Development and Implementation of Intensity Modulated Radiation Therapy for Small Animal Irradiator

by

Jacob Kodra

Graduate Program in Medical Physics
Duke University

Date:_______________________
Approved:

___________________________
Mark Oldham, Supervisor

___________________________
Justus Adamson

___________________________
David Kirsch

Thesis submitted in partial fulfillment of
the requirements for the degree of Master of Science in the Graduate Program in
Medical Physics in the Graduate School
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2018
ABSTRACT

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Abstract

Translational cancer research has been around for many years and has resulted in many advancements in cancer treatment. Preclinical radiation therapy is an important tool used in some studies to better understand the biological effects due to radiation. Current preclinical radiation treatment techniques do not emulate the advanced techniques used in cancer clinics, such as intensity modulated radiation therapy (IMRT). In this work we explore the possibility of developing and implementing an IMRT treatment capability for an orthovoltage micro irradiator used for small animal research.

In order to implement IMRT to the micro irradiator, every step of the radiation therapy treatment process had to be evaluated, developed, and tested. The first step was to develop and treatment planning software that can be used for small animal studies. Using the open source Computational Environment for Radiotherapy Research (CERR) and adapting it for use with an orthovoltage irradiator, Monte Carlo dose calculations could be performed for small animal data sets. CERR does not have the ability to optimize dose calculations, so a Matlab script was developed and written for inverse optimization for treatment planning. Treatment plans were designed and optimized for several small animal cases to evaluate the optimization algorithm. Following successful simulation development, treatment delivery techniques needed to be developed. 3D printing was used as a tool to create physical compensators that could be used as an
add-on device to the micro irradiator. With the capability of submillimeter printing resolution, 3D printing has the capability to handle the high resolution required for very small structures inside of small animals. Using the simulation data, another Matlab script was developed to create both compensator and inverse compensator 3D models. Many materials and techniques were evaluated to determine the best method for compensator production. Materials were tested for attenuation properties, printing capabilities, and ease of use until a satisfactory result was achieved.

Once the simulation and delivery techniques were developed to a satisfactory level, an end to end test was designed to verify the IMRT capability. Using a 2.2 cm diameter cylindrical Presage® dosimeter as the quality assurance (QA) device/patient, a treatment plan was created based on the geometry of the Radiologic Physics Center (RPC), which is now the Imaging and Radiation Oncology Core (IROC), Head and Neck phantom design. The dose tolerances used for the inverse optimization were the same as the RPC Head and Neck protocol with a stricter tolerance for the organ at risk (OAR). Compensators were produced for the plan and both 2D and 3D analysis was performed. Radiochromic film was used for 2D dose map analysis. Gamma analysis was performed using 2D film data with varying criteria for distance to agreement and dose difference. 3D analysis was done by delivering the treatment plan to the Presage® dosimeter. Using optical-CT for dose readout of the dosimeter, qualitative analysis was performed to show the 3D delivered dose data.
The end to end test showed strong evidence that IMRT could be implemented on the small animal irradiator. The 9 field treatment plan was delivered in under 30 minutes with no mechanical or collisional issues. The 2D dose analysis showed 7 out of 9 treatment fields had a passing rate greater than 90% for a gamma analysis using 10%/0.5 mm tolerances. 3D dose analysis showed promising spatial resolution of the dose modulation. Basic feasibility of using 3D printed compensators to modulate dose with high spatial precision and moderately accurate dose delivery has been established, and further recommendations on how to improve the accuracy of this new technique have been included.
Dedication

To my beautiful wife and children. Without their love and support I would not be where I am today. They give me the drive to work hard and be successful.

To my wife. Thank you for always standing by my side, and being a perfect wife and mother. You are the one who keeps our family happy, healthy, and moving toward a better future.

To my kids. This is for you. This is a step toward our future and the future I want to give you.
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1. Introduction

1.1 Pre-Clinical Cancer Modelling

Cancer is the second leading cause of death in the United States. It was predicted that in the United States, over 1.6 million new cases would be diagnosed and over 0.6 million cancer related deaths would occur in 2017 [1]. For this reason, research is very important in improving the understanding of this aggressive disease. With better understanding, treatment methods will continue to improve. One major component of cancer research happens in the preclinical realm where cells and small animals provide valuable insights to cancer biology.

In 1951 the first cell line, HeLa, was cultured using cervical cancer cells from Henrietta Lacks [2, 3]. This was just the beginning, and since that time many more cell lines have been developed [4, 5]. Cultured cell lines are used in many ways for pre-clinical cancer research. They are used in both medical oncology and radiation oncology research [6-8]. As time has progressed, so have the preclinical modelling methods. Based off of the development of cell lines, the ability to do in-vivo studies through orthotopic xenografts has been implemented [9-12]. This development has allowed researchers the ability to study the microenvironment of cancers rather than in-vitro tumor cells alone [13, 14]. Another modelling type that has been developed is genetically engineered
mouse models (GEMMs). These models allow for autochthonous tumor growth, which has many advantages for cancer biology research [15].

**1.2 Small Animal Radiation Therapy**

As mentioned previously, these preclinical cancer models are used in many ways for cancer research, with radiation oncology being a major focus. Radiation therapy treatment is used on roughly 50% of all cancer patients and is therefore an important translational research topic. Using the many types of models mentioned, researchers have the ability to study the effects of radiation therapy on cancer biology, such as fractionation, linear energy transfer, radiosensitivity, tumor growth rate and many more [16-19]. Depending on the type of experiment being performed, the type of radiation used varies, but in terms of small animal studies, preclinical irradiators are the predominant choice. There are several commercial options on the market today with each unit having varying characteristics [20].

Some of the features that can be seen on the many devices are built-in imaging, adjustable/interchangeable collimator sizes, variable dose rate, beam energy selection, and fixed or arc fields. The use of these features allow for a wide range of treatment methods from conformal dose delivery, using small circular collimators and high resolution imaging, to less intricate experiments like whole body radiation or cell culture irradiations. Here at Duke, the X-Rad 225Cx seen in figure 1, developed at Princess
Margaret Hospital and distributed by Precision X-Ray Inc. (PXI, North Branford, CT, USA), is used for small animal radiotherapy studies. The X-Rad 225Cx is equipped with an x-ray tube capable of generating photon energies up to 225 keV, built in cone beam CT imaging panel, interchangeable collimator (1 mm diameter to 40x40 mm²) and an adjustable stage in 3 dimensions (x, y, and z). This fully shielded unit allows for it to be placed in a clean room environment for direct access in the small animal facility.

![Figure 1: Precision X-Ray Inc. X-Rad 225Cx small animal irradiator. Features gantry mounted x-ray tube and imaging panel. Figure courtesy of pxinc.com.](image)

Although these machines have improved the ability for small animal radiation therapy studies, there are still limitations to each machine. One of the common limitations of these machines are the fixed field shapes. Of the machines that have been developed, one unit developed at Stanford University does have an adjustable field size collimator, but it is fixed to only circularly shaped fields [21]. The reason fixed field shapes is a point of interest is because this treatment method is not translatable to most
clinical methods. Treatment methods such as intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) have been used clinically for many years [22-26] and have the ability to use multi-leaf collimators (MLCs) or physical compensators to create custom field shapes.

This work aims to enhance the abilities of the X-Rad irradiator by implementing a method of delivering IMRT treatment plans. Building on previous work using the irradiator for special procedures [27], here we present data showing a treatment plan designed based off of the Radiologic Physics Center (RPC), now Imaging and Radiation Oncology Core (IROC), Head and Neck phantom design [28]. Using the open source Computational Environment for Radiological Research (CERR) [29] for Monte Carlo simulations and treatment planning, and advanced 3D printing techniques for photon modulation, a 9 field plan was designed. Verification of the plan delivery was done both in 2D, using radiochromic film, and 3D, using a Presage® dosimeter (Heuris Inc., Skillman, NJ) and high resolution optical CT.
2. Materials and Methods

2.1 Overview

In order to develop a novel IMRT treatment delivery for the small animal irradiator, three main tasks had to be evaluated and developed. These three parts were simulation and treatment planning, compensator design and manufacturing, and a complete end to end test of the whole process. Various tools and equipment had to be used throughout.

Initial testing and development of the simulation and treatment planning processes focused on using small animal data sets. This allowed testing of various parameters such as anatomy and target location.

The final two steps, compensator design and manufacturing and end to end testing, were based off of a treatment plan designed for a phantom. The phantom used in this work was a 3D Presage® dosimeter.

2.2 Developing a Micro-IMRT Treatment Planning Capability for Small Animals

2.2.1 CT Data Input

CERR is a powerful open source research platform that has been used for a wide range of research projects [29]. In order to use it for a small animal research, some adaptations needed to be implemented and accounted for.
The first step before using CERR is to obtain a CT set for a patient or cohort of mice. This was done using the CBCT on the irradiator. This CT set can be imported into CERR for further evaluation. The CBCT images used here were provided from previous small animal studies. The CBCT data used the standard protocol techniques for the X-RAD 225Cx.

### 2.2.2 Structure Segmentation

Here at Duke, most small animal studies using X-Rad 225Cx irradiator use a preset treatment protocol. In some cases, however, more sophisticated planning is done. PXI, in collaboration with the Maestro Clinic, developed a Monte Carlo small animal treatment planning system, SmART-Plan. This software can be used for structure segmentation. This capability becomes important in some studies where dose toxicities may be of concern and researchers would like to know how much dose certain organs at risk (OARs) receive.

The structure set from SmART-Plan software can be exported and imported into CERR if desired, but the two programs do not communicate well and a third software needs to be used to properly register the image data with the structure data.

For the work in this study, 3D slicer was used to properly register the data. The structure set and CT set are exported in DICOM format and imported into 3D slicer.
Using a rigid registration method, the structure set and CT set are registered. This new registered data is exported and can then be imported into CERR for plan evaluation.

2.2.3 CERR Treatment Planning

IMRT capabilities are partially built-in to the CERR interface using the IMRTp guided user interface (GUI). Figure 2 shows the GUI interface with the many parameters that can be used.

Within the interface the user selects the target structure(s) and chooses how many beams to use. Beam orientation can be done manually or automatically spaced equidistant. These beams are centered on the isocenter. Isocenter can be automatically determined using the center of mass of the target structure(s), or manually put in. In this work we allowed the software to determine isocenter.

Many of the other options of the GUI were not used in this study because they have no function for a small animal irradiator. These inputs were either set to zero or set to not applicable.
Figure 2: IMRTp guided user interface built into the CERR platform. User has the ability to create sophisticated treatment plans using all the parameters seen.

2.2.4 Dose Calculation Algorithm

Beam energy is a selection not mentioned in the previous section. This selection is important for the dose calculation algorithm.

IMRTp has the capability of running a fast dose calculation using the quadrant infinite beam (QIB) algorithm. This method, however, is limited to the preset megavoltage photon energies. IMRTp also comes with the capability of performing a Monte Carlo dose calculation using voxel-based Monte Carlo (VMC++) [30, 31]. As an input to the Monte Carlo algorithm, a spectrum file can be input for a specific energy source. The typical use of the Monte Carlo algorithm is for megavoltage energies, but the VMC++ algorithm has been shown to be accurate at orthovoltage energies [32].
The x-ray tube installed in the irradiator uses a tungsten target with inherent filtration of 0.8 mm of beryllium. Added filtration of 0.9 mm copper is used while delivering therapeutic x rays. The beam spectrum file was obtained by extracting the data from the treatment planning software that is integrated with irradiator treatment planning software. Figure 3 shows the spectrum file that was obtained and used for the Monte Carlo simulations.

![X-Rad 225Cx Beam Spectrum](image)

**Figure 3: X-Rad 225Cx beam spectrum used for Monte Carlo calculations. The characteristic bremsstrahlung photons due to the tungsten target can be seen.**

At orthovoltage energies, the photoelectric interaction is the dominant form of photon interactions. Understanding of this principle allowed for verification that the Monte Carlo simulation was properly using the input spectrum file. By running a dose calculation, it was expected that the surface dose and high density regions would have the highest doses. Many simulations were run using various inputs such as beam angle,
number of targets, beamlet size, and number of particles to gain experience using the software.

### 2.2.5 Fluence Modulation and Inverse Optimization

The Monte Carlo dose simulation outputs uniform fluence for each beam. The IMRTp interface does not have the capability to optimize each beam. This must be done using an external solver. There are many methods for IMRT optimization, but the one used in this work is the fast and accurate method of gradient descent.

The fluence matrix generated from the IMRTp calculation is first extracted from the global variable created during simulation. From here an IMRT input script was written to be used for the target and OAR dose constraints and weightings. This script allows for an upper and a lower constraint to be set for each structure. The script extracts the data for each structure to determine the number of voxels (volume) each structure contains.

Once the constraints are set, the optimization is run. Several scripts were written to implement the gradient descent method. To begin, a uniform initial starting fluence is created. The objective function for this starting fluence is calculated using equation 1 for the target objective and equation 2 for the OARs. The total objective function is a sum of all OARs and target structures individual $\Omega$ values.
Equation 1: This is the objective function component for target structures. Here \(d\) is the dose criteria, \(w\) is the priority, and \(N\) is the volume input

\[
\Omega^{\text{target}} = w_{\text{target}} \times \sum_{i \in \text{target}} \frac{\max (d_i^\text{target} - d_i^\text{max})^2}{N_{\text{target}}} + w_{\text{target}} \times \sum_{i \in \text{target}} \frac{\max (d_{\min}^\text{target} - d_i^\text{target})^2}{N_{\text{target}}}
\]

Next, the steepest decent direction is determined by using equation 3. In this work we used a numerical method approach for steepest decent calculations using equations 4 and 5.

\[
g = -\frac{\vec{v}}{||\vec{v}||} = \left[ \frac{\partial \Omega}{\partial f_1}, \frac{\partial \Omega}{\partial f_2}, \frac{\partial \Omega}{\partial f_3}, \frac{\partial \Omega}{\partial f_4}, \ldots \right]
\]

Equation 3: This equation is used to determine the steepest descent toward the minimum objective function value for all beamlet \(s\) and constraints. \(f\) represents individual beamlets.
Equation 4: Numerical method approach to finding the steepest descent direction of the objective function.

\[
\frac{\partial \Omega}{\partial f_1} \approx \frac{\Omega(f_1 + \Delta f_1) - \Omega(f_1)}{\Delta f_1}
\]

Equation 5: Supporting equation used in the numerical method approach for steepest descent direction.

\[\Delta f_1 = \max (0.01 \cdot |f_1|, 0.001 \cdot \text{avg}(|f_1|, |f_2|, \ldots))\]

Once the direction is determined, a line search is then performed along the steepest gradient direction. For each step along the steepest descent, the objective function must be calculated. The line search continues until equation 6 is no longer satisfied. Once the initial line search has completed, the process begins again and a new steepest decent direction is determined. This cycle continues until the objective function reaches a minimum value.

Following optimization, this process outputs a fluence weighting vector for each beamlet. This vector is then used as input in the IMRTp GUI where a new optimized dose distribution is calculated.

\[\frac{(\Omega_{\text{line start}} - \Omega_{\text{line end}})}{\Omega_{\text{line start}}} > 10^{-5}\]

Equation 6: Conditional statement for the line search step of the optimization. When the statement is no longer satisfied the line search ends.
2.3 A Novel Method for Implementing IMRT Treatment Delivery

3D printing is a technology that allows for rapid prototyping. There are many types of 3D printing technologies but a common and inexpensive method is fused deposition modelling. This method uses continuous heating of a thermoplastic filament to deposit layer by layer of a 3D model. There are a wide range of commercial printer options with a range of printing qualities.

For this work we used an Ultimaker 2+ (Ultimaker, Geldermalsen, Netherlands) as can be seen in figure 4. This printer has the capability of submillimeter printing resolution based on the diameter of the printing nozzle and the settings used for printing. In this work we use 3D printing as a tool to create physical compensators that can be used for IMRT treatment delivery on the micro irradiator.

Figure 4: Ultimaker 2+ 3D desktop printer. Printer capable of submillimeter printing resolution. Photo courtesy of Ultimaker.com
2.3.1 Automatic 3D Modeling

Once the treatment planning process had been completed, the delivery technique needed to be developed. Using the optimized fluences, we are able to create planned fluence maps for each beam within a plan. In order to deliver a modulated fluence, a modulation device needed to be created. A physical compensator can do just this and a method for creating was developed.

A Matlab (MathWorks, Natick, Massachusetts) script was written to convert a 2D fluence map to a 3D compensator model. By taking the fluence weights for each beamlet, all fields are normalized together. This was done to simplify the delivery process. This normalization will allow for the same treatment time for each field. Although this is not the most efficient method, it is the most user friendly method for the micro irradiator operator. Each normalized beamlet is converted to the number of half value layers (HVL) required for modulation using equation 7. By multiplying the HVL of the material being used, the thickness is then determined for each beamlet.

\[
\text{number of HVLs} = -\log_2\left(\frac{f_n}{f_{\text{max}}}\right)
\]

Equation 7: Equation used to determine the number of HVLs needed to modulate each beamlet.
Once the thickness for each beamlet is determined, the data must to be converted to a 3D model. Using an open source Matlab function, a surface in Matlab is converted to a 3D model compensator file. We are also able to modify this code to make an inverse compensator and use this as a mold.

Other inputs to the Matlab script are beamlet resolution, thickness limit, and collimator size. These inputs are all used for generating the 3D model.

The beamlet resolution from simulation is used to correct the size of the model. The position of the compensator is placed in the beam path at $\frac{3}{4}$ of the distance from the treatment plane. This means the size of the model needs to be corrected because the fluence map shows the treatment field size at the isocenter distance.

Thickness limit is used as a hard cutoff of the compensator thickness. As space is limited within the irradiator, the compensator must have a practical size as not to impede on treatments as well as to avoid collisions with the treatment couch. The thickness limit used here was 6 HVLs of a given material. 6 HVLs of material corresponds to 1.25% transmission. This was chosen as an acceptable transmission level for regions trying to achieve 0% transmission.

Collimator size is an important input so the model is the correct size. As the size of the treatment field differs, regions outside the field need to be blocked. The script uses this input to match the size of the model to the size of the collimator field size to block all portions of the open beam.
2.3.2 Comprehensive Material Evaluation

2.3.2.1 Compensator

With high interest in the field of 3D printing, there are many types of filament available for purchase. As we are trying to use 3D printing filament for x-ray attenuation, we had to find a material that would work properly for our beam energy as well as have high printing qualities.

As the 3D printing world has developed, the filaments have as well. Popular types of filament are thermoplastic materials such as acrylonitrile butadiene styrene (ABS) or polylactic acid (PLA) doped with some sort of other material. These additives allow 3D printed models to have unique textural features. Some of these filaments are doped with metal particles as to give a metallic look to models. Some of these metal-doped filaments were tested for potential use. These filaments were tungsten filled ABS, tungsten filled PLA and copper filled PLA. These materials were tested by setting them up to print simple but detailed 3D models that test various printing parameters.

The attenuation properties of the tungsten filled filaments was also tested by printing known thicknesses of material and performing an HVL test. This was done by using an ionization chamber placed slightly above the treatment couch to avoid backscatter readings and placed along the central axis of the beam. A small field was used to avoid additional scatter as well. Successive readings were made by adding additional material in the beam path. Collected charge readings were taken for each
amount of material. The HVL was determined by finding the amount of material needed to reduce the collected charge to \( \frac{1}{2} \) of the unfiltered beam.

Another approach that was tested was making custom 3D printing filament. This allowed for using materials that cannot be commercially purchased. Using mass attenuation to estimate the HVL of a given material, several materials were compared. Table 1 shows a list of materials that were evaluated and their corresponding HVL estimation at the peak energy and the average energy of the micro irradiator beam.

<table>
<thead>
<tr>
<th>Material</th>
<th>HVL (cm) 225 keV</th>
<th>HVL (cm) 80 keV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bismuth</td>
<td>0.080902113</td>
<td>0.028191435</td>
</tr>
<tr>
<td>Lead</td>
<td>0.071861671</td>
<td>0.025240706</td>
</tr>
<tr>
<td>Tin</td>
<td>0.332083866</td>
<td>0.031298</td>
</tr>
<tr>
<td>Cadmium</td>
<td>0.299918042</td>
<td>0.029122358</td>
</tr>
<tr>
<td>Cerrobend</td>
<td>0.100859747</td>
<td>0.028521568</td>
</tr>
</tbody>
</table>

From this list, tin was chosen as a potential suitable material. Small samples of tin-doped PLA with differing mass ratios were manufactured. To test the attenuation properties, these samples were placed in the micro irradiator beam path and attenuation was measured using EBT Gafchromic Film as can be seen in figure 5. EBT Gafchromic film has been shown to have a small dependence at low energies and therefore is a reliable tool [33]. Resulting from this test, a mass ratio of 1:1 tin to PLA was chosen as the desired composition for filament manufacturing.
Figure 5: Various materials tested for attenuation with change in optical density as the scale. A, B, C are tin-PLA composites of 40%, 50%, and 60% tin respectively. D and E are tungsten-PLA composites with one being commercial and the other custom. F is cerrobend. All samples were approximately the same thickness (1 cm).

The filament making process is a multi-step process. First the base thermoplastic is dissolved with a 10:1 volume ratio of dichloromethane (DCM) to thermoplastic PLA pellets. These are combined in a sealed glass jar and stirred for at least 12 hours. Once the thermoplastic pellets are dissolved, tin was added to the desired ratio and mixed for 12 hours to ensure even mixing of the two materials. Once fully combined, the solution is casted on a flat pan so all DCM can evaporate. The casted solution should be approximately 2 cm thick prior. 12 hours was allotted for full evaporation. Following evaporation, a flat sheet, approximately 2 mm thick, of tin-PLA remains and is chopped down to pellet form. These pellets are then fed into an auger driven filament extruder which melts down and shapes the material into a filament form.
2.3.2.2 Inverse Compensator

Another approach to compensator manufacturing was 3D printing inverse compensator molds and filling this mold with an appropriate attenuating material. Various materials were tested as part of this process.

The first trial was to use the tin-PLA solution that was used for filament manufacturing. As this was a pourable mixture, it was able to be poured directly into a mold but there were concerns the DCM would dissolve a 3D printed mold before the evaporation occurred. Also after the DCM evaporated, gaps were left in the mold where the DCM gases escaped. More solution had to be poured into the gaps to ensure the compensator was 100% solid with no air pockets. This process was repeated until all gaps were visibly filled.

Next, metal casting was attempted for compensator production. Cerrobend is a widely used material in radiation therapy. It is used for custom field shapes for electron beam treatments. With its effective attenuating property and low melting point, it was hypothesized that this material could be used to create compensators. As seen in figure 5, cerrobend proved too highly attenuating for orthovoltage x rays.

Another metal with a low melting point called pewter, which is composed of 85-99% tin, and varying percentages of bismuth, antimony, copper and lead, seemed potentially another viable option as a casting material. With a melting point below the
melting point of PLA, pewter blocks were placed into a desktop cast iron melting pot and poured into 3D printed molds to test the feasibility of metal casted compensators.

One final method that was tested was to use a powdered material. This would allow the material to be reusable. The powder needed to have high density, very fine particles, and non-toxic. After some research into various choices, sodium iodide was chosen. The HVL was tested by creating molds of a known thickness filled with sodium iodide powder. The HVL was measured by placing the molds in the beam path and measuring the ionization signal with radiochromic film.

2.4 End to End Verification of the Entire Micro-IMRT Treatment Chain

2.4.1 Overview

Following development of the simulations, treatment planning, and material testing, an end to end test was designed to test the feasibility of this new IMRT capability. Building on previous substantial lab work and development in 3D dosimetry [34-41], a treatment plan was designed for a 3D Presage® dosimeter. The plan designed was based off the geometry of the RPC Head and Neck phantom which is commonly used for IMRT quality assurance.

2.4.2 Treatment Design

A CBCT set of a cylindrical Presage® dosimeter with a diameter of 2.2 cm was acquired on the micro irradiator. The CT set was imported into CERR for structure contouring. There were 4 structure sets contoured (body, primary planning target
volume (PTV), secondary PTV, and a single OAR). Figure 6 shows an axial slice through the dosimeter showing the geometry each structure. Once the contouring was completed, a slight simplification was made to the CT by overriding the CT values within the body of the dosimeter to be uniform. This simplification would allow for simpler optimization and compensator manufacturing.

![Secondary PTV](image)

Figure 6: Axial slice of the cylindrical 3D Presage® dosimeter used for end-to-end testing. The three structures of interest are shown with a similar geometry to the RPC Head and Neck phantom.

Following contouring, the initial Monte Carlo dose calculation was performed in the IMRTp interface. The primary and secondary PTVs were selected as the target structures. The plan used 9 beams spaced equidistant apart starting at 0 degrees. The simulation was run using 100,000 particles and beamlet resolution of 1.25 mm in both x and y directions. The beamlet resolution is limited by the slice thickness of the image set.

After completion of the Monte Carlo simulation, the dose optimization was implemented. The dose constraints used for the clinical RPC Head and Neck Phantom were used here with the exception of the OAR. Here we used a lower dose constraint for the OAR to further test the capabilities and attempt to spare as much dose to the OAR as possible.
possible. Table 2 shows the dose constraints for each structure used in the optimization.

Following the optimization algorithm, the new beamlet weights were input back into IMRTp for the final dose calculation.

Table 2: Dose constraints used for the inverse optimization for the Presage® cylindrical dosimeter.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Max Dose (Gy)</th>
<th>Volume Percentage</th>
<th>Min Dose (Gy)</th>
<th>Volume Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV Primary</td>
<td>7</td>
<td>0</td>
<td>6.6</td>
<td>0.95</td>
</tr>
<tr>
<td>PTV Secondary</td>
<td>6</td>
<td>0</td>
<td>5.4</td>
<td>0.95</td>
</tr>
<tr>
<td>OAR</td>
<td>2</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Using the 3D modeling script and the optimized beamlet fluence, the 9 compensator mold models were created and printed on the Ultimaker 2+ printer. Sodium iodide was added into each mold and sealed using a 3D printed lid. These molds are then attached to a mounting tray that slides into a custom mounting block attached to the irradiator collimator. This can be seen in figure 7.

Figure 7: 3D printed compensator attached to mounting tray and positioned on the collimator mounting block inside the X-RAD 225Cx irradiator
One final step needed before irradiation, was to convert the fluence to dose. A first order approximation was done by creating a dose calculation simulation using uniform beamlet fluence \( f \) values of 500, 1000, and 1500 from a single anterior to posterior field if the Presage® dosimeter. The surface dose of the dose calculation was measured for each beam weighting scheme along the central axis. By dividing the calculated dose for each specific beamlet weight, it was determined that the simulation modeled 0.12 cGy/f. By taking the max fluence value from the optimization and simply multiplying 0.12cGy/f and the max f, each fluence map was converted to a dose map. Using the commissioning data values of the micro irradiator output of .05 Gy/s at the surface, a beam on time of 72 seconds was to be used for each field. This approximation would result in slightly higher dose to the 3D phantom because the attenuation at varying depths was not accounted for.

### 2.4.3 Dose Delivery Quality Assurance

#### 2.4.3.1 Overview

One of the many roles of a clinical physicist is to perform patient specific quality assurance (QA). It is vital to be able to test treatment plans before they are used on patients to ensure patient safety and successful treatment. This is the case as well for this new treatment technique for the small animal irradiator. For this work we had the ability to test the treatment using both 2D and 3D dose analysis.
2.4.3.2 Compensator Reproducibility

Typical clinical workflow for IMRT QA is to deliver fluence maps for each beam to a calibrated QA device. The delivered fluence and planned fluence are compared using a gamma analysis. This work used a similar workflow but in this case, EBT Gafchromic film was used to measure the fluence. This QA approach was used to test a key feature of the process, compensator production reproducibility. If this treatment technique is to be implemented into real small animal studies, it is important that the compensators can be manufactured reliably.

Reproducibility was tested by using the generated 3D model for beam 1 of the 9 field beam plan. This model was printed three times using the same printing settings. Each compensator was filled with sodium iodide and attached to separate mounting trays. Each compensator was placed on the irradiator collimator with the gantry at 0 degrees and delivered for the planned 72 seconds with a sheet of radiochromic film placed at isocenter on the couch. Separately, 5 films were used for dose calibration of the film. Each film was irradiated to known doses ranging from 0 to 5 Gy. The film readout process is explained further below.

EBT film was cut into small pieces to be used individually for each field. Each film was scanned prior to irradiation on an Epson flatbed scanner (Epson American Inc., Long Beach, CA) following 1 hour of scanner warm-up time. Following pre-scans, the films were stored in a black envelope.
Following irradiation, the films were stored in a black envelope and given a full 24 hours to stabilize before scanning. Each film was scanned following the same pre-scan protocol. These images were then brought into the open source image analysis software ImageJ (National Institute of Health, Bethesda, MD) for analysis.

In ImageJ, the change in optical density (OD) was calculated using equation 8 for the irradiated films. This was done on both the delivered fluence fields as well as the dose calibration fields. By taking the average change in OD for each known dose delivered, a change in OD to dose curve was created and applied to the delivered fluence fields. These dose map images were saved and imported into Matlab for further analysis.

$$\Delta OD = \log_{10} \left( \frac{I_{\text{Before}}}{I_{\text{After}}} \right)$$

Equation 8: Change in optical density equation used for film analysis. I represents the intensity values of the pre-scan and post-scans.

The delivered dose maps and planned dose maps were analyzed in Matlab. Each field was analyzed using the gamma analysis method as shown in equation 9. Each delivered map was compared with the planned map. Various gamma criteria were used for both distance to agreement (DTA) and dose difference ($\Delta D$). In order for a pixel to pass a gamma analysis, a value less than 1 must be achieved. A Matlab script was
written to show a line profile across both the planned and delivered dose maps to show spatial modulation.

Statistical analysis of the reproducibility was done by creating an average dose map from the three separate dose maps. From here an isodose plot using average dose map with one standard deviation margins shows how much variability there was between the compensators.

$$\gamma = \min \left( \frac{\Delta D}{\Delta D_t} + \frac{\Delta d}{\Delta d_t} \right)$$

Equation 9: Gamma analysis equation used for 2D dose analysis. $\Delta D$ corresponds to dose and $\Delta d$ corresponds to distance to agreement.

2.4.3.3 9 Field 2D Dose Analysis

Once reproducibility had been established for the compensator production, the entire 9 field plan was to be analyzed. All 9 compensators were printed and filled with sodium iodide. Each of the compensators for were attached to separate trays. Using 225 kVp tube potential, 13 mAs, and a 0-degree gantry angle, each compensator was placed on the mounting block and x rays were delivered for 72 seconds to a piece of film placed on the treatment couch at isocenter. The film readout and dose analysis performed here used the same procedure as that of the reproducibility test.
2.4.3.4 3D Dose Analysis

This whole treatment plan was designed for a cylindrical Presage® dosimeter. To perform a 3D dose analysis, the plan needed to be delivered to a dosimeter and scanned using our in-house optical-CT scanner.

Prior to irradiation, the dosimeter was scanned in order to get the pre-irradiation background signal. 1 image projection was taken every 1 degree for a total of 360 projection images. Next, using the same compensators used for the 2D analysis, the dosimeter was positioned on the treatment couch and taped in place to prevent it from moving. Using fluoroscopy, the couch was shifted to the treatment isocenter. The treatment was then delivered using all 9 fields. The dosimeter was then stored in a dark bag for 24 hours and then scanned again using the same pre-scan technique in the optical-CT.

In order to convert the data to a dose value, calibration cuvettes were used. Using an AP-PA technique, 1 cm thick cuvettes filled with the same batch of Presage® as the dosimeter were irradiated to doses of 3, 6, and 8 Gy. These cuvettes were placed in a spectrophotometer in order to obtain the change in OD per cm calibration points.

Using an in-house reconstruction GUI in Matlab, the dosimeter pre and post scan data were used to create a reconstructed volume set with values as the change in OD of the Presage®. The change in OD to dose conversion from the calibration cuvettes was applied to the reconstructed volume in ImageJ.
As an additional plan verification method, a film measurement was implemented to measure a single axial dose slice of the whole treatment plan. A single sheet of Gafchromic film was placed in the plane parallel to the beam rotation as to measure the transverse dose distribution. The entire treatment plan was delivered using the same parameters as mention previously. Dose analysis for the film followed the same procedures as mentioned earlier.
3. Results

3.1 Simulations and Dose Calculations

Many simulations were run using various CT sets to confirm the Monte Carlo simulation was working as expected. Figure 8 shows a sample CT set for a 5 field rat prostate case prior to beam optimization. Figure 9 shows that the tumor targeting feature is working properly.

Figure 8: Rat Prostate with open field Monte Carlo dose distribution for both 6 MV (A) and using the 225 kVp spectrum (B). It can be seen that the Monte Carlo appears to be using the orthovoltage energy spectrum. The dominant photoelectric effect is noticeable in the high Z bony regions.

Figure 9: This is a mouse with a single lung tumor as contoured in yellow. The simulation properly shifted to make the isocenter of the treatment to be within the tumor. This is shown because the beam orientation has two sets of parallel opposed beams (AP-PA and laterals) and a single oblique field.
3.2 Fluence Optimization

Various cases were simulated and optimized to test the robustness and ability of the inverse optimization algorithm. Figures 10-12 show several cases that were run.

Figure 10: Here is a single lung tumor case showing lung and esophagus as the critical structures. The left image shows an axial slice and with the varying beam angles and the right image is the corresponding dose volume histogram. This plan was designed to deliver 20 Gy to the tumor.

Figure 11: Rat prostate case. (A) shows the optimized dose distribution with the PTV as the red contoured structure with the rectum as the OAR. The yellow dashed line corresponds to the line profile image in (B) comparing the optimized and non-optimized dose distributions. Note the line profile passes through the rectum and the dose sparing in this region of the optimized line profile.
Figure 12: Relative fluence map for single beam of rat prostate case. This is a PA beam for a prone rat. Note the central dose sparing where the rectum is positioned.

3.3 Compensator 3D Model Generation

Using the script that was generated, figures 13 and 14 show sample 3D models that were created for both compensators and compensator molds from optimized fluences. For all compensator molds, standard PLA filament was used.

Figure 13: (A) A simulated fluence map used to generate a compensator 3D model in (B). The thick regions designated by the arrows represent the regions to be blocked more showing the Matlab script is working properly.
3.4 Materials

3.4.1 Filament and Compensators

Various types of filament were used as potential for compensator manufacturing. Figures 15-17 show results for some of this testing. Each of them had positive and negative properties.

The copper filament (figure 15) had a 91% by mass composition that made it intriguing for compensator production. However, it was quickly determined this filament would not be suitable. The filament itself was very brittle causing many problems in the extrusion process. Extrusion was not smooth resulting in very choppy and rough prints. We were unable to produce any high quality prints using this filament which meant it would not work for the high resolution required for the project.
Figure 15: Copper PLA tested for potential use. This filament was very brittle and was very difficult to use. Printing resolution was poor and inconsistent printing can be seen toward the right side of the rectangular model.

The tungsten PLA that was commercially purchased had promising results. The printer had no problems using this filament. It was easy to use and high resolution prints were made using it as seen in figure 16. The specifications for the material composition were not available so we were unsure of its attenuation capabilities. Quick irradiation results using EBT film showed high spatial modulation.

Figure 16: Commercial tungsten PLA used. Top row shows three models with varying spatial resolution and design. Bottom row shows irradiated film images for each model placed in the beam path. Darker regions correspond to blocked regions. This filament had good printing properties and some good attenuation properties.
Figure 17: (A) Shows fluence map generated from the rat prostate case with lighter regions corresponding to blocked regions. (B) An early stage printed compensator using the tungsten PLA. (C) Film measurement using compensator. Film measurement shows promising modulation capabilities using tungsten PLA. Grayscales in (A) and (C) are relative.

Tungsten PLA was determined to have promising characteristics. Work proceeded with this filament as the current option. Figure 17 shows one of the first fluence maps and corresponding compensators that was printed using the tungsten PLA. This quick result using radiochromic film was very encouraging that this filament would work. The end to end test proceeded with this as the choice. To show feasibility, a compensator for the Presage® dosimeter was printed and used for a fluence film measurement as can be seen in figure 18. Again this result was a relative in nature but it showed that the tungsten PLA could be used to modulate the dose from totally blocked to almost completely open.
Figure 18: (A) shows a planned fluence map for the Presage® dosimeter. (B) A delivered fluence using a tungsten PLA compensator showing a relative fluence distribution. This result was promising but the compensator was 15 cm thick which is not practical for real cases.

To better characterize the tungsten PLA, the HVL was measured. Figure 19 shows the measurements made for tungsten PLA and tungsten ABS that had been previously used in the lab. The HVL for the PLA was determined to be too thick to continue using it. The ABS filament had a better HVL at approximately 5 mm but the printing quality of the ABS was not satisfactory.

Figure 19: HVL measurement of the tungsten PLA and tungsten ABS. PLA had too thick of an HVL while ABS was better but has poor printing qualities.
The next approach for filament was to create a custom made tin filament. Following the procedure, the tin PLA composition was made and chopped to create the filament. During the filament extrusion process, the appropriate extrusion temperature was unknown and had to be determined. It was determined that the tin PLA had a high thermal conductivity and the melting temperature of this composition was well below typical PLA melting temperature. Due to this, many attempts lead to the tin PLA filament not holding its filament shape. In most cases the filament would liquefy and drip out of the filament extruder instead of being a semi-solid filament.

### 3.4.2 Compensator molds

Once it was decided that a different approach was needed for compensator design, the mold technique was tested. Figures 20 and 21 show usage of the tin PLA solution poured into a 3D printed mold. This option was determined to not be successful due to the fact that the DCM began to dissolve the mold and therefore render it unusable. Also, due to it being a liquid, there was a noticeable meniscus effect occurring and a non-uniform thickness across the width of the compensator would occur. Other filaments were used that do not react with DCM but no viable options were successful.
Figure 20: 3D printed compensator mold filled with tin PLA and DCM solution. (A) shows the bottom side of the mold that was flat prior to adding the solution. The base is now deformed and non-uniform. (B) Shows the top view of the mold where the meniscus effect is apparent and the top surface is not flat.

Figure 21: Second mold filled with the tin PLA solution. The evaporation of the DCM caused the walls of the mold to be deformed as well as dissolve features of the mold.

Use of cerrobend and pewter metals were feasible due to their low melting point. Figure 22 shows a mold filled with pewter metal. Both metals were difficult to cast into a mold. They quickly began to solidify once poured into the mold. This caused uneven molds with gaps and varying thickness. Also the meniscus effect occurred at the edges of the mold. These metals had a thicker HVL and were highly attenuating, so the molds would need to be very thin and left little room for error. This method was determined to be unusable.
Figure 22: Pewter casted compensator. The large non-uniformities on the surface make this manufacturing method not a viable approach.

The final mold method was using the sodium iodide powder. The HVL that was measured was 2.3 mm. The film measurements used to determine this value can be seen in figure 23. This HVL was close to ideal because it allowed for high quality molds to be printed and was not too thick that the molds would cause collision issues. Sodium iodide compensators were chosen as the method for creating compensators.

Figure 23: HVL measurement for the sodium iodide powder. The film measurement resulted in a value of 2.3 mm HVL. This HVL is a desirable thickness in order to create high quality compensators and not be too thick.
3.5 *Presage® Phantom End to End Test*

The simulated *Presage®* phantom dose distribution can be seen in figure 24. The dose distribution shows dose sparing to the OAR and dose being pushed to both the primary and secondary PTVs. No normalization was given to the dose distribution and was taken as is from the optimization. The dose volume histogram (DVH) for the treatment plan can be seen in figure 25.

![Axial slice with overlaid dose distribution from optimized plan. The primary PTV (green) and secondary PTV (red) are receiving most of the dose with dose sparing to the single OAR (violet).](image)

**Figure 24:** Axial slice with overlaid dose distribution from optimized plan. The primary PTV (green) and secondary PTV (red) are receiving most of the dose with dose sparing to the single OAR (violet).

![Dose Volume Histogram](image)

**Figure 25:** Planned DVH for cylindrical Presage dosimeter. DVH shows the primary and secondary PTVs have satisfactory dose coverage and the OAR is being spared.
As mentioned, the reproducibility of the compensators was tested first following treatment planning completion. The results for these film measurements can be seen in the following figures. The reproducibility was shown to be robust. Using gamma criteria of 10% and 0.5mm for the planned versus delivered dose maps, each of the 3 molds passing rate was within a 2.5% range, with all of them above 96% passing. Even at a very tight tolerance of 3% and 0.5mm all were above 88% passing and within a 5% range. The line profile image shows very similar profiles for all three molds as well as the average of all three. The dose modulation and spatial modulation were very consistent among all three compensators.

Another metric to compare the 3 molds was to use isodose curves as seen in figure 28. The average dose map was normalized to the 75% of the maximum value as not to skew the results towards the hot spot. Variation within one standard deviation were limited to only a few regions throughout the dose map.
Figure 26: Gamma analysis for three separate compensators (1-3) printed using the same computer 3D model. (4) corresponds to the average delivered dose map of all three. Dose maps were compared to simulation and red contour regions correspond to failure using 10%/0.5 mm gamma criteria. The dashed lines indicate the line profile location in figure 27.

Figure 27: Line profiles for three separate compensators printed from the same 3D model as indicated in figure 26. The average of all three is shown as well to show the reproducible nature of the compensators. The spatial modulation of each is very consistent.
Figure 28: Isodose curves from the average delivered dose of the 3 beam 1 compensator molds with a 2 standard deviation window for each level. Regions with good agreement are shown by nearly overlapping isodose lines.

Following simulation, the 9 field plan was then prepared for treatment. The 9 compensator molds were printed and the sodium iodide powder was added to them. Figure 29 shows a completed compensator attached to a mounting tray. These 9 compensators were then used for 2D film analysis. The calibration data used to convert change in OD to dose for the EBT film can be seen in figure 30. Delivered dose map results can be seen in figures 31-33.
Figure 29: (A) 3D printed compensator mold. (B) Compensator filled with sodium iodide powder. (C) Completed compensator mold attached to mounting tray.

\[ y = 0.0663x + 0.0227 \]
\[ R^2 = 0.98416 \]

Figure 30: Dose calibration data for EBT Gafchromic film. 5 data points were acquired to get a dependable curve. Gafchromic film is known to be very stable and linear across a practical dose range in this data shows to be linear across a range of 0 to 5 Gy.
Figure 31: Planned dose maps vs corresponding delivered dose maps for beam angles of 0, 40, and 80 degrees. Delivered dose maps on EBT film shows overall promising results in both dose and spatial resolution.
Figure 32: Planned dose maps vs corresponding delivered dose maps for beam angles of 120, 160, and 200 degrees. Delivered dose maps on EBT film shows overall promising results in both dose and spatial resolution.
Figure 33: Planned dose maps vs corresponding delivered dose maps for beam angles of 240, 280, and 320 degrees. Delivered dose maps on EBT film shows overall promising results in both dose and spatial resolution.
Further analysis including gamma analysis and line profiles of the delivered dose maps can be seen in the following figures. Overall, the results are very promising. The dose maps show the capability of the compensator to modulate the dose from low to high dose in both directions. These delivered dose maps show the scaling of the compensators was done accurately. It is highly important that the spatial resolution of the compensators be accurate because slight positional issues could cause the small targets to be missed. The dose that was delivered was also very promising. This shows that the HVL measurement of the sodium iodide and dose conversion of the simulation were roughly accurate. As encouraging as these results are, there are some issues that stand out as well.

As seen in figure 34, the peak dose region is much higher than the surrounding areas. This steep dose gradient is hard to handle for the physical compensator. The compensator must print a single steep peak to create such a hot spot and this is difficult to do at a high spatial resolution. It can be noticed in all of the maps that the background dose is higher for the delivered than the plan. This is due to the cutoff limit of the compensator thickness. The model plans zero dose outside of the field and the compensator design cuts off the outside dose to 6 HVLs of the maximum beamlet. Depending on the treatment plan or treatment field, a lot of background dose could be delivered in these regions.
Figure 34: Beam 1 (0 degrees) line profile and gamma analysis. (C) Shows the line profile from the planned and delivered fields as shown by the line in (A) and (B). (D) Red contoured regions that did not pass the gamma analysis with 0.5 mm DTA and 10% ∆D. This field had promising spatial resolution and fairly acceptable dose values.
Figure 35: Beam 5 (160 degrees) line profile and gamma analysis. (C) Shows the line profile from the planned and delivered fields as shown by the line in (A) and (B). (D) Red contoured regions that did not pass the gamma analysis with 0.5 mm DTA and 10% ΔD. Both the dose and spatial aspects for this field were encouraging.

Table 3 shows some of the various gamma criteria used and pass rates for each field. Various criteria were used in order to understand where the modulation is mostly effected. It can be seen that the standard clinical criteria of 3%/3mm has near complete pass rates for all fields except beam 6. Using tighter DTA tolerances shows that the pass rate drops significantly. This is due to the size of the fields are so small. A 3 mm DTA can reach a significant portion of the field. By looking at more reasonable criteria for this study (10%/0.5mm), 7 out of the 9 fields have greater than 85% of the pixels passing. By changing this to 5%/0.5mm, 6 out of the 9 fields still have greater than 85% of the pixels.
passing. This shows that the high spatial resolution of the compensators is accurate and the dose coverage is promising for an initial attempt.

**Table 3**

Table showing various gamma criteria and passing rates for all fields

<table>
<thead>
<tr>
<th>Field</th>
<th>Pass Rate 3% 0.5 mm</th>
<th>Pass Rate 3% 0.75 mm</th>
<th>Pass Rate 5% 0.5 mm</th>
<th>Pass Rate 5% 0.75 mm</th>
<th>Pass Rate 10% 0.5 mm</th>
<th>Pass Rate 3% 3 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (0°)</td>
<td>88.73%</td>
<td>90.79%</td>
<td>91.47%</td>
<td>93.23%</td>
<td>97.65%</td>
<td>98.81%</td>
</tr>
<tr>
<td>2 (40°)</td>
<td>80.58%</td>
<td>84.32%</td>
<td>81.53%</td>
<td>84.96%</td>
<td>84.30%</td>
<td>97.85%</td>
</tr>
<tr>
<td>3 (80°)</td>
<td>88.93%</td>
<td>90.95%</td>
<td>89.41%</td>
<td>91.38%</td>
<td>90.95%</td>
<td>100%</td>
</tr>
<tr>
<td>4 (120°)</td>
<td>85.81%</td>
<td>91.77%</td>
<td>87.33%</td>
<td>92.46%</td>
<td>91.17%</td>
<td>98.78%</td>
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<tr>
<td>5 (160°)</td>
<td>92.26%</td>
<td>95.99%</td>
<td>93.49%</td>
<td>96.72%</td>
<td>97.02%</td>
<td>99.43%</td>
</tr>
<tr>
<td>6 (200°)</td>
<td>52.87%</td>
<td>59.17%</td>
<td>53.71%</td>
<td>59.83%</td>
<td>56.70%</td>
<td>88.77%</td>
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<td>7 (240°)</td>
<td>91.67%</td>
<td>95.37%</td>
<td>92.05%</td>
<td>95.55%</td>
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<td>99.72%</td>
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<td>8 (280°)</td>
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<td>89.65%</td>
<td>87.05%</td>
<td>90.08%</td>
<td>88.58%</td>
<td>100%</td>
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<td>9 (320°)</td>
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<td>83.27%</td>
<td>87.16%</td>
<td>87.00%</td>
<td>98.65%</td>
</tr>
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</table>

Some of the fields did have problems, especially beams 3 and 6. Figure 36 shows the analysis for beam 6. Here, there seems to be a problem with the compensator. However, when looking at the details a little closer, this beam had a much lower planned dose than the other fields. This means that the background dose was very
significant and played a role in the gamma analysis failure. Beam 3, as seen in figure 37 has a region that was blocked significantly. This can be contributed to the 3D printed mold. Small gaps in the surface of the mold allowed sodium iodide crystals to fall inside the mold where they should not have been. Had this issue not been there, this field would have performed very well.

Figure 36: Beam 6 (160 degrees) line profile and gamma analysis. (C) Shows the line profile from the planned and delivered fields as shown by the line in (A) and (B). (D) Red contoured regions that did not pass the gamma analysis with 0.5 mm DTA and 10% ΔD. Significant failure occurred for this beam but the line profile shows good spatial resolution of the varying regions.
Figure 37: Beam 3 (80 degrees) line profile and gamma analysis. (C) Shows the line profile from the planned and delivered fields as shown by the line in (A) and (B). (D) Red contoured regions that did not pass the gamma analysis with 0.5 mm DTA and 10% ΔD. Failure for this beam occurred on only part of the field. Region of blocked dose on the delivered map did not match the planned map.

Following the 2D dose analysis and verifying that the compensators were created in a satisfactory manner, they were used again on a 3D Presage® phantom. Figure 38 shows a single axial slice of the delivered dose compared to the planned dose. It can be seen that there are noticeable differences between the planned and delivered dose but there is still dose sparing to the OAR which is a key result. After analyzing the 2D dose maps, it was expected that there would be a discrepancy for the dose delivered in 3D.
One thing that was fairly consistent for the 2D dose maps, however, was the dose sparing regions in each field. This can be seen in the 3D axial slice because there is a dose difference between the primary and secondary PTVs and the OAR. Figure 39 shows a line profile for both the planned and delivered doses passing through the OAR and the primary PTV. This line profile shows the steep dose gradient that was created between the two structures. This result is very encouraging because this allows for sufficient target coverage and better OAR sparing.

The planned dose was highly conformal to the primary PTV and less conformal to the secondary PTV but there was acceptable dose coverage for both structures. This effect was much less significant for the 3D dosimeter phantom but it can be seen that there was some conformal dose distribution to the primary PTV. Although the 3D phantom was not perfect, the results showed feasibility for IMRT to be implemented onto the micro irradiator. More work needs to be done and some details still need to be adjusted to make the system more robust.

Figure 40 shows the film measurement taken with the film placed within the dosimeter. This film measurement gives a better representation of the IMRT capability than the 3D phantom. The dose is highly conformal to both the primary and secondary PTVs. There is also significant dose sparing to the OAR. The absolute dose did not match the planned dose, but this was expected.
Figure 38: 3D dose analysis for the Presage dosimeter compared to the planned dose distribution. This single slice of the delivered dose distribution shows higher dose to the PTVs and less dose to the OAR.

Figure 39: Dose profile of planned and delivered dose. The absolute dose values do not match but are similar and the overall shape is consistent for both.

Figure 40: Axial slice dose distribution for the planned (A) and delivered (B). The delivered dose was measured using EBT film placed in the axial plane of the 3D dosimeter. The measured distribution shows strong modulation agreement with the planned fluence.
4. Conclusions

This work aimed to improve the current techniques used on the micro irradiator used at Duke. It was shown through an end to end test that IMRT capabilities are feasible for this machine with some work still left to do. The 3D printed compensators were able to modulate dose with promising spatial and dose accuracy.

The tools have been created for a systematic workflow to be implemented for treatment planning, compensator production, plan delivery, and quality assurance, but each step along the way can be improved more.

The compensator production proved to be a fairly robust method as seen in figure 28. Once the treatment has been planned and optimized, the 3D models are created automatically and need no further modifications prior to printing. By using the printer settings established in this work, high resolution compensator molds can be produced rather quickly. Adding the sodium iodide powder takes time, but by following the procedure will allow for reproducible results.

Plan delivery in the end to end test was much more simple than a true small animal case will be. The on board imaging capabilities of the micro irradiator is better than 0.5 mm, so taking advantage of this will be important for accurate treatments.

Quality assurance is important at any level and played an important role in this project. The 2D film analysis procedure should be implemented for all future IMRT plans. Using the Matlab script that was written, a quick film analysis can be done to
determine any major problems that may have occurred throughout the treatment
planning process. As many small animals are treated using the same treatment protocol,
a quick quality assurance check will allow verification that the treatment will be
delivered accurately and precisely for an entire cohort of small animals.

This work has laid the fundamental groundwork for complete implementation of
IMRT on the micro irradiator. With some adjustments based off of the results in this
work, IMRT may become standard practice for preclinical cancer research. A list of
recommendations following will help improve this system even more.
5. Recommendations

Below are recommendations for each step of the process that should be focused on to improve the accuracy and bring this treatment technique into use. Each of them will enhance the abilities of delivering IMRT and should be evaluated. Each of these recommendations call on different skillsets and should be approached differently depending on the researcher.

5.1 Simulation and Treatment Planning

- Integration between SmART-Plan and CERR
- Plan normalization
  - Determine method to normalize optimization in CERR and adjust simulated dose maps

5.2 Compensator Manufacturing

- 3D printing materials testing
  - Ongoing exploration of new filaments or mold materials
- 3D printing resolution testing
  - Determine a way to analyze the quality of the 3D printed compensators comparing to the computer 3D model. Due to high accuracy needed, prints should have submillimeter errors.

5.3 Treatment Delivery

- Coordinate system integration
- Determine the correlation between the couch coordinate systems between the treatment planning system and the micro irradiator.

- TG-61 machine calibration
  - This will be useful for accurate dose calculations.
6. References


