8-9-2022

Quantifying the Dosimetric Impact of Target Margins in the Oligometastatic Setting

Jessica E. Strang
Grand Valley State University

Quantifying the Dosimetric Impact of Target Margins in the Oligometastatic Setting

Jessica Strang

Grand Valley State University

Medical Dosimetry Class of 2022

Abstract

Introduction

With advancements in cancer treatment therapies, patients are living longer with oligometastatic disease. These patients may have multiple targets and may be treated in a single isocenter to reduce overall treatment time. However, the most considerable risk of treating multiple lesions in a single isocenter is a geometric miss. It can be challenging to perform daily alignment of multiple lesions creating a need to prioritize one lesion alignment over others or abort treatment.

Methods

This study quantified the dosimetric impact of total lung exposure as the planning target volume (PTV) margin incrementally increased for multiple intrathoracic lesions.
The analysis consisted of 15 patients treated at mid-inspiration breath-hold to 2-3 intrathoracic targets in the same lung. Each patient had three treatment plans (5, 7, and 9 mm isotropic margins on the gross tumor volume (GTV)) generated to treat all lesions in a single isocenter. Plans were generated using the same optimization objectives and beam arrangements for all plans.

Results

Each plan was evaluated for the dose to the lung minus the GTVs with V20 serving as the primary lung dose metric for plan quality. In addition, plans were assessed for conformity and meeting standard RTOG 0915 endpoints for lung V20, V5, chest wall, heart, esophagus, and spinal cord. When the isotropic margin to the GTVs increased from 5 mm to 9 mm, V5 increased from 12.9% to 18.5%, V20 increased from 1.9% to 3.8%, and mean lung dose (MLD) increased by 1.2 Gy. All these dosimetric endpoints met constraints outlined by RTOG 0915.

Discussion

From large breathing motion to the location of GTVs, the patient may benefit from treating multiple targets with a single isocenter. In these situations, the data in this study shows for small GTV targets, you can safely expand your PTV margin up to 9 mm. Further studies could show which PTV expansion is most applicable using treatment images acquired.

Introduction

As medical imaging and cancer treatment therapies continue to become more precise, patients are living longer with their disease. Today, even metastatic disease is being treated aggressively for curative intent.[1] The standard of care for metastatic cancer, of the lung and other sites, has been systemic therapy providing progression-free and overall survival.[2] Palliative radiotherapy would be enlisted for metastatic disease when patients have bleeding, pain, or obstruction.[2] While there have been tremendous strides in systemic therapy for metastatic cancer, it is expected a patient's disease will eventually become resistant to systemic therapy and need to switch to a new regimen.[2] Eventually, patients may run out of systemic treatment options.[2] Recent studies have shown that radiotherapy can provide equally effective results for overall survival if utilized with more curative intent.[1,2.3] Radiotherapy is also cited as equally effective as surgery, as well as more appealing for elderly patients or patients who do not qualify for or want to undergo surgery.[3,4] Finally, it is a non-invasive, relatively quick treatment (typically 1-5 appointments).[3]

Not all metastatic diseases should be treated aggressively. Patients who have widely metastatic disease or are thought to be in their final six months of life should only be treated for the palliative reasons listed above. However, patients with oligometastatic disease who show good performance status should be treated with curative intent. Oligometastatic disease is defined as a stage of the disease where cancer has spread beyond the primary tumor to a limited number of sites but is not yet widely metastatic.[2,5] This typically is describing 1-5 sites of metastases.[2,5,6] Treating oligometastatic disease with radiotherapy is pivotal in keeping patients with a reasonable quality of life and from succumbing to their disease.[6] Sanford et al. quoted

local control rates at one and two years after stereotactic body radiotherapy (SBRT) as 100% and 96% respectively for oligometastatic patients.[1]

Other studies have found success in treating oligometastatic disease as well. Palma et al conducted a Phase II study across Canada, the Netherlands, Scotland, and Australia, titled Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastases (SABR-COMET). This study focused on oligometastatic disease in patients with controlled primary tumors, one to five metastatic lesions, and an Eastern Cooperative Oncology Group (ECOG) score between 0-1, indicating good performance status. Results deduced "the use of SBRT in patients with controlled primary tumors in the body and one to five oligometastatic sites achieved a 13-month improvement in overall survival with a doubling of progression-free survival at the cost of an increased risk of toxicity, including a 4.5% risk of grade 5 toxicity."[5] These studies show there is a return on investment when treating oligometastatic disease curatively (the investment) yielding increased survival periods (the return) with limited toxicity risks.

The primary limiting factor(s) for radiotherapy treatment in metastatic disease settings is dose limits for organs at risk near the target(s). When looking at serial structures (such as the spinal cord), the maximum dose point will be the limiting factor. For parallel structures, such as the lungs, the volume of the organ receiving a specific dose is the main restriction.[2] When analyzing volume doses in the lung, the volume receiving 5 Gray (Gy) (V5), 10 Gy (V10), or 20 Gy (V20), in addition, to the mean lung dose (MLD) are the main factors.[1,6,7] Endpoints of concern for the unaffected lung is the main organ at risk with the potential for radiation-induced lung damage (RILD), radiation pneumonitis (RP), or pneumothorax.[8]

There are various guidelines for what constraints should be placed on lung doses. In a study of 106 patients treated for non-small cell lung cancer (NSCLC) with SABR, RILD was evaluated. According to Cella et al, 24% of patients in their study developed greater than a grade 2 dyspnea within six months of radiotherapy.[4] This coincides with Käsmann et al who stated that with the advances in VMAT, the occurrence of radiation-induced pneumonitis (RIP) has decreased from 30-47% with traditional 2D radiotherapy, to 30-35% for three-dimensional (3D), to 24-29% for VMAT plans.[8] One of the main references used for lung constraints is RTOG 0915, a submitted protocol. According to RTOG 0915, the dose to 1500 cubic centimeters (cc) of the lung should be less than 7 Gy, and the dose to 1000 cc should be less than 7.4 Gy to avoid a greater than grade 3 late toxicity for the lungs. Additionally, the V20 of the lung should be kept below 10-15%.[6] Käsmann et al suggested V20 be limited to less than 30-35%, and MLD less than 20-23 Gy to limit the risk of RIP to less than 20%.[8] Muller et al found V5 had the strongest correlation with at least grade 2 RP, no relation was found with higher dose levels such as V50 or V60.[6]

Regardless of the limits placed, one challenge presented in all lung treatments is motion due to breathing. There are a variety of tools that can be utilized from 4D computed tomography (CT), acquiring 10 images over time to show all of the respiratory cycles, or respiratory gating management (RPM), where the patient is to hold their breath (typically at mid inspiration) to reduce motion.[9] Regardless of the technique selected, target volumes often require unique planning target volume (PTV) margins due to the potential of the patient taking a different breath than what was simulated. Liu et al evaluated 22 patients treated for NSCLC with SABR retrospectively and analyzed the effect of various uncorrected rotations (1, 2, 3, and 5 degrees). In this study, researchers noted tumors of the lung could have a motion range of 10-30 mm.[9] The

largest tumor motion is detected in the lower lobe and the superior to inferior direction.[4] Typical PTV margins for lung targets are 5 millimeters (mm) but can be as large as 10-20 mm if treated without image-guided radiotherapy (IGRT).[10] As reported through multiple studies, 5 mm is the standard expansion for internal target volume (ITV) to PTV, but, some programs are arguing PTV margins should be patient-dependent.[1,7,10]

Motion can be even more challenging when there are multiple oligometastatic disease targets in the lung that need treatment. Several studies have been conducted to review dosimetric comparisons between a single isocenter for each lesion versus combining lesions into a single set-up isocenter. [1,7] Benefits of combining targets into a single isocenter, specifically with flattening filter-free (FFF) energies, range from optimizing gantry speed, to multileaf collimator (MLC) position, reducing treatment time and improving patient cooperation, and reducing error due to motion.[1,7] Sanford et al. reviewed 14 patients with metastatic NSCLC treated for two to five lesions in a single isocenter in their retrospective study.[1] In summary, clinically acceptable dosimetric parameters were achievable (0.35 cc spinal cord, 5 cc esophageal, 4 cc bronchial tree and trachea, 1 cc of ribs, and 10 cc of rib doses) for multi-target lung SBRT plans with a single isocenter. Additionally, the lungs minus GTV V10, V5, MLD, and a maximum dose to 1000 cc were all clinically acceptable per RTOG 0915 standards.[1]

Despite the benefits, there are risks involved when treating multiple targets with one setup isocenter. The biggest risk of treating multiple lesions in a single isocenter is a geometric miss, as it can be challenging to perform daily alignment of multiple lesions, which creates a need to prioritize one lesion alignment over others. In that case, an uncorrected misposition may have a larger impact on patient outcome and this impact will be greater in non-isocentric points than in isocentric points.[9] Liu et al found that rotations around the setup isocenter of up to 2

degrees may cause significant errors in delivering the planned dose.[1,4,8,9] Liu stated the "mean probability that the PTV D95 is at least 98% of the original plan would be less than 95% if rotations of 2° are not corrected".[9] Critchield et al stated that "despite the growing interest in single-isocenter/multi-lesion VMAT lung SBRT treatments, accuracy is more likely to decrease when treating multiple lesions synchronously compared to treating the lesions individually."[3] To support this statement, Critchfield et al utilized a random number generator to create misalignments of target volumes and recalculated the original plan with the uncorrected random shifts simulating setup error in synchronously treated lung lesions treated with SBRT. The researchers found that setup errors resulted in the average PTV coverage loss of 27.4 ± 14.6%, and up to 72%, which was most dramatic in smaller target (>10cc) volumes. The group queries alternative planning strategies that could reduce the risk of geometric misses.[3] Challenges in setup may arise when treating multiple lesions or when they are further apart (closer to the machine limit). Additionally, lesions in the lower lobe of the lung are more likely to be affected by breathing motion, therefore making alignment more difficult.[1] Larger PTV margins could help allow for more setup variances during treatment but at the risk of exposing more healthy lung tissue.

An increasingly utilized lung treatment, for primary and oligometastatic disease, is SBRT.[1,2,4,10] SBRT is a plan that treats a relatively small area (typically less than 3 cm) with a higher dose (5-12 Gy) per fraction and lower total dose. Research supports a variety of total doses and number of fractions ranging from 30- 60 Gy in 1-5 fractions.[2.3] The best way to compare the efficacy of varying schemas is by evaluating the biologically effective dose (BED). Many studies state a BED of at least 100 is necessary for superior local control and overall survival.[1,3,6] Practitioners aim to minimize the amount of normal lung that gets treated to avoid

RILD. However, the risk of geometric miss is increased when combining targets and using smaller PTV margins. Sanford et al concluded, "further studies are required to validate the standard 5 mm ITV to PTV expansions that would be adequate or not...while fulfilling the RTOG compliance."[1] Critchfield et al questioned if a 5 mm margin around the gross tumor volume (GTV) was sufficient to achieve greater than 100 BED to the GTV.[3] Pokhrel et al expressed there is "little guidance concerning PTV margins in the case of a single-isocenter/multi lesion SBRT treatment."[7]

This study will be evaluating what PTV margin should be used when combining multiple oligometastatic lung targets into a single isocenter to ensure full coverage of the tumors and minimize healthy lung dose. In this retrospective study, 15 patients were treated at mid-inspiration breath-hold to two to three intrathoracic targets in the same lung. Each patient had three treatment plans (5, 7, and 9 mm isotropic margins on the GTV) generated to treat all lesions in a single isocenter. Plans were generated using the same optimization objectives and beam arrangements for all cases (See Table 1). Each plan was evaluated for the lung dose minus the GTVs with V20 serving as the primary lung dose endpoint for plan quality.

Methods

Technology

This IRB-approved, retrospective study was conducted to guide appropriate PTV margins when combining multiple targets into a single isocenter for oligometastatic cancer. Fifteen patients with multiple lung lesions treated in the calendar year of 2021 were anonymized and brought into the training institution of Raystation version 10 for planning. MIM software version 6.9.7 was used for the Doctor of Medicine (MD) contouring of the targets. For treatment delivery, VMAT plans were generated for the Varian TruebeamSTX with micro leaves using two

partial planar arcs. Six FFF Mega Voltage (MV) beams were used for optimal planning, as is standard practice at the overseeing institution.

Patient Selection

Fifteen patients between the ages of 37 and 87 years, with an average age of 59.6 years, were evaluated for their oligometastatic lung targets. The retrospective study included patients with two to three intrathoracic oligometastases. Lesions had to be contained in one lung and PTVs must be contained within the mechanical limits of the Varian TruebeamSTX. Persons with pneumothorax were excluded from the study.

Simulation

Patients were simulated on a Siemens SOMATOM Definition Edge (2 mm slice thickness) scanner utilizing Varian's Real-Time Position Management Respiratory Gating System (version 1.7) for RPM data collection. For simulation, patients were imaged head first, supine with their arms above their head. Custom BodyFix immobilization devices were created for each patient without compression. The placement of the RPM box was documented for consistent patient set-up. Standard RPM box placement is at the xiphoid process but could be moved if deemed necessary by the simulation team. Five total deep inspiration breath-hold (DIBH) scans were performed. Images were reviewed by a board-certified radiation physicist who selected the median breath-hold image for MD contouring.

Treatment Planning

For each patient, three treatment plans were generated to treat all intrathoracic lesions in a single isocenter with differing PTV margins. In contouring, the MD delineated targets, using supplemental PET-CT images when deemed appropriate by the physician. The MD or dosimetrist added the esophagus, chest wall, spinal cord, heart, and lungs (individual and

collective) contours. Planning risk volumes (PRVs) of 5 mm were generated for the spinal cord and esophagus. Planning objectives are detailed in Table 1. For isocenter placement, Raystation software placed the isocenter in the center of the combined PTV volumes (See Figure 1). Collimation angles were selected to vary between arcs to reduce inter-leaf leakage in the same positions, and so that MLCs could maximize unaffected lung blockage between target volumes. A total dose of 50 Gy administered in 5 fractions was prescribed to 98% of the PTV (See Figure 2). Patients were to be treated 2 to 3 days per week and a daily cone-beam computed tomography (CBCT) was acquired before treatment.

PTV Margins

When respiratory motion is accounted for, typical PTV margins vary from 5 mm to 10mm.[2] The first plan expanded the GTV 5 mm uniformly to create the PTV (PTV5mm) used for treatment planning. Next, the plan was designed with a 7 mm expansion of the GTV (PTV7mm), and a plan was generated with the same optimization objectives and beam arrangements to ensure reliability between treatment plans. Finally, a 9 mm expansion was uniformly generated around the GTV (PTV9mm). The same isocenter placement was used for each plan within one patient. Additionally, planning objectives were kept the same between the three plans for one patient.

Each plan was evaluated for the lung dose minus the GTVs. To do so, the GTVs were summed together and removed from the total lung contour to create a Lungs-GTVs structure. As discussed in the previous section, the V5 and V20 are the primary lung metrics evaluated for plan quality and risk of RP.[3] These metrics were compared between the three plans and calculated for statistical significance. A table of results was generated for further analysis.

Evaluation of Plans

Each plan had to meet the constraints displayed in Table 1 to be clinically acceptable. These constraints are used at the overseeing institution for lung SBRT treatments. The V20 for lung was evaluated in addition to V5, dose to 1000 cc's and 1500 cc's. Chest wall, esophagus, spinal cord, and heart doses were evaluated as well. The conformity index (CI) was compared between plans and was intended to be similar between cases for single patients. To calculate CI per RTOG 0915, one over the volume receiving 100% of the prescription dose was divided by the total volume of the PTVs. The ideal CI would be 1.0 reflecting a perfectly conformal plan.

Statistical Analysis

A one-way repeated measures test was conducted to evaluate dosimetric outcomes. All lung parameters evaluated were deemed statistically significant. Each endpoint was tested using Wilks' Lambda, Pillar's Trace, Hotelling-Lawley Trace, and Roy's Greatest Root.

Results

Target sample

Of the fifteen subjects, 40% had three targets and 60% had two targets planned with a single isocenter. The average GTV volume was 0.57 ± 0.50 cc (range: 0.08 cc - 2.27 cc) of a total 37 GTV lesions planned for. Some patients had more targets than were treated, but the study was limited to 2-3 targets.

Lung doses

The dose to normal lung was evaluated between three different isotropic PTV margin expansions. To be expected, the normal lung dose increased with increasing margin expansions. This study found the difference in V5, $F(2,13)= 106.69$, $p<.0001$ was statistically significant. Mean V5 doses were 5 mm (M=12.92, SD= 4.39), 7 mm (M=15.93, SD=05.00) and 9 mm (M=18.53, SD=5.43) (See Figure 3, Table 2). The V20 was also statistically significant, $F(2,13)=$

57.44, p<.0001. Mean doses to the V20 were 5 mm (M=1.98, SD= 0.98), 7 mm (M=2.86, SD=1.44) and 9 mm (M=3.76, SD=3.76) (See Figure 4, Table 3). MLD was significant, F(2,13)= 137.01, p<.0001. Mean doses were 5 mm (M=2.41, SD= 0.70), 7 mm (M=3.02, SD=0.86) and 9 mm (M=3.58, SD=0.95) (See Figure 5, Table 4).

As a percentage, this study found that an increase from a 5 mm margin to a 7 mm margin increased the V5 from 12.9% to 15.9%, the V20 increased from 1.9% to 2.9% and the MLD increased by 0.6 Gy. When the isotropic margin to the GTVs increased from 5 mm to 9 mm, V5 increased from 12.9% to 18.5%, V20 increased from 1.9% to 3.8%, and MLD increased by 1.2 Gy. All of these dosimetric endpoints met constraints outlined by RTOG 0915.

OAR doses

Other dosimetric endpoints were analyzed for other organs at risk, such as the spinal cord, chest wall, and esophagus. The maximum dose to the chest wall F(2,13)= 5.08, p<.0235 increased by 2.1 and 3.9 Gy when increased from 5 mm to 7 mm and 9 mm respectively. Spinal cord maximum dose F(2,13)= 14.11, p<.0006 increased by 0.9 Gy and 2.4 Gy when increased from 5 mm to 7 mm and 9 mm respectively. The average maximum dose to the esophagus was 10.98 Gy with a standard deviation of 4.65. Heart dose constraints were 0 ccs for all cases.

Discussion

This study quantified the dosimetric impact of increasing PTV margins to reduce potential geometric misses during radiation delivery. For the 15 subjects in the study, the PTV margin could be safely increased to 9 mm without compromising normal tissue constraints. Increased PTV margins yielded increased MLD, V20, and V5. Per the literature, MLD should be less than 20-23 Gy, and the data from this study ranged from 2.41-3.58 Gy for 5mm-9mm margins, which is well below the guidance. RTOG 0915 states V20 should be less than 10-15%.

In this study, V20 averages ranged from 1.98-3.76%, again far below the protocol. The overseeing institution requires V5 to be less than 50% which was again well met in this study at all margin levels with average V5 ranging from 12.92-18.53%. These results all satisfied the levels detailed in the literature considered safe to treat.

Opening literature described the increased risk of a geometric miss when combining multiple targets into a single isocenter. A larger PTV margin provides greater assurance that the GTVs will be contained within the PTVs during the several breath-holds required for gated treatments when multiple lesions are being treated simultaneously with one isocenter. It is important to note, that one should not increase margins unwarranted as this is contradictory to the as low as reasonably achievable (ALARA) principle. However, when combining targets into a single isocenter, the risk of a geometric miss arises. Worse than increasing the margin would be missing one of the targets in treatment and not treating it to a curative dose. The therapeutic ratio weighs the risk of exposing healthy tissues to the probability of tumor control. If tumor control is not achieved, the dose to the lung is doing more harm than good.

Reasons a patient may need a larger than 5 mm PTV margin would include the patient struggling with a reproducible breath-hold, one or more targets being by the diaphragm, or if a radiation oncology facility does not have a couch with 6 degrees of freedom. Firstly, patients sometimes do not qualify for RPM treatment because they are not consistent enough with their breath-hold. However, with a larger margin, people who are not as consistent could be treated with RPM which may help position the heart more favorably or increase normal lung volume. Second, as shown in the literature, lesions closer to the diaphragm are prone to greater breathing motion. The type of breath-hold taken greatly impacts the position of targets in that region. This may drive the need for different shifts to align different targets, which can be alleviated by an

increased treatment margin. Finally, a six degrees of freedom couch allows correction for pitch, yaw, and rotation in addition to planar movements. This can help better align on-treatment images and would be missed if a particular institution did not have this feature and would benefit from an increased treatment margin.

As with any study, there were some limitations to discuss. One limitation of the application of these results is the GTVs targeted were all small (range: 0.08 cc - 2.27 cc). The results of this study are only applicable for patients with multiple targets within the size range listed in the results. Specific to patients with oligometastatic disease, there is an increased chance the patient will need more treatment. This is another reason GTV size and margin selection are crucial for this patient population. Treating patients with multiple targets in a single isocenter should be reserved for patients who can tolerate larger treatment margins and the increased lung dose outlined in the results. Another limitation of this technique is when targets fall in the same axial plane. In the study, patient number five was marked as an outlier in the graph for V20. This case in particular had three lesions in the same axial plane. Because of this, the crosstalk, when high doses fall between lesions because they are in the same plane, increased the V20 between the three lesions, shown in Figure 6. Planners can add a structure between lesions and set a maximum dose limit to that structure. This method was employed for several patients in the study. The majority of the time, this was used for lesions in the same axial plane, but a few patients had crosstalk structures to separate lesions in the same sagittal plane.

One unanticipated result noted in the statistical analysis was the increased CI with increased PTV margin. Extending from 5 mm to 7 mm to 9 mm PTV margins increased the average CI from 0.81 to 0.85 to 0.87, respectively. This was not found in the literature previously and was not a focus of this study. However, this finding should be investigated further.

Future studies could repeat this methodology with more than two to three lesions in a single target, or focus on larger targets. This study could be applied to on-treatment imaging for the selected patients and see which margin expansion would be most appropriate for each of these patients. This would show how much the targets did or did not line up in relation to one another, identifying which margin level is most demanded by day-to-day setup. Finally, this study could be conducted amongst other respiratory management devices such as MR, AVG CTs, etc.

Conclusion

This study quantified the dosimetric impact of increasing PTV margins to reduce potential geometric misses during radiation delivery. For the 15 patients considered, the PTV margin could be safely increased to 9 mm without compromising normal tissue constraints. This provides greater assurance that the GTVs will be contained within the PTVs during the several breath-holds required for gated treatments when multiple lesions are being treated simultaneously with one isocenter. Future studies could apply margins to onboard images to determine setup reproducibility and further validate the final margin expansion to yield safe and effective radiation therapy treatments for oligometastatic patients.

Bibliography

1. Sanford L, Molloy J, Kumar S, Randall M, McGarry R, Pokhrel D. Evaluation of plan quality and treatment efficiency for single-isocenter/two-lesion lung stereotactic body
2. Bauman GS, Corkum MT, Fakir H, Nguyen TK, Palma DA. Ablative radiation therapy to restrain everything safely treatable (ARREST): study protocol for a phase I trial treating polymetastatic cancer with stereotactic radiotherapy. *BMC Cancer*. 2021;21(1):405. doi:10.1186/s12885-021-08020-2
3. Critchfield LC, Bernard ME, Randall ME, McGarry RC, 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*. 2021;22(1):251-260. doi:10.1002/acm2.13145
4. Cella L, Monti S, Thor M, Rimner A, Deasy JO, Palma G. Radiation-Induced Dyspnea in Lung Cancer Patients Treated with Stereotactic Body Radiation Therapy. *Cancers*. 2021;13(15):3734. doi:10.3390/cancers13153734
5. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *The Lancet*. 2019;393(10185):2051-2058. doi:10.1016/S0140-6736(18)32487-5
6. Muller DA, Dutta SW, Aliotta E, et al. Clinical Outcomes and Predictors of Lung Toxicity After Multiple Courses of Lung Stereotactic Body Radiotherapy for Early-Stage Non–Small Cell Lung Cancer. *Clin Lung Cancer*. 2021;22(3):234-241. doi:10.1016/j.cllc.2020.06.006
7. Pokhrel D, Sanford L, Larkin S, et al. On the use of single-isocenter VMAT plans for SBRT treatment of synchronous multiple lung lesions: Plan quality, treatment efficiency, and early clinical outcomes. *J Appl Clin Med Phys*. 2020;21(8):160-167. doi:10.1002/acm2.12938radiation therapy. *J Appl Clin Med Phys*. 2018;20(1):118-127. doi:10.1002/acm2.12500
8. Käsmann L, Dietrich A, Staab-Weijnitz CA, et al. Radiation-induced lung toxicity – cellular and molecular mechanisms of pathogenesis, management, and literature review. *Radiat Oncol*. 2020;15(1):214. doi:10.1186/s13014-020-01654-9
9. Liu H, Andrews M, Markovich A, Zhuang T. Dosimetric effect of uncorrected rotations in lung SBRT with stereotactic imaging guidance. *Phys Med*. 2017;42:197-202. doi:10.1016/j.ejmp.2017.09.135
10. Li H, Chang JY. Accounting for, Mitigating, and Choice of Margins for Moving Tumors. *Semin Radiat Oncol*. 2018;28(3):194-200. doi:10.1016/j.semradonc.2018.02.004

Tables

Metric for Lungs-GTV	Goal/Constraint
V20Gy	< 10-15%
Mean Lung Dose (MLD)	< 20 Gy
V1000cc	< 7.4 Gy
V1500cc	< 7 Gy

Table 1. Constraints placed on lung volumes for study

Analysis of LungV5%
Descriptive Statistics

Variable	*Label*	*N*	*Mean*	*Std Dev*	*Std Error*	*Lower 95% CL for Mean*	*Upper 95% CL for Mean*
VAR6_5	LungV5(%)	15	12.92	4.39	1.13	10.49	15.35
VAR6_7	LungV5(%)	15	15.93	5.00	1.29	13.16	18.70
VAR6_9	LungV5(%)	15	18.53	5.43	1.40	15.53	21.54

Table 2. Statistics for V5 in study

Analysis of LungV20%
Descriptive Statistics

Variable	*Label*	*N*	*Mean*	*Std Dev*	*Std Error*	*Lower 95% CL for Mean*	*Upper 95% CL for Mean*
VAR7_5	LungV20(%)	15	1.90	0.98	0.25	1.36	2.44
VAR7_7	LungV20(%)	15	2.86	1.44	0.37	2.06	3.66
VAR7_9	LungV20(%)	15	3.76	1.60	0.41	2.87	4.64

Table 3. Statistics of V20 in study

Analysis of CI (%)
Descriptive Statistics

The MEANS Procedure

Variable	*Label*	*N*	*Mean*	*Std Dev*	*Std Error*	*Lower 95% CL for Mean*	*Upper 95% CL for Mean*
VAR10_5	CI (%)	15	0.81	0.03	0.01	0.79	0.83
VAR10_7	CI (%)	15	0.85	0.04	0.01	0.83	0.87
VAR10_9	CI (%)	15	0.87	0.03	0.01	0.86	0.89

Table 4. Statistics of MLD in the study

Figures

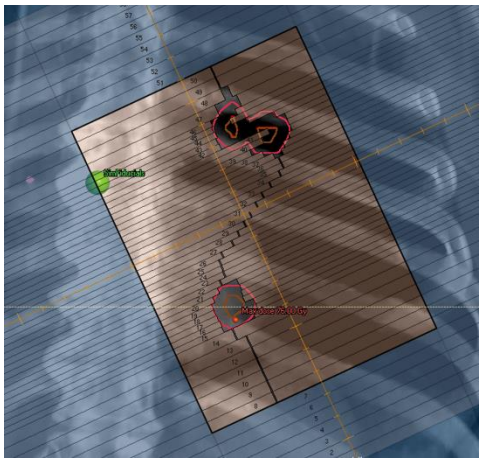

Figure 1. Display of isocenter placement and collimator selection

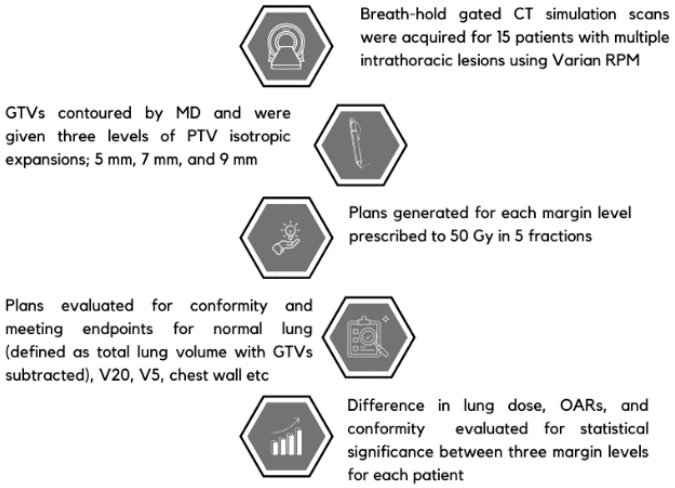

Figure 2. Visual aid of methods for study

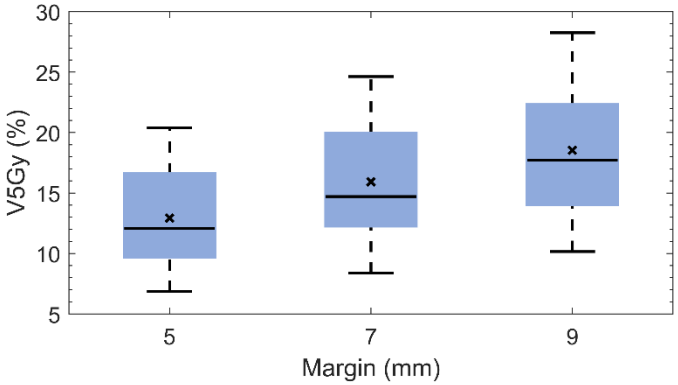

Figure 3. Box plot of V5 compared to margin expansion

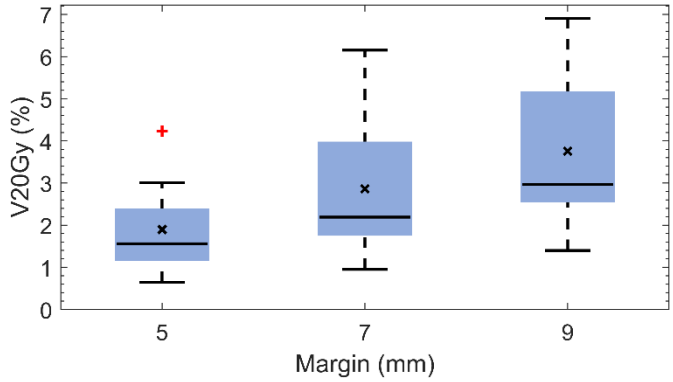

Figure 4. Boxplot of V20 compared to margin expansion

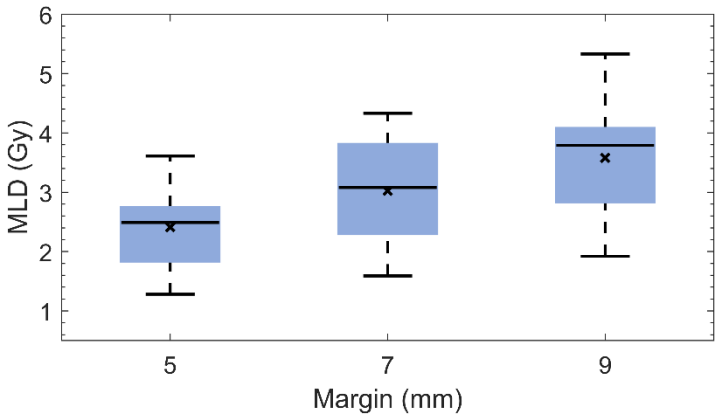

Figure 5. Boxplot of MLD compared to margin expansion

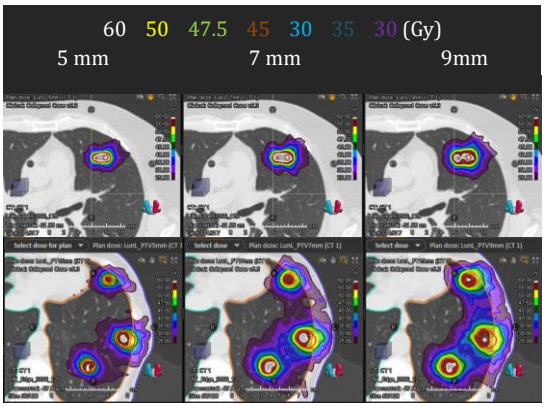

Figure 6. Axial slices comparing isodose lines for a typical patient (top) and for the outlier patient (bottom) described in Figure 4.

Acknowledgment: This research was the product of collaborative work. The author was involved with all aspects, but I would like to take a moment to thank Dr. Gemma Davies for her knowledge, brainstorming and plan review, Alyx Alfson for her education and plan review, Dr. Carri Glide-Hurst for her brainstorming and unmatched editing skills, and finally Kristen Vu for her brainstorming and editing.