Verification of Proton Range Predictions in Proton Treatment Planning Using X-Ray CT or Proton CT Imaging

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The objective of this paper is to compare the range errors for two treatment plans; one using x-ray CT and the other using proton CT for calculating dose distributions in an animal tissue phantom. We shot 150 MeV proton beam through a meat phantom to a film stack to measure the exponential drop of dose at the Bragg peak until zero dose remained. Plotting the depth dose curves and performing gamma analyses are two ways to quantify the proton range errors when comparing them to depth dose curves from film measurements in the phantom. The depth dose curves give us a visual representation of both treatment plans and the measured dose response on film.

The proton CT’s treatment plan range error was smaller than the x-ray CT’s. However, both treatment plans were within a millimeter of each other. Both the proton CT and x-ray CT treatment plans showed range errors less than 2% of the range. Both are within the clinical tolerances of $\pm 3.5\%$. The Proton CT treatment plan showed slightly better accuracy than the x-ray CT treatment plan. This study is the second experiment to compare range measurements using proton CT and x-ray
CT and is important in testing the image quality of the ProtonVDA’s scanner. In addition, proton CT can be used to create proton DRR’s (digital reconstructed radiographs), which can then be used for daily proton range verification in the treatment room by comparing the DRR to daily proton radiographs.
VERIFICATION OF PROTON RANGE PREDICTIONS IN PROTON TREATMENT PLANNING USING X-RAY CT OR PROTON CT IMAGING

BY

NICHOLAS S. YEE, M.S.
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A THESIS SUBMITTED TO THE GRADUATE SCHOOL IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE MASTER OF SCIENCE

DEPARTMENT OF PHYSICS

Thesis Director:
Dr. George Coutrakon
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DEDICATION

To "Ning Ning" - Betty Yee, my grandmother, your battle against Hodgkin’s lymphoma inspired me to pursue my research in the medical field and to devote this thesis to you.

May you rest in peace in heaven.
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CHAPTER 1
THEORY

1.1 Benefits of Protons

Traditionally, patients will receive radiation therapy via x-rays, i.e., photons in the mega voltage range. However, the use of protons as the beam source have benefits that photons cannot compete with, such as lower risk brain damage when treating pediatric brain tumors. Also, computed tomography (CT) scans using protons, create less image distortion, i.e. streaking artifacts from high density implants. A CT scan is a 3D image of the anatomy of a patient. In our case, the most important aspect of the proton treatment is the energy deposition of the proton along its track up to its end of range in the patient. The Bragg peak gives much higher dose at the tumor relative to the entrance dose as shown in Figure 1.1. Dose is defined as

\[ PhysicalDose = \Phi \times \frac{dE}{dx} \times \rho_x, \]  

(1.1)

where \( \Phi \) is the fluence in \( \text{protons/cm}^2 \), \( \frac{dE}{dx} \) is the stopping power of the medium, and \( \rho_x \) is the density of the material. Dose is given in units of energy deposited per unit mass of tissue. This unit is known as the Gray (Gy), which is equal to \( 1 \frac{\text{Joule}}{\text{kg}} \) of tissue or \( 10^4 \frac{\text{ergs}}{\text{gram}} \) of tissue. In the context of this thesis, we will use the protons’ “biological” dose which is defined as RBE weighted dose or \( Co^{60} \) equivalent dose (CGE) and given by

\[ CGE = PhysicalDose \times RBE, \]  

(1.2)
where CGE is the $\text{Co}^{60}$ Gray Equivalent and RBE is the relative biological effectiveness, relative to x-rays.

Protons start with low dose at the entrance. The dose then increases as it slows down through a medium until it reaches its peak dose at the end of range, where the dose then falls to zero as shown in Figure 1.1. The sum of all mono-energetic Bragg peaks form the spread out Bragg peak (SOBP) with uniform high dose in the tumor volume.

![Figure 1.1: Dose of protons and x-rays as it traverses further into tissue. The combination of each proton’s Bragg peak combine to form the SOBP which delivers a constant dose to the tumor, while the x-rays deliver a steady decrease of dose to the target volume and beyond. Taken from [6].](image)

X-rays follow the dose distribution in Figure 1.1. They deposit the highest dose close to the skin followed by an exponential attenuation with depth. The x-ray’s dose distribution can become harmful if sensitive organs are in front or behind the tumor since they will receive significant amounts of unwanted radiation.

Note: the Intensity Modulated Radiation Therapy (IMRT) often gives highly conformal dose to the tumor volume (similar to multi-field proton treatments) by using much larger number of fields with x-rays as the primary beam source. However, the integral (or total dose) to healthy tissues will always be higher with photons than with protons. A low dose to
healthy tissue spread over a larger volume may or may not give higher toxicity (side effects) than proton treatments. This is still an open question in clinical research.

We want to compare the predicted stopping distance, or range, of the protons from treatment planning with measurements of where the protons actually stop in our meat phantom. This is known as the range error. In our case, we wanted to use animal tissue as the medium for the radiation to traverse to emulate as close as we could to human tissue. To measure the proton range, or the end of the distal edge of the Bragg peak, we used a stack of 36 films, each 0.28 mm thick, to observe the location of the distal edge falloff of the Bragg peak.

1.2 Standard X-Ray Imaging for Proton Dose Distributions

Each x-ray CT scan (xCT) is composed of a Hounsfield Unit (HU) per each 1 mm$^3$ voxel (3D pixel) and a dose distribution of the entire medium. The HU determines the linear attenuation coefficient for the photons relative to water and its formula is

\[ HU = \frac{\mu_x}{\mu_w} \times 1000, \]  

where $\mu_w$ and $\mu_x$ are the linear attenuation coefficient in each cubic millimeter voxel in terms of its electron density and effective atomic number of the medium. In general

\[ \mu_x = \rho_{e,x}[Z_x^4 F(E, Z_x) + G(E, Z_x)], \]  

where $\rho_{e,x}$ is the electron density of the material, $Z$ is the atomic number, and $E$ is the x-ray energy. $\rho_{e,x}Z_x^4 F(E, Z_x)$ and $\rho_{e}G(E, Z_x)$ are the contributions of the photoelectric effect and the Compton scattering, and coherent interactions, respectively. The linear attenuation
coefficient, \( \mu \), changes when traversing through a composite material of poly-energetic x-rays with peak energies less than 1.02 MeV to be

\[
\mu_x = \rho_{e,x} \sum_{i=1}^{N} w_i [Z_x^4 F(E_i, Z_x) + G(E_i, Z_x)],
\]

(1.5)

where \( w_i \) is the weight factor for the photon energy, \( E_i \), using the x-ray energy spectrum of the beam. With Equation 1.3, the HU formula becomes

\[
HU = \frac{\rho_{e,x} \sum_{i=1}^{N} w_i [Z_x^4 F(E_i, Z_x) + G(E_i, Z_x)]}{\rho_{e,w} \sum_{i=1}^{N} w_i [Z_w^4 F(E_i, Z_w) + G(E_i, Z_w)]}.
\]

(1.6)

The photoelectric effect, Compton scattering, and coherent scattering factors are interpolated based on the XCOM database provided by the NIST (Berger et al., 2005). We can now map out the linear attenuation relative to every millimeter voxel of our phantom.

The proton dose in each voxel is calculated from the proton fluence and the energy deposited for each proton passing through that voxel. To create a dose map for protons, we need the water equivalent depth (WED) of the proton pencil beam at each voxel in our patient. The WED (Equation 1.10) allows us to calculate the dose in each voxel by using the water depth dose curve for the delivered proton beam. The WED for each voxel that the proton beam traverses is first calculated. Then the WED value is used to look up the proton dose from the measured proton depth dose curve in water. The WED is calculated by finding the relative stopping power (RSP) at each voxel. The RSP is the ratio of the stopping power of the medium to the stopping power of water

\[
RSP = \frac{\frac{dE}{dx}}{\frac{dE}{dx}}_w.
\]

(1.7)

Schulte et al. [4] have calculated the stopping power of a medium to be Equation 1.8.
\[
\frac{dE}{dx})_x = 170 \text{keV cm} \beta^2 \rho_{e,x} \rho_{e,w} \left[ \ln \left( \frac{2m_e c^2 \beta^2}{I(z)(1 - \beta^2)} \right) - \beta^2 \right],
\]

where \( \beta \) is velocity of the proton relative to the speed of light, \( m_e \) is the mass of an electron, \( c \) is the speed of light, and \( I(z) \) is the mean ionization energy of the material.

Using Equation 1.6, Equation 1.5 becomes

\[
RSP = \frac{\rho_{e,x} \ln \left( \frac{2m_e c^2 \beta^2}{I_x(z)(1 - \beta^2)} \right) - \beta^2}{\rho_{e,w} \ln \left( \frac{2m_e c^2 \beta^2}{I_w(z)(1 - \beta^2)} \right) - \beta^2},
\]

where \( I_x(z) \) and \( I_w(z) \) are the mean ionization energies of the material and water. The water equivalent depth is defined by

\[
WED = \sum_{i=1}^{N} RSP(i) L_i.
\]

The WED is used to find the dose in the \( N^{th} \) voxel from the measured depth versus dose tables in a water tank. This is why correct RSPs are important for accurate dose maps. We integrate all the RSP values to the last voxel to reach the range.

Once the WED reaches the range, \( r \) in water, Equation 1.8 becomes

\[
r = \sum_{i=1}^{N_{\text{max}}} RSP(i) L_i,
\]

where \( N_{\text{max}} \) is the last voxel that the proton traverses at the end of its range.

Figure 2.1 is the dose distribution mapped onto a CT slice taken from our experiment. The beam enters from the top of the image and stops in the target volume shown in red.
1.3 Largest Source of Proton Range Uncertainty in Human Tissues (HU Conversion to RSP)

To calculate RSP from xCT voxels, we need to convert HU to RSP. Equations 1.4 and 1.7 do not allow for a direct conversion of HU to RSP because, for example, two tissues with different \((Z_{\text{eff}}, \rho_e)\) can yield the same HU but different RSP and visa versa. The ambiguity can be (hopefully) resolved with dual energy x-ray CT, but that is still an ongoing research topic when applied to proton therapy treatments. HU equation depends on \(Z^4\) and cross sections of the photoelectric effect, Compton scattering, and coherent scattering, while the RSP equation depends on the mean ionization energy, which is also depends on \(Z\). (See Figure 1.3). Any errors in this conversion will cause the patient to receive improper dose, in which the consequences are emphasized at the distal falloff, where the dose declines rapidly. This could lead to a insufficient amount of dose received at the target volume or healthy tissue in front or behind the tumor to receive large amounts of unwanted dose. The conversion error is heightened as the atomic number \(Z\) of the material the protons are traversing through can change such as protons traveling through tissue, bone, and other organs composed of different elements. To combat this the beam shoots protons at multiple energies to compensate for the protons traveling through more dense material or mediums with a lower net atomic numbers.

The Equation 1.12 allows us to find the effective atomic number \((Z_{\text{eff}})\) when the protons traverse through a molecule and more complex atoms

\[
Z_{\text{eff}} = E \sqrt{\frac{\sum_{i=1}^{N} w_i Z_i}{\sum_{i=1}^{N} w_i A_i Z_i^E} / \left(\sum_{i=1}^{N} w_i Z_i / A_i\right)},
\]  

(1.12)
where $A_i$ is the mass number of the $i$th element and $E$ is chosen to be 3.3 to represent tissue or bone since these are the only materials the protons will travel through. Using Equation 1.10, we can find the effective atomic number ($Z_{eff}$) for the HU and RSP calculations.

To calculate the mean excitation energy for tissue and bone, we used the Bragg additivity rule:

$$\ln I_m = \frac{\sum_{i=1}^{N} \frac{w_i Z_i}{A_i} \times \ln I_{m,i}}{\sum_{i=1}^{N} \frac{w_i Z_i}{A_i}},$$  \hspace{1cm} (1.13)

where $I_{m,i}$ represents the $i$th element of a composite material, which composes a large percentage of the overall material. Equations 1.10 and 1.11 allow us to completely solve the RSP and HU equations for every voxel in our phantom.

Figure 1.2 further emphasizes the lack of proportionality of the atomic number in Equations 1.4 and 1.7. The best-fit lines for bone and soft tissue do not align, causing error more error in our conversion from HU to RSP. We plotted well-known elemental compositions to graph accurate mean ionization potentials and effective atomic numbers.

Figure 1.2: Graph illustrating the misalignment of the bone and soft tissue curves for effective atomic number and mean ionization potential Taken from Reference [3].
There is already a disconnect with well-known elemental compositions. This error is exacerbated when the composition of the medium is unclear such as humans since tissue types can vary for patients that are even of the same age, forcing an interpolation of an error-rigged conversion curve. The tumor volume is increased in the beam direction by \( \pm 3.5\% \) of the range of the protons to correct for possible underdosing of the distal edge or proximal edge of the tumor. This comes at the expense of possible dose increases to surrounding healthy tissue due to RSP errors.

The direct HU to RSP conversion for multiple tissues is plotted from a previous study in Figure 1.3.

![Figure 1.3: Plot of proton RSP to x-ray HU conversion from Reference [3].](image)

Each best-fit line for does not align with the data points leading to an error-filled conversion from HU to RSP. This is especially shown with soft tissues in Figure 1.3 (b).

### 1.4 pCT Measures RSP Directly

Due to the advancements in proton detectors, proton CT scans (pCT) can directly obtain an RSP map from proton energy loss measurements through the patient anatomy and proton path through the patient voxels as shown in Figure 1.4. This skips need to convert xCT from HU to RSP, leading to less error in range measurements. Protons, used for imaging, are
tracked using (X,Y) sensing detectors to inform us about the protons’ position and direction, before and after the phantom. This information is used to calculate the most likely path through the phantom and determines which voxels are crossed and should be included in the RSP reconstruction algorithm. (See Figure 1.4) Note that the imaging requires accumulating data from 100 or more beam angles, from 0 to 360° around the phantom, similar to x-ray CT. The stopping power, $\frac{dE}{dx}$, can also be calculated for each voxel using the image reconstruction software. Using readings from a calorimeter (in Figure 1.4) and the proton’s most likely path, one can calculate the RSP integrals for each protons’ path. Acquiring data from many beam angles, like x-ray CT, one can reconstruct the RSP for each voxel.

![Figure 1.4: Diagram of a single-proton tracking pCT scanner. Protons enter from the left and pass 4 silicon strip detectors while their exit energy is read by the calorimeter at the end on the right hand side of the figure. Taken from Reference [4].](image)

Bypassing the HU to RSP conversion leads to smaller range uncertainty for pCT. As a result, the pCT treatment plan range error will be less than the xCT treatment plan range error.
1.5 xCT Must Be Converted from HU to RSP

To compare the range errors of the pCT and xCT treatment plans using the RSP maps described in the Section 1.4, the xCT images that are labeled in terms of HU must be converted to RSP. Figure 1.3 illustrates the discrepancy between RSP and HU conversion, especially in the case of soft tissue. Since the conversion is not one-to-one, the interpolated curves give incorrect values when we want to convert the xCT’s HU to RSP.
CHAPTER 2

METHODS AND MATERIALS

2.1 Treatment Plan for Meat Phantom

A 9 × 3 × 3 cm target volume was created near the center of a 25 cm diameter cylinder containing cow tissues obtained from a local butcher. Each film is a 6 × 1 cm in area and 0.28 mm thick. We wanted to observe the distal falloff of the beam source, so we calculated the distance from the entrance of the meat phantom to the edge of the plateau region starting at the entrance of the film stack, so that the beam ultimately stops before the end of our film stack. The goal of the xCT-based treatment plan was to make the dose on each film as uniform as possible. Because of the large heterogeneity of tissues this was not entirely possible. So for the first analysis in which we plotted the dose vs depth for the two treatment plans and films, we restricted the analysis to the average dose in a 5 × 5 mm area in the central region of each film. To create the proton treatment plan, we scanned the non-radiated beef tissue (composed of ribs, liver, and kidney) and the film stack to divide the phantom into individual CT images (of 1 mm in width) that were orientated perpendicular to the beam so that each dose plane matched the orientation of the film stack. The dose in each CT plane was calculated by taking the average dose in a 1 mm square at the center of the film relative to the CT plane. We then uploaded them to the RayStation Treatment Planning System (RaySearch, Stockholm, Sweden). RayStation is a Monte Carlo-based, clinical treatment planning system that converts each image’s pixels from HU to RSP. Using the proton energies, spot positions and intensities of the pencil beam delivery (derived from
the xCT treatment plan), these same pencil beam parameters were delivered in RayStation to create the new dose wash onto the proton CT. The treatment plan was designed so that the distal region of the SOBP (180cGy) was recorded on some of the entrance films so that the entire dose falloff at the end of the SOBP falls completely within our film stack. The average physical dose delivered to the target volume was about 180 cGy. A horizontal CT slice through the target volume is shown in Figure 2.1.

Figure 2.1: A single CT slice through the middle of the cubic target used in our experiment, for purposes of illustration. Dose distribution produced by the proton beam is color coded. The green box represents the boundary of the film stack located at the distal dose falloff region.
2.2 Single xCT Slice with Dose Distribution Through Target Volume

We wanted to test the range error of protons in organic tissue so we used a phantom to hold beef ribs and our film stack. Radiating the film stack twice for pCT and xCT proved to be a problem since the orientation of the ribs in the phantom is almost impossible to replicate when replacing films for the second beam test using a proton CT based treatment plan. Finding the exact rib dimensions, shape, and arranging the ribs in the same orientation would be challenging. For the study, we were required to image the phantom twice with the film stack: once with xCT and once with pCT. The phantom with the film stack could only be irradiated once to high dose, so we chose to irradiate the phantom using the xCT based treatment plan. This would give us a predicted range of xCT based treatment plan versus the measured range with film. However, we could not test the pCT based treatment plan the same way because inserting a new film stack would disturb the meat phantom. We use the technique described earlier to evaluate the accuracy of the pCT plan.

2.3 Calibrating Film Exposure to Dose Using Treatment Plan

Once the experiment is complete a series of steps must be completed in order to read the dose on each film. We must (1) scan the experimental films into the computer, (2) orientate the films properly, (3) apply calibration curve, and (4) set offsets.

Note: All forms of dose in this thesis are labeled either in terms of RBE weighted dose or physical dose. RBE weighted dose is the physical dose, Equation 2.5, multiplied by the relative biological effectiveness (RBE), relative to Co\textsuperscript{60} irradiation. For therapeutic protons, the RBE is 1.1 at all treatment centers. The RBE weighted dose is also referred to as Cobalt
(or x-ray) equivalent dose (CGE). The RBE of 1.1 indicates that protons are more effective at cell kill than x-rays.

To scan the films into the computer, we warm up the Epson Perfection V700 Photo Scanner 11 times before scanning in any films. The Epson V700 scanner was used to create a 2D digital map of the film darkness (or exposure) in each 1 $mm^2$ pixel of each $16 \times 62\ mm^2$ film. The data for each film was stored in a computer as a 2D map of ADC counts. Later these ADC counts would be converted to dose for each pixel in each film. We mark the right corner of each film as to not confuse which side of the film was facing the incident proton beam. Using a vertical envelope and horizontal envelope that fit into the scanner, we can create a wedge at the corner where the two envelopes meet to place one film in the exact same spot each time (the long side of the film being parallel to the longer side of the scanner). We used this method so that if different areas of the scanner bed are exposed to various light then this technique would alleviate any abnormalities in radiation readings. Some other scanning settings to note are films are scanned using 48-bit pixels with 400 dpi resolution and film type positive.

The scanned films are saved in a directory accessible at the Chicago Northwestern Proton Center and are opened up in the Omni-Pro i’mRT software, developed by Ion Beam Applications (Louvain La Neuve, Belgium). The films need to be flipped horizontally to be facing the same position as when they were scanned in. We crop the film images to the exact size of the films so the software can focus in on the films to mitigate any edge effects that can alter our experimental results.

When all the films are orientated correctly, we can apply a calibration curve to change the Analog Digital Converter (ADC) counts to dose. Each box of films from the vendor needs a unique calibration curve, since each batch of EBT3 film is expected to have slightly different dose responses. The calibration curve converts ADC counts to dose through every pixel on the film. The attenuation of the light due to the film darkness (or opacity) provides
a measurement of the transmission of the film at that point. The darker the pixel, the more
dose was radiated at that point and the fewer the ADC counts due to lower transmission.
Radiation changes ADC counts because the radiation breaks apart chemical bonds in the
film, which releases blue dye. The more bonds that are broken in the film, the more dye is
released and the darker the film will become. A previous study [1] with EBT3 film (from the
same vendor) showed that the calibration curve was in good agreement with the parabolic
shape so we assume the same for our data also. We then used the curvature from that
experiment for our parabolic fit. ADC counts and dose have an inverse relationship. The
film darkens as it is exposed to more dose, since chemically, the active layer is releases more
blue dye the more radiation the film is exposed to. Less light is able to pass through the
film from the scanner bed, leading to lower ADC counts. Due to the abrupt Bragg Peak
shape of protons and the treatment plan for the experiment and the depth versus dose plot
in Figure 1.1, the protons are set up to reach their maximum dose at the beginning of the
SOBP which continues to the entrance of the film (185 cGy) and decline rapidly in dose at
the end of the SOBP. Thus, they will not penetrate much further. Therefore, in a stack of
36 films, we can safely assume that films 32-36 will have no dose (0 cGy). We average the
ADC counts for films 32-36 to be the average ADC counts for 0 cGy. Therefore, we have our
two points: (29,249 counts, 181.81 cGy) and (41,004 counts, 0 cGy). Note: films 32-36 had
a range of ADC counts from 39,700 to 41,200 counts and the first two films were averaged to
represent our entrance dose of 181 cGy (as prescribed in treatment planning) with average
ADC counts of 29,250. The shape of the calibration curve is assumed to be parabolic, so we
can formulate our calibration curve to follow the general form of a parabola in vertex form
which is

\[ y = m(x - a)^2 + k, \]  \hspace{1cm} (2.1)
where $y$ is dose, $m$ is the curvature or rate of change of the slope, $x$ is ADC counts, $a$ is the horizontal shift of ADC counts, and $k$ is a vertical shift in dose (if needed). Thus a more practical way to rewrite Equation 2.1 would be

$$D = m(ADC - A_0)^2 + h. \quad (2.2)$$

To obtain our curvature, $m$, we recorded and plotted the ADC and dose values from an earlier published experiment [1] with EBT3 film. See Table 2.1.

Table 2.1: Calibration film values for the past calibration curve. Taken from Reference [1].

<table>
<thead>
<tr>
<th>ADC Counts</th>
<th>RBE Weighted Dose (cGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>36802</td>
<td>0</td>
</tr>
<tr>
<td>34937</td>
<td>25</td>
</tr>
<tr>
<td>32957</td>
<td>50</td>
</tr>
<tr>
<td>31624</td>
<td>75</td>
</tr>
<tr>
<td>30067</td>
<td>100</td>
</tr>
<tr>
<td>25322</td>
<td>200</td>
</tr>
<tr>
<td>18399</td>
<td>400</td>
</tr>
<tr>
<td>15258</td>
<td>600</td>
</tr>
</tbody>
</table>

We calculated the curvature, i.e. 2nd derivative, of the calibration curve from a previous study of the EBT3 film. By plotting dose versus ADC counts and applying a best-fit parabola, the curvature of the calibration curve was obtained for our data.
Factoring out the coefficient of the best-fit line in Figure 2.2, we have our curvature for our calibration curve: $9.758 \times 10^{-7}$. Now we can solve for the last variable in our calibration parabola equation by using the entrance and exit dose of our films to create 2 system of equations and solve for $A_0$.

$$0 = 9.758 \times 10^{-7} (41004 - A_0)^2 + h \quad (2.3)$$

$$181.81 = 9.758 \times 10^{-7} (29249 - A_0)^2 + h \quad (2.4)$$

Solving for $A_0$ and $h$, our final equation for the interpolated calibration curve becomes

$$D = 9.758 \times 10^{-7} (ADC - 43052)^2 - 4.094. \quad (2.5)$$

We can create a table similar to Table 2.1 for our specific film set. Using Table 2.2 and Equation 2.5, we can graph our new interpolated calibration curve.
Table 2.2: ADC and dose values found using the calibration curve passing through the known doses and measured ADC counts at 0 cGy and 180 cGy.

<table>
<thead>
<tr>
<th>ADC Counts</th>
<th>RBE Weighted Dose (cGy)</th>
<th>Physical Dose (cGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>41004</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>36986</td>
<td>35</td>
<td>31.81</td>
</tr>
<tr>
<td>34721</td>
<td>70</td>
<td>63.63</td>
</tr>
<tr>
<td>32952</td>
<td>105</td>
<td>95.45</td>
</tr>
<tr>
<td>31449</td>
<td>140</td>
<td>127.27</td>
</tr>
<tr>
<td>30120</td>
<td>175</td>
<td>159.09</td>
</tr>
<tr>
<td>29249</td>
<td>200</td>
<td>181.81</td>
</tr>
<tr>
<td>28430</td>
<td>225</td>
<td>204.54</td>
</tr>
<tr>
<td>27654</td>
<td>250</td>
<td>227.27</td>
</tr>
<tr>
<td>26915</td>
<td>275</td>
<td>250</td>
</tr>
<tr>
<td>26209</td>
<td>300</td>
<td>272.72</td>
</tr>
</tbody>
</table>

Figure 2.3: Interpolated calibration curve with best-fit parabola equation. First 4 films and last 4 films are averaged in the 180 cGy point and end points of the calibration curve, which are 29249 ADC counts at about 180 cGy and 41004 ADC counts at 0 cGy.
The best-fit equations in Figure 2.2 and Figure 2.3 are very similar to one another and the fitted quadratic function well represents our data, Figure 2.3.

We can now read the treatment plans and film stack in terms of physical dose. To determine the difference between measured range in the film and predicted range from the TPS, we plot the dose vs depth (starting with film number 1) for film and the two treatment plans. For the first analysis we measured the proton range for each curve at the depth where the dose falls to 50% of D(max) and calculated the error from the measured proton range in the film. We then apply a technique called gamma analysis [7], which uses all of the dose values on the distal edge for the films and treatment plan doses by comparing each film to every CT plane, which will be discussed in further detail in a later section.

2.4 Measurement of Range Error Using Depth Dose Curves

To check if the experiment followed the Bragg peak shape we expect from treatment planning, we plotted a depth versus dose curve to map out the change in dose as the protons travel further in the film stack. We extracted the value of the average dose at the center of each film using $5 \times 5$ mm square areas.
Each film width is 0.28 mm and the entrance film reads 185.2 cGy. The statistical errors, $\sigma/\sqrt{N}$ are calculated from the standard deviation of the dose values in a 5 × 5 mm square areas with N=25 dose points.

The film stack followed the exponential dose fall off that we expect at the end of the Bragg Peak as seen in Figure 2.4.

Plotting the depth versus dose curve of a treatment plan and the film stack, we can find the horizontal shift needed for the two curves to align with one another which becomes our range error. We can then visually convey which treatment plan has a smaller range error by plotting the depth versus dose of the pCT and xCT treatment plans along with the film stack data. This is shown in Figure 3.13 and will be discussed later.
Figure 2.5: The arrow represents the difference in range needed for the two curves to align.

2.5 Measurement of Range Error Using Gamma Analysis

In these next subsections, we will cover the proper steps needed to evaluate our film stack using gamma analysis.

2.5.1 Transverse Alignment of Film Plane and CT Plane

Omni-Pro I’mRT divides each film into 1x1 mm square pixels. Each pixel’s ADC counts is converted to dose using the calibration curve in the previous section. The software also converts the pixels on each film plane to match the same pixel size as the CT planes’ pixels. To finish setting up our films for gamma analysis, we needed to build a 3D cube by stacking the films in Omni-Pro I’mRT. We can stack the film data so that adjacent films are separated in depth by 0.28 mm (since this is the thickness of each film). Figures 2.6 and 2.7 are
dose distributions on two of our films; one at the depth of the first film and the 18th film, respectively.

Figure 2.6: First film in stack; mean physical dose: 187.36 cGy (Figure labeled in RBE weighted dose). \( \sigma = 2.63 \) cGy for the 5 \( \times \) 5 mm area of the center of the film.

Figure 2.7: Film 18 in stack; mean physical dose: 91.91 cGy of dose (Figure labeled in RBE weighted dose). \( \sigma = 15.48 \) cGy for the 5 \( \times \) 5 mm area of the center of the film.
2.5.2 Gamma Analysis - Comparisons Between Doses on Film and CT planes

Figure 2.8: Dose distribution in treatment plan for the CT slice corresponding to the depth of the first film in the stack. The bright orange/red area represents the high dose target region from treatment planning. Mean physical dose: 182.73 cGy (dose in Figure is labeled in RBE weighted dose). The dashed rectangle represents the film alignment with respect to the target volume, which will be used for comparison in gamma analysis. The dose for the CT plane was taken at the center of the film.
Figure 2.9: Dose distribution in treatment plan for the CT slice corresponding to the depth of the 18th CT plane. Mean physical dose: 85.45 cGy (Figure labeled in RBE weighted dose). The dashed rectangle represents the film alignment with respect to the target volume. The dose for the CT plane was taken at the center of the film.

Once the 3D dose cube is built, we loaded in the treatment plan from RTDOSE files, which includes 1 mm-thick dose planes from the beam source to the end of the film stack as seen in Figures 2.8 and 2.9. We compared every film in our film stack to each treatment plan dose plane to obtain a gamma score between every possible plane to film as depicted in Figure 2.10. In this technique, we are repeating 2D gamma analysis but at different film and CT plane depths to give us 3 dimensions. The gamma score for each pixel is calculated using

\[ \Gamma = \sqrt{(\frac{DTA}{3mm})^2 + \left(\frac{\% Diff}{3\%}\right)^2}, \]  

(2.6)
where DTA is the distance to the pixel with the closest dose agreement and % Diff is the percent difference between the dose of the two pixels. We chose to use 3 mm and 3% as our threshold for perfect agreement, since these values are widely accepted in clinical practice. The gamma pass rate (also referred to as the gamma score) is the percent of pixels with $\Gamma < 1$.

To find the range error, we first find which CT slice has the highest agreement with each film. This is determined by finding which CT slice has the highest gamma score for each film. The difference between a given film depth and the corresponding CT slice depth with the highest gamma pass rate gives the range error for that particular film. We wish to include data from all films for obtaining range error so we plot film depth versus CT slice depth that has the highest gamma pass rate and draw a straight line through the graph. The y-intercept of the line is used to calculate the proton range error of the treatment plans for both xCT and pCT treatment plans. If the dose planes aligned perfectly with the film stack, we would see a y-intercept of zero.

Figure 2.10: Illustration of search for the CT dose plane with the highest gamma score when using the 5th film in the stack.
2.5.3 Range Difference of xCT and pCT

We can find the range error by taking the highest agreement gamma scores for each film depth (or film number) versus the shift in the CT dose planes from treatment planning. We plotted the percentage of pixels in a given film that had a gamma score less than 1, when compared to a corresponding CT slice. We then found the best-fit line through the points with the highest gamma pass rates (See Figure 2.11). The y-intercept of this line is our range error.

Figure 2.11: Gamma scores for film number versus CT slice. The black line shows the best fit for the highest gamma scores between film numbers 4 and 18 (films 1-3 were not used due to discussions in the Appendix A.1). The y-intercept, 2.5 mm, is the range error for the xCT treatment plan.
2.6 LET Correction

Linear energy transfer (LET) is the average energy delivered by an ionizing particle to a medium per unit path length and given in units of KeV/\(\mu m\). In our case, protons have a high LET, greater than 10 KeV/\(\mu m\), near the end of range. Radiochromic film is known to have a decreased response to dose as the LET of the film is increased leading to concerns about the accuracy of the range measurements [8]. At the distal falloff of the SOBP, the attenuation of protons increases, leading to a decline in dose radiated on our EBT3 film stack. To measure the effect of LET on our film doses, we found the dose at 17 depths at the distal falloff and 3 dose at the plateau region of the SOBP using the same water equivalent depths as our phantom. To ensure each dose reading was correct, we took 2 measurements at each depth for both the ion chamber and film stack, then averaged the dose readings. We compared these average doses to the ion chamber with the same water equivalent depths on 5x5 cm EBT3 films. Figure 2.12 plots the total measurements taken at various depths of ion chamber dose and the EBT3 films.

We can see from Figure 2.12, the film and ion chamber follow the SOBP shape from the beam source to the end of where our film stack should be in depth. Thus, we can trust that the data we took for the LET corrections should be accurate for the EBT3 film. A separate film dose calibration was performed using 5 × 5 cm films exposed in the proximal edge of a well calibrated 6 cm SOBP. 8 films were exposed to 8 doses (not shown here) that provided the calibration for film doses in Figures 2.12 and 2.13.
Table 2.3: Average ion chamber and film doses at various depths from the beam source to the end of the SOBP.

<table>
<thead>
<tr>
<th>Ion Chamber Depth (mm)</th>
<th>Ion Chamber Physical Dose (cGy)</th>
<th>EBT3 Film Depth (mm)</th>
<th>DEBT3 Film Dose (cGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.92</td>
<td>151.92</td>
<td>0</td>
<td>151.90</td>
</tr>
<tr>
<td>4.94</td>
<td>155.17</td>
<td>3.02</td>
<td>153.80</td>
</tr>
<tr>
<td>103.22</td>
<td>200.08</td>
<td>101.30</td>
<td>201.18</td>
</tr>
<tr>
<td>154.92</td>
<td>202.40</td>
<td>153.00</td>
<td>200.80</td>
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<td>155.00</td>
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</tr>
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<td>158.12</td>
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</tr>
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<td>159.02</td>
<td>199.10</td>
<td>157.10</td>
<td>199.25</td>
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<td>160.42</td>
<td>182.38</td>
<td>158.5</td>
<td>197.85</td>
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<td>187.80</td>
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<td>111.20</td>
<td>160.5</td>
<td>164.45</td>
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<td>163.22</td>
<td>77.30</td>
<td>161.30</td>
<td>133.20</td>
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<td>42.9</td>
<td>162.60</td>
<td>92.70</td>
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<td>22.7</td>
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<td>61.55</td>
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<td>166.12</td>
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<td>45.80</td>
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<td>167.23</td>
<td>0.03</td>
<td>165.35</td>
<td>12.05</td>
</tr>
<tr>
<td>168.27</td>
<td>0.01</td>
<td>166.35</td>
<td>10.6</td>
</tr>
<tr>
<td>169.28</td>
<td>0.01</td>
<td>167.36</td>
<td>9.70</td>
</tr>
</tbody>
</table>

Figure 2.12: Average ion chamber and film doses at depths starting at the distal falloff.
Plotting the distal falloff values only from Table 2.3, we can see the films corresponded very closely to the ion chamber in dose. (See Figure 2.12). The proton range measured with the ion chamber was 0.5 mm higher than the range measured with the EBT3 film. We include this effect in the conclusion section when we discuss the range errors for xCT and pCT based treatment plans.

Figure 2.13: Average ion chamber and film doses at depths starting at the distal falloff.
CHAPTER 3
RESULTS AND DATA ANALYSIS

3.1 Uniformity Checks - Scanned in Films and Dose Histograms

One of our first film checks was to verify that the dose falls to zero at the end of range within the film stack as expected from the Bragg peak. To do this, we visibly check the films after scanning them into the computer to confirm we have captured the distal edge of the Bragg peak on the films. As the beam travels further into the film stack, the films (not just the center of the films) becomes lighter since the dose is decreasing with depth. However, the figures below show the negatives of selected films, which show darkening with depth.

Figure 3.1: Entrance film scan
Figure 3.2: 5th film scan
Protons experience different stopping distances in tissue depending on the path they take through heterogeneous tissues. The treatment plan tries to make all the protons stop at the same depth by modulating the energy and intensity of each pencil beam. However, some dose variations are still visible on each film as seen in Figures 3.1 and 3.8. Another check we can use to determine if the dose was spread equally through the center of the films is to create histograms of the dose of the first few films in the film stack. In Figures 3.9-3.12, the dose distributions of four films are shown within the central $5 \times 5 \text{ mm}^2$ areas of each film. Ideally these doses should be as uniform as possible, but there are variations shown by the standard deviation calculations. These standard deviations were used for our error calculations of the average dose in each film as shown in Figures 2.4 and 3.13.
Figure 3.9: Entrance film dose distribution of a $5 \times 5$ center area of the film. The average dose was 200.55 cGy and the standard deviation was 2.44 cGy for this film.

Figure 3.10: Film 6 dose distribution of a $5 \times 5$ center area of the film. The average dose was 166.49 cGy and the standard deviation was 4.09 cGy for this film.
Figure 3.11: Film 11 dose distribution of a $5 \times 5$ center area of the film. The average dose was 142.21 cGy and the standard deviation was 10.99 cGy for this film.

Figure 3.12: Film 16 dose distribution of a $5 \times 5$ center area of the film. The average dose was 99.19 cGy and the standard deviation was 15.48 cGy for this film.

As depicted in figures 3.9-3.12, the dose on each film becomes more spread out the further we go into the film stack. This is due to the various cow tissue the protons attenuated through. Since there was a diversity of tissue (liver, kidney, and bone), some protons ex-
experienced a more significant dose drop off if the material they were traversing through was more dense, which is illustrated in the increase in standard deviation as we increase in film number. However, the average dose remains as predicted with an exponential drop in dose as we increase in film number.

3.2 Depth Dose Curves for pCT, xCT and Film Stack

Figure 3.13 shows the depth dose curves through the center of the film stack for x-ray CT and proton CT based treatment plans. Also shown is the measured depth dose curve using the film stack. The horizontal shift needed to align the film data with our treatment plans is our range error. As conveyed by the figure, we can see that pCT and xCT treatment plans’ range error are measured using the depth at which the dose falls to 50% of $D_{\text{max}}$. To obtain the most accurate range error measurement, we look to our gamma analysis results in the next few sections.
Figure 3.13: Plot of xCT vs pCT treatment plans in comparison to the film stack. Doses for each CT plane were recorded from the pixels at the center of each film. Dose points on the CT slices at 1 mm increments of depth lie on the green and orange curves but are not shown explicitly. The statistical errors, \( \sigma = \sqrt{N} \) are calculated from the standard deviation of the dose values in a 5 x 5 mm square areas with N=25 dose points. The red points represent the CT plane depth at the distal 50% falloff that align with the 18\(^{th}\) film used for the range error measurements.

Based on Figure 3.13, the range errors for the xCT and pCT treatment plans are shown in Table 3.1.

Table 3.1: Range error for xCT and pCT treatment plans using depth versus dose curves.

<table>
<thead>
<tr>
<th></th>
<th>xCT</th>
<th>pCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta r )</td>
<td>2.44 mm</td>
<td>0.94 mm</td>
</tr>
</tbody>
</table>

The range error values in Table 3.1 are measured using the depth at the distal 50% dose falloff. Gamma analysis uses multiple films to measure the range error and will be discussed in the later sections.
3.3 Distributions of Gamma Pass Rates

We can see from each heat map, the red, turquoise band, that these specific dose planes have the highest match with our films. As we continued to progress further into the film stack, the gamma scores started to significantly decrease, which is the reason we decided to not use films 19 through 36. Based off the gamma score tables in the appendix section, we plot the percentages of agreement between each TPS dose plane and the film stack as color coded plots. Figures 3.14 and 3.15 depicts the gamma scores (also referred to as gamma pass rates) from 0% (purple) to 100% (red). The beginning of the two plots represent the entrance film of the film stack to the right-hand side being the exit.

Figure 3.14: $\Gamma$ scores for each combination of film and TPS dose plane in the xCT treatment plan.
3.4 Range Error Plots

We obtain our final range errors for the pCT and xCT treatment plans by extrapolating the 2 lines in Figures 3.16 and 3.17 to 0 film depth which is the y-intercept of the 2 lines. We first set the slope of our best-fit line equal to 1 to compare our best-fit line to the line corresponding to no range error between the film and the treatment plan (the orange dashed line), which also has a slope of one and y-intercept of zero in Figures 3.16 and 3.17. We can set our slope equal to one since the shape of the depth versus dose curves measuring the energy falloff at the end of range of the xCT treatment plan, pCT treatment plan, and film stack are the same. The final range errors are obtained by taking the y-intercept of the treatment plan (at film depth=0).
Figure 3.16: Blue data points were taken from the highest gamma scores in Figure 3.14 using films 6-24. Range error for the xCT treatment plan is 3.1 mm.

Note: because the first 4 films were exposed to the plateau region of the spread out Bragg peak (SOBP), we did not use the first 4 films in our y-intercept plot of xCT. Since there were 3 or 4 CT slices that gave nearly equal gamma scores for each of the entrance films (with 180 cGy), we did not use many of the gamma scores that were in close proximity to one another.
Figure 3.17: Blue data points were taken from the highest gamma scores in Figure 3.15 using films 4-18. Range error for the pCT treatment plan is 1.8 mm.

Our final range errors for pCT and xCT treatment plans using gamma analysis are shown in Table 3.2.

Table 3.2: Range error for xCT and pCT treatment plans using gamma analysis.

<table>
<thead>
<tr>
<th></th>
<th>xCT</th>
<th>pCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta r$</td>
<td>3.13 mm</td>
<td>1.78 mm</td>
</tr>
</tbody>
</table>

As we can see from Table 3.1, the pCT treatment plan had a better range error than the xCT treatment plan by about 1mm, which is what we expected. Both tests, the depth dose curves and gamma analysis, show that the pCT treatment plan has better range error than xCT’s.

### 3.5 Uncertainties in Range Error Measurements

There are 4 uncertainties that could have affected our range error calculations. Multiple CT planes of the same depth had the best gamma pass rate percentages. (See Tables A.1
and A.2). We averaged the film depths with the same corresponding CT plane depths with the best gamma pass rates. Then we plotted these averages in our y-intercept range plots. However, the actual film depth that best matched a given CT plane could have been anywhere from the first to the last film of the same CT depth match if there was no correlation between the two curves. In addition, the film stack (the dashed rectangles) in Figures 2.8 and 2.9 are not centered on the target volume CT, which could lead to slightly different dose readings if the films were centered relative to the target volume. Furthermore, the dose on our treatment plans’ CT planes were calculated using $1 \times 1$ mm square areas relative to the center of the films, rather than $5 \times 5$ mm areas we used to calculate the dose for each film. This further emphasizes the importance that the films be centered on each CT plane. Perhaps our largest uncertainty is due to the CT slice thickness of 1 mm. We were unsure if dose was measured at the entrance of each CT plane or at the middle of each CT plane in the Omni-Pro I’mRT software, leading up to a possible 0.5 mm shift in our range error measurement since each CT plane was measured to be 1.0 mm as seen in Figure 3.18. Note: Since the films have a much smaller thickness of 0.28 mm, the CT slices would contribute more to the overall error.

![Diagram](image)

Figure 3.18: Possible depths of the dose readings on the 1 mm CT slice leading to $\pm 0.5$ mm depth uncertainty.
CHAPTER 4

CONCLUSION

Our depth versus dose curves measured our range error to be 0.94 mm for the pCT treatment plan and 2.44 for the xCT treatment plan. However these range errors were measured at the dose 50% mark and did not include the points before or after. For this analysis, the xCT treatment plan had a range error 1.5 mm worse than the pCT treatment plan when compared to the film stack. The gamma analysis range error measurements consider more than one of the film depths in comparison to the CT plane depths.

With respect to our film measurements in the gamma analysis comparisons, the pCT based treatment plan had a range error of 1.78 mm and the xCT had a range error of 3.13 mm. This means that xCT treatment plan had a range error 1.35 mm worse than the pCT treatment plan when compared to our film stack.

If we include the 0.5 mm increase in the film depth dose curve due to LET saturation of the film (See Figure 2.12), the errors for the depth versus dose curves reduce to 1.94 mm for xCT treatment plan and 0.44 for the pCT treatment plan. The gamma analysis range errors reduce to 1.28 mm for the pCT treatment plan and 2.63 mm for the xCT treatment plan. Our final range error calculations are listed in Figure 4.1.
Figure 4.1: Range error measurements using depth versus dose curves, gamma analysis, and LET corrections.

For the LET-corrected, gamma analysis range error calculation, the xCT treatment plan’s range was within 1.75% of the film stack range and the pCT treatment plan’s range was within 0.9% of the film stack range. Thus, both of these are within the ±3.5% (of proton range) errors that are expected in xCT based treatment planning with a slight improvement provided by pCT.

However, our experiment only had 8 cm of cow tissue in front of the films and larger volumes of cow tissue would have likely made the errors and differences between xCT, pCT, and film more noticeable. For future experiments, we would like to test higher and lower beam energies. We predict the higher the beam energy, the longer the range and the greater the range error. We would also like to experiment with different tissues and tissue depths to observe how different tissue densities and distances affect our range error measurements. We believe that the heterogeneity of the tissues would lead to larger range errors in treatment planning since the RSP errors lead to larger range errors when integrating the RSPs over more voxels.
REFERENCES


APPENDIX

GAMMA SCORE TABLES
Table A.1: Gamma scores for xCT listed as percentages of agreement comparing treatment plan depth to film depth. The bolded values represent the best agreement between the film and every CT plane. The first 5 films were determined to be in the plateau region of the SOBP so they were not counted toward the range error measurement and were therefore not bolded.

<table>
<thead>
<tr>
<th>Film Depth (mm)</th>
<th>0</th>
<th>0.20</th>
<th>0.52</th>
<th>0.78</th>
<th>1.04</th>
<th>1.30</th>
<th>1.56</th>
<th>1.82</th>
<th>2.08</th>
<th>2.34</th>
<th>2.60</th>
<th>2.86</th>
<th>3.12</th>
<th>3.38</th>
<th>3.64</th>
<th>3.90</th>
<th>4.16</th>
<th>4.42</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>68.4</td>
<td>89.13</td>
<td>87.03</td>
<td>80.39</td>
<td>73.34</td>
<td>65.79</td>
<td>57.49</td>
<td>48.43</td>
<td>38.76</td>
<td>28.54</td>
<td>17.86</td>
<td>13.17</td>
<td>9.49</td>
<td>6.81</td>
<td>4.13</td>
<td>1.46</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>1</td>
<td>92.21</td>
<td>92.35</td>
<td>91.34</td>
<td>90.58</td>
<td>88.07</td>
<td>85.47</td>
<td>80.14</td>
<td>73.64</td>
<td>66.79</td>
<td>58.84</td>
<td>50.94</td>
<td>41.47</td>
<td>31.91</td>
<td>22.35</td>
<td>13.79</td>
<td>6.23</td>
<td>0.00</td>
<td>0.00</td>
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<tr>
<td>2</td>
<td>83.41</td>
<td>92.95</td>
<td>92.08</td>
<td>89.36</td>
<td>87.24</td>
<td>84.44</td>
<td>79.14</td>
<td>71.79</td>
<td>64.58</td>
<td>56.10</td>
<td>48.56</td>
<td>40.03</td>
<td>31.59</td>
<td>23.10</td>
<td>14.64</td>
<td>7.18</td>
<td>0.00</td>
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<tr>
<td>3</td>
<td>78.92</td>
<td>88.46</td>
<td>87.58</td>
<td>84.10</td>
<td>82.07</td>
<td>79.68</td>
<td>75.38</td>
<td>68.93</td>
<td>61.59</td>
<td>54.02</td>
<td>45.49</td>
<td>36.96</td>
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<td>19.91</td>
<td>11.39</td>
<td>3.97</td>
<td>0.00</td>
<td>0.00</td>
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<tr>
<td>4</td>
<td>77.93</td>
<td>87.46</td>
<td>86.58</td>
<td>83.09</td>
<td>81.06</td>
<td>78.67</td>
<td>74.37</td>
<td>67.92</td>
<td>60.49</td>
<td>53.03</td>
<td>44.50</td>
<td>35.97</td>
<td>27.45</td>
<td>18.92</td>
<td>10.39</td>
<td>2.97</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Table A.2: Gamma scores for pCT listed as percentages of agreement comparing treatment plan depth to film depth. The bolded values represent the best agreement between the film and every CT plane. The first 5 films were determined to be in the plateau region of the SOBP so they were not counted toward the range error measurement and were therefore not bolded.