently with SBRT has led investigators to study synchronous VMAT treatments.[4-8] These fast treatments employ a single-isocenter shared between multiple lesions and high dose rate flattening filter free (FFF) beams, which reduces out of field dose and provides better dose coverage at tumor-lung interface compared to standard flattened beams.[9-11] To further reduce treatment time and plan complexity, tools like dynamic conformal arc (DCA), aperture shape controller (ASC), and photon optimizer (PO) MLC algorithm are beginning to be utilized.[12-14] Reduction of plan

complexity can reduce MLC positioning errors, resulting in more accurate dose delivery with the additional benefit of decreasing treatment time. However, with the complexity of single-isocenter/multiple lesion SBRT treatment plans and the vast array of planning options available, consistency in plan quality and treatment delivery efficiency may prove problematic. Therefore, a robust treatment planning method for single-isocenter/multiple lesion lung SBRT is needed.

Image-guidance procedures such as CBCT scans prior to treatment have become standard of care for lung SBRT. It has been demonstrated that bony anatomy cannot be used as a surrogate for tumor-to-tumor matching for lung SBRT.[15] Due to tumor motion and possible tumor deformation, aligning multiple lung tumors using a single daily CBCT can be difficult and may lead to misalignment with the potential of geometric misses. Correcting for setup errors for multiple tumors is improved when utilizing a six-degree-of-freedom (6DOF) couch.[16] Previously demonstrated are potential large target coverage losses (up to 72% loss from the prescribed dose) associated with small setup errors in single-isocenter/multiple lesion lung SBRT treatments using a single daily CBCT.[17] Dosimetric errors were the largest for small lesions. These errors are likely with clinics inexperienced with multi-lesion SBRT. Therefore, creation of a robust SBRT treatment approach for synchronous multiple lung lesions that decreases the difficulty of patient setup and minimizes setup errors while still maintaining fast treatment times is a major goal.

Herein, we have developed a novel Restricted Single-Isocenter Stereotactic Body Radiotherapy (RESIST) method to minimize setup uncertainties and simplify synchronous multiple lesion treatments. RESIST used for multiple lung lesions improves target localization by matching tumor-to-tumor, provides better target conformity and gradient

indices and reduces doses to organs-at-risk (OAR), while improving treatment times from traditional lung SBRT. The RESIST method presented here will guide planners to use the optimal treatment geometry and planning options and allow more treatment flexibility for physicians and therapists. This study aims to compare plan quality and treatment delivery parameters for RESIST with single-isocenter/multiple lesion VMAT lung SBRT plans.

4.2   Materials and Methods

After obtaining Institutional Review Board Approval, 21 patients with two synchronous lung tumors who underwent a single-isocenter VMAT lung SBRT treatment of 54 Gy in 3 fractions (n = 7) or 50 Gy in 5 fractions (n = 14) in our clinic were included in this study.

4.2.1   Patient Setup and Target Delineation

Patients were immobilized with the Body Pro-Lok^{TM} SBRT system (CIVCO, Orange City, IA) in the supine position with arms up. Patients received a free-breathing simulation CT scan on a GE Lightspeed 16 slice CT scanner (General Electric Medical Systems, Waukesha, WI) with 512×512 pixel image size and 2.5 mm slice thickness in the axial helical mode. Abdominal compression was employed for most patients or a 4D-CT scan was obtained, utilizing Varian RPM system (version 1.7). Simulation images were imported into Eclipse Treatment Planning System (TPS, Version 15.6, Varian Medical Systems, Palo Alto, CA). Gross tumor volumes (GTVs) were contoured based on the observable tumor mass from the free-breathing CT or, if a 4D-CT was obtained, internal target volumes (ITVs equal to GTVs) were contoured based on maximum intensity projection (MIP) registered with the planning CT images. A planning target volume (PTV)

was created by expanding the GTV by 10 mm in the superior-inferior direction and 5 mm in the lateral direction (free-breathing CT) or with a uniform 5 mm margin (4D-CT). Critical structures were contoured per RTOG protocol and included uninvolved lung (right, left and combined), spinal cord, heart, bronchus, trachea, esophagus, skin and ribs (right, left and combined). **Table 4.1** summarizes the tumor characteristics for the 21 patients included in this study.

Table 4.1: Main tumor characteristics of the 21 lung SBRT patients included in this study. Each patient had 2 tumors. STD = standard deviation.

Parameters	Mean ± STD (range or n = no. of patients)
Tumor 1, PTV1 (cc) Tumor 2, PTV2 (cc)	23.3 ± 20.6 (5.0 – 80.9) 25.9 ± 27.5 (6.38 – 137.2)
Prescribed dose to each lesion	54 Gy in 3 fractions (n = 7)
	50 Gy in 5 fractions (n = 14)
Tumor location (left/right/bi-lateral lungs)	(n = 6 / 3 / 12)
Uninvolved lung (cc)	3673.8 ± 1012.8 (1892 – 6542)

4.2.2   Clinical VMAT Plans

For each patient, a single-isocenter lung SBRT plan was generated in Eclipse TPS for a Truebeam Linac (Varian Medical Systems, Palo Alto, CA) with Millennium 120 MLC. Plans were VMAT utilizing a 6MV-FFF (1400 MU/min) beams. The isocenter was placed approximately between the two tumors. In order to maintain use of the 0.5 cm MLC leaves, the maximum distance between the distal edge of the two lesions should be 20 cm, although a greater distance is possible but a degradation in plan quality would be observed. Collimator angles were manually chosen based on the tumor arrangement to reduce MLC leakage dose between each arc along with utilization of the jaw-tracking feature. For optimal MLC use, the collimator is rotated such that the tumors are oriented with the y-jaw. Two to three full arcs (coplanar) were utilized for bilateral lungs tumors and three to

five partial non-coplanar arcs, with couch rotations of ± 10° for unilateral lung tumors. Doses were 54 Gy or 50 Gy in 3 or 5 fractions, respectively. Both PTVs (PTV 1 and PTV 2) were planned with the prescription dose at the 70-80% isodose lines and optimized such that at least 95% of each PTV received 100% of the prescription dose. The maximum dose to each target was planned to fall inside the GTV. Dose was calculated using Boltzmann transport based AcurosXB algorithm in Eclipse for heterogeneity corrections and reporting dose to medium.[18] Although single-isocenter SBRT was designed for synchronous two lesions, planning objectives per RTOG protocols were followed.[19, 20]

4.2.3   RESIST VMAT Plans

Each patient was re-planned with the new RESIST method. A single-isocenter was placed at the patient's midline. If the lesions shared an axial plane, the isocenter location corresponded with that plane. However, if the lesions were axially separated, the isocenter location was placed at the mid-plane of the lesions still at midline. Due to the MLC overtravel limitations of the Truebeam Linac, the maximum distance between the distal edge of each lesion and isocenter in the x-jaw direction is ±14.5 cm. In order to maintain use of the 0.5 cm MLC leaves, the maximum distance between the distal edge of each lesion and the isocenter in the y-jaw direction is ±10 cm. Collimator angles were manually optimized based on PTV shape and offset from one another to reduce leakage dose and to ensure the MLC leaves can travel to each PTV. Treatment planning for PTV 1 began by deploying 3 partial arcs with 6 MV FFF (1400 MU/min) beam with couch rotations of 0°, 10°, and 350°. In the Calculation Models tab (in Eclipse TPS), the PO MLC calculation options were assigned to select the strength of aperture shape controller (ASC) to be "very high" instead of default "low" in the clinical VMAT plans. A few recent studies have

shown that utilizing the ASC in DCA-based VMAT can reduce the total number of monitor units and reduce plan complexity and improve the plan quality.[13, 14] The MLC aperture was fit to the first tumor, PTV 1, with a margin of 0.2 cm and dynamic conformal arc (DCA) dose was calculated. After the initial DCA dose calculation, VMAT optimization began for target coverage to the PTV 1 (and GTV 1) and to spare adjacent normal structures. Jaw tracking option was utilized to further reduce leakage dose to uninvolved lung.[21] **Figure 4.1** describes the RESIST planning method for synchronous multiple lung SBRT treatments.
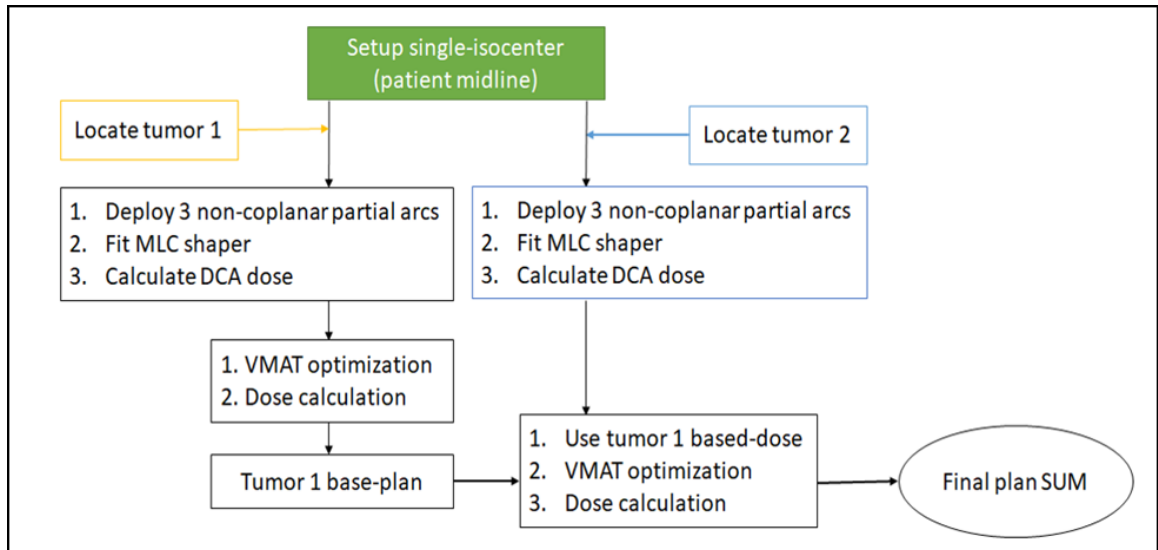
Figure 4.1: The proposed RESIST treatment planning workflow for single-isocenter/multiple-lesions lung SBRT.
Using RESIST, initially DCA-based dose plan can be used to reduce the modulation factor, thus reducing treatment time and the plan complexity.

A separate plan was created for the second tumor, PTV 2, utilizing the same isocenter location used in the previous plan for PTV 1. The same steps were followed as above, now with the partial arcs being deployed on the PTV 2 side of the patient, which may be the same configuration as for PTV 1. Before VMAT optimization, the plan for PTV 1 was chosen as the base dose plan. This plan was optimized for coverage to PTV 2 (and GTV 2) and to spare adjacent critical structures. Once optimized and calculated, the plan

sum was created. In the plan sum module, to obtain optimal coverage of both tumors, the dose can be re-normalized to account for the dose contribution from one plan to the other.

4.2.4   Plan Comparison and Data Analysis

All plans were compared per RTOG guidelines for each target conformity, tumor heterogeneity and intermediate dose-spillage as follows:

- Conformality Index (CI_{RTOG}): Ratio of prescription isodose volume to the PTV volume. Values between 1.0–1.2 are desirable, but values between 1.2–1.5 would be acceptable per SBRT protocol with minor deviations. Therefore, for prescription isodose volume (V_{RI}),

$$CI_{RTOG} = \frac{V_{RI}}{PTV} \qquad (4.1)$$

- Paddick Conformation Number ($PCN_{Paddick}$): Determines the overlap of the prescription isodose volume and the *PTV* volume. [22] Ideally, PCN = 1.0 is anticipated. For target volume covered by the prescription dose (*PIV*), and total volume covered by the prescription dose (V_{RI}),

$$PCN_{Paddick} = \frac{PTV_{PIV}^2}{(PTV \times V_{RI})} \qquad (4.2)$$

- Heterogeneity Index (*HI*): Evaluates the target(s) dose heterogeneity inside the each PTV and is given by:

$$HI = \frac{D_{Max}}{Rx} \qquad (4.3)$$

- Gradient Index (*GI*): Used to evaluate the intermediate dose-spillage and calculated as:

$$GI = \frac{50\% IsodoseVolume}{PIV} \tag{4.4}$$

- Maximum dose at 2 cm away from the PTV in any direction (D2cm): Acceptable values depend on PTV size.

Doses to OAR that were evaluated included maximum dose to 0.03 cc of ribs, spinal cord, heart, bronchial tree, esophagus and skin. Volumetric doses evaluated included dose to 1 cc of ribs, 0.35 cc of spinal cord, 15 cc of heart, 4 cc of bronchial tree/trachea, 5 cc of esophagus and 10 cc of skin. Lung doses were evaluated using the mean lung dose (MLD) and percentage of lung receiving 10 Gy (V10Gy) and 20 Gy (V20Gy) or more. Total monitor units (MU), beam modulation factor (MF) and beam on time was recorded. Overall treatment time (including CBCT scan time) was estimated between the 2 methods. MF was defined as the ratio of total number of MU to the prescription dose in cGy. Data was assessed for normality, then either a paired two-tail Student's t-test (Microsoft Excel, Microsoft Corp., Redmond, WA) or a Mann-Whitney test (Minitab, Minitab LLC, Chicago, IL) was used to compare the data for the clinical VMAT versus simulated VMAT plans for all parameters of target coverage and dose tolerances to OAR. A value of $p < 0.05$ was considered statistically significant.

4.3   Results

4.3.1   Target Coverage and Dose to OAR

All RESIST plans demonstrated equivalent PTV coverage compared to the clinical VMAT plans, but provided better conformity indices, heterogeneity index, gradient index and D2cm, as shown in **Table 4.2**. Overall, the GTV doses were similar except, in some cases, the minimum dose to the GTV was improved with RESIST from 91.4% to 96.5% of

the prescribed dose. The RESIST plans exhibited RTOG conformity index and PCN values closer to unity than the single-isocenter VMAT plans, suggesting that the RESIST method can produce more conformal dose distributions than the original clinical method. Gradient index ($p < 0.001$) and maximum dose 2 cm away from the PTV in any direction ($p = 0.02$) were improved significantly with RESIST suggesting less intermediate dose-spillage in the uninvolved lung.

Table 4.2: Analysis of the target coverage of the dosimetric parameters for all 21 lung SBRT patients treated with single-isocenter/multiple-lesions VMAT compared to RESIST plans. Mean ± STD (range) and p-values were reported. Significant values are highlighted in bold. STD = standard deviation. PCN = Paddick Conformation Number. CI = conformity index. HI = heterogeneity index.

Target	Parameter	Clinical VMAT plans	RESIST VMAT plans	*p*-value
PTV (n = 42)	% Vol. covered by Rx dose (%)	96.3 ± 1.3 (94.8–99.3)	96.1 ± 0.8 (94.9–98.3)	*p = 0.1*
	CI	1.04 ± 0.05 (0.96–1.21)	1.02 ± 0.03 (0.97–1.09)	***p = 0.003***
	PCN	0.88 ± 0.03 (0.81–0.96)	0.90 ± 0.03 (0.85–0.95)	***p < 0.001***
	HI	1.21 ± 0.3 (1.13–1.31)	1.19 ± 0.04 (1.11–1.28)	***p = 0.005***
	GI	5.77 ± 2.46 (3.60–17.6)	4.92 ± 0.98 (3.45–8.15)	***p < 0.001***
	D2cm (%)	53.3 ± 5.3 (46.5–67.0)	51.6 ± 3.6 (45.0–61.3)	***p = 0.02***
GTV (n = 42)	Minimum dose (%)	108.4 ± 4.7 (91.4–117.3)	107.5 ± 4.9 (95.6–117.1)	*p = 0.1*
	Maximum dose (%)	120.9 ± 3.6 (113.2–129.4)	119.1 ± 3.7 (111.7–128.1)	***p = 0.001***
	Mean dose (%)	114.8 ± 2.8 (110.1–120.3)	113.7 ± 3.8 (107.8–122.6)	***p = 0.04***

Table 4.3 shows the dose differences for the OAR between the clinical VMAT and RESIST VMAT plans. The average differences between all OAR maximum and volumetric doses were positive values, demonstrating that on average RESIST can decrease the dose to all OAR. Furthermore, RESIST significantly reduced the uninvolved

lung V10Gy by 3.4% (up to 13.9%) and, in all cases, reduced MLD by about 0.7 Gy (up to

2.0 Gy) and V20Gy by 1.0% (up to 3.2%), on average. On a case-by-case basis, some OAR

doses slightly increased using the RESIST method shown as negative values (see **Table

4.3**). This can be attributed to the fact that for certain tumor arrangements (unilateral lesions

in the same axial plane), more arcs utilized similar geometry and thus deliver more MU to

the same organ. However, this increase in dose was minimal, with the biggest difference

being seen for 1 cc of ribs where one RESIST plan delivered was about 4.0 Gy more than

the clinical plan, still well below the SBRT protocol limits. For many cases, the decrease

in OAR dose from the clinical VMAT plan to the RESIST plan was dramatic due to better

beam geometry. For example, a decrease of 5.8 Gy for the spinal cord maximum is

observed in an example case. This dose drop can be attributed to optimal arc geometry

decreasing the need to treat the target through critical structures, such as the spinal cord.

Similarly, in some instances, the maximal dose to heart and esophagus were decreased by

up to 7.2 Gy and 9.2 Gy (see **Table 4.3**), respectively.

Table 4.3: Evaluation of dose to OAR for all 21 multi-lesions lung SBRT patients for both plans. Mean ± SD (range) was reported. SD = standard deviation. MLD = mean lung dose. Statistically significant p-values are highlighted in bold.

Dose to OAR	Parameters	Difference = Clinical minus RESIST plan	*p*-value
Spinal cord (Gy)	D_{max}	0.73 ± 1.98 (-2.02 – 5.81)	*p = 0.06*
	$D_{0.35cc}$	0.68 ± 1.8 (-1.97 – 5.07)	*p = 0.05*
Heart/pericardium (Gy)	D_{max}	2.21 ± 2.6 (-1.61 – 7.17)	***p < 0.001***
	D_{15cc}	2.61 ± 1.82 (0.03 – 6.94)	***p < 0.001***
Esophagus (Gy)	D_{max}	1.83 ± 2.99 (-1.9 – 9.14)	***p < 0.001***
	D_{5cc}	2.43 ± 2.67 (-0.95 – 7.87)	***p < 0.001***
Trachea/bronchus (Gy)	D_{max}	1.15 ± 2.53 (-2.24 – 6.46)	***p = 0.03***
	D_{4cc}	2.08 ± 2.48 (-1.31 – 6.93)	***p < 0.001***
Skin (Gy)	D_{max}	0.32 ± 1.59 (-2.76 – 3.68)	*p = 0.2*
	D_{10cc}	0.88 ± 0.93 (-0.7 – 2.94)	***p < 0.001***
Ribs (Gy)	D_{max}	1.58 ± 2.07 (-2.0 – 7.73)	***p = 0.001***
	D_{1cc}	0.13 ± 1.61 (-4.36 – 3.16)	*p = 0.4*

Table 4.3 (Continued)

Uninvolved lung	MLD (Gy)	$0.65 \pm 0.53 \ (0.01 - 1.96)$	*p < 0.001*
	V_{20Gy} (%)	$0.99 \pm 0.87 \ (0.03 - 3.14)$	**p < 0.001**
	V_{10Gy} (%)	$3.43 \pm 3.46 \ (-2.02 - 13.9)$	**p < 0.001**

In **Figures 4.2** and **4.3**, the benefits of RESIST beam geometry are demonstrated. With RESIST, because the isocenter is always placed at the patient's midline, partial arcs of 180° arc length are always achievable on the tumor side of the patient. With RESIST, highly conformal and much tighter target dose distributions with less 50% isodose spillage were achieved (**Figure 4.2**). RESIST isocenter placement avoids collisions and minimizes uninvolved lung dose with local jaw tracking to each tumor one at a time. Smaller jaw tracking field sizes are seen with the RESIST plan. Additionally, a significantly lower dose to the critical structures including ribs was achieved due to the patient's midline isocenter placement allowing for arcs to be utilized on both sides of the patient (**Figure 4.3**).
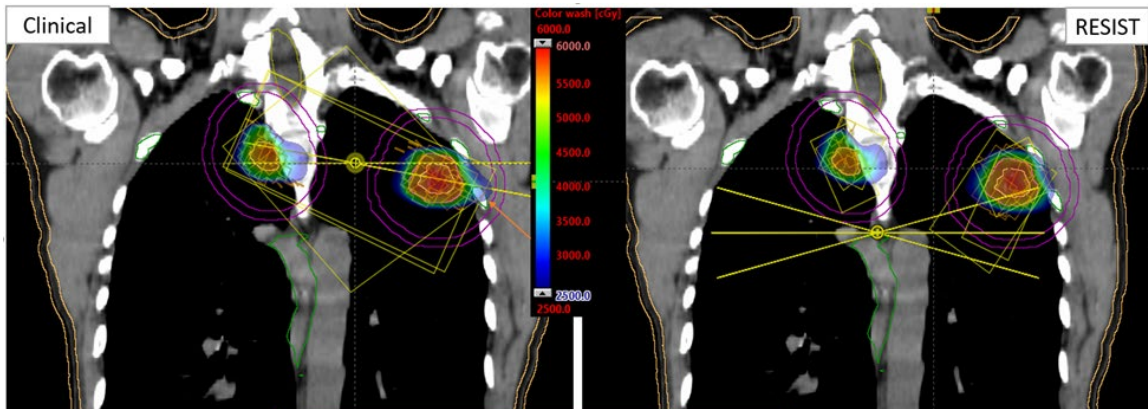
Figure 4.2: Coronal view for an example clinical plan (left panel) and the RESIST plan sum (right panel), each lesion was treated for 50 Gy in 5 fractions synchronously. The isocenter placement at the patient's mediastinum is shown for RESIST, allowing for optimal partial non-coplanar arcs to be utilized in both directions, compared to only one couch rotation was possible in the clinical plan for this patient due to possible collisions.
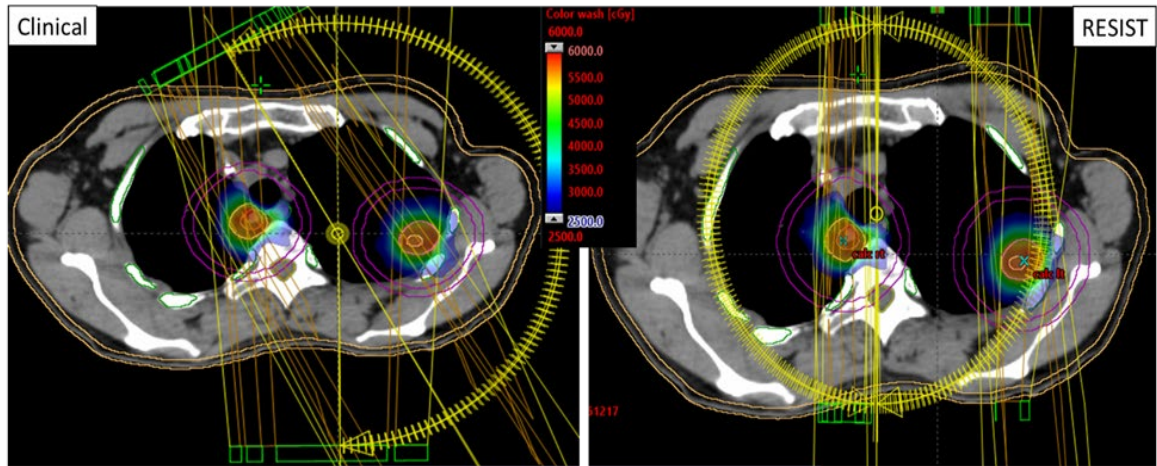
Figure 4.3: Axial view for the same example patient.
In the clinical VMAT plan, the isocenter placement restricted dose delivery for the lesion in the right lung to be primarily exit dose through the critical structures such as spinal cord, esophagus and left lung. The patient midline isocenter placement with RESIST allowed for optimal arcs on both sides of the patient, permitting lower OAR doses as well as more conformal target dose distribution to each lesion.

Figure 4.4 demonstrates the special case when both lesions are in close proximity of one another. Placing the isocenter at patient's midline allowed for non-coplanar arc geometry without risk of patient collision, which was beneficial even in the case like this. Because both lesions are planned separately, with RESIST the MLCs are not required to move between the lesions and jaw tracking was restricted to one single lesion at a time. Thus, the uninvolved lung dose between the lesions was reduced significantly as demonstrated by the reduced 50% isodose volume. Likewise, it lowered V20Gy by 1.5%, V10Gy by 1.7% and MLD by 0.7 Gy. RESIST significantly improved the GI for both targets at 5.2 and 6.3 compared to 12.7 and 17.6 for the original clinical VMAT plan.
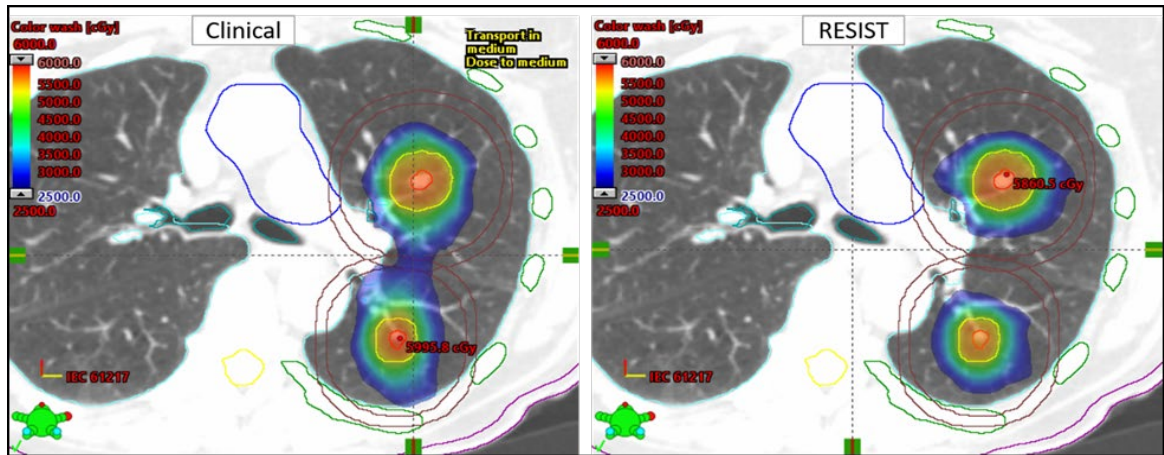
Figure 4.4: This is an example case of two lesions near one another.
Each lesion was prescribed 50 Gy in 5 fractions synchronously using a clinical single-isocenter VMAT plan. Structures contoured include total lung (light blue), heart (blue), cord (yellow), ribs (green), and skin (purple), PTVs (orange) and the GTVs (red). A 2 cm expansion is contoured around each PTV (brown). RESIST plan sum (right panel) demonstrated a highly conformal dose distribution to both lesions with no 50% dose bridging between the lesions (see blue dose color wash)

4.3.2 Treatment Delivery Parameters

The improvement of treatment delivery efficiency and accuracy is associated with Eclipse's new feature of adjustable aperture shape control priority and the initial DCA-based dose calculation before the VMAT optimization (Eclipse, Version 15.6). With this new feature, less beam modulation through the PTVs was observed thus reducing the uncertainty of modeling small-field dosimetry. Total MU per fraction for the RESIST plans (2 plans with a single-isocenter placed at patient's midline) increased by a factor of 1.7 on average, compared to single-isocenter clinical VMAT. Although the beam on time is increased for the RESIST plans, the average modulation factor for these plans is reduced significantly ($p < 0.001$), as shown in **Table 4.4**, potentially improving the treatment delivery accuracy.

Table 4.4: Comparison of average values of treatment delivery parameters (and range) between clinical VMAT and RESIST plans for all 21 lung SBRT patients. Mean ± SD (range) was reported. SD = standard deviation. Statistically significant p-values are highlighted in bold.

Beam delivery parameters	Clinical VMAT	RESIST VMAT	*p*-value
Total MU per fraction	5130 ± 1977 (2784–10727)	8793 ± 2572 (5605–15537)	***p < 0.001***
Modulation factor (MF)	4.2 ± 1.3 (2.8–8.6)	3.5 ± 0.7 (1.9–5.1)	***p < 0.001***
Beam-on time (min)	3.7 ± 1.4 (2.0–7.7)	6.3 ± 1.8 (4.0–11.1)	***p = 0.01***
Treatment time (min)	17.7 ± 1.4 (16.0–21.7)	24.3 ± 1.8 (22.0–29.1)	***p < 0.001***

The estimated mean treatment time for both plans (including patient setup, CBCT imaging, and tumor matching) was 17.7 minutes for clinical VMAT versus 24.3 minutes for RESIST. The estimated time for initial patient setup on the machine is about 10 minutes and the estimated time to complete one CBCT is 1 minute followed by another about 3 minutes for tumor matching and applying shifts. Although the treatment time is longer for RESIST when accounting for the possibility of a second CBCT scan and tumor matching, there will be reduced geometric uncertainties and reduced likelihood of a geometric miss. The RESIST treatments are still reasonably achievable in the standard 30-minute time slot usually allotted to treat SBRT patients. As previously demonstrated, small setup errors in single-isocenter SBRT treatments to two lesions at the same time could potentially produce a large decrement in target coverage if the tumors could not line up correctly on a single daily CBCT. These errors could be avoided by setting up and treating one lesion at a time using the novel RESIST method.

4.4   Discussion

A novel and clinically useful RESIST method for synchronous multiple lung lesions that minimizes setup uncertainties is described. Twenty-one patients with two

lesions were treated with a single-isocenter VMAT-SBRT plan with the isocenter placed between the lesions. Each patient was replanned using the RESIST method with a single isocenter placed at the patient's midline and each tumor was separately optimized in an individual plan. Each RESIST plan utilized the same number of arcs, couch rotations, and planning selections including the use of DCA-based dose, ASC, PO MLC algorithm and advanced AcurosXB dose calculation. RESIST plans exhibited more conformal target dose distribution with improved conformity and gradient indices compared to clinical single-isocenter VMAT plans. Additionally, the average dose to all adjacent critical structures was decreased, including the uninvolved lung dose potentially reducing the rate of radiation-induced pneumonitis.[23]

The average modulation factor for the individual RESIST plans was reduced compared to the original clinical plans. This reduction in plan complexity can be attributed to the use of an initial DCA-based dose calculation, ASC, and PO MLC algorithm. Although multiple studies suggest that interplay effect is minimal in multi-fraction lung SBRT treated with VMAT[24, 25], reducing plan complexity can also reduce treatment time and MLC position errors, improving accurate dose delivery by reducing small-field dosimetry errors.[26, 27] The RESIST method further improves accurate dose delivery by allowing each lesion to be lined up individually during daily pre-treatment CBCT scan. **Figure 4.5** describes the treatment delivery workflow for the RESIST patients. With the current clinical VMAT plan, the physician must line up both lesions on a single CBCT scan. If both lesions do not line up, possibly due to tumor deformation or a change in tumor motion, the physician must make one of two decisions: they may "split-the-difference" between the lesions (which is not recommended), risking target coverage loss due to

geometric misalignment, or they may need to setup and re-image the patient again. If they opt for the second option and the lesions do not line up, the physician may need to abandon the treatment and try again another day or re-plan the treatment thus adding burden to the radiation therapists and SBRT team.

In a study by Quan *et al*, it was suggested that when treating multiple lesions with VMAT or intensity-modulated radiosurgery the event of multiple lesions not lining up during pre-treatment imaging would cause the treatment to be abandoned.[7] Using the RESIST method, if both lesions do not line up during the first daily CBCT the physician can choose to line up the first tumor and treat the first plan then repeat the second CBCT, match the second tumor and treat the second plan. In between the plans, the therapists do not need to enter the room to reposition the patient because the plans share the same isocenter and the isocenter placement at patient midline ensures the CBCT will clear the patient without applying a couch shift (shift needed for Varian Linac/couch for off-center patients > 5 cm laterally). Likewise, the physician can choose to treat only one lesion per treatment without causing any error in dose tracking. We have demonstrated that in the case of two CBCT scans needed, the treatment still falls within the usually allotted 30-min treatment time slot for SBRT patients. In addition to minimizing the potential geometric misses, this workflow allows for more flexibility for treating synchronous multiple lung SBRT lesions by allowing patients to take breaks in between tumors or allowing physician to treat different tumors at different days to manage lung toxicity.
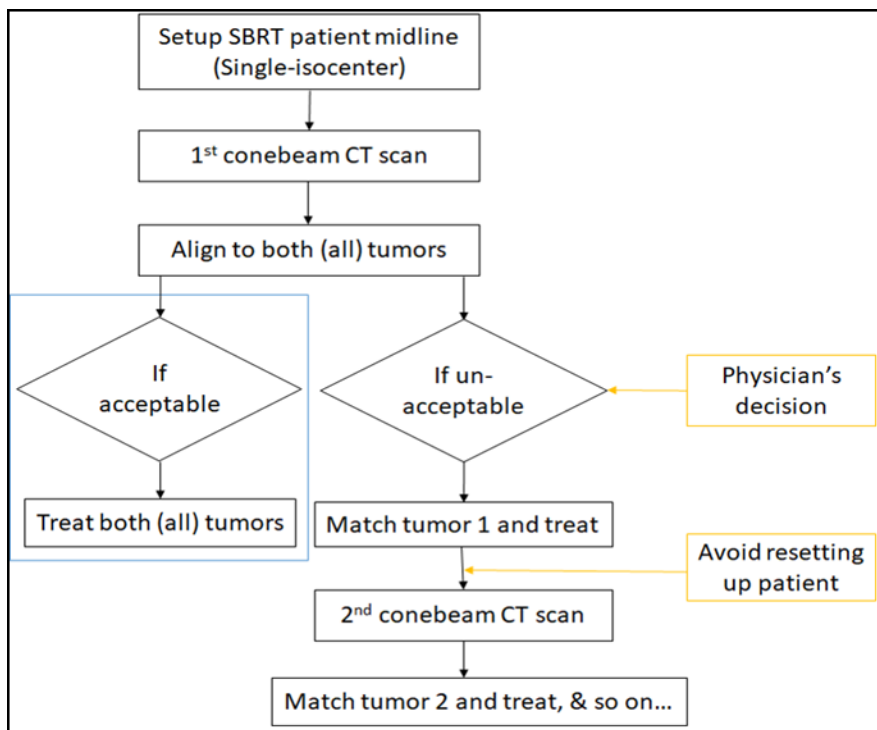
Figure 4.5: The proposed RESIST treatment delivery workflow for single-isocenter/multiple-lesions VMAT lung SBRT.
The physician has the option to set up all tumors at the same time (left blue box) or match one tumor at a time and treat without entering the treatment room for resetting up the patient for the second CBCT scan.

Trager *et al* from Duke University Medical Center devised a method for mitigating setup uncertainties in single-isocenter/multiple lesion SBRT treatments.[28] The authors determined that approximately 30% of fractions required a correction in order to accurately line up both lesions. Their solution to this problem utilized a single-isocenter shared between two lesions, but each lesion was optimized with its own arc. The authors also identified that beginning each plan with DCA-based dose calculation decreased the plan complexity. Although their method is a viable option for minimizing setup uncertainties, the study primarily focused on phantom-based plans with only one lung plan demonstrated. With only one arc per plan and the use of inferior dose calculation algorithm, Anisotropic Analytical Algorithm (Varian Medical Systems, Palo Alto, CA), their method does not take

full advantage of the proven benefit of non-coplanar arc geometry and the improved dose calculation abilities of AcurosXB.[29-31] Furthermore, their method did not provide further guidance for treatment planners concerning isocenter placement and clearance issues. In contrast, this study has presented a comprehensive treatment planning and more accurate delivery approach for the cohort of two lesion lung SBRT patients. This method minimizes setup uncertainties, improves target dose conformality, reduces dose to adjacent critical structures and reduces plan complexity in addition to simplifying treatment planning and treatment delivery. Although, overall treatment time was longer with RESIST method compared to clinical VMAT plans, the treatment time using RESIST will still be much shorter than utilizing traditional multiple isocenters 3D-conformal or VMAT SBRT treatments, robotic CyberKnife treatment to lung lesions (45 minutes for one tumor) or SBRT treatments on Tomotherapy unit (40-50 minutes).[32-34] Future work includes clinical implementation of RESIST technique including more than two tumors in the same session. Moreover, to further simplify the RESIST planning process, the creation of a template treatment plan module in Eclipse TPS is ongoing. This template treatment plan will further simplify the treatment planning process and improve delivery accuracy of RESIST. This method can be expanded further to other treatment sites such as multiple lesion liver SBRT or abdominal and pelvic node SBRT.

4.5 Conclusion

Using RESIST to treat synchronous lung lesions with VMAT-SBRT can significantly improve target dose conformality, reduce dose to adjacent OAR while reducing the chance of a geometric miss due to setup uncertainties by allowing for individual tumor matching. Placement of single-isocenter at patient's mediastinum will

avoid potential patient's collision with the gantry head, provide greater degrees of non-coplanar arcs and eliminate the need for multiple couch movements during CBCT imaging for off-center lesions. RESIST has been demonstrated for two tumors but can be used for more. Further clinical validation of this novel technique is ongoing.

CHAPTER 5. AUTOMATION AND INTEGRATION OF RESTRICTED SINGLE-ISOCENTER STEREOTACTIC BODY RADIOTHERAPY (RESIST) METHOD FOR SYNCHRONOUS MULTIPLE LUNG LESIONS

The following chapter has been adapted from a manuscript currently under review for publication: Lana Sanford Critchfield, Justin Visak, Mark Bernard, Marcus Randall, Ronald McGarry, Damodar Pokhrel, "Automation and Integration of Restricted Single-Isocenter Stereotactic Body Radiotherapy (RESIST) Method for Synchronous Multiple Lung Lesions", *J Appl Clin Med Phys,* September 29, 2020.

Abstract

Synchronous treatment of two lung lesions using a single-isocenter volumetric modulated arc therapy (VMAT) stereotactic body radiation therapy (SBRT) plan can decrease treatment time and reduce the impact of intrafraction motion. However, alignment on a single cone beam CT (CBCT) can prove difficult and may lead to setup errors and unacceptable target coverage loss. A Restricted Single-Isocenter Stereotactic Body Radiotherapy (RESIST) method was created to minimize setup uncertainties and provide treatment delivery flexibility. RESIST utilizes a single isocenter placed at midline and allows both lesions to be planned separately but treated in the same session. Herein is described a process of automation for the RESIST method. Automation of RESIST significantly reduced treatment planning time while maintaining the benefits of RESIST. To demonstrate feasibility, ten patients with two lung lesions previously treated with single-isocenter clinical VMAT plan were replanned manually with RESIST (*m*-RESIST) and with automated RESIST (*a*-RESIST). The *a*-RESIST method automatically sets isocenter, creates beam geometry, choses appropriate dose calculation algorithms, and performs VMAT optimization using an in-house trained knowledge-based planning model

for lung SBRT. Both *m*-RESIST and *a*-RESIST showed lower dose to normal tissues compared to manually planned clinical VMAT although *a*-RESIST provided slightly inferior, but still clinically acceptable, dose conformity and gradient indices. However, *a*-RESIST significantly reduced the planning time to less than 20 minutes and provided a higher dose to the lung tumors. The *a*-RESIST method provides guidance for inexperienced planners by standardizing beam geometry and plan optimization using DVH estimates. It produces clinically acceptable two lesion VMAT lung SBRT plans efficiently. Further development of *a*-RESIST for more than two lung lesions and refining this approach for extracranial oligometastastic abdominal/pelvic SBRT, including development of simulated collision detection, merits future investigation.

5.1 Introduction

Stereotactic body radiation therapy (SBRT) of synchronous multiple primary or metastatic lung lesions can result in excessively long treatment times for patients and busy clinics. To alleviate this, a single-isocenter intensity modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) SBRT plan is a feasible treatment option for patients presenting with synchronous multiple metastatic or primary lung lesions. [1-5] SBRT of two lung lesions with a single-isocenter VMAT plan decreases treatment delivery time, increases patient comfort, and reduces the chance of intrafraction tumor motion errors.[5] However, small setup errors may occur due to the difficulties of multiple lung lesion alignment on a single cone beam CT (CBCT) scan. These small setup errors may lead to unacceptable loss in target coverage due to lung heterogeneities and the steep dose gradients obtained in SBRT. [6] Thus, a Restricted Single-Isocenter Stereotactic Body Radiotherapy (RESIST) method was developed to minimize the problems associated with

single-isocenter VMAT lung SBRT (e.g., setup errors, collision issues). [7] It has been reported that patient outcome is related to a clinic's experience in delivery of SBRT.[8] There are no definitive planning guidelines for inexperienced clinics in the treatment of multiple lesion lung SBRT who wish to treat their patients efficiently and accurately.

Recently, investigators have presented work on the use of automation for generating lung SBRT treatment plans using a knowledge-based planning (KBP) approach with dose volume histogram estimates via RapidPlan (RP) modeling (Varian Medical Systems, Palo Alto CA).[9-11] KBP models can generate plans quickly and improve plan quality and consistency by reducing inter-planner variability. These models are trained using previously treated high quality treatment plans and provide a good starting point for subsequent plan optimization. However, there has yet to be a KBP model to automate treatment planning for multi-lesion lung SBRT. In order to guide planners in generating single-isocenter/two-lesion VMAT lung SBRT plans, an automated treatment planning routine (*a*-RESIST) has been developed using the RESIST planning geometry, which is further optimized using an in-house trained KBP lung SBRT model. [10] This report aims to demonstrate the feasibility of the *a*-RESIST planning technique and its ability to assist planners in improving planning efficiency, consistency and accuracy. Further, this report also provides guidance for automating treatments for fast and effective synchronous multiple lesion lung SBRT.

5.2   Materials and Methods

After obtaining institutional review board approval, ten patients were selected with two lung tumors each who were previously treated to 50 Gy in 5 fractions using a single-

isocenter VMAT lung SBRT. For each patient, both lesions were treated at the same time every other day.

5.2.1 CT Simulation and Contouring

Patients were immobilized with the Body Pro-Lok[TM] SBRT system (CIVCO, Orange City, IA) in the supine position with arms up. A simulation CT scan was obtained on a GE Lightspeed 16 slice CT scanner (General Electric Medical Systems, Waukesha, WI) with 512×512 pixel image size and 2.5 mm slice thickness in the axial helical mode. For respiratory control, most patients tolerated abdominal compression, if not a 4D-CT scan was obtained by utilizing Varian RPM system (version 1.7). Images were imported into the Eclipse Treatment Planning System (TPS, Version 15.6, Varian Medical Systems, Palo Alto, CA).[12] Gross tumor volumes (GTVs) were contoured based on the observable tumor mass. If a 4D-CT was obtained, internal target volumes (ITVs) were contoured based on maximum intensity projection (MIP) co-registered with the free breathing planning CT images. A planning target volume (PTV) was created by expanding the GTV by 10 mm in the superior-inferior direction and 5 mm in the lateral directions (abdominal compression) or expanding the ITV with a uniform 5 mm margin (4D-CT). Critical structures were contoured, including normal lung (right, left and combined), spinal cord, heart, bronchus, trachea, esophagus, skin and individual ribs (right, left and combined) per RTOG requirements.[13, 14] **Table 5.1** summarizes the tumor characteristics and tumor distance to isocenter for the ten multi-lesions lung SBRT patients included. Distance to isocenter was calculated by finding the Cartesian coordinates of the PTV geometric center and determining the Euclidian 3D distance with the isocenter coordinates for each plan.

Table 5.1: Main tumor characteristics of the 10 lung SBRT patients included in this study. Each patient had 2 tumors. STD = standard deviation.

Parameters and plans		Mean ± STD (range or n = no. of patients)
Tumor 1, PTV1 (cc) Tumor 2, PTV2 (cc)		21.35 ± 17.16 (6.5 – 69.6) 21.95 ± 13.06 (6.38 – 40.9)
Prescribed dose to each lesion		50 Gy in 5 fractions
Tumor location (left/right/bi-lateral lungs)		(n = 4 / 1 / 5)
Normal lung (cc)		3837.3 ± 1171.2 (2041 – 6542)
Isocenter to tumor distance (cm)	Clinical plans	5.5 ± 2.3 (2.4 – 9.2)
	m-RESIST plans	7.4 ± 2.0 (3.2 – 11.3)
	a-RESIST plans	8.1 ± 2.1 (4.5 – 10.9)

5.2.2   Clinical VMAT Plans

A single-isocenter lung SBRT plan was generated in Eclipse TPS to be treated with a Truebeam Linac (Varian Medical Systems, Palo Alto, CA) with the Millennium 120 MLC. All plans were VMAT utilizing 6MV-FFF (1400 MU/min) beams. The isocenter was placed approximately between the two tumors. For patients who presented with bilateral tumors or select unilateral tumors, two to three full coplanar arcs were used for treatment. For the remaining unilateral cases, three to five partial coplanner or non-coplanar arcs with couch rotations up to ± 10° were utilized (planner preference). Collimator angles were manually chosen to reduce the MLC leakage dose between each arc with the jaw-tracking feature enabled.[16] Dose was 50 Gy in 5 fractions for all patients. Target naming convention (PTV1 or PTV2) was chosen by the treating physician. Both PTVs were planned with dose prescribed to the 70-80% isodose lines and optimized such that at least 95% of each PTV received 100% of the prescription dose. The maximum dose to each target was planned to fall inside the GTV. Dose was calculated using the Boltzmann transport based AcurosXB algorithm in Eclipse with heterogeneity corrections with a 1.25

mm calculation grid size (CGS).[12] Reporting dose to medium and photon optimizer (PO) MLC algorithm was used. Although single-isocenter SBRT was designed for synchronous treatment of two lesions, planning objectives per RTOG protocols and NRG-BR001 were utilized for the organs-at-risk (OAR).[1, 13-15] Each patient was treated every other day with the VMAT planning technique using an in-house CBCT-guided lung SBRT protocol.

5.2.3   *m*-RESIST VMAT Plans

Each patient's clinical treatment plan was replanned using the manual RESIST (*m*-RESIST) method. The *m*-RESIST method places isocenter at the patient's midline and both tumors share the treatment isocenter. If the lesions are separated in the x-direction, the isocenter is placed approximately between the lesions in the mid-coronal plane of the patient. A separate plan is made for PTV1 and PTV2. Each plan has 3 partial non-coplanar VMAT arcs with a 6 MV FFF (1400 MU/min) beam deployed on the tumor side of the patient. Couch rotations were 0°, 10° and 350° for each beam, respectively. Collimator angles were offset by 30° to reduce leakage dose in the same plane and were chosen to ensure the MLCs can travel to the PTV locations. The aperture shape controller (ACS) in the PO MLC algorithm was set to 'very high' in order to reduce the total number of monitor units, reduce plan complexity and improve plan quality.[17, 18] The m-RESIST plans were created by fitting the MLCs to PTV1 and then calculating the dynamic conformal arc (DCA) dose for the respective plan. Next, standard manual VMAT optimization began for PTV1 and GTV1 coverage. The jaw tracking option was employed to reduce leakage dose to normal lung as described above.[16] Once dose calculation was complete, the plan for PTV1 was used as a base-dose plan before VMAT optimization in the plan for PTV2. The

PTV2 plan was optimized for coverage to PTV2 and GTV2 and to spare the OAR. Once optimized and calculated, a *m*-RESIST plan summation was created with both plans and re-normalized to account for contribution from each plan. The plans were then evaluated per lung SBRT protocols.

5.2.4 *a*-RESIST VMAT Plans

Varian Eclipse Scripting Application Programming Interface (ESAPI, Version 15.5) allows for integration of writable scripts and supports the automation of SBRT plans.[19] A script (*a*-RESIST) was developed using Microsoft Visual Studio written in C# with guidance from the Varian APIs handbook. [20] Running the script in external beam planning will begin the *a*-RESIST treatment planning method and selects the appropriate patient's planning CT dataset and structure set. Utilizing *a*-RESIST automation requires precise structure naming convention chosen based on institution standards (such as PTV1, PTV2, Lt ribs etc.). The *a*-RESIST automation routine includes the following:

1. Creation of treatment course *AutoPlan RESIST* and creation of two plans: *RESIST PTV1* and *RESIST PTV2*.

2. Placement of single treatment isocenter with x- and y- based on the coordinates of the spinal cord contour and z- being the axial plane between the two PTVs.

3. Selection of machine (Truebeam Linac), energy (6MV FFF), VMAT arc geometry, and dose rate (1400 MU/min).

4. Creation of 3 partial arcs from 0° to 180° (CW and CCW direction) on the PTV side of the patient.

5.   Offset collimator angles based on PTVs distance to isocenter to allow for optimal MLC travel distance to PTVs.

6.   Selection of appropriate dose calculation algorithms (AcurosXB, PO, VMAT optimization, DVH Estimates algorithm).

7.   Application of normal tissue objective and jaw tracking to be used in optimization.

8.   Optimization of plans using an in-house KBP model for lung SBRT.[11]

Figure 5.1 demonstrates the automated (dashed box) and user input sections of the planning workflow for *a*-RESIST. After dose calculation of the first plan (*RESIST PTV1*), this plan is chosen as the base-dose plan for the second plan (*RESIST PTV2)*. The second plan is optimized and dose is calculated. A plan summation is then created by the user and plans are renormalized (if needed) together such that 95% of each PTV receives 100% of the prescription dose. The user can adjust the plans from there, further re-optimizing the plans (if needed) including adjusting the beam geometry for better coverage or normal tissue sparing.
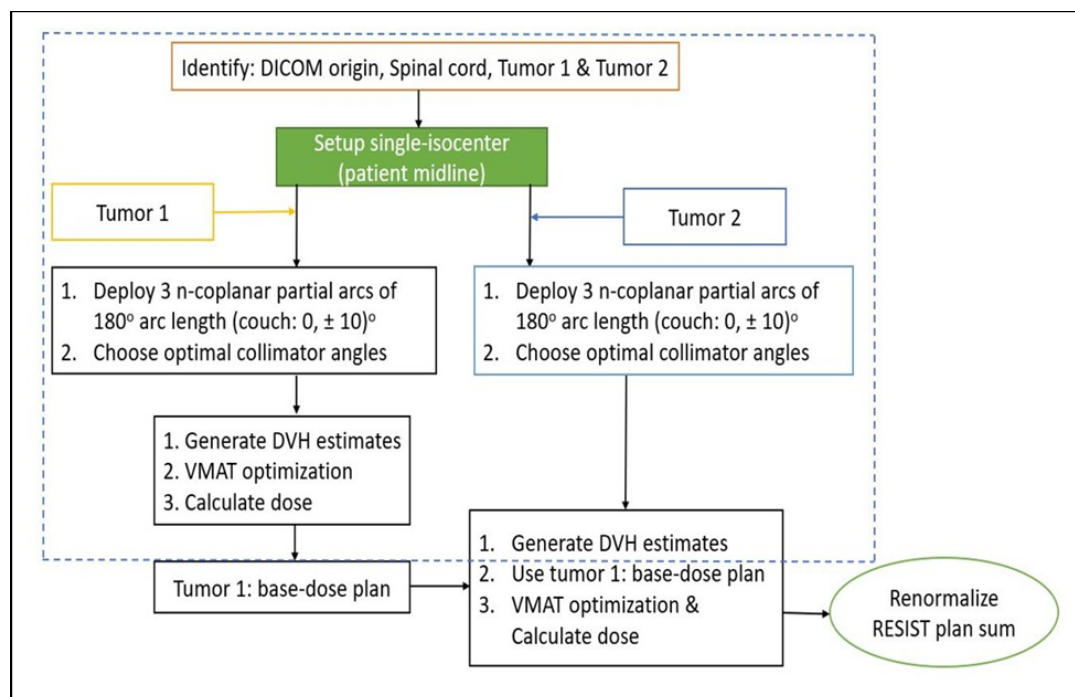
Figure 5.1: The *a*-RESIST treatment planning workflow for a single-isocenter/two lesions VMAT lung SBRT.
The selections in the dashed blue box were deployed by the automated treatment planning script. Utilizing *a*-RESIST reduces the treatment planning time and ensures standardized plans for synchronous multi-lesion lung SBRT.

5.2.5   Plan Comparison and Data Analysis

Plans were compared per RTOG guidelines for target conformity (CI), tumor dose heterogeneity (HI), gradient index (GI) and intermediate dose spillage at 2 cm away in any direction for each target (D2cm).[1,5,14,15]Additionally, Paddick conformation number (PCN) was calculated for each target.[21] Minimum, maximum and mean dose to each GTV was assessed. Doses to OAR that were evaluated included maximum dose to 0.03 cc of ribs, spinal cord, heart, bronchial tree, esophagus and skin. Volumetric doses to OAR's were also evaluated for 1 cc of ribs, 0.35 cc of spinal cord, 15 cc of heart, 4 cc of bronchial tree/trachea, 5 cc of esophagus and 10 cc of skin. Lung doses were evaluated for percentage of normal lung receiving 10 Gy (V10Gy) and 20 Gy (V20Gy) or more and the mean lung dose (MLD). Moreover, overall treatment planning time was estimated for all 3 plans.

Statistical analysis was performed using Microsoft Excel (Microsoft Corp, Redmond WA) program. Mean, standard deviation (STD) and range values for each of the dose metrics were compared for all 3 plans.

5.3 Results

5.3.1 Target Coverage and Dose to OAR

All *a*-RESIST plans demonstrated acceptable target coverage per SBRT protocols, as shown in **Table 5.2**. For similar target coverage, *a*-RESIST plans provided slightly inferior CI and D2cm compared to both clinical VMAT and *m*-RESIST plans; however, GI was slightly better with *a*-RESIST plan. The large GI values reported for clinical VMAT are due to dose bridging between lesions that is eliminated using RESIST methods. Likewise, *a*-RESIST show inferior PCN compared to *m*-RESIST plan. These discrepancies are likely attributed to the use of KBP model generating *a*-RESIST plans slightly inferior to manually optimized treatment plans. This slight degradation can be accounted for given that the KBP model was originally developed for single-lesion SBRT plans, i.e. the input data in the model did not include plans that included a base dose thus affecting model performance. However, the KBP model helped to produce *a*-RESIST plans with higher GTV minimum, maximum and mean doses compared to the other planning strategies (see **Table 5.2**). This dose escalation is desirable in SBRT since normal tissue dosing was still acceptable. For instance, the mean GTV dose for *a*-RESIST was 7% and 6% higher (up to 3.5 Gy) compared to *m*-RESIST and clinical VMAT plans, respectively.

Table 5.2: Analysis of the target coverage of the dosimetric parameters for 10 lung SBRT patients. Mean ± STD (range). STD = standard deviation. PCN = Paddick Conformation Number. CI = conformity index. HI = heterogeneity index. n = number of targets.

Target	Parameter	Clinical VMAT	m-RESIST	a-RESIST
PTV (n = 20)	% Vol. covered by Rx dose (%)	96.2 ± 1.0 (94.8–99.0)	95.8 ± 0.4 (95.1–96.8)	95.9 ± 0.7 (95.2–98.1)
	CI	1.04 ± 0.05 (0.97–1.21)	1.02 ± 0.03 (0.97–1.09)	1.06 ± 0.03 (0.99–1.16)
	PCN	0.88 ± 0.03 (0.81–0.94)	0.90 ± 0.02 (0.85–0.93)	0.88± 0.02 (0.80–0.92)
	HI	1.21 ± 0.3 (1.15–1.26)	1.19 ± 0.04 (1.16–1.28)	1.26 ± 0.04 (1.20–1.34)
	GI	6.13 ± 3.20 (3.60–17.6)	4.83 ± 0.76 (3.53–6.28)	4.56 ± 0.65 (3.71–5.93)
	D2cm (%)	54.4 ± 5.8 (47.6–67.0)	51.0 ± 3.7 (44.9–61.3)	55.2 ± 4.9 (43.7–64.3)
GTV (n = 20)	Minimum dose (%)	107.9 ± 3.5 (102.8–114.4)	106.5 ± 4.5 (98.9–115.5)	114.6 ± 3.3 (106.8–120.9)
	Maximum dose (%)	121.1 ± 2.9 (114.8–125.5)	118.8 ± 3.9 (113.4–128.1)	126.1 ± 4.2 (120–134.1)
	Mean dose (%)	114.3 ± 2.1 (111.5–119.2)	113.0 ± 3.6 (107.8–122.6)	120.4 ± 4.9 (106.9–130.3)

Figure 5.2 demonstrates the pairwise differences for the OAR doses for m-RESIST and a-RESIST plans with respect to clinical VMAT plans. The average difference between clinical VMAT and m-RESIST for all maximum and volumetric OAR doses is a positive value, suggesting that in all cases the doses to OAR were lower using m-RESIST compared to clinical VMAT plans. In comparison, the majority of the average differences between clinical VMAT and a-RESIST were positive values. However, the average difference for 0.03 cc and 0.35 cc of spinal cord and 5 cc of esophagus were all negative values, at -0.7 Gy, -0.8 Gy and -0.4 Gy, respectively. These small OAR sparing discrepancies (< 1.0 Gy) suggest a-RESIST plans were as good as clinical VMAT and m-RESIST plans.
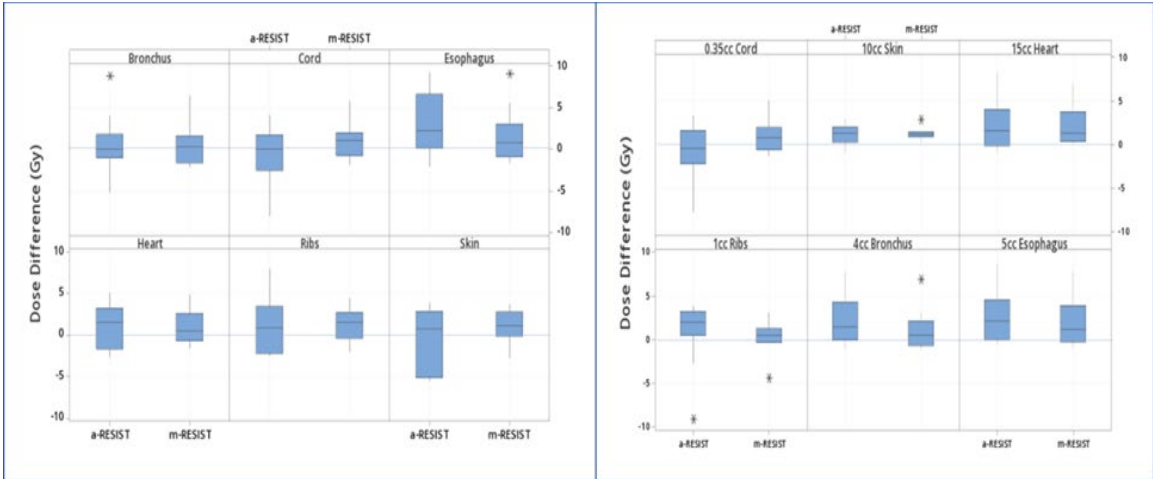
Figure 5.2: The pairwise differences between clinical VMAT and *a*-RESIST plans and clinical VMAT and *m*-RESIST for maximum (left panel) and volumetric (right panel) doses to OAR. The stars represent outlier data points.

The average difference between clinical VMAT and *m*-RESIST for normal lung V20Gy, V10Gy and MLD was $0.8 \pm 0.9\%$ (0.03–2.9%), $3.1 \pm 4.3\%$ (-2.0–13.9%), 0.5 ± 0.6 Gy (0.01–1.8 Gy), respectively. Corresponding average difference for those variables between the clinical VMAT and *a*-RESIST were $0.8 \pm 1.9\%$ (-3.6–3.8%), $3.2 \pm 7.0\%$ (-12.6–16.4%), 0.3 ± 1.3 Gy (-2.9–2.2 Gy), respectively. This data indicates that, in general, both *m*-RESIST and *a*-RESIST can provide better normal lung sparing compared to original clinical VMAT plans. However, occasionally *a*-RESIST produces plans with more lung dose as can be seen by the negative values for V20Gy, V10Gy and MLD. This can be attributed to less than ideal isocenter placement and more intermediate dose-spillage associated with the KBP model for VMAT optimization. An example of isocenter placement and beam geometry used by all 3 planning approaches can be seen in **Figure 5.3** (unilateral lung lesions). For the clinical VMAT plan, the isocenter placement is between the lesions and was planned with coplanar geometry. The yellow box around the lesions represents the jaw size to cover both lesions. This larger field size is due to treating both lesions at the same time, and although the jaw tracking was enabled, the jaws must

track both lesions at once to allow to MLC travel between the lesions. For both *a*-RESIST and *m*-RESIST, the jaw tracking can be utilized more effectively, which can be seen by the small jaw sizes (i. e., jaw tracking locally around each target, one at a time). The upper limit for the dose color wash is much higher for the *a*-RESIST plan at 67 Gy compared to 60 Gy for *m*-RESIST and 62.4 Gy for clinical VMAT. This is due to the higher GTV maximum dose obtained with *a*-RESIST planning approach. A higher GTV maximum dose is clinically desirable for lung SBRT as long as low doses to normal tissues are maintained. The dose color wash in the axial plane of a different patient is demonstrated in **Figure 5.4** (bilateral lung lesions). For this patient, comparable dose distribution can be seen for all three plans. However, both *m*-RESIST and *a*-RESIST exhibited higher dose to GTVs. For the *a*-RESIST plan, higher intermediate dose spillage can be seen for the posterior lesion.
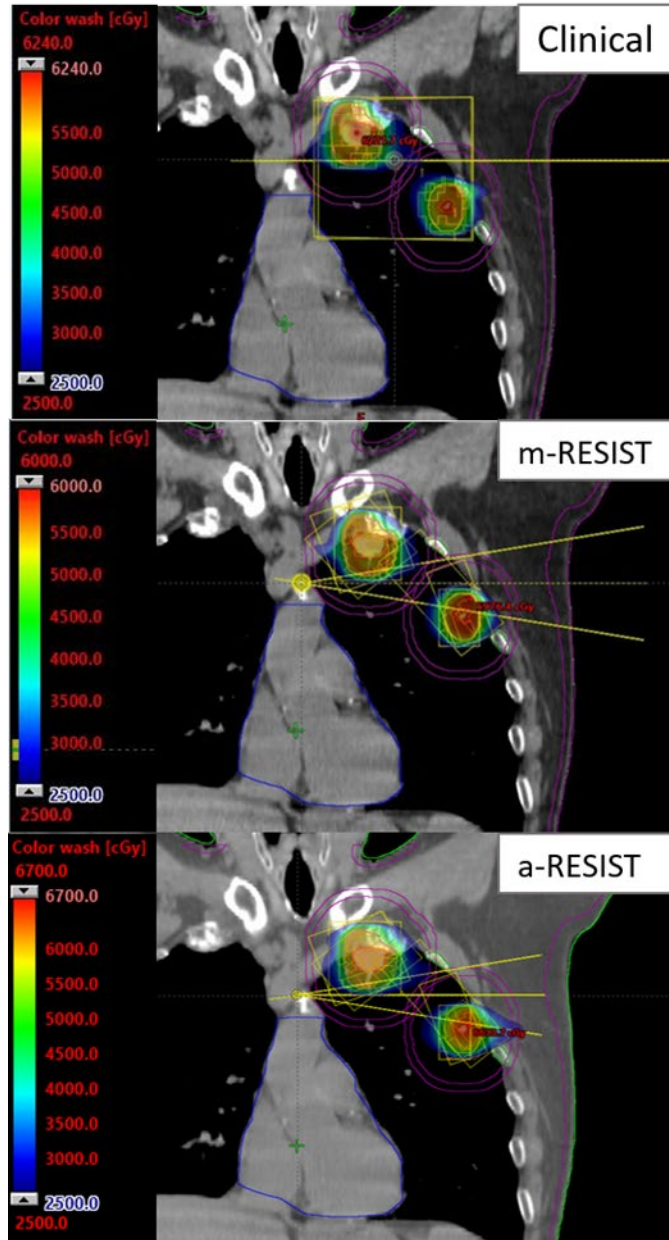
Figure 5.3: Coronal beam geometry and dose color wash for clinical VMAT, *m*-RESIST and *a*-RESIST plans.
Targets shown are PTVs (orange) and GTVs (red). Rings 2 cm away from the PTVs are in purple. OAR shown are skin (purple), heart (blue), ribs (green). The isocenter placement at the patient's midline for both *m*-RESIST and *a*-RESIST allow for non-coplanar arc geometry, improving planning efficiency and plan quality, escalating tumor dose and avoiding potential collisions.
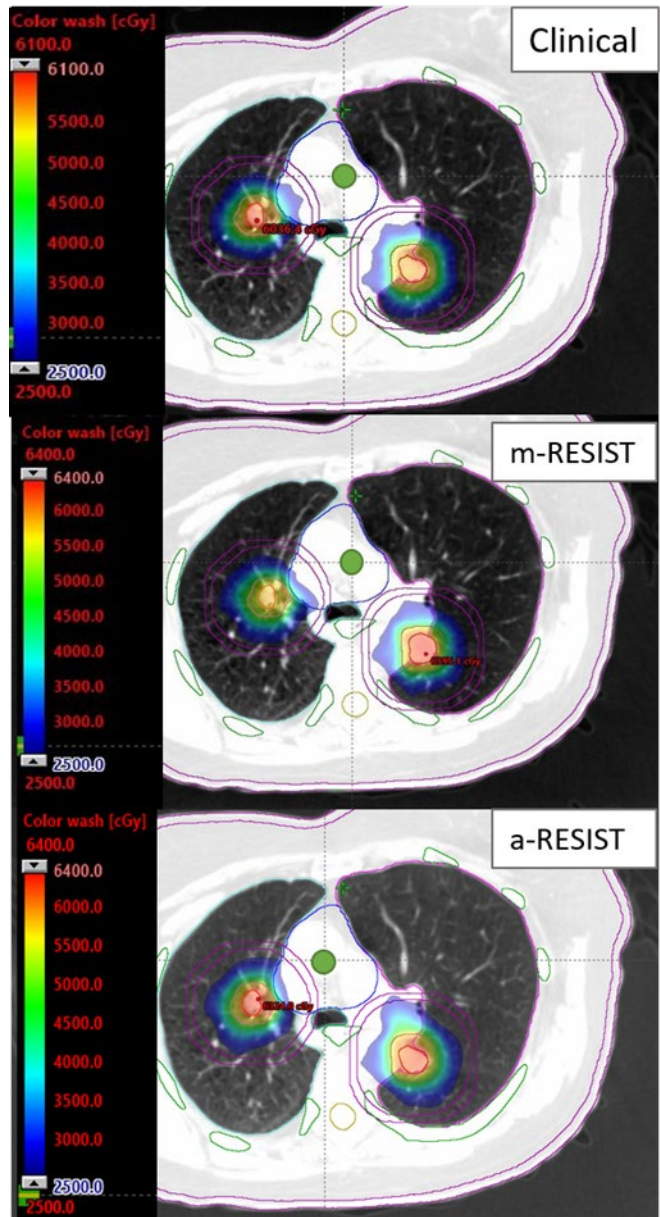
Figure 5.4: Dose color wash in the axial plan of a patient with bi-lateral lesions.
Shown are PTVs (orange), GTVs (red), D2cm ring (purple), ribs (green), heart (blue), esophagus (green), cord (yellow), right lung (blue), left lung (pink) and skin (purple). Green dot at the viewing plane intersection is the isocenter location. The *a*-RESIST plan provided higher GTV dose and slightly higher intermediate dose spills, which can be seen for the posterior lesion but it was within the protocol requirements.

5.3.2 Treatment Planning Parameters

The average total treatment planning time for the *a*-RESIST script to complete all 10 lung SBRT patients with two lesions was 12.5 ± 3.5 min (9.1–21.1 min). Time was recorded on average 66 min for *m*-RESIST plans to complete the same tasks as *a*-RESIST. The significant reduction of treatment planning time can be attributed to both the automation of arc geometry for *a*-RESIST as well as the use of the in-house KBP model for the VMAT optimization. Specifically, the KBP helped create a clinically acceptable and similar plan much quicker than manually inputting and adjusting optimization objectives. As can be seen with slightly higher dose to some OAR and inferior CI, PCN, HI and D2cm, *a*-RESIST plans are less desirable, although clinically acceptable and protocol compliant, compared to *m*-RESIST. However, the dramatic treatment planning time savings and plan consistency is desirable for a busy clinic. Like *m*-RESIST plans, *a*-RESIST plans allow for additional manual intervention to help improve OAR sparing and target coverage with minimal additional treatment planning time.

5.3.3 Treatment Delivery Parameters

The total number of monitor units for *m*-RESIST and *a*-RESIST is about 1.8 times higher than for the clinical VMAT plans, as can be seen in **Table 5.3**. However, due to both PTVs being planned separately with separate prescriptions, the average modulation factor for the RESIST methods are lower compared to the clinical VMAT method, could potentially improve treatment delivery accuracy. The estimated treatment time was calculated by adding 10 minutes for initial patient setup, 1 minute to complete a single CBCT (two CBCT scans available with RESIST methods) and 3 minutes for tumor

matching and applying shifts per CBCT. Although the treatment time is longer for both *m*-RESIST and *a*-RESIST, these treatments can still be delivered during the typical 30-minute treatment slot.

Table 5.3: Comparison of average values of treatment delivery parameters (and range) between clinical VMAT, m-RESIST and a-RESIST plans for all 10 lung SBRT patients. Mean ± SD (range) was reported. SD = standard deviation.

Beam delivery parameters	Clinical VMAT	*m*-RESIST	*a*-RESIST
Total MU per fraction	4020 ± 612 (3091–5010)	7272 ± 1136 (5605–10010)	7065 ± 605 (6021–7982)
Modulation factor (MF)	4.0 ± 0.6 (3.1–5.0)	3.36 ± 0.7 (1.9–5.1)	3.5 ± 0.5 (2.7–4.9)
Beam-on time (min)	2.8 ± 0.4 (2.2–3.6)	5.2 ± 0.8 (4.0–7.2)	5.0 ± 0.4 (4.3–5.7)
Treatment time (min)	16.8 ± 0.4 (16.2–17.6)	23.2 ± 0.8 (22.0–25.2)	23.0 ± 0.4 (22.3–23.7)

5.4   Discussion

This report describes and assesses the feasibility of the automated RESIST method for treating two synchronous lung lesions with SBRT that aims to minimize setup uncertainties and significantly improve treatment planning time. The method was validated by retroactively planning 10 patients with two lesions who previously underwent VMAT SBRT with a single isocenter placed between the two lesions. RESIST consists of a single isocenter placed at the patient's midline and both lesions sharing the isocenter. Unlike clinical VMAT, in RESIST plans both lesions have an individual plan which are then evaluated with a plan summation. Allowing each lesion to be planned individually allows for optimal collimator angles and the best use of the jaw tracking feature to aid in the reduction of the normal lung dose. Furthermore, two plans sharing the same isocenter allows for more flexibility during patient treatment as demonstrated in **Figure 5.5**.
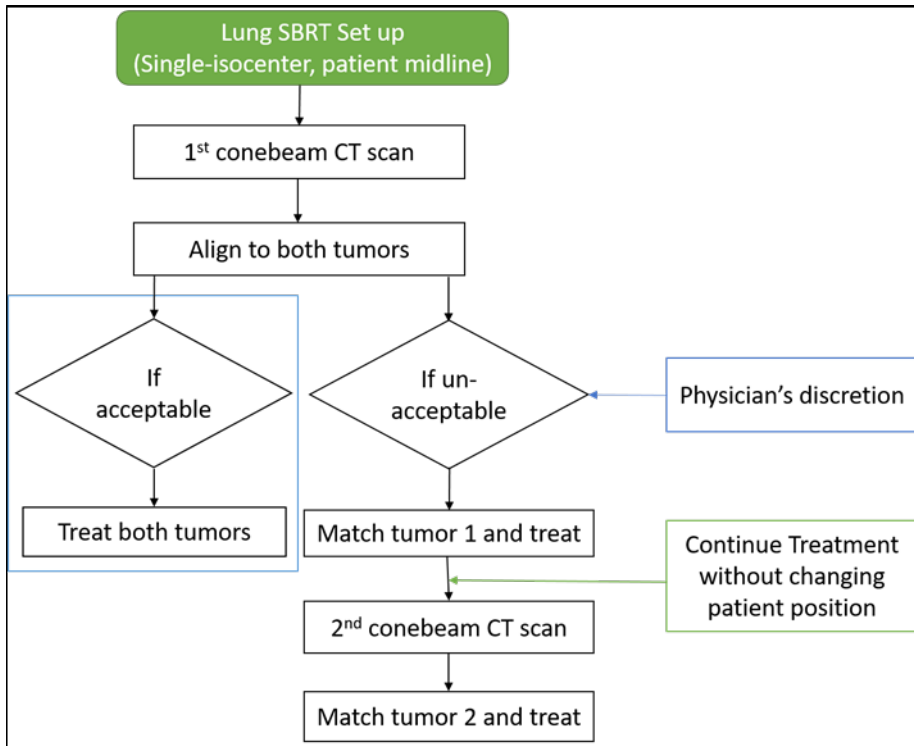
Figure 5.5: The *a*-RESIST treatment delivery workflow for single-isocenter/two-lesion VMAT lung SBRT.
The physician has the option to line up both tumors on the first daily CBCT and deliver both plans (blue box) or match one lesion at a time and treat without entering the room to re-setup the patient for the second CBCT (demonstrated on the right side of the flow chart) thus improving treatment delivery efficiency and accuracy by reducing the chance of a geometric miss. Placement of an isocenter at the mediastinum avoids potential patient/gantry collisions, provides greater flexibility of non-coplanar arc geometry and eliminates the need for multiple couch movements during CBCT imaging.

Single-isocenter VMAT plans have become a popular treatment option for intracranial stereotactic radiosurgery (SRS) and more recently, are becoming of interest for extracranial lesions. A few studies have shown the use and feasibility of treating multiple lung lesions with a single isocenter approach.[22, 23] However, these studies fail to acknowledge the treatment planning difficulties or provide solutions to treatment delivery uncertainties. The *a*-RESIST planning method decreases the treatment planning difficulties for two lesion lung SBRT plans as well as provides appropriate guidance for more accurate treatment delivery, eliminating unwanted stress on the entire SBRT team. Furthermore, to

our knowledge, *a*-RESIST is the first approach to automate single isocenter/multiple lesion lung SBRT plans. Automated treatment planning is a fast-developing area of research and, with the recent availability of writeable scripting using Varian ESAPI, will continue to gain favor. A recent study demonstrated the use of automation in an existing clinical workflow and showed the feasibility of automation for improving clinical efficiency and safety for total body irradiation (TBI).[24] Similar to TBI procedures, lung SBRT procedures are high risk, involving large doses. The *a*-RESIST method can be used to reduce planning errors and potentially reduce the chance of tumor misalignment for treatment. Recent publications have explored automation of planning for various treatment of other sites[25-27] although *a*-RESIST is the first of its kind for multiple lesions VMAT lung SBRT treatment. Further validation and clinical implementation of *a*-RESIST method for multi-lesions lung SBRT treatment is ongoing.

Further improvement of *a*-RESIST is ongoing in our center including improvement of the KBP optimization model for two-lesion lung SBRT plans and a more "patient-specific" approach to isocenter placement. Simulated collision detection is a feature available when using Varian HyperArc module for intracranial SRS treatments and has been further developed by multiple researchers.[28,29,30] However, simulated collision detection for extracranial SBRT has yet to be studied and would be the next step to the *a*-RESIST method to further ensure an efficient treatment delivery. Efficacy of *a*-RESIST has been demonstrated for two lung lesions and can potentially be used for more than two lung lesions as well as other extracranial treatment sites such as multi-lesion liver SBRT or oligometastastic abdominal/pelvic lymph nodes SBRT

5.5   Conclusion

Using the *a*-RESIST planning method for synchronous lung lesions can decrease planning time and allow planners to create clinically acceptable lung SBRT treatment plans. The RESIST method reduces the chance of a geometric miss due to setup uncertainties by allowing for planning and setup of each lesion individually. Furthermore, automation of the planning technique will allow for standardized treatment plans while allowing user input to further increase the plan quality and treatment efficiency. Utilizing an in-house trained lung SBRT RP model helps ensure treatment plans are of consistent high quality. Further improvement of the *a*-RESIST script to ensure more precise isocenter location as well as well-trained KBP models for patient-specific multi-targets could further improve plan quality, reduce inter-planner variability and inconsistency and improve patient safety and clinic workflow.

CHAPTER 6. STUDY CONCLUSIONS

6.1   Study Summary

This dissertation has described the development of a methodology for treating multiple lung lesions efficiently and accurately with single-isocenter VMAT SBRT. Beginning in **Chapter 1,** a brief history of SBRT is presented followed by a discussion of synchronous multiple lesion treatments and the current clinical limitations. Chapter 1 is concluded with a presentation of the dissertation outline and the major clinical innovations presented in each chapter.

Chapter 2 presented a dosimetric study of two common treatment planning methods for multiple lesion lung VMAT SBRT. The first technique consists of two plans and two different isocenters, one for each lesion. The isocenter is placed in the center of the lesion. The second technique plans for both lesions at the same time using a single-isocenter VMAT SBRT plan. The isocenter is placed approximately between the two lesions. This study validated the hypothesis that the single-isocenter plans would be dosimetrically equivalent to the multi-isocenter and would provide more efficient treatments. Treating both lesions with a single isocenter reduced the beam-on time by a factor of 1.5, thus improving patient convenience. Efficient treatments can help ensure the patient remains in the ideal treatment position while releasing the treatment machine to be used for more patient treatments. However, there was no evidence that the single isocenter plans were more accurate upon patient setup and delivery. Small setup errors were observed upon evaluation of the pre-treatment CBCTs of patients previously treated with a single-isocenter VMAT SBRT plan. Unfortunately, there is no method available in

Eclipse TPS to quantitate the dosimetric effects of these setup errors on targets or uninvolved structures.

For the study in **Chapter 3** a novel transformation method was created to more accurately simulate the dosimetric impact of patient setup errors. This method was used to quantitate the effect of possible small setup errors in dose distribution of the treatment of multiple lesion VMAT SBRT using a single isocenter. This method produced random translations and rotations on the patient CT, similar to the observable patient setup errors, in order for a dose calculation to be performed, per treatment fraction. This study validated the hypothesis that small patient setup errors could lead to clinically unacceptable target coverage loss. Using this method, the study demonstrated that the largest risk of target dose coverage loss of up to 72% was observed for the smallest lesion volumes. Likewise, it was determined that a loss in optimal BED was possible for many targets, potentially compromising tumor local control.

Before completion of this study, a linear relationship between target coverage loss and target distance to isocenter was expected, as shown by multiple sources in the treatment of multi-lesion brain SRS.[1,2] However, in this cohort, upon analyzing the target coverage data, no clear relationship was found. This is likely due to multiple confounding factors including the drastic change in tissue densities in the thorax, the large variability in lung tumor sizes and lung tumor locations. For lung lesions, small rotations and translations will lead to larger changes in source to surface distance (SSD) than for lesions of the brain due to the oval shape of the thorax in comparison to the spherical shape of the brain. Likewise, small rotation and translations may result in more or less of the beam going through dense structures like the ribs, potentially resulting in a large dosimetric change to both targets and

normal tissues. The previous brain SRS studies calculated coverage loss based on one simulation of the dose distribution. In contrast, our study simulated a different transformation for each treatment fraction. The method used in Chapter 3 likely produced a more accurate representation of target coverage loss for multiple fraction treatments.

To create a more accurate treatment alternative for these patients, the Restricted Single-Isocenter Stereotactic Body Radiotherapy (RESIST) method was created and described in **Chapter 4.** RESIST utilizes a simplified approach by placing a single-isocenter at the mediastinum. It uses partial arcs to minimize dose to the other lung. It allows for an individual plan to be created for each tumor, using the first plan as the base-dose for the second plan, while still allowing both tumors to be treated in the same session. The technique uses novel features in Eclipse TPS to provide better target dose conformity and gradient indices and lower doses to adjacent normal structures when compared to the single-isocenter VMAT treatment described in Chapter 2. Using RESIST to treat synchronous lung lesions with VMAT SBRT significantly reduces plan complexity, as demonstrated by smaller beam modulation factors, without unreasonably increasing treatment time. RESIST reduces the chance of a geometric miss due by allowing CBCT matching of one tumor at a time. Placement of isocenter at the mediastinum avoids potential patient/linac gantry collisions, provides greater flexibility of non-coplanar arcs and eliminates the need for multiple couch movements during CBCT imaging, thus reducing the number of times a therapist must enter the treatment room.

Automation of the RESIST method is presented in **Chapter 5.** This automated RESIST (*a*-RESIST) method is the first automated treatment planning method for synchronous multiple lung lesion VMAT SBRT. This study validated the hypothesis that

a-RESIST would produce acceptable treatment plans quicker and more consistently than manually created plans. Not only does the automation significantly reduce the treatment planning time, from over 1 hour to about 20 minutes, it can reduce treatment planning errors and is adaptable to fit the preferences of the physician. The *a*-RESIST method automatically sets isocenter, creates partial arc beam geometry, choses appropriate dose calculation algorithms, and performs VMAT optimization using an in-house trained knowledge-based planning model for lung SBRT. The *a*-RESIST method provides guidance for inexperienced planners by standardizing beam geometry and plan optimization using DVH estimates. It produces clinically acceptable two lesion VMAT lung SBRT plans efficiently.

Following the guidance presented in this dissertation, treatment planners with minimal experience in multi-lesion lung SBRT will be able to produce efficient and accurate treatment plans. The methods presented are adaptable and are a proof-of-concept that these complicated treatment plans can not only be created more resourcefully and consistently, but can be automated with the clinic's aims in mind.

6.2   Study Limitations and Future Perspectives

This study aimed to create a protocol for the safe, effective, accurate and efficient treatment of multiple lung lesions with VMAT SBRT. Although there is confidence this dissertation will improve these complicated treatments, the study is not without limitations. In all chapters, the statistical analysis is limited by the number of patients. Patient number was chosen based on the cohort available in the clinic at The University of Kentucky, and therefore will affect the study power. Nevertheless, these studies are important and provide the groundwork for potential larger studies that could involve more patient data.

Due to the novelty of this study, patient follow up is needed to support the conclusions made in a few of the chapters. In **Chapter 2**, two treatment planning techniques are described and determined to be dosimetrically equivalent. However, further follow up of clinically treated patients is warranted to determine if the dosimetric equivalency translates to equivalent local control. Furthermore, **Chapter 3** suggests that the small setup errors observed in the pre-treatment imaging of patients treated with single-isocenter VMAT SBRT will result in dose coverage loss that may impact the local control of the lesions. So far, The University of Kentucky Radiation Oncology clinic has used this treatment technique on approximately 30 patients with two synchronous lung lesions each in the last 2 years and further follow up of these patients is needed to determine if the observed setup errors resulted in inferior rates of local control. Early follow up results of 14 patients (mean, 9 months) showed high local control rates (100%)[3], however longer follow up is needed to determine overall survival and future local control. For these patients, the conclusion was made that dose coverage loss is magnified in smaller lesions, however, due to the complicated relationships between tumor location, tumor size, and heterogeneous densities in lung treatments no definitive relationship can be determined regarding tumor size and coverage loss.

In **Chapter 3**, a novel technique for the simulation of patient setup errors in Eclipse TPS is presented. In the current version, the script integrates with the Image Registration module in Eclipse TPS. Thus, this method is currently only available to users with Eclipse TPS. Although this TPS is widely used, a different method may need to be created for alternative TPS.

Chapter 4 describes the RESIST method for treating synchronous multiple lung lesions utilizing novel features available in the Eclipse TPS (version 15.5), such as aperture shape controller. These features will not be available to all users with previous versions; thus, adaptation may be necessary when trying to implement this method. The RESIST method has been used to treat three patients. This method can continue to be used for multiple lesion SBRT and clinical follow-up can be performed to determine the advantages in overall survival and local control rates, if any. Furthermore, the *a*-RESIST method in **Chapter 5** is restricted to users with the Eclipse TPS (version 15.5). Although *a*-RESIST provides acceptable treatment plans, they are slightly inferior to manually created plans. Further refinement of the automation could provide more optimal and patient specific isocenter placement. Currently, the knowledge-based planning (KBP) approach with dose volume histogram (DVH) estimates via RapidPlan (RP) model used in *a*-RESIST was trained using single-isocenter/single-lesion lung SBRT plans. Although the dose to each lesion is optimized individually, the plans are evaluated in a plan summation containing plans to both lesions. The KBP approach does not take this into account during optimization resulting in an inferior plan. A model trained on single-isocenter/two-lesion plans could further improve the plan quality of *a*-RESIST.

The isocenter location in *a*-RESIST is chosen at patient midline to reduce the chance of a patient collision while the linac gantry rotates around the patient. However, there is no way to ensure patient safety without a "dry-run" of the treatment before delivery. This may increase the time the patient must remain on the table and there is currently no way to simulate this in the TPS. The development and implementation of a simulated collision detection module in Eclipse TPS for extracranial lesions could further improve *a*-

RESIST and could be used for lesions in other sites. Fully integrating and automating the RESIST method with the TPS could further improve the technique.

As an expansion of this thesis, a grant proposal has been accepted and funded (at Varian Medical Systems, Palo Alto CA) regarding the treatment of synchronous multiple extracranial lesions with SBRT on the recently introduced Varian Halcyon Linac.[4] The Halcyon linac has a single 6MV-FFF beam and allows for quick gantry rotations with fast dual-stacked and staggered MLCs, but does not allow for non-coplanar beam geometry. Currently, the Halcyon can only correct translational set up errors for patient set up and verification. Therefore, there is a tremendous interest on quantifying the dosimetric effects of rotational setup uncertainties and developing a novel approach to minimize those errors for multiple lesions on Halcyon, analogous to the novel technique used to quantify those previously treated on the Varian Truebeam and discussed in this dissertation.

Further expanding on RESIST, studies can be performed about the efficacy of the method on different machines, such as the Varian Halcyon. Likewise, RESIST can be expanded to other treatment sites including the liver and for multi-site/multi-lesion SBRT. Utilizing the RESIST approach to minimize dose to normal brain and improve localization accuracy in the treatment of multiple brain lesions for linac-bases SRS in another avenue of research. Exploration of RESIST's potential to escalate dose to large tumors with simultaneous integrated boost while sparing normal tissues could prove to be a useful treatment option and merits future investigation.

APPENDICES

APPENDIX 1. GLOSSARY

6DOF	six-degrees-of-freedom
ACR	American College of Radiology
a-RESIST	Automated Restricted Single-Isocenter Stereotactic Body Radiotherapy
ASTRO	American Society for Therapeutic Radiology and Oncology
BED	Biological Effective Dose
BOT	Beam on time
CBCT	Cone Beam Computed Tomography
CGS	Calculation Grid Size
CI	Conformity Index
CN	Conformation Number
D	Dose
DCA	Dynamic Conformal Arc
DTA	Distance to Agreement
DVH	Dose Volume Histogram
ESAPI	Eclipse Scripting Application Programming Interface
ESR	Extracranial Stereotactic Radioablation
FFF	Flattening Filter Free
GD	Gradient Distance
GI	Gradient Index
GTV	Gross Tumor Volume
HI	Heterogeneity Index
IMRT	Intensity Modulated Radiation Therapy
ITV	Internal Target Volume
KBP	Knowledge-based planning
LLL	Left Lower Lobe
LUL	Left Upper Lobe
MF	Modulation Factor
MIP	Maximum Intensity Projection
MLC	Multi-leaf Collimator
MLD	Mean Lung Dose
m-RESIST	Manual Restricted Single-Isocenter Stereotactic Body Radiotherapy
MU	Monitor Units
NSCLC	Non-Small Cell Lung Cancer

NTO	Normal Tissue Objective
OAR	Organ at Risk
PIV	Prescription Isodose Volume
PO	Photon Optimizer
PTV	Planning Target Volume
QA	Quality Assurance
RESIST	Restricted Single-Isocenter Stereotactic Body Radiotherapy
RLL	Right Lower Lobe
RP	RapidPlan
RTOG	Radiation Therapy Oncology Group
RUL	Right Upper Lobe
SBRT	Stereotactic Body Radiation Therapy
SRS	Stereotactic Radiosurgery
SSD	Source to Surface Distance
STD	Standard Deviation
TPS	Treatment Planning System
TV	Target Volume
V	Volume
VMAT	Volumetric Modulated Arc Therapy

APPENDIX 2. MATLAB SCRIPT FOR SIMULATION OF RANDOM SETUP
ERRORS

```
%Before starting, replace the current registration file with whatever
%patient you are working with. Change the number of fractions to correspond
%with the current patient.

fractionnumber=1;
while fractionnumber<6

% thetax, thetay and thetaz represent the random rotations between -2 and 2
% degrees.

thetax=rand*4-2;
thetay=rand*4-2;
thetaz=rand*4-2;

%Rotx, roty and rotz are the three rotation matrices.

rotx=[1,0,0,0;0,cosd(thetax),sind(thetax),0;0,sind(thetax),cosd(thetax),0;0,0,0,1];
roty=[cosd(thetay),0,sind(thetay),0;0,1,0,0;sind(thetay),0,cosd(thetay),0;0,0,0,1];
rotz=[cosd(thetaz),sind(thetaz),0,0;0,sind(thetaz),cosd(thetaz),0,0;0,0,1,0;0,0,0,1];

%Multiplying the matrices together will get my rotation matrix in 3D.

rotationmatrix=rotx*roty*rotz;

%x, y and z are the random translation between -5mm and 5mm

x=rand*10-5;
y=rand*10-5;
z=rand*10-5;
translationmatrix=[1,0,0,x;0,1,0,y;0,0,1,z;0,0,0,1];

%Multiplying the rotationmatrix and the translation matrix will get the
%transformation matrix needed for the RE DICOM file

transformationmatrix=rotationmatrix*translationmatrix;
transformationmatrix=transpose(transformationmatrix);
newtransformationmatrix=reshape(transformationmatrix,16,1);

%Replacing the current DICOM transformation matrix with my new randomly
%generated transformation matrix and saving the DICOM file under the
%specified name

info=dicominfo('');
```

```matlab
read=dicomread('');
t=newtransformationmatrix;
info.RegistrationSequence.Item_2.MatrixRegistrationSequence.Item_1.MatrixSequence.Item_1.FrameOfReferenceTransformationMatrix=t;
basename='fraction';
name=[basename,num2str(fractionnumber)];
dicomwrite(read,name,info, 'CreateMode', 'copy');
fractionnumber=fractionnumber+1;
end
```

APPENDIX 3. ESAPI SCRIPT FOR *a*-RESIST

```
1   using System; using
2   System.Linq;
3   using System.Text;
4
5   using System.Collections.Generic;
6   using System.Reflection;
7   using System.Runtime.CompilerServices; using
8   VMS.TPS.Common.Model.API;
9   using VMS.TPS.Common.Model.Types;
10
11  using System.IO;
12  using System.Security;
13  using System.Security.Cryptography;
14
15  // TODO: Replace the following version attributes by creating AssemblyInfo.cs.
        You can do this in the properties of the Visual Studio project.
16  //[assembly: AssemblyVersion("1.0.0.1")]
17  //[assembly: AssemblyFileVersion("1.0.0.1")]
18  //[assembly: AssemblyInformationalVersion("1.0")]
19  [assembly: ESAPIScript(IsWriteable = true)]
20  // TODO: Uncomment the following line if the script requires write access.
21
22
23  namespace VMS.TPS
24  {
25      public class Script   {
26
27          public Script()
28      {
29      }
30
31          [MethodImpl(MethodImplOptions.NoInlining)]
32      public void Execute(ScriptContext context )
33      {
34              StructureSet ss = context.StructureSet;   Patient patient
35          = context.Patient;   Course course = context.Course;
36          patient.BeginModifications();
37            //Add new course
38
39
40      {
41              course = patient.AddCourse();   course.Id
42          = "AutoPlan RESIST";
43      }
44
45          //Add a new plan in current course called RESIST PTV 1
46
47
48          ExternalPlanSetup eps = course.AddExternalPlanSetup(ss);   eps.Id = "RESIST
49      PTV 1";
50
```

```
51
52
53          Structure ptv1 = ss.Structures.First(x => x.Id == "PTV 1");
54          Structure ptv2 = ss.Structures.First(x => x.Id == "PTV 2");
55          Structure cord = ss.Structures.First(x => x.Id == "Cord");
56          Structure gtv1 = ss.Structures.First(x => x.Id == "GTV 1");
57          Structure gtv2 = ss.Structures.First(x => x.Id == "GTV 2");
58          Structure bronchialtree = ss.Structures.First(x => x.Id == "Bronchial
               Tree");
59          Structure D2cm1 = ss.Structures.First(x => x.Id == "D2cm+5mm1");
60          Structure D2cm2 = ss.Structures.First(x => x.Id == "D2cm+5mm2");
61          Structure esophagus = ss.Structures.First(x => x.Id == "Esophagus");
62          Structure heart = ss.Structures.First(x => x.Id == "Heart");
63          Structure lung1 = ss.Structures.First(x => x.Id == "Lungs-PTV1");
64          Structure lung2 = ss.Structures.First(x => x.Id == "Lungs-PTV2");
65          Structure skin = ss.Structures.First(x => x.Id == "Skin(-)0.5cm");
66          Structure trachea = ss.Structures.First(x => x.Id == "Trachea");
67          Structure ribsleft = ss.Structures.First(x => x.Id == "LT Ribs");
68          Structure ribsright = ss.Structures.First(x => x.Id == "RT Ribs");
69          // Structure ribs = ss.Structures.First(x => x.Id == "Ribs");
70
71
72
73
74          //Set Isocenter
75          VVector isocenter = new VVector(Math.Round(cord.CenterPoint.x /
               10.0f) * 10.0f, Math.Round(cord.CenterPoint.y) + -60, Math.Round
               ((ptv1.CenterPoint.z + ptv2.CenterPoint.z) / 2));
76
77          //Set dose
78          eps.SetPrescription(5, new DoseValue(1000, DoseValue.DoseUnit.cGy),
               1.0);
79
80          //Add beams
81
82          if (ptv1.CenterPoint.x > isocenter.x)
83          {
84              var ebmp = new ExternalBeamMachineParameters("TrueBeamSN2004",
                   "6X", 1400, "ARC", "FFF");
85              Beam A1 = eps.AddArcBeam(ebmp, new VRect<double>(-100, -100, 100,
                   100), 30, 0, 179, GantryDirection.Clockwise, 10, isocenter);
86              Beam A2 = eps.AddArcBeam(ebmp, new VRect<double>(-100, -100, 100,
                   100), 330, 179, 0, GantryDirection.CounterClockwise, 350,
                 isocenter);
87              if (ptv1.CenterPoint.x > 60 || ptv1.CenterPoint.x < -60)
88              {
89                  Beam A3 = eps.AddArcBeam(ebmp, new VRect<double>(-100, -100,
                       100, 100), 90, 0, 179, GantryDirection.Clockwise, 0,
                     isocenter);
90                  A3.Id = "A3";
91              }
92              else
```

113

```
93                      {
94                          Beam A3 = eps.AddArcBeam(ebmp, new VRect<double>(-100, -100,
                              100, 100), 0, 0, 179, GantryDirection.Clockwise, 0,
                              isocenter);
95                          A3.Id = "A3";
96                      }
97                      A1.Id = "A1";
98                      A2.Id = "A2";
99                  }
100                 if (ptv1.CenterPoint.x < isocenter.x)
101                 {
102                     var ebmp = new ExternalBeamMachineParameters("TrueBeamSN2004",
                          "6X", 1400, "ARC", "FFF");
103                     Beam A1 = eps.AddArcBeam(ebmp, new VRect<double>(-100, -100, 100,
                          100), 30, 0, 181, GantryDirection.CounterClockwise, 10,
                          isocenter);
104                     Beam A2 = eps.AddArcBeam(ebmp, new VRect<double>(-100, -100, 100,
                          100), 330, 181, 0, GantryDirection.Clockwise, 350, isocenter);
105                     if (ptv1.CenterPoint.x > 60 || ptv1.CenterPoint.x < -60)
106                     {
107                         Beam A3 = eps.AddArcBeam(ebmp, new VRect<double>(-100, -100,
                              100, 100), 90, 0, 179, GantryDirection.Clockwise, 0,
                              isocenter);
108                         A3.Id = "A3";
109                     }
110                     else
111                     {
112                         Beam A3 = eps.AddArcBeam(ebmp, new VRect<double>(-100, -100,
                              100, 100), 0, 0, 179, GantryDirection.Clockwise, 0,      ⏎
                              isocenter);
113                         A3.Id = "A3";
114                     }
115                     A1.Id = "A1";
116                     A2.Id = "A2";
117                 }
118             //Set Calc Models
119             eps.SetCalculationModel(CalculationType.PhotonVolumeDose,              ⏎
                  "AcurosXB_15605");
120             eps.SetCalculationModel(CalculationType.PhotonVMATOptimization,        ⏎
                  "PO_15605");
121             eps.SetCalculationModel(CalculationType.DVHEstimation, "DVH            ⏎
                  Estimation Algorithm [15.6.05]");
122             eps.OptimizationSetup.AddNormalTissueObjective(140.0f, 1.0f, 90.0f,    ⏎
                  60.0f, 0.45f);
123
124             //Set Rapid Plan structures
125
126
127             Dictionary<string, DoseValue> levels = new Dictionary<string,          ⏎
                  DoseValue>();
128             Dictionary<string, string> matches = new Dictionary<string, string>    ⏎
                  ();
```

```csharp
129              levels.Add(ptv1.Id, new DoseValue(5000, "cGy"));
130              levels.Add(gtv1.Id, new DoseValue(5000, "cGy"));
131              matches.Add(ptv1.Id, "PTV");
132              matches.Add(cord.Id, "Cord");
133              matches.Add(bronchialtree.Id, "Bronchial Tree");
134              matches.Add(gtv1.Id, "GTV");
135              matches.Add(lung1.Id, "Lungs");
136              matches.Add(D2cm1.Id, "D2cm");
137              matches.Add(heart.Id, "Heart");
138              matches.Add(esophagus.Id, "Esophagus");
139              matches.Add(trachea.Id, "Trachea");
140              if (ptv1.CenterPoint.x > isocenter.x)
141              {
142                  matches.Add(ribsleft.Id, "Ribs");
143              }
144              else
145              {
146                  matches.Add(ribsright.Id, "Ribs");
147              }
148              eps.CalculateDVHEstimates(modelId: "UK VMAT LUNG SBRT Central_Final",
                    targetDoseLevels: levels, structureMatches: matches);
149              eps.OptimizationSetup.UseJawTracking = true;
150              eps.OptimizeVMAT();
151
152
153              //Add new plan for PTV 2
154
155              ExternalPlanSetup eps2 = course.AddExternalPlanSetup(ss);
156              eps2.Id = "RESIST PTV 2";
157
158
159              //Set dose
160              eps2.SetPrescription(5, new DoseValue(1000, DoseValue.DoseUnit.cGy),
                    1.0);
161
162              if (ptv2.CenterPoint.x > isocenter.x)
163              {
164                  var ebmp = new ExternalBeamMachineParameters("TrueBeamSN2004",
                        "6X", 1400, "ARC", "FFF");
165                  Beam A4 = eps2.AddArcBeam(ebmp, new VRect<double>(-100, -100,
                        100, 100), 30, 0, 179, GantryDirection.Clockwise, 10,
                        isocenter);
166                  Beam A5 = eps2.AddArcBeam(ebmp, new VRect<double>(-100, -100,
                        100, 100), 330, 179, 0, GantryDirection.CounterClockwise, 350,
                        isocenter);
167                  if (ptv2.CenterPoint.x > 60 || ptv2.CenterPoint.x < -60)
168                  {
169                      Beam A6 = eps2.AddArcBeam(ebmp, new VRect<double>(-100, -100,
                            100, 100), 90, 0, 179, GantryDirection.Clockwise, 0,
                            isocenter);
170                      A6.Id = "A6";
171                  }
```

```csharp
172                     else
173                     {
174                         Beam A6 = eps2.AddArcBeam(ebmp, new VRect<double>(-100, -100,
                              100, 100), 0, 0, 179, GantryDirection.Clockwise, 0,
                              isocenter);
175                         A6.Id = "A6";
176                     }
177                     A4.Id = "A4";
178                     A5.Id = "A5";
179
180                 }
181             if (ptv2.CenterPoint.x < isocenter.x)
182             {
183                 var ebmp = new ExternalBeamMachineParameters("TrueBeamSN2004",
                          "6X", 1400, "ARC", "FFF");
184                 Beam A4 = eps2.AddArcBeam(ebmp, new VRect<double>(-100, -100,
                          100, 100), 30, 0, 181, GantryDirection.CounterClockwise, 10,
                          isocenter);
185                 Beam A5 = eps2.AddArcBeam(ebmp, new VRect<double>(-100, -100,
                          100, 100), 330, 181, 0, GantryDirection.Clockwise, 350,
                          isocenter);
186                 if (ptv2.CenterPoint.x > 60 || ptv2.CenterPoint.x < -60)
187                 {
188                     Beam A6 = eps2.AddArcBeam(ebmp, new VRect<double>(-100, -100,
                              100, 100), 90, 0, 179, GantryDirection.Clockwise, 0,
                              isocenter);
189                     A6.Id = "A6";
190                 }
191                 else
192                 {
193                     Beam A6 = eps2.AddArcBeam(ebmp, new VRect<double>(-100, -100,
                              100, 100), 0, 0, 179, GantryDirection.Clockwise, 0,
                              isocenter);
194                     A6.Id = "A6";
195                 }
196                 A4.Id = "A4";
197                 A5.Id = "A5";
198             }
199             //Set Calc Model
200             eps2.SetCalculationModel(CalculationType.PhotonVolumeDose,
                      "AcurosXB_15605");
201             eps2.SetCalculationModel(CalculationType.PhotonVMATOptimization,
                      "PO_15605");
202             eps2.SetCalculationModel(CalculationType.DVHEstimation, "DVH
                      Estimation Algorithm [15.6.05]");
203             eps2.OptimizationSetup.AddNormalTissueObjective(140.0f, 1.0f, 90.0f,
                      60.0f, 0.45f);
204
205             Dictionary<string, DoseValue> levels2 = new Dictionary<string,
                      DoseValue>();
206             Dictionary<string, string> matches2 = new Dictionary<string, string>
                      ();
```

```
207            levels2.Add(ptv2.Id, new DoseValue(5000, "cGy"));
208            levels2.Add(gtv2.Id, new DoseValue(5000, "cGy"));
209            matches2.Add(ptv2.Id, "PTV");
210            matches2.Add(cord.Id, "Cord");
211            matches2.Add(bronchialtree.Id, "Bronchial Tree");
212            matches2.Add(gtv2.Id, "GTV");
213            matches2.Add(lung2.Id, "Lungs");
214            matches2.Add(D2cm2.Id, "D2cm");
215            matches2.Add(heart.Id, "Heart");
216            matches2.Add(esophagus.Id, "Esophagus");
217            matches2.Add(trachea.Id, "Trachea");
218            if (ptv2.CenterPoint.x > isocenter.x)
219            {
220                matches2.Add(ribsleft.Id, "Ribs");
221            }
222            else
223            {
224                matches2.Add(ribsright.Id, "Ribs");
225            }
226        eps2.CalculateDVHEstimates(modelId: "UK VMAT LUNG SBRT
             Central_Final", targetDoseLevels: levels2, structureMatches:
             matches2);
227        eps2.OptimizationSetup.UseJawTracking = true;
228        }
229    }
230 }
```

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4. Principle Investigator (Damodar Pokhrel, PhD), Co-PIs (Mark E Bernard, MD, & Lana Critchfield, MS): Halcyon Linac for Single-Isocenter/Multi-Lesion Stereotactic Body Radiotherapy (SBRT) Treatments – Accepted Full Grant Proposal to Varian Medical System (Palo Alto, CA), July 2020.

VITA

Lana Catherine Critchfield

Education

University of Kentucky, Lexington, KY
Doctor of Philosophy, Radiation and Radiological Sciences   Expected Fall 2020
    Dissertation: "Development of a Robust Treatment Delivery Framework for Stereotactic Body Radiotherapy (SBRT) of Synchronous Multiple Lung Lesions"
    Advisor: Damodar Pokhrel, PhD, DABR

University of Kentucky, Lexington, KY
Masters of Science, Radiological Medical Physics   2015-2017

Lewis & Clark College, Portland, OR
Bachelor of Arts, Mathematics & Physics   2011-2015

Professional Experience
Medical Physicist
Department of Radiation Oncology at the University of Kentucky   July 2019-Present

Resident in Medical Physics
Department of Radiation Oncology at the University of Kentucky   July 2017-July 2019

Teaching Experience
Teaching Assistant
Department of Physics at the University of Kentucky   Fall 2016

Submitted Manuscripts Relevant to Thesis (3)

1. **Critchfield L**, Bernard M, Randall M, McGarry R, Pokhrel D. Risk of Target Coverage Loss for Stereotactic Body Radiotherapy Treatment of Synchronous Lung Lesions via Single-Isocenter Volumetric Modulated Arc Therapy. *J Appl Clin Med Phys,* August 22, 2020.

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(RESIST) Method for Synchronous Multiple Lung Lesions", *J Appl Clin Med Phys,* September 29, 2020.

Peer-Reviewed Journal Publications Relevant to Thesis (10)

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

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Other Peer-Reviewed Journal Publications (2)

1. Pokhrel D, Halfman M, **Sanford L**, Chen Q, Kudrimoti M. A novel, yet simple MLC-based 3D-crossfire technique for spatially fractionated GRID therapy treatment of deep-seated bulky tumors. *J Appl Clin Med Phys.*, 2020;21(3), 68-74.

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