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Investigation of Respiratory Motion Management Techniques for Proton and Photon Radiotherapy of Lung Cancer

Jason E. Matney

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INVESTIGATION OF RESPIRATORY MOTION MANAGEMENT TECHNIQUES FOR PROTON AND PHOTON RADIOTHERAPY OF LUNG CANCER

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INVESTIGATION OF RESPIRATORY MOTION MANAGEMENT TECHNIQUES FOR PROTON AND PHOTON RADIOTHERAPY OF LUNG CANCER

A DISSERTATION

Presented to the Faculty of
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of the Requirements

for the Degree of

DOCTOR OF PHILOSOPHY

by
Jason E. Matney, M.S.
Houston, Texas

December 2013
DEDICATION

To my dear brother, Alex Santos, who lost his battle with cancer four days before his twenty-second birthday.
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ABSTRACT

INVESTIGATION OF RESPIRATORY MOTION MANAGEMENT TECHNIQUES FOR PROTON AND PHOTON RADIOTHERAPY OF LUNG CANCER

Jason E. Matney, MS

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Protons as a source of therapeutic radiation can provide a substantial improvement over dose distributions that can be achieved with conventional sources of radiation such as high-energy photons. However, respiratory motion can significantly impact the delivered proton and photon dose distributions during lung cancer radiotherapy. The goals of this dissertation research were to evaluate the impact of respiratory motion and to estimate the benefit of respiratory gating for passively scattered proton therapy (PSPT) and intensity modulated photon therapy (IMRT).

The first aim of this project was to determine the impact of respiratory motion in PSPT and IMRT. Four dimensional dose distributions were calculated in both modalities for a cohort of 20 patients. The mean changes in normal tissue dose-volume indices were indistinguishable except proton therapy had a greater increase in lung V5, heart V5 and spinal cord maximum dose. The effects of respiratory motion on the calculated dose were not correlated to the tumor motion.
The second aim estimated the benefit of PSPT and IMRT respiratory gating by simulating end-exhale gated treatment plans. The results demonstrated that respiratory gating showed a benefit for a majority of proton and photon treatment plans. PSPT gating, compared to IMRT gating, allowed for larger reduction of all lung and intermediate esophagus dose-volume indices. The third aim attempted to correlate the benefit of respiratory gating to the extent of tumor motion. For the cohort, the benefit of respiratory gating in PSPT and IMRT cannot be predicted by the extent of tumor motion. This aim showed that the tumor motion was inadequate to predict the benefit of respiratory gating.

In an additional fourth aim, we proposed a new metric to quantify respiratory motion in proton therapy: the water equivalent thickness (WET). The change in WET between the inhale and exhale phases of respiration (ΔWET) was significantly correlated to the change in dose during respiration. Additionally, ΔWET analysis was used to create treatment plans that were more robust to respiratory motion. The use of ΔWET gives a powerful new tool, especially in proton therapy, to quantify the anatomical variations of all irradiated tissues along the beam path.
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ABBREVIATIONS

3D = Three dimensional
4D = Four dimensional
BEV = Beam’s eye view
CT = Computed tomography
CTV = Clinical target volume
DIBH = Deep inspiration breath hold
DICOM = Digital imaging and communication in medicine
DIR = Deformable image registration
DVH = Dose-volume histogram
DVF = Deformable vector field
GTV = Gross tumor volume
Gy = Gray
HU = Hounsfield Unit
IMRT = Intensity modulation radiotherapy
ITV = Internal target volume
MCS = Multiple Coulomb scattering
MDA PTC = MD Anderson Proton Therapy Center
MeV = Megaelectron Volt
MLD = Mean lung dose
MED = Mean esophagus dose
MHD = Mean heart dose
OAR = Organ at risk
PSPT = Passively scattered proton therapy
PTV = Planning target volume
RMW = Range modulation wheel
RSP = Relative stopping power
SOBP = Spread out Bragg peak
TPS = Treatment planning system
WET = Water equivalent thickness
CHAPTER 1: INTRODUCTION TO RADIOThERAPY, PROTON THERAPY AND RESPIRATORY MOTION

1.1 Radiation Therapy for Cancer Treatment

The goal of radiation therapy is to maximize the absorbed dose in a target volume while minimizing dose to normal, healthy tissue. After x-rays were discovered by Wilhelm Röentgen in 1895, the medical community quickly adopted x-rays for both diagnostic and therapeutic use. Leopold Fruend is credited as the founder of radiotherapy when he documented the first therapeutic irradiation in Austria in 1896 on a young girl with melanoma. New York Cancer Hospital was one of the first institutions in the United States to recognize the potential of x-rays for the treatment of cancer by installing two low voltage X-ray machines in the hospital in 1902. While the equipment and techniques have advanced tremendously over the past century, the basic principles remain unchanged: to deliver ionizing radiation to tumorous cells while limiting the dose to normal tissue. The radiobiological effect of ionizing radiation is attributed to the destruction of chemical bonds in deoxyribonucleic acid in the cell nucleus. This damage can halt cell proliferation and induce cellular death. The challenge is that radiation does not distinguish between cancerous
cells and healthy cells. Modern advances in radiation therapy have been directed at maximizing the dose deposited in tumorous tissues while limiting the dose to neighboring healthy tissues.

The field of radiation oncology has changed rapidly over the past few decades due to new technologies in linear accelerators and computerized treatment planning systems. These recent advances in radiation therapy have promoted great improvements in the current treatment of cancer. The 5-year relative survival rate for all cancers diagnosed between 2002 and 2008 is 68%, up from 49% in the years 1975-1977. The improvement in survival reflects both progress in diagnosing some cancers at earlier stages and improvements in treatment. Radiation therapy has proven to be an effective form of treatment in many cancer types. However, survival statistics vary widely depending on the cancer type and stage at the time of diagnosis. The estimated new cases and resultant fatalities from the various types of cancers are shown in Figure 1-1. Lung cancer is associated with one of the highest mortality and is also one of the most prevalent.
Figure 1-1: Estimates from the American Cancer Society of the expected new cases of cancer (left columns) and the expected deaths from each type of cancer (right columns) for both men and women. Figure from the American Cancer Society’s Cancer Facts and Figures 2013: http://www.cancer.org/research/cancerfactsstatistics/

1.2 Radiation Therapy in Lung Cancer

The American Cancer Society estimates that 228,190 new cases of lung cancer will be diagnosed in the United States in 2013\textsuperscript{3}. Lung cancer accounts for an estimated 27% of all cancer deaths, more than any other cancer in both men and women. A majority (84%) of lung cancer cases are classified as non-small cell lung cancer. The current 5-year survival rate for non-small cell lung cancer is approximately 18%. Radiation therapy has proven to be a valuable component in the treatment of lung cancer\textsuperscript{4-8}. There is evidence that an escalation in prescription dose could increase local control rates\textsuperscript{9-11}. As the treatment dose is
increased to the target, surrounding normal tissue would also receive a higher dose. Thus, one limiting factor in dose escalation is the risk of lung complications due to the possible increase in the dose to the healthy lung. Mean lung dose\textsuperscript{12, 13} and other dose volume indices such as lung volume receiving 20 Gy (V20)\textsuperscript{14, 15} have been shown to be correlated with normal tissue complications in the lung, such as pneumonitis. Since lung cancer may not be diagnosed until it is at an advanced stage, radiation therapy and chemotherapy are often administered concurrently. This combination can increase sensitivity to radiation\textsuperscript{16}, leading to increased probability of normal tissue complications\textsuperscript{17, 18}. Thus, one of the goals of modern radiation therapy is to find novel ways to deliver higher doses to the target while reducing dose outside the target as much as possible\textsuperscript{19}. Proton therapy is a potential modality that can achieve this goal by reducing patient integral dose while maintaining target dose\textsuperscript{20}. Radiotherapy delivery using protons is advantageous compared to widely-used high-energy photons due to normal tissue dose sparing potential beyond the range of the proton beam.

1.3 History of Proton Radiotherapy

Proton therapy is a relatively new technology as compared to photons in radiation oncology\textsuperscript{21}. The use of protons in radiotherapy was first proposed in 1946 by Robert
Wilson\textsuperscript{22}. Wilson theorized that it would be possible to accelerate the relatively heavier protons to energies able to irradiate a localized region of the body while limiting skin dose compared to photons. After Wilson proposed the medical usage of protons, cancers of the pituitary gland were treated with protons in the 1950’s\textsuperscript{23,24}. During this period, only research laboratories had access to high energy proton accelerators. The first hospital-based proton accelerator was not built until the early 1990’s, which was at Loma Linda University Medical Center\textsuperscript{25}. As the accelerator technology advanced, more hospital-based proton therapy facilities were established. Proton therapy could be considered a relatively immature technology compared to that of photon therapy, which has been in widespread use for many decades prior. In recent years, the availability of hospital-based proton therapy facilities has increased dramatically. According to the Particle Therapy Co-Operative Group website\textsuperscript{26}, as of 2012, over 83,000 patients have been treated with protons at 42 facilities worldwide. There are at least 24 new proton therapy centers that are planned to open worldwide from 2013 through 2015. As an early adopter of proton therapy, the University of Texas MD Anderson Proton Therapy Center (MDA PTC) treated its first patient in 2006\textsuperscript{27}. 
1.4 Introduction to Proton Radiotherapy

The benefit of protons in radiotherapy is basic: protons have a dose distribution with a finite range in a medium, unlike that of photons. Protons are heavy charged particles that interact mainly through Coulomb electric force with the electrons and nucleus of the penetrated medium. Protons lose energy primarily through multiple Coulomb scattering (MCS) until all initial kinetic energy is lost. Protons exhibit a relatively low ionization density, or energy loss per unit path length, at the surface that slowly increases to near the end of the beam range when there is a narrow region of high ionization density. Protons exhibit the highest linear energy transfer just before the end of range, which is referred to as the Bragg peak\textsuperscript{22, 28, 29} named for William Henry Bragg who discovered it in 1903. Beyond the proton range in a medium, virtually no dose is deposited. The finite range of protons in tissue can be used to spare dose to non-cancerous tissue distal to the tumor\textsuperscript{30}. A conceptual depth dose profile for a mono-energetic proton beam is shown in Figure 1-2.
Figure 1-2: Conceptual sketch of depth dose curve for a mono-energetic proton beam. The Bragg peak occurs near the end of the proton range in the medium. The shape of the Bragg peak is a result of the proton stopping power being inversely proportional to the square of the proton velocity \( \propto \beta^{-2} \). Note the relatively low entrance dose proximal and the sharp falloff of dose distal to the Bragg Peak.

The expectation value of the proton energy \( (E) \) loss per unit path length \( (x) \) is called the proton stopping power \( \frac{dE}{dx} \) and typically is reported in units of Megaelectron-volts per centimeter \( \frac{MeV}{cm} \). The stopping power is described using the Bethe formula\(^{31}\) and is valid for ionized and charged particles traversing a medium. For protons the formula is given by:

\[
-\frac{dE}{dx} = \frac{4\pi}{m_p c^2} \cdot \frac{ne^2}{\beta^2} \left( \frac{e^2}{4\pi\epsilon_0} \right)^2 \left[ \ln \left( \frac{2m_p c^2 \beta^2}{I(1 - \beta^2)} \right) - \beta^2 \right]
\]  

(1)

where \( m_p \) is the rest mass of the proton, \( c \) is the speed of light constant, \( \beta \) represents the velocity of the proton expressed as a fraction of the speed of light, \( e \) is the charge of the proton, \( \epsilon_0 \) is the vacuum permittivity, \( I \) is the mean excitation potential of the medium, and \( n \) is...
is the electron number density of the medium. The electron number density for a medium can be calculated by:

\[ n = \frac{N_A \cdot Z \cdot \rho}{M_u} \]  

(2)

where \( N_A \) is the constant Avogadro number, \( \rho \) is the density of the material, \( Z \) is the atomic number and \( M_u \) is the Molar mass constant of the medium.

The range of the charged particles is defined by Attix\(^{31}\) as the expectation value of path length that the particle follows until coming to rest. Calculating precise range of each individual proton constituting a beam is a stochastic process; the position of the Bragg peak is determined by the mean path length of the proton beam. Typically, the proton range is approximated using the continuously slowing down approximation (CSDA)\(^{32, 33}\), which assumes the rate of energy loss along the particle track is equal to the total stopping power. The range of the proton based on CSDA can be calculated using:

\[ Range_{CSDA} = \int_0^{E_0} \left( \frac{dE}{\rho \, dx} \right)^{-1} dE \]  

(3)

where \( E_0 \) is the initial energy of the proton incident on the material. The mean path length must be calculated in order to determine the initial energy required to position the Bragg peak at the intended depth. For dose calculation purposes, the CSDA approximation is used to determine the proton range.
In theory, the finite range of protons may spare distal normal tissues, but this aspect of proton therapy can also be a potential weakness. Uncertainties exist in the determination of range in the heterogeneous anatomy of a patient. The proton beam can be designed to deliver therapeutic levels of dose to cancerous tumor cells while sparing normal tissue distal to the target beyond the proton range. However, any difference in the calculated proton range can alter the planned dose distribution.

A single Bragg peak is often not sufficient to cover the typical tumor size; therefore multiple Bragg peaks must be used to effectively cover a range of depths. To overcome this issue, there are two methods currently employed to cover the tumor target in proton radiotherapy: passively scattered proton therapy (PSPT) and active scanning proton therapy.

The basis of PSPT was originally suggested by Wilson; he suggested to “impose a rotating wheel of variable thickness, corresponding to the tumor thickness.” This produced what is referred to as the spread-out Bragg peak (SOBP), which can be conceptualized as the summation of individual Bragg peaks from multiple, mono-energetic proton beams. This concept is illustrated in Figure 1-3. The modulation is achieved by a range modulator wheel (RMW), shown in Figure 1-4. The RMWs at the MD Anderson Proton Therapy Center (MDA PTC) rotate at 400 revolutions per minute and produce six modulations per
revolution. The incident beam of protons at MDA PTC is accelerated to the necessary energy using a synchrotron, shown in Figure 1-5. The proton beam can be gated on and off during RMW revolution to produce SOBP’s in 1 gm/cm² increments, up to maximum of 16 gm/cm². The initial, narrow beam of protons incident on the RMW must be of sufficient energy to penetrate to the distal end of the target. To cover tumor targets in the lateral direction, a scattering system is used to spread the protons laterally and collimators are used to create the desired field shape. In the MDA PTC facility, the RMW acts as the first scattering device, and a dedicated second contoured scatterer is located downstream of the RMW. This double scattering system is designed to provide uniform proton fluence over the desired region. The MDA PTC passive scattering system is limited to three predetermined square field sizes: 10x10, 18x18, and 25x25 centimeters. For patient-specific treatments, the lateral edges of the field are defined using a brass block collimator ("aperture") which is placed after the scattering system. A compensator is a block made of Lucite that is milled to provide energy absorbing material to conform the proton beam range to the distal surface of the target. An example of an aperture block and compensator are shown in Figure 1-6. A diagram of the MDA PTC PSPT nozzle (treatment head) is shown in Figure 1-7 from Smith et al. The theory and design of energy, RMW, aperture, and compensator creation will be
covered in the following chapters.

Figure 1-3: Example of creation of spread-out Bragg peak (SOBP). In passively scattered proton therapy, the dose delivered by each Bragg peak (various colors) sums to create the SOBP shown in white.
Figure 1-4: Image of a range modulator wheel. When the wheel is rotated, the various step thicknesses are used to absorb energy from the incident proton beam in order to produce the spread out Bragg peak in passively scattered proton therapy. The beam can be gated off/on to create a series of various SOBP widths. The modulation wheel also acts as a primary scatterer which works in conjunction with secondary scatterers to produce a broad beam useful for radiotherapy treatment. Photograph courtesy of R. Mohan.

Figure 1-5: Protons are accelerated using a synchrotron at MDA PTC. A batch of protons is initially accelerated by a linear accelerator and injected into the synchrotron ring, shown above. Protons are accelerated in each rotation in the ring by a wide band radiofrequency cavity. The protons are steered in a ring using bending magnets using increasingly stronger magnetic fields. When the accelerated protons have obtained the desired energy, the protons are extracted and directed towards the treatment gantry. Photograph courtesy of R. Mohan.
Figure 1-6: Brass apertures (left) are used to shape every passively scattered field to the intended target shape in the lateral direction. A compensator (right) is made of Lucite to conform each proton field’s range to the distal surface of the target. Photographs courtesy of R. Mohan.

Figure 1-7: In passive scattered proton therapy, the proton beam is scattered into a flat field by the range modulation wheel and secondary scatterers. The spread out Bragg peak is generated by passing the incident narrow proton beam through a rapidly rotating wheel of various thicknesses. This absorbs energy to produce multiple Bragg peaks which sum together to achieve the desired spread out Bragg peak.
The second type of proton delivery is known as active scanning\textsuperscript{35}. During active scanning proton therapy, magnets are used to scan a narrow pencil beam of protons in the desired lateral profile. The desired proton range can be achieved by varying the initial energy of the proton beam and the desired lateral dose profile can be created by using magnets to steer the proton beam to predetermined locations in the lateral direction. This method of proton delivery requires less patient-specific hardware for delivery compared to passive scattering techniques. No blocks are required in active scanning because the lateral dose distribution of any desired shape is created by steering proton pencil beams to suitable locations using scanning magnets. Also, compensators are not required because the proton range is modulated by changing the energy of protons from the accelerator. Active scanning has additional uncertainties not present in passive scattering, such as the interplay between scanned beam delivery and target motion\textsuperscript{36}. Over time, it is expected that scanned beam proton therapy will become more widely used. The delivery of scanned beam proton therapy is technically challenging but holds great potential for future applications. Many researchers are actively working towards implementing and improving scanned beam proton therapy for the treatment of lung cancer\textsuperscript{37-40}.

The patient cohort in this study was drawn from an IRB-approved randomized
clinical trial which compares PSPT with intensity modulated photon therapy (IMRT). When this study was activated in 2008, PSPT was the delivery system of choice for proton therapy of the lung. The remainder of this work will focus on PSPT as the method for proton treatment delivery.

1.5 Intensity Modulated Photon Radiotherapy

Historically, most forms of external beam radiotherapy have involved high energy photons. Photons are uncharged particles and are attenuated exponentially. Thus, photon beams deposit dose throughout the beam path in a patient. In contrast, protons have a finite range in a patient’s tissues. A comparison of photon and proton depth dose curves is shown in Figure 1-8. IMRT uses inverse planning methods to optimize intensity distributions of non-uniform photon beams. At the MD Anderson Cancer Center, IMRT has been designated as the standard of care for lung radiotherapy to improve target dose conformity and reduce normal lung dose. Modern IMRT makes use of moveable tungsten blocks, called leaves, to shape and modulate the treatment beam. This system is known as the multileaf collimator (MLC). A computerized control system shapes the leaves and conforms the field aperture to the projected target shape for any desired angle about the patient.
A common form of IMRT consists of a multiple series of MLC shapes, or segments, delivered sequentially for a selected number of angles around the patient. The leaf shapes of an individual segment may obscure regions of the target during dose delivery in order to produce the desired composite dose distribution, as shown in Figure 1-9. The radiation delivery is enabled for a prescribed amount of time in each segment, before terminating the beam and moving to the next segment. This process is called “step-and-shoot” IMRT delivery. The step-and-shoot delivery of IMRT will be the method considered in subsequent when PSPT and IMRT are compared. The methods of IMRT planning will be
discussed in an upcoming chapter.

Figure 1-9: An example of beam’s eye views of IMRT segment series to deliver a modulated photon dose to the tumor target (red volume). The multileaf collimator shapes the field via computer controlled tungsten “leaves”, drawn in white. The summation of dose delivered by each segment provides the desired modulated dose to the target.

1.6 Uncertainties in Radiation Therapy

The identification and management of uncertainty in radiotherapy is a complicated but important task. The only way to minimize and account for potential uncertainties is to carefully evaluate the potential sources of error. One of the first potential errors encountered during radiotherapy plan creation is uncertainty in delineating the anatomical volumes due to inaccuracy in the imaging modality. Uncertainties also arise in the calculation of dose in patient anatomy. The delivery of external beam radiation can experience geometrical target miss from anatomical variation due to tumor shrinkage/expansion, internal variation, patient weight variation, respiratory motion and interfractional setup variations. These sources of uncertainty are present in all types of external beam radiation therapy.
The International Commission on Radiation Units and Measurements (ICRU) has defined several volumes to ensure proper treatment of a patient with malignant disease\textsuperscript{54}. To account for anticipated uncertainties in external beam radiotherapy, typically the irradiated volume is expanded to maintain target coverage, as shown in Figure 1-10. The gross tumor volume (GTV) is defined as the gross demonstrable extent and location of the malignant growth. The GTV includes the primary tumor site and any metastatic lymph nodes. Commonly, the GTV is assessed using computed tomography for tumors in the lung. The clinical target volume (CTV) is defined as the volume containing microscopic disease not detectable on imaging studies. Typically an isotropic expansion of the GTV is used to define the CTV. The planning target volume (PTV) is defined in ICRU 50 as a geometrical concept used for photon treatment planning to ensure the prescribed dose is actually delivered to the CTV. ICRU 62 further breaks the PTV margin down into two different components, the internal target volume (ITV) margin which accounts for target motion and the setup margin which accounts for interfractional setup uncertainty\textsuperscript{55}. The ITV margin is added to compensate for expected physiological movements and variations in size, shape and position during therapy. The set up margin is added to account specifically for uncertainties in patient positioning and alignment of the treatment beams during the course of all treatment.
fractions. In practice, a clinician may consider nearby critical structures and modify the CTV or PTV margin accordingly.

Van Herk\textsuperscript{56} developed an analytical method for determining photon PTV margin based on all possible systematic ($\Sigma$) and random errors ($\sigma$):

\[ Margin_{PTV} = \alpha \sqrt{\left( \Sigma_i^2 + \Sigma_e^2 \right)} + \beta \sqrt{\left( \sigma_i^2 + \sigma_e^2 + \sigma_p^2 \right)} - \beta \sigma_p \]  

(4)

where $i$, $e$ and $p$ respectively denote internal, external, and penumbra. In this equation, sources of errors ($\sigma$ and $\Sigma$ terms) were assumed to be statistically independent, thus adding in quadrature. The value of $\sigma_p$ is the standard deviation describing the width of the penumbra. In Van Herk’s equation, alpha and beta are chosen to ensure confidence level that
a desired percentage of patients receive a desired dose coverage. For example, to ensure that the minimum dose of 95% of prescription dose is delivered to 90% of the patient population, Van Herk estimated that values of $\alpha$ and $\beta$ to be 2.5 and 1.64, respectively. Other authors have suggested other, similar methods of margin generation to account for uncertainty and anticipated uncertainties in photon therapy\textsuperscript{57, 58}. By identifying and quantifying the potential for random and systematic uncertainties, it is possible and necessary to formulate margins to ensure adequate target coverage over the course of radiotherapy.

The impact of these uncertainties may be greater for proton therapy due to the physical range of protons is a function of the stopping power of the tissue traversed. Any variation of tissue along the beam path can significantly alter the location of the Bragg peak, and thus cause significant perturbation of delivered dose distribution relative to the planned dose distribution. For example, if a proton beam encounters additional tissue than was originally planned for, it is possible for no dose at all to reach the intended target. Understanding and mitigating all forms of uncertainty are important, especially in proton therapy. In this research, our focus will be uncertainty introduced by respiratory motion on the planned dose distribution in proton therapy, and the relative effects compared to photon therapy.
1.7 Respiratory Motion in Radiotherapy

Respiratory motion has been shown to affect tumor sites in the thorax, liver, and abdomen, and is of particular concern in the treatment of lung cancer. Literature has shown that respiratory motion is an important component of geometric uncertainty in lung cancer. Respiratory motion is patient-specific and individual respiratory characteristics can vary in period, amplitude, and regularity during observation. Furthermore, respiratory motion patterns can vary between fractions and over the course of treatment the tumor may change in mobility as well as size and shape. Figure 1-11 shows a fluoroscopic assessment of respiratory motion for 21 tumors.

Some algorithms attempt to predict individual breathing parameters. Typically, tumor respiratory motion is not predictable by tumor size or location. A study by Liu et al reported that tumor motion is primarily influenced by diaphragm motion because the largest tumor motions were observed in the lower lung. As seen in Figure 1-12, the measured tumor motion was largest in the superior-inferior direction, with increasingly smaller components in the anterior posterior and left-right direction. In Liu’s study of over 150 patients, ~40% of patients displayed respiratory motion over 5 millimeters and ~10% of lung tumors exhibited respiratory motion greater than 10 millimeters.
Figure 1-11: Orthogonal projection motion data for 21 patients showing fluoroscopic tracking of tumor position over the respiratory cycle. Tumors that were affixed to neighboring anatomy are circled. Hysteresis, the difference between the inhalation and exhalation motion trajectory, can be observed for some patients (e.g. #8, 19). This figure is reprinted from reference 68 with permission from Elsevier.

Figure 1-12: Measured fraction of tumors with motion greater than a specified value in the superior-inferior (SI), anterior-posterior (AP) and lateral (LR) directional components for 152 stage III lung cancer patients. This figure is reprinted from reference 74 with permission from Elsevier.
Changes in patient anatomy due to respiration have been shown to negatively affect dose delivery during proton therapy\textsuperscript{75}. Literature has also shown that photon therapy is susceptible to respiratory motion\textsuperscript{76-79}. Other studies have concluded that systematic setup uncertainties were of greater concern for delivery accuracy than random errors or respiratory motion\textsuperscript{80}. As systematic sources of uncertainty are reduced and the delivery of external beam radiation therapy becomes more precise, the margins that are used to account for uncertainty may be reduced. Unavoidable intrafractional variations such as respiratory motion become more important as other treatment margins shrink.

1.8 Respiratory Motion Management

Traditionally, intrafractional motion was accounted for in ICRU report 62 by creating an ITV margin\textsuperscript{55}. This method expands the clinical target volume by an “internal margin” to cover the CTV position over all phases of respiration\textsuperscript{81}. This expansion increases the amount of healthy tissue that receives the therapeutic dose. This “motion-encompassing” technique to account for respiratory motion leads to enlarged treatment fields, larger normal tissue dose, and potential for increased normal tissue complications. The treatment plans that were developed using this method will be referred to as the “non-gated” or “nominal” plan
throughout the following chapters.

One proposed technique to minimize the effect of respiratory motion is respiratory gating\textsuperscript{82, 83}. Respiratory gating is the technique of limiting the delivery of the treatment beam to a specific portion, or “gate”, of the patient’s respiratory cycle. This requires a (nearly) real-time method of monitoring the patient’s respiration. Gated treatment is often delivered by observing the external or internal motions of the patient. Examples of proposed monitoring systems include infrared reflector markers\textsuperscript{84}, spirometers\textsuperscript{85}, strain gauge belts\textsuperscript{86} or x-ray imaging of internal fiducial markers\textsuperscript{87}. Figure 1-13 shows examples of proposed devices for monitoring patient respiratory motion. It is important to note that these devices are often surrogates for the true respiratory motion of the tumor. Literature has reported on the varying correlations between external surrogates and internal motion of the target\textsuperscript{88}.

One type of respiratory gated therapy involves gating during a given phase of normal or free-breathing respiration, typically during full exhale\textsuperscript{89}. As shown in Figure 1-14, when a patient is observed to be within the predetermined gating window, the linear accelerator is enabled and treatment is delivered until the patient respiratory position exits the gating window. Due to the mechanics of human respiration, it has been reported that exhale is the longest, most geometrically stable and most repeatable phase of respiration\textsuperscript{90, 91}.
Figure 1-13: Several methods of observing patient respiratory motion are shown above. One of the most common methods involves (a) optical tracking using an infrared camera/light source to monitor reflective markers placed on the patient abdomen. Other proposed methods of observing respiratory motion include using (b) measuring respiratory airflow using a spirometer, (c) imaging the tumor or implanted fiducials directly with fluoroscopic imaging, or (d) monitoring abdominal movement of the patient using respiratory strain gauge belt. Photographs courtesy of Isaac Rosen, Ph.D.
Figure 1-14: An illustration of end-exhale respiratory gated treatment. Respiratory motion is shown as a sinusoidal trace representing a patient’s external respiratory motion from full-inhale (0% phase) to full-exhale (50% phase). Also shown is a sample gating sequence centered at the full-exhalation phase of respiration. When the patient’s respiratory trace falls within a predetermined range, or gating window shown in pink, the treatment beam delivery is enabled (bottom).

Another proposed variation of gating is referred to as deep-inspiration (video-guided) breath hold (DIBH) gating. In DIBH gating, the patient actively inhales deeply and holds their breath. Some treatment systems provide feedback to the patient with audio or video cues generated by monitoring an external respiratory motion surrogate. When the patient’s respiratory signal is within tolerance of the planned criteria, the treatment beam is
enabled. The theoretical benefit of using DIBH is that the increased lung volume reduces lung dose-volume (DV) indices (e.g. Lung V20)\textsuperscript{97}. A study by Starkschall\textsuperscript{98} concluded that end-exhale gating was as reliable in reproducibility as voluntary breath hold methods.

Breath hold techniques usually require a more active role of the patient to inhale and maintain breath hold position. Lung cancer patients with compromised lung function may not be able to comply with the demands of breath hold techniques. Breath holding must be closely monitored to insure the tumor remains properly positioned and constant during each gate of the treatment beam. It could be argued that the simplest form of beam gating for lung cancer patients to comply with is free breathing gating. At most institutions, the method of free breathing gating is considered to be the most readily available and easiest to implement. This research will focus on free-breathing exhale gating techniques for the reasons previously listed. The technique of free-breathing full-exhale gated delivery will be referred as “gating” for the remainder of this work.

1.9 Significance of Project

As the number of centers and availability of proton therapy grows rapidly, it is important translate clinical experiences from photon therapy. Proton therapy is not as mature
as photons in radiation therapy. For the increasing number of patients that are treated with proton therapy, there are many uncertainties that must be addressed. One perceived weakness of proton therapy is that protons may be more susceptible to the effects of respiratory motion. In order to treat patients with proton therapy, we must determine how respiratory motion affects the planned dose. Most comparative studies of proton and photon modalities compared conformal (instead of IMRT) photon radiotherapy and proton therapy\textsuperscript{99}. One study by Chang et al.\textsuperscript{100} included a comparison of five IMRT plans to proton therapy plans, however the planning methodology used in this study is now outdated and recent advances in IMRT technology call into question the conclusions of this study. No study to date has focused on comparing the effects of respiratory motion between proton and photon therapy.

If proton therapy is indeed more sensitive to respiration motion, it must be determined if current treatment methods could be improved. If respiratory motion affects the planned dose distribution, it may be advantageous to consider the use of motion management. Respiratory motion management is a very active research topic in many clinics. There is a wealth of literature on techniques such as gating\textsuperscript{82, 86, 101, 102} and breath hold\textsuperscript{93, 94, 97, 103} for conformal photon therapy. Recently there have been publications on
gated\textsuperscript{78, 104, 105} and breath hold\textsuperscript{106} IMRT. Also, there are studies that have investigated the implementation of gated\textsuperscript{99, 107, 108} and breath held\textsuperscript{75} proton therapy treatments for a small number of patients. In these studies, patients with large (typically greater than 1 centimeter) respiratory motion were selected in order to showcase the benefit of respiratory motion management. In general, only \(~10\%\) of lung cancer patients exhibit respiratory motion greater than 1 centimeter\textsuperscript{74}. If proton therapy demonstrated larger uncertainty due to respiration motion, it could be hypothesized that proton therapy could benefit from respiratory gating for small respiratory motions. Therefore, more proton therapy patients could benefit from gated motion management techniques. However, to date, there are no such comparisons of respiratory gated techniques between proton and photon modalities. Such research would be instrumental in directing future research initiatives and equipment acquisition.

The application of gated therapy requires additional effort from the radiation therapy team. Additional equipment, quality assurance, patient compliance, and staff time are necessary when adding respiratory gating to the workflow of a typical radiotherapy treatment. Therefore, we must carefully choose when to consider the application of respiratory gating. An expert task group has suggested 5 mm respiratory motion the
“threshold” above which to consider implementing an unspecified form of respiratory motion management\textsuperscript{63}. However, the selection of this 5 mm recommendation was not evidence-based. This recommendation was given for photon therapy and issues pertaining to proton therapy delivery were not explicitly addressed in the report. The implementation of respiratory gating requires extended treatment times and additional equipment, quality assurance and time investment from the clinical staff. Therefore, it is prudent to administer respiratory gating only when it is beneficial to the patient. No literature has quantified a “threshold of respiratory motion”, above which respiratory gating would be beneficial to consider for the patient in proton or photon therapy.

1.10 Objective

The overall theme of this research was to assess the differences between proton and photon therapy in terms of respiratory motion. The first objective was to compare the effects of respiratory motion on planned dose in proton and photon therapy. The second objective was to estimate the benefit of gated motion management techniques in proton and photon therapy. The next objective was to compare the benefit of respiratory gating for both modalities and to determine if the extent of tumor motion could predict the benefit of
respiratory gating. The final objective of this work was to attempt to predict the need for respiratory gating based on respiratory motion metrics.

1.11 Hypothesis

We hypothesized that proton therapy planned dose (1) would be more affected by respiratory motion, (2) would demonstrate a larger dosimetric benefit when implementing gated motion management, and (3) that the magnitude of respiratory motion to demonstrate a benefit from gated motion management would be smaller compared to photon therapy.

1.12 Specific Aims

1. Quantify and compare the impact of respiratory motion on proton and photon radiotherapy plans for a selected cohort of locally advanced non-small cell lung cancer patients with a wide range of respiratory motion.

2. Estimate the benefit of gating for proton and photon therapy by simulating respiratory gated plans for the patient cohort.

3. Determine if a threshold motion exists above which gated therapy demonstrates
dosimetric improvement in either modality by comparing the gated and non-gated plan dose for both proton and photon radiotherapy.

4. Investigate metrics to quantify global respiratory motion for proton therapy by calculating the change in water equivalent path length during respiration.
CHAPTER 2: QUANTIFYING THE EFFECTS OF RESPIRATORY MOTION ON DOSE IN PROTON AND PHOTON RADIOTHERAPY

Chapter 2 is based on material that was published in the International Journal of Radiation Oncology, Biology, and Physics in November 2013 by the author of this dissertation [Int. J. Radiat. Oncol. Biol. Phys. 2013: 87(3): 576-582]. Written permission has been obtained from Elsevier for use of these materials in this dissertation.

2.1 Introduction

As discussed in the previous chapter, respiratory motion has been demonstrated to affect radiation dose distributions in the thorax and is of concern in the treatment of lung cancer.\textsuperscript{63} Review of literature has indicated that respiratory motion can impact the planned dose for intensity modulated photon therapy (IMRT)\textsuperscript{109} and passively scattered proton therapy (PSPT)\textsuperscript{75}. In general, it is often thought that the dose perturbation due to respiratory motion is greater for proton therapy because of proton range uncertainties. Proton range in a medium is determined by its initial energy and the density of the materials traversed. However, the increased sensitivity of PSPT to respiratory motion, when compared to IMRT, has not been clearly established. One potential reason is that the treatment planning methods
and the margins used to create PSPT plan are vastly different from IMRT\textsuperscript{110}. Following sections will discuss the methodology of PSPT and IMRT treatment planning.

The purpose of this chapter was to assess the changes in calculated dose distribution for both PSPT and IMRT when considering respiration motion. Due to the range uncertainty of proton therapy, we have hypothesized that proton therapy will demonstrate larger variation of the planned dose distribution due to respiratory motion. If the calculated dose variation is greater in proton therapy compared to photon therapy, this uncertainty may affect long term patient outcome reporting. Any potential differences in the effect of respiratory motion is important information to be considered in order to support or judge previous\textsuperscript{37, 100} or future work that compares PSPT vs. IMRT for lung cancer. This chapter sought to identify the deviation introduced in our current dose calculation methodology and to determine if the magnitude of planned dose variation due to respiratory motion was greater for PSPT compared to IMRT.

It is possible to explicitly account for the effects of respiratory motion on the planned dose to the patient by calculating four dimensional (4D) dose. Calculation of the 4D dose to moving anatomy is a complex process. First, it was necessary to first recalculate the planned dose delivered during respiratory motion. Secondly, the dose to each tissue element, or
voxel, must be accumulated over all phases of respiration. The tissue element represented by a voxel may move between respiratory phases. Due to this motion, spatial correlation between tissues must be determined. In order to calculate the dose to each phase of respiration, we need representations of the patient at various time points in the respiratory cycle. We first outline a method to image the patient anatomy throughout the respiratory cycle.

2.1.1 Four Dimensional Computed Tomography

In radiation therapy planning, respiratory motion can present a significant challenge to imaging anatomical features of the thorax. In regards to radiotherapy, respiratory motion can cause significant distortion in the shape of anatomy in computer tomography (CT) imaging\textsuperscript{111}. Motion artifacts can occur at boundaries of anatomical structures, resulting in uncertainty in the delineation of anatomical structures\textsuperscript{83}. Figure 2-1 taken from Rietzel et al.\textsuperscript{112} demonstrates a static sphere (left) and the potential of respiratory motion to distort a moving sphere in CT imaging. The sphere, depending on the interplay between slice scanning and object motion, can be depicted as separate structures. Such artifacts lead to uncertainty when delineating targets for radiotherapy planning.
A widely used approach to imaging anatomical motion was to obtain time-resolved or respiratory-correlated CT images. Vedam et al. proposed the method referred to as four-dimensional computed tomography or 4DCT\textsuperscript{113}. This imaging allowed for the incorporation of anatomical motion in the resulting images. Essentially, 4DCT involved sorting an over-sampled cine CT where each axial slice of the patient was imaged for at least one full respiratory period. Simultaneously, the patient’s respiratory position/phase was monitored and correlated in time to CT data acquisition. The sorting process is illustrated in Figure 2-2 taken from Pan et al.\textsuperscript{114} Patient respiratory motion was monitored using external markers affixed to the patient chest/abdomen. Such setup assumed correlation between internal anatomical motion and the motion of the external markers. Each reconstructed CT image was retrospectively sorted in phase bins based on the patient’s respiratory phase/amplitude at time of image acquisition\textsuperscript{112, 114}. After the images have been sorted and binned, the resultant
image sets depict various phases of respiration. In our clinic, the CT images are sorted into ten phases. Following the nomenclature by Pan et al., ten phases of respiration are defined as 0% to 90%, in increments of 10%. The 0%, full-inhale phase of respiration is often referred to as T0; the 50% phase or T50 represents the full-exhale phase of respiration. Multiple studies have demonstrated that 4DCT exhibits fewer motion artifacts compared to standard CT datasets\(^7\).\(^{74, 91, 112-115}\). An example coronal slice of an example patient’s standard spiral CT is compared to the 4DCT exhale phase in Figure 2-3.

![Diagram](image)

Figure 2-2: An illustration from Pan et al. demonstrating the sorting of reconstructed images from a multi-slice CT scanner. Each dot represents the scan time of the acquired image set shown at the bottom. The table translates after imaging each section for greater than one respiratory cycle. The images are then resorted based on the phase of respiration that the images were acquired in.
While the advent of 4DCT has improved images and reduced artifacts, even these time-resolved images exhibit geometric uncertainties. Several investigators have reported that motion artifacts are still present in 4DCT imaging techniques\textsuperscript{116-118}. Three important sources of uncertainty are the detector slice thickness, respiratory sorting accuracy, and partial projection effects. Spatial resolution is always dependent on the finite CT detector slice thickness, but can be reduced through future detector design improvements. Respiratory sorting uncertainties will always be present and result in 4DCT artifacts. Such artifacts can be minimized through coaching to improve respiratory reproducibility of patient respiration\textsuperscript{95}. Other investigators have proposed using internal anatomical
information to sort the CT images instead of using external surrogate information\textsuperscript{119, 120}.

Unlike the previous two sources of uncertainty, partial projection artifacts are due to the residual motion of an object during the acquisition of the CT image. During CT tube rotation, imaged anatomy can move into or out of the current imaging plane. Rietzel et al. has demonstrated that this effect is similar to the partial volume effect in computed tomography\textsuperscript{112}. In this case, the artifacts were caused by partial projection data for a moving object. Partial projection effects on an image can be seen in Figure 2-1 as a spiraled representation of the imaged sphere. Nakamura et al. have quantified artifacts for a deformable phantom and concluded that motion-induced artifacts are directly related to target velocity\textsuperscript{117}.

Uncertainties in 4DCT image construction must be well understood and incorporated into the patient-specific margins that are used during radiotherapy planning. Watkins et al. reported that if a patient can breathe consistently and reproducibly, the uncertainties due to motion artifacts can be predicted\textsuperscript{116}. In practice, the 4DCT scan is monitored by the attending physicist and staff to ensure images are free from significant artifacts. Furthermore, the delineation of treatment contours by the attending physician is assumed to cover the anatomical targets in the presence of any remaining uncertainty.
2.1.2 Deformable Image Registration

The motion of anatomy during respiration is represented by the various phases of the 4DCT dataset. To quantify temporal and position-dependent variations in images of patient anatomy, deformable image registration is necessary. Deformable image registration is the process of transforming one image into the coordinate system of a reference image through spatial mapping of corresponding regions. The concept of deformable image registration is illustrated in Figure 2-4.

Figure 2-4: Illustration of deformable image registration between two images. Two points denoted by the blue pixel are spatially correlated under the transformation that deforms the fixed image (left) to the moving image (right).
Non-rigid or deformable image registration (DIR) methods can be classified into two groups: feature-based or intensity-based. Feature-based algorithms match contours, landmarks, or structure boundaries in the deforming or ‘moving’ image with the same features in the reference or ‘static’ image. In contrast, intensity-based algorithms use pixel or voxel information directly to match to the reference image. CT images are suited to this latter method because values of each CT voxels are given in Hounsfield units (HU). These units are calibrated to the attenuation coefficient of water. Because of this consistency in CT image intensities, intensity-based methods of DIR have been reported in literature for use on CT datasets\textsuperscript{61, 121, 122}. One method of deformable image registration is based on a version of the Horn and Schunck’s optical flow\textsuperscript{123} algorithm known as Thiron’s “demons” algorithm\textsuperscript{124}.

In the demon’s algorithm, the estimated displacement ($\vec{d}$) required to match a point of static image $S$ with intensity $s$ to a corresponding point in the moving image $M$ with intensity $m$ was given by Thiron as:

$$\vec{d} = \frac{(m - s)\vec{\nabla}s}{|\vec{\nabla}s|^2 + (m - s)^2}$$

(5)

where $\vec{d} = (d_x, d_y, d_z)$, and $\vec{\nabla}s$ was the gradient of the reference image. Diffusion between two images was driven by a ‘force’ determined by the gradient and the difference in image
intensity at each point. In the demon’s algorithm, the gradient driving the deformation force is taken from the static image. An additional term added by Wang et al.\textsuperscript{125} treats the deformation between two images as having an equal and opposite force, drawing from Newton’s third law of motion. This term adds a new deforming force opposite to that of equation 5:

$$\bar{f}_m = -\frac{(s - m)\bar{v}_m}{|\bar{v}_m|^2 + (s - m)^2}$$ \hspace{1cm} (6)

where $\bar{f}_m$ represented the force of the moving image towards the static image. Combining the equations 5 and 6 yields:

$$\tilde{f} = (m - s)\left(\frac{\bar{v}_s}{|\bar{v}_s|^2 + (m - s)^2} + \frac{\bar{v}_m}{|\bar{v}_m|^2 + (s - m)^2}\right)$$ \hspace{1cm} (7)

$$\tilde{f} = (m - s)\left(\frac{\bar{v}_s}{|\bar{v}_s|^2 + \alpha^2(m - s)^2} + \frac{\bar{v}_m}{|\bar{v}_m|^2 + \alpha^2(s - m)^2}\right)$$ \hspace{1cm} (8)

where $\tilde{f}$ is a combination of the two forces. To further speed up the calculation, the variable of $\alpha$ was added to iteratively adapt the force strength as the two images converged. Wang reported that the implementation of the accelerated demon’s algorithm to be 40% faster than the original demon’s algorithm. This algorithm was implemented at MD Anderson Cancer Center in a software platform called CT-Assisted Targeting (CAT) for Radiation Therapy.
The accurate validation of any deformable image registration is difficult to measure because the ground truth of clinical patient anatomical deformation is unknown. It should be noted that dose accumulation through DIR is not well established in clinical use due to the difficulty in interpreting and validating results\textsuperscript{126}. In a recent point/counterpoint article in Medical Physics on the use of deformable image registration, the use of DIR to adapt treatment plans was debated\textsuperscript{127}. The three most common methods to validate voxel-by-voxel DIR use anatomical landmarks\textsuperscript{128, 129}, anthropomorphic phantoms\textsuperscript{130, 131}, and mathematical phantoms\textsuperscript{132, 133}.

Deformations of mathematical and anthropomorphic phantoms have been reported to validate the CAT software. Validation results of the CAT software demonstrated that more than 96\% of voxels were within 2 mm of expected position using mathematically simulated deformation on patient datasets\textsuperscript{125}. A follow-up paper reported the absolute registration accuracy of CAT was about 1 mm in a deformable phantom study\textsuperscript{134}. In these two reports, the in-house implementation was demonstrated as an accurate DIR platform for tracking voxel displacements between CT datasets.

The accuracy of DIR is a controversial topic. The calculation of deformation between any two images will have uncertainties. One of the largest sources of uncertainties is the
“missing tissue” problem. Examples of this issue include patient weight loss, tumor shrinkage, surgical removal of tissues, bladder filling and stomach content variations. Such missing tissues can violate the initial assumptions of DIR algorithms and can create spurious distortions in regions of tissue mismatch. In this aim, we calculate the deformations present during respiration as imaged during 4DCT. This largely avoids the uncertainties involved with the “missing tissue” problem in DIR. We anticipate that our use of DIR to track deformation during respiration should minimize the uncertainties inherent in the use of DIR.

2.2 Methods and Materials

In this chapter, we calculated and compared 4D dose for a cohort of proton and photon radiotherapy plans. For each plan, dose was recalculated for each phase of the simulation 4DCT. Deformable image registration accumulated the 4D dose received by a voxel over all phases of respiration. The 4D dose was compared to the standard method of calculating dose, which we term the 3D dose. Lastly, this chapter sought to predict the effects of respiratory motion on delivered dose by correlating the 4D vs. 3D dose changes to the tumor motion.

2.2.1 Randomized Clinical Trial
This study obtained a twenty patient cohort taken from an institutional review board approved trial randomizing treatment between PSPT and IMRT for locally advanced lung cancer. The primary objective of the clinical trial was to compare the incidence and time to develop grade 3 treatment related pneumonitis or local failure. Clinical endpoints for the study included treatment related pneumonitis and tumor response. Figure 2-5 shows the study design flowchart for randomization. Inclusion to the randomized trial required the patient to have unresected, locally advanced non-small cell lung cancer (stage II-IIIB disease according to the 7th edition of the AJCC Staging Manual\textsuperscript{136}), without distant metastases, aged 18-85, and eligible for concurrent chemotherapy. Patients on the study had a Karnofsky performance score $\geq 70$ and forced exhalatory volume $\geq 1$ liter. Each patient had physician-approved PSPT and IMRT plans designed which both achieved the common dose objectives shown in Table 2-1. A comparison of the PSPT and IMRT plan pair is shown for an example patient in Figure 2-6. Once the PSPT and IMRT plans were approved for a patient, treatment was randomized between the two modalities based on a Bayesian adaptive randomization method\textsuperscript{137}. This adaptive randomization would allocate more patients to the treatment modality that yielded more favorable outcomes.

From the randomized clinical trial, this work selected a cohort of patients that
demonstrated a range of respiratory motion amplitudes. Many studies in literature have defined tumor motion based on the centroid displacement of the observable tumor volume\textsuperscript{59}.\textsuperscript{98, 138} Based upon historical recommendations, we defined tumor motion extent to be the distance from the centroid of the GTV on the 50% phase to the centroid on the 0% phase of respiration. The range of the extent of tumor motion observed for cohort patients for this study was 3-17 mm. Table 2-2 lists the extent of tumor motion, the tumor volume, histology and the prescribed radiation dose for each patient.
Figure 2-5: The radiation therapy workflow of the randomized clinical trial is shown. Once an acceptable pair of plans was found at one of the prescription dose levels (74, 66, or 60 Cobalt Grey Equivalent), the patient is randomized between proton and photon therapy.
Figure 2-6: Example patient’s plan comparison using dose-volume histograms (DVH) to compare target, total lung (Tot Lung), esophagus (Eso), spinal cord, and heart doses between proton (dashed line) and photon (solid line) therapy.

Table 2-1: Both proton and photon plans were designed to achieve the normal tissue constraints shown.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Constraints</th>
<th>Minor Deviation</th>
<th>End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Lung (Left Lung + Right Lung – GTV)</td>
<td>V20 ≤ 37%; MLD ≤ 20 CGE</td>
<td>V20 ≤ 40%; MLD ≤ 22 CGE</td>
<td>Clinical pneumonitis</td>
</tr>
<tr>
<td>Esophagus</td>
<td>V45 ≤ 100%</td>
<td>V55 ≤ 66%</td>
<td>Not Permitted</td>
</tr>
<tr>
<td></td>
<td>V65 ≤ 33%</td>
<td>V70 ≤ 10%</td>
<td>Clinical stricture and perforation</td>
</tr>
<tr>
<td></td>
<td>V75 ≤ 5%</td>
<td>V78 ≤ 1.0 cc</td>
<td></td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>V50 ≤ 2 cc</td>
<td>Not Permitted</td>
<td>Myelitis</td>
</tr>
<tr>
<td>Heart</td>
<td>MHD ≤ 30 CGE</td>
<td>V33 ≤ 100%</td>
<td>Not Permitted</td>
</tr>
<tr>
<td></td>
<td>V45 ≤ 70%</td>
<td>V60 ≤ 35%</td>
<td>Clinical pericarditis</td>
</tr>
</tbody>
</table>

Abbreviations: MLD = mean lung dose, CGE = cobalt gray equivalent, MHD = mean heart dose, Vxx = volume of structure receiving at xx or higher dose in Grays.
Table 2-2: Patients, tumor motion, prescription dose, tumor location, size, histology, and the modality patients were randomized to for treatment.

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Motion [mm]</th>
<th>Rx [Gy]</th>
<th>Location</th>
<th>iGTVall [cc]</th>
<th>Histology</th>
<th>Randomized</th>
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<td>378</td>
<td>Squamous</td>
<td>PSPT</td>
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<td>4</td>
<td>74</td>
<td>RUL</td>
<td>240</td>
<td>Squamous</td>
<td>IMRT</td>
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<td>5</td>
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<tr>
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<td>6</td>
<td>74</td>
<td>RUL</td>
<td>709</td>
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<td>6</td>
<td>6</td>
<td>74</td>
<td>RUL</td>
<td>50</td>
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<tr>
<td>7</td>
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<td>94</td>
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<td>PSPT</td>
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<tr>
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<td>74</td>
<td>RLL</td>
<td>67</td>
<td>NOS</td>
<td>PSPT</td>
</tr>
</tbody>
</table>

Abbreviations: Rx = prescription dose, GTV = gross tumor volume, RLL = right lower lobe, RUL = right upper lobe, LLL = left lower lobe, LUL = left upper lobe, Squamous = Squamous-cell carcinoma, Adeno = adenocarcinoma, Large Cell = large cell carcinoma, NOS = not otherwise specified

2.2.2 4DCT Simulation

For all patients in this study, respiration-correlated 4DCT images were created using GE Advantage 4DCT software from image data acquired from a multi-slice helical CT scanner (Discovery PET/CT: General Electric Company, Waukesha, WI). The Varian Real-Time Positioning Management (RPM) System (Varian Oncology Systems, Palo Alto, CA) was used as the external monitoring device, which served as a surrogate for internal motion. The patient’s abdominal motion was monitored by the RPM system shown in Figure 2-7. On
right is the front view of the camera/light source system used to illuminate and observe the moving marker box. The reflective box was illuminated by infrared emitting diodes surrounding the camera and the marker box position was recorded by the camera at 30 frames per second. Patients were simulated in the supine position and immobilization was achieved by using T-bar, wing boards and Vac-Lok (Civco Medical Solutions, Orange City, IA) customizable cushions. If patients are non-compliant with repeatable respiratory motion, audio coaching may be used to promote regular respiration during 4DCT acquisition\textsuperscript{95}.

![Figure 2-7](image.png)

Figure 2-7: An example of (a) the Varian RPM system camera that is attached to the CT couch to illuminate and monitor (b) a reflective marker box (outlined in red) that is used to track respiratory motion of the patient during 4DCT acquisition.

Scanner x-ray tube rotation time was 0.5 seconds. Scans were acquired that covered the entire thoracic region using a 50 cm field of view and 2.5 mm slice spacing. Scan
parameters were set to a 360° scan 120 kilovolts, 150 milliamperes, and cine duration of at least one respiratory period plus one second. During the scan, an attending physicist was present to observe for any abnormalities in respiratory amplitude or period. If any significant artifacts were present in the 4DCT data, the scan was repeated to ensure accurate imaging data for treatment planning. Depending on the scan parameters and cine duration, up to 3000 images were reconstructed by the scanner.

The reconstructed CT images were exported from the CT scanner to the GE Advantage 4D Workstation (General Electric, Waukesha, WI). Each reconstructed image of the patient was matched to the patient’s respiratory motion trace. Figure 2-8 shows a screen capture of the retrospective sorting process to recreate the 4DCT phase datasets. For each desired bin, the reconstructed image at each couch position that most closely matched the respiratory phase was selected. The selected images were binned into the appropriate phase. From the binned images, 10 volumetric datasets were created that corresponded to ten different phases of respiration. The sorting computer also calculated a maximum, average, and minimum intensity projection for every voxel of the ten phases of respiration. These images have proven useful in current treatment plan design workflow. In our clinical practice, the maximum intensity projection can be used to determine the volume that
encompasses the overall motion of the GTV. As described in a later section, the averaged 4DCT dataset was used for the original clinical dose calculation. Completed 4DCT datasets were archived on an image server (Evercore; TeraMedica, Milwaukee, WI).

Figure 2-8: In the GE Advantage 4D workstation, the CT image acquisition time is matched to the respiratory trace as observed by the Varian RPM system. For each desired phase of respiration, the image at each couch position is selected that best represents that phase. For this example, the full-inhale T0 phase is currently selected. Light blue dots indicate a CT image that has been retrospectively sorted to represent the T0 image reconstruction.

Before the 4DCT data could be used for treatment planning efforts, imaging/treatment couch differences must be addressed. The CT imaging couch and treatment couches are constructed differently. Lung radiotherapy plans can involve posterior fields, thus it was necessary to accurately model the treatment couch that the field passes through. This is very important for proton therapy, since the range of protons is affected by all materials they traverse. Before any proton therapy planning, we removed the CT couch and inserted a virtual representation of the treatment couch at the MDACC proton therapy
center. The couch replacement was completed using an in-house MATLAB program developed by Drs. Lei Dong and Yongbin Zhang. An example of the couch replacement program along with an example of images with the CT couch and proton couch is shown in Figure 2-9. In IMRT planning, described in a later section, the CT imaging couch is ignored during dose calculation within the treatment planning system (TPS).

Figure 2-9 Sample axial image of a 4DCT phase showing the CT imaging couch (left) and the same image with the proton therapy center treatment couch that has been inserted (right) using the digital couch converter program (bottom).
2.2.3 Contour Delineation

Plan contour delineation was performed manually by the physician and clinical dosimetry staff for every patient on the clinical trial. After the simulation 4DCT scan, the physician delineated the gross tumor volume (GTV) using the TPS software. The physician determined the GTV contours from macroscopically identifiable tumor disease, including lymph nodes, as observed on the planning CT. The diseased volumes were modified as deemed necessary based on other clinical studies and imaging modalities such as position emission tomography. Figure 2-10 shows an example of the volumes creating the total GTV.

Figure 2-10: Radiograph projection of sample patient overlaid with primary tumor outlined in red. Nodal GTV volumes to be treated are colored green and blue. The union of the primary tumor and any nodal involvement was used to create the GTV.
A structure defined as the iGTV (internal gross tumor volume) was created that was equal to the union of the GTV on all phases of the simulation 4DCT. This was created by propagation of the GTV from one phase to another, or by directly contouring on a maximum intensity project (MIP) 4DCT image. The iGTV structure encompasses the GTV over all phases of respiration. The clinical target volume (CTV) is designed to encompass subclinical disease around the GTV. The CTV was defined as the GTV plus an isotropic 8 mm margin for microscopic extension of the tumor. When respiratory motion is present, the internal target volume (ITV) was defined as the envelope of the CTV during all phases of respiration. The ITV was created by expanding the iGTV by 8 mm. These volumes were reviewed and edited if necessary based on the physician’s clinical experience. The ITV was expanded by 5 mm margin to create the planning target volume (PTV) for photon therapy planning. The PTV is a geometrical construct to account for multiple sources of variation in delivery over the course of treatment. Figure 2-11 illustrates how the volumes of the ITV and PTV were created.

Following the identification of the tumor target volumes, the normal tissue anatomy was contoured. Structures delineated included, but not limited to, right lung, left lung, esophagus, spinal cord, heart, and external body contours. The total lung volume was
defined as the union of left and right lung volume excluding the GTV. All normal tissue contours were delineated on the average CT dataset. The resulting structures were approved by the physician and used in plan evaluation.

Figure 2-11: For each patient, the GTV (red) was outlined in red on the T0 and T50 phases of the 4DCT dataset. A margin of 8 mm for subclinical disease expansion was added to each GTV to create the CTV, shown in yellow. The union of CTV volumes over all phases of respiration in the 4DCT created the ITV (yellow shaded region). An expansion of the ITV by 5 mm for additional uncertainties over the course of radiotherapy denotes the PTV (blue) on the average CT dataset.

2.2.4 IMRT Planning

The basis of IMRT is to treat the patient with a series of fields with non-uniform fluence. The fluence of each field is optimized such that the sum over all beams achieves a high dose to the target structure and acceptably low doses to surrounding normal tissues.
The IMRT treatment planning system divides each beam into a large number of beamlets and optimizes the weighting or intensities to produce a composite plan. Individual beam fluence is optimized using “inverse planning” methods. In IMRT inverse planning, individual beamlet weights are adjusted in an attempt to meet predefined dose distribution goals for the composite plan. These goals were selected to meet shared normal tissue constraints shown in Table 2-1.

The TPS represents these objectives in a cost function. The cost function quantitatively represents the deviation from the desired goal. As given by Khan\textsuperscript{139}, the cost function may be a least square function of the form:

$$C_n = \sqrt{\left(\frac{1}{N}\right) \sum_i W(i) \times ((D_0(i) - D_n(i))^2}$$

(9)

where $C_n$ was the cost function of the $n^{th}$ iteration, $D_0(i)$ was the desired dose at a point $i$, $D_n(i)$ was the currently computed dose at the same point, $W(i)$ was the weighting or relative importance factor, and $N$ is the number of dose points. The overall cost is the sum of the costs for the target and the normal tissue structures based on the weighting. The optimization algorithm attempted to minimize the cost function until the best approximation to the desired goal or dose distribution was achieved. An example of the optimization
structures, goals, and weighting factors for a patient in this study is shown in Figure 2-12.

The difference between the actual and desired value for each criteria is weighted by factor in the “weight” column to calculate an objective value for each structure. The IMRT optimization algorithm attempts to minimize the composite objective value by adjusting beamlet weighting.

<table>
<thead>
<tr>
<th>ROI</th>
<th>Type</th>
<th>Constrain</th>
<th>Target cGy</th>
<th>% Volume</th>
<th>% Variation</th>
<th>Weight</th>
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Figure 2-12: An example of the dose-volume objectives optimized for IMRT plans for this study. Abbreviations: EUD = equivalent uniform dose, NT = normal tissue, PRV = planning organ at risk volume, ILung = ipsilateral lung, CLung = contralateral lung
For each patient in this study, an IMRT plan was designed to treat the PTV with any combination of coplanar or non-coplanar fields. The number and angle of fields were selected based on criteria such as tumor size and location. Fields were either manually selected by the dosimetry team or determined by using “AutoPlan”, an automatic IMRT planning program developed by Zhang et al\textsuperscript{140}. For the cohort in this study, between 5 and 12 fields were selected for patient treatment in the Pinnacle treatment planning system (Philips Medical Systems, Madison, WI).

After an acceptable IMRT plan was generated, the intensity profiles for each beam were converted into a series of control points, or multi-leaf collimator shaped fields. A final plan dose was calculated as the composite of the dose delivered from each control point. For all patients on study, the physician reviewed the dosimetrist and AutoPlan designed plans. The plan deemed superior by the physician was selected as the patient’s IMRT plan for purposes of this study. The IMRT plan dose as calculated on the average 4DCT dataset was defined as the 3D IMRT dose. This 3D IMRT dose method represents the current clinical standard in calculating and reporting photon dose-volume indices.
2.2.5 PSPT Planning

The PSPT plans considered in this work were designed by dosimetrists skilled in proton therapy treatment planning. The approved anatomical contours were imported into the proton treatment planning system; for our work, the Eclipse treatment planning system was used (Varian Medical Systems, Palo Alto, CA). To ensure target coverage despite any GTV displacement, our clinic adopted a conservative approach in which the iGTV volume was overwritten with the maximum HU value within the iGTV\textsuperscript{141}.

As mentioned previously, the methodology of proton therapy planning was vastly different than that for photons. In contrast to the “inverse planning” of IMRT in the previous section, the planning of PSPT is considered a “forward planning” process. For PSPT planning, the dosimetrist initially selected the number of fields, incident angles and weighting for each field is used for creating a PSPT plan. After the treatment fields were designed, dose was calculated for each individual proton beam. The fields were modified as needed until planning criteria were met. A major difference is the use of beam-specific margins to design PSPT plans in place of traditional PTV as described by Moyers et al\textsuperscript{110}.

It is important to note that the PTV concept for plan generation may not be appropriate for proton therapy planning. Van Herk’s\textsuperscript{56, 142} margin formalisms for PTV
creation assumed that the dose cloud is invariant to small shifts in the patient. This is a valid assumption in photon therapy planning, as photons are attenuated exponentially. Thus, for small variations of patient anatomy, the change in planned dose should be minimal. Cho et al. reported that for a majority of clinical cases, the anatomical displacement and variation of tissue inhomogeneity has a negligible impact on the planned dose distribution in photon therapy\textsuperscript{143}. In contrast, Moyers reported that the PTV concept was inadequate for proton therapy because the dose with depth decreases rapidly beyond the spread-out Bragg peak\textsuperscript{110}. This is demonstrated in Figure 2-13 where we insert a high-Z object simulating a bone proximal to the tumor target. As the bone object moves, it is observed that a severe under-dose is present in the distal region of the target due to change in the water equivalent depth of the material in the path of the proton beam.

Figure 2-13: Dose was calculated in Eclipse of as a spherical heterogeneity simulating a rib bone moved into the path of the proton beam in this example. The original dose (left) is perturbed as the bone moves proximal to the target (red box) in the center and right images. Note that there are regions of the target receiving no dose as the heterogeneity moves in the beam path.
In the design of treatment plans for PSPT patients in the clinical protocol, the target for the prescription dose was designed with appropriate margins to the ITV structure; No PTV was used in the design of the fields. Individual proton fields were conformed to the target generated using lateral and longitudinal margins around the ITV. The dose conformity in the lateral direction (perpendicular to the field axis) was achieved by using custom apertures. The dose coverage of the target in the longitudinal (parallel to field axis) was achieved by appropriate selection of range and spread out Bragg peak (SOBP) width. Margins around the ITV were determined for each field based on beam and patient-specific parameters. For each field, an estimate of the incident proton energy (or range) and required SOBP width to cover the ITV. An example of the range and SOBP calculation is illustrated in Figure 2-14.
To be consistent with the PTV concept, lateral margins were used to define the field aperture shape. Aperture edges were designed to project outside of the ITV by a distance that accounts for setup uncertainty and the 90-50% penumbra width. The penumbra width was determined during clinical commissioning of each passively scattered proton beam selection available at our center. For example, the equation to calculate the lateral penumbra (LP) for the medium field size (18x18 cm) scattering system used at our proton therapy center is given by:
\[ LP \, [\text{cm}] = 0.0005 \times d^2 + 0.0258 \times d + 0.1822 \]  

(10)

where \( d \) is the depth to the center of the SOBP. These lateral margins were set to ensure that the prescribed dose from each proton field in the treatment plan encompassed the ITV in the plane perpendicular to the field axis.

Proximal and distal margins were added to the ITV for each field to ensure the dose coverage along the longitudinal direction under range uncertainties. The equation used to calculate distal margin (DM) and proximal margin (PM) are given by:

\[
DM \, [\text{cm}] = (0.035 \times \text{Range}) + 0.3 \, \text{cm}
\]

(11)

\[
PM \, [\text{cm}] = (0.035 \times (\text{Range} - \text{SOBP width})) + 0.3 \, \text{cm}
\]

(12)

where range is the distance in centimeters (cm) to the most distal edge of the ITV. The uncertainty in the value of CT and the subsequent conversion to relative linear stopping power is historically assumed to be 3.5\%\textsuperscript{144}. The additional 0.3 cm was to account for additional uncertainties such as beam energy, thickness of the beam line components in the nozzle, and compensator manufacturing/design uncertainties. The final range and SOBP width were recalculated to cover the distal and proximal margins added to the ITV.

Field-specific range compensator was designed to match the proton range to the distal surface of the tumor target. In the Eclipse TPS, a ray trace algorithm initially calculates the desired thickness of the compensator at each point over the target surface. To
design the compensator to cover the target due to possible misalignment of heterogeneities in the beam path, Urie\textsuperscript{145} proposed that the compensator be “smeared” with a smearing radius (SR). The compensator thickness at a point is replaced by the minimum thickness calculated within a distance ±SR. The compensator smearing radius is calculated using the following equation\textsuperscript{110}:

\[
SR = \sqrt{(IM + SM)^2 + (0.03 \times Range)^2}
\]  

(13)

where SM is the setup and IM is the internal margin, which is already accounted for in the ITV contour, thus equals zero for our purposes. The setup margin is assumed to be 5 mm, which is the same as for photon planning. The second term of equation 9 is from Urie et al\textsuperscript{145}. where it was determined that 3% of the proton range is comparable to the root mean square multiple scattering distance for protons.

After each field has been designed as described above, they were weighted manually to provide adequate tumor coverage and sparing of the normal tissues. Typical number of fields for each plan was between 2 and 4. If necessary, the PSPT field weighting was altered until the planning criteria in Table 2-1 was met and the physician approved the plan. The final plan dose was calculated on the average 4DCT dataset. This was defined as the 3D PSPT dose. The 3D PSPT dose calculation represents the current clinical standard in
calculating and reporting proton dose-volume indices.

2.2.6 4DCT Dose Recalculation

To accurately determine the dose delivered to a patient with moving anatomy over a series of 4DCT phase CT images, it must be known how the moving anatomical voxels deforms and corresponds between images. Deformable registration allows for the correlation of points between two deformed images. To accumulate the dose delivered to each voxel of the patient anatomy, the spatial location of the voxel must be followed from one CT image to another using deformable vector fields.

To calculate the 4D dose in each plan, the dose delivered during each phase of respiration must first be calculated. This requires dose calculation be performed using each of the ten phases of the 4DCT instead of the average CT. In both treatment planning systems, this can currently only be accomplished by recreating the clinical plan on each of the 4DCT phases. Currently, commercial treatment planning systems are not designed with 4D dose calculation needs in mind.

The recalculation of the PSPT plan was relatively straightforward in the Eclipse TPS. As in the original plan, the CT imaging couch was first replaced with a virtual representation
of the proton therapy center treatment couch. Once the 4DCT phase images were loaded into the Eclipse TPS, copies of the clinical plan were created using each of the 4DCT phases as the primary dataset. The proton beam line, aperture blocks, compensator, and all other plan settings were copied onto the new “plan” unchanged. The proton dose recalculation was completed for all ten phases. The 4DCT images and corresponding PSPT doses were exported for further processing before being imported into the CAT software.

For the IMRT plan, the process of recalculating the dose to each respiratory phase was not straight-forward in the Pinnacle TPS. To copy the IMRT plan from the average CT to each 4DCT phase, several steps were followed:

1. Express the prescription dose as monitor units per field,
2. Record the isocenter location name and location,
3. Save beam data/parameters to a file using Pinnacle scripting,
4. Created a series of “plans” each with a different 4DCT phase as the primary dataset,
5. Recreate isocenter in new “plan” matching the location in original plan,
6. Load relevant plan data (prescription, treatment fields, MLC control points, etc.) at plan isocenter,
7. Recalculate dose for each field,

8. Repeat for all 10 phases of 4DCT

As in the original IMRT dose calculation, the CT imaging couch in each 4DCT phase was replaced with air in the Pinnacle TPS. The removal of the couch is shown in Figure 2-15. The current clinical practice is to assume the couch introduces negligible effect on the calculated IMRT dose. Consistency of the prescription, field weighting values, couch removal location, dose grid dimensions and resolution was verified before final dose calculation in each phase. This process was repeated for all ten phases of the 4DCT. The resulting IMRT dose calculations and 4DCT images were exported from the Pinnacle TPS to the CAT software for deformable image registration.

Figure 2-15: The CT imaging couch is removed in the Pinnacle TPS for each IMRT dose calculation. It is assumed in our clinic that the photon treatment couch does not impact the delivered dose significantly. However, this is not the case in proton therapy, where the couch is replaced with a virtual representation of the proton therapy couch seen in Figure 2-9.
2.2.7 Deformable Image Registration

After calculating the dose on each 4DCT phase, it is important to know the dose delivered to the moving patient anatomy during respiration. As previously mentioned, deformable image registration allows for the correlation of the location of a voxel in one phase of the image to another phase. The CT Assisted Targeting (CAT) program has been designed to perform CT-to-CT registration using the demons algorithm. After importing the 4DCT datasets into CAT, we selected the T50, full-exhale phase of respiration as our static/reference image to deform towards. The T50 set was chosen because it is reported that the lung at exhale is the most geometrically stable and repeatable phase of respiration \(^{90}\). Each 4DCT simulation image from T0 to T90 was deformed towards the T50 image. An example of the CAT graphical user interface is shown in Figure 2-16.

The CAT program calculated the deformation of each voxel between each 4DCT phase and T50 phase; this is known as the deformable vector field (DVF). An example of how an anatomy is deformed between the T0 and T50 phase is shown in Figure 2-17. The DVF was used to calculate how the dose distribution corresponding to each phase deformed onto the T50 image coordinate system. This was not necessary for the dose calculated on the T50 phase. This process was repeated for the nine remaining PSPT/IMRT 4DCT phase
doses. The dose deformed to the T50 phase for all 4DCT phases was saved for dose summation.

Previously, we have stated that deformation between 4DCT phases acquired at the same time should minimize the uncertainties associated with deformable image registration. It should be noted that the same DVF was used to deform both the PSPT and IMRT doses. Any uncertainties in the calculation of the DVF should equally affect the resulting 4D PSPT and IMRT dose accumulations.

Figure 2-16: Example of the graphical user interface of the CAT software. This is a user-friendly platform in which the daily (moving) and reference (static) images are compared. The deformable vector field is overlaid on the reference image in this example (bottom right). The resulting deformed dose or structural files can be exported to the treatment planning systems for further analysis.
Figure 2-17: An example of how a 4DCT T0 phase (left) was deformed towards the reference, T50 phase (right) of respiration using the deformable image registration software. A coronal slice of the deformable vector field (middle) demonstrates the deformation of each voxel from the moving image (T0) to the reference image (T50). A yellow line is drawn to serve as a reference between the two images.

2.2.8 4D Dose Summation

After the dose to each phase was deformed to the T50 coordinate system, a final dose summation to each voxel of the patient was calculated for the PSPT and IMRT plan. Each phase represented one tenth of the patient’s respiratory cycle. Therefore, the dose delivered to each voxel in a particular phase contributed one tenth of the total dose to the patient. As shown in Figure 2-18, the CAT software was used to compute the dose accumulated over the ten phases of the 4DCT. This deformed, weighted, and accumulated dose distribution is defined as the 4D dose. The 4D PSPT and 4D IMRT dose distributions were imported into the treatment planning systems to compare against the 3D dose. It is our assumption that the explicit inclusion of respiratory motion into the calculation of 4D dose is more accurate than traditional 3D dose calculation methods using motion averaged CT datasets.
2.2.9 4D versus 3D Dose Comparison

This chapter quantified the difference between the 4D and 3D dose calculations for both PSPT and IMRT. The 4D dose distribution was defined as the dose accumulated on the T50 phase of the 4DCT. The 3D dose was calculated on the average CT. It is important to note that the anatomy as represented on the average CT does not correspond to anatomy on an individual 4DCT phase. The average CT is a composite of the 10 phases of the 4DCT. Anatomical structures appear “blurred” due to this averaging and do not necessarily correspond to the patient anatomy as observed during the individual phases of respiration. In
Figure 2-11, the anatomical structures between the T0 and T50 appear shifted, but similar. However, in Figure 2-11, the anatomical structures appear blurred in the average CT image. This is pronounced in the diaphragm region of the average CT. The anatomical structures as observed from the average CT do not represent the true patient anatomy. For example, the deformation software would have difficulty matching the blurred diaphragm anatomy to the anatomy in the individual phases. Thus, it can be anticipated that DIR software would exhibit much greater uncertainty in deformably registering the average CT images to 4DCT phase images. For this reason, we did not deform the 4D dose on the T50 to directly compare with the 3D dose as calculated on the average 4DCT image.

To compare 4D versus 3D dose, dose volume histograms (DVH) were calculated and compared for both PSPT and IMRT. Dose-volume (DV) indices that were observed are listed in Table 2-3. The 3D DVH was calculated using contours that were originally designed on the average CT. To compute the 4D DVH, a new set of volume structures were defined on the T50 for the PTV, total lung, heart, esophagus and spinal cord. Any uncertainty in contour delineation on the average CT or T50 CT should affect both modalities equally in the analysis. Previously it was stated that the PTV concept is not valid for PSPT plan creation, however, PTV is still used as a method of evaluating and reporting
dose to the target in proton therapy.

Table 2-3: Twenty seven dose-volume indices were collected for analysis in this study. The anatomical structures of interest were the tumor target, total lung, esophagus, heart, and spinal cord.

<table>
<thead>
<tr>
<th>Structure</th>
<th>DVH criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>PTV D95, ITV D95, H.I.</td>
</tr>
<tr>
<td>Total Lung</td>
<td>MLD, Lung V5, V10, V20, V30, V40, V50, V60, V70</td>
</tr>
<tr>
<td>Esophagus</td>
<td>MED, Esophagus V20, V30, V40, V55, V60, V65, V70</td>
</tr>
<tr>
<td>Heart</td>
<td>MHD, Heart V5, V30, V45, V60</td>
</tr>
<tr>
<td>Cord</td>
<td>Cord 1%, Cord V45</td>
</tr>
</tbody>
</table>

Abbreviations: MLD = mean lung dose, MED = mean esophagus dose, MHD = mean heart dose, Cord 1% = maximum dose to 1% of cord, PTV D95 = Dose to 95% of PTV, ITV D95 = dose to 95% of ITV, H.I. = heterogeneity index

The target dose heterogeneity index (H.I) was calculated using the equation:

\[ H.I. = \frac{D_2 - D_{98}}{D_{RX}} \]  

(14)

where \(D_2\) represented the highest dose to 2% of the target, \(D_{98}\) represented the dose to at least 98% of the target, and the prescription dose is represented by \(D_{RX}\).

To model the differences between 4D and 3D DVH indices based on the extent of tumor motion, we hoped to observe a correlation between the effect of respiration on the planned dose (4D-3D) and tumor motion. As a first order approximation, we assumed that the tumor motion would exhibit a linear relationship to the dosimetric variation during respiration.
Pearson correlation coefficients were calculated to determine the correlation between tumor motion and the 4D - 3D dose differences.

2.2.10 Weekly 4D Dose Accumulation Example

Each patient enrolled in the randomized clinical trial was reimaged with weekly, repeat 4DCT. This presented a unique opportunity to calculate the effect of respiratory motion over multiple weeks of treatment. For a typical prescription dose of 74 Gy delivered over 37 fractions, the full course of treatment would take at least 7 weeks. The proposed workflow to calculate the weekly accumulated dose is shown in Figure 2-19.

This chapter identified an example patient from the cohort with 9 mm tumor motion with 7 weeks of repeat weekly 4DCT imaging. For this patient, this work wanted to demonstrate the feasibility of using the 4D dose calculation technique to estimate dose accumulated over all weeks of treatment. Essentially, the 4D dose calculation method is repeated every week that weekly 4DCT is available. One issue is that the setup position between 4DCT imaging sessions can vary. It is possible to shift the simulation week (week 0) isocenter to the corresponding location on the weekly 4DCT image. After shifting the treatment fields based on the isocenter shift, the planned dose can be recalculated for that particular week.
Figure 2-19: Workflow for calculation of weekly (5D) accumulated dose over the seven week course of radiotherapy treatment.
The CAT software was used to calculate a shift between the week 0 dataset and each subsequent weekly 4DCT image. As previously stated, the T50 phase of respiration is regarded as the most stable phase of respiration. Our method was to rigidly align the primary GTV as delineated on the T50 with the corresponding structure in the weekly T50 image. This could be analogous to using 4D cone beam CT to align to the tumor target during the exhale phase of respiration. An example of the rigid shift between week 0 and week 3 is shown in Figure 2-20. The CAT system calculated the rigid shift as shown in Figure 2-21. The original plan isocenter shift was recorded for each weekly image.

Once the shift was calculated for all seven weeks of repeat 4DCT imaging, the new isocenter point was exported to the treatment planning system. The original plan’s treatment fields in both PSPT and IMRT were applied to the new, shifted isocenter in each weekly image. Following the workflow outlined earlier, the weekly 4D dose was calculated for each week of treatment.
Figure 2-20: Example of the rigid shift calculated using the CAT software. The GTV (red), CTV (khaki) and PTV (light blue) are shown with the external body contour (yellow) and spinal cord (dark red). The original contours on week 0 (top) were overlaid on the week 3 T50 image (middle). A shift was calculated to align the GTV structure to the corresponding anatomy in the week 3 image (bottom). The shift is used to determine the isocenter location in the week 3 image.
Figure 2-21: Example of the isocenter shift between the week 3 and week 0 T50 phase. The primary GTV on the week 0 T50 image (GTVp_T50) was rigidly aligned with the corresponding tumor on the weekly T50 image. The vertical (VRT), longitudinal (LNG) and latitude (LAT) of the shift gives the location of the isocenter in the weekly T50 image.

To calculate the weekly accumulated dose for PSPT or IMRT over 7 weeks of treatments, the proposed workflow required 70 dose recalculations and 70 deformable image registrations. The resulting weekly 4D dose files were exported back to the CAT software to estimate the accumulated dose over all weeks of treatment. The week 1-7 T50 image was deformably registered and mapped to the week 0 T50 image. This process was repeated for each week of treatment for both PSPT and IMRT. The accumulated weekly dose was calculated from equally weighting the weekly 4D dose contributions. The deformed weekly dose was weighted by $1/7^{th}$ (due to treatment over seven weeks) and accumulated over all
weeks. The final dose accumulated was defined as the weekly 4D (5D) dose.

2.3 Results

For the cohort of 20 patients, 4D doses have been calculated for PSPT and IMRT modalities. An example of 4D and 3D dose from a sample patient is shown in Figure 2-22. The top two images show a slice of the 4D dose as calculated in the previous sections, and the bottom two images show a slice of the voxel-by-voxel 4D-3D dose differences. The difference between the two calculation methods is presented to visually demonstrate the differences between the 4D and 3D dose clouds. It should be noted that this image is not a measure of the 4D vs. 3D dose difference for the patient tissue elements. As previously stated, registering between patient anatomy represented on T50 and average CT would be incorrect and introduce unacceptable uncertainty. In general, we found that the dosimetric variation was most pronounced in the normal tissue around the target volume in IMRT, and for PSPT, the largest variation was typically in normal tissue distal to the target volume from each beam.

The goal of this chapter was to determine if PSPT or IMRT planned dose was more affected by respiratory motion. Our proposed method was to evaluate the 4D vs. 3D dose
differences by DV index comparison. An example of the 4D vs. 3D DVH curves for PSPT and IMRT are given in Figure 2-23 and Figure 2-24, respectively. It should be emphasized that the structural volumes used to calculate the DVH in 4D and 3D were delineated on different datasets (T50 and Average CT, respectively), but consistent between PSPT and IMRT.

First, we report the DV indices for the tumor target. The ITV and PTV 95% dose coverage (ITV D95 and PTV D95, respectively) were evaluated for the cohort. The mean change in ITV D95 was close to zero; In 19/20 patients; the 4D ITV D95 value was within ±1% of 3D values. The cohort average 4D vs. 3D increased by 0.5 Gy in both modalities. The 4D-3D PTV D95 changes are shown in Figure 2-25 and Figure 2-26; the 4D PTV coverage values were within ±3% of the 3D value for all PSPT plans and 18/20 IMRT plans. Differences in the heterogeneity index between 4D and 3D are demonstrated in Figure 2-27. A paired t-test found no statistical difference between the mean 4D-3D DV values for PSPT and IMRT PTV D95, ITV D95 or H.I.
Figure 2-22: An example of the 4D PSPT and IMRT plans and the differences of the 4D – 3D dose clouds overlaid on the T50 image for reference. Note that largest PSPT 4D-3D dosimetric variation occurs distal to the PTV (outlined structure) from two treatment fields and the largest IMRT dose variation occurs just outside the PTV target in the high dose gradient regions present in the IMRT plan.
Figure 2-23: Dose volume histogram of 4D and 3D PSPT plans for the example patient in Figure 2-22.

Figure 2-24: Dose volume histogram of 4D and 3D IMRT for the example patient in Figure 2-22.
Figure 2-25: Before-after plots showing the PTV 95% coverage for the coverage demonstrating the 3D and 4D dose for the 20 patient cohort.

Figure 2-26: Change in PTV 95% volume coverage dose between 4D and 3D calculation for PSPT (red) and IMRT (blue). For a majority (>75%) of the patients, the PTV dose coverage was higher in 4D than in 3D in both modalities.
Figure 2-27: The change in heterogeneity index between 4D and 3D is shown for each patient in the cohort. For a majority of the patients, the 4D plan has a lower heterogeneity index, signifying the plan was more homogeneous when calculating the 4D dose.

For both PSPT and IMRT, the mean of the 4D-3D difference was calculated for all DV indices. A paired t-test was used to determine if the mean 4D-3D difference in DV indices was greater for PSPT or IMRT. Only three values of the mean 4D-3D DVH change were found to be significantly different (p<0.05) for the cohort. Table 2-4 lists the 3 values found to have mean 4D-3D values that were significantly different between PSPT and IMRT. The increases in mean value of 4D-3D Lung V5 and Heart V5 for the PSPT cohort suggest that protons tend to range deeper than originally calculated with PSPT 3D methods.

The mean change in 4D maximum cord dose was greater for PSPT than IMRT. It should be
noted that the population average of absolute maximum cord dose was significantly lower for PSPT (PSPT = 29.8±18.0 Gy, IMRT = 40.0±4.5 Gy). The 4D PSPT spinal cord dose increase can be attributed to cases where the proton beam ranges extend into cord volumes that were assumed completely spared in the 3D calculation method.

Table 2-4: Of the 24 DVH indices listed in Table 2-3, only three criteria had mean values which were determined to be statistically different. The results demonstrate that the low dose to lung and heart structures, and maximum cord dose increased by a significant, but small amount in PSPT. All other criteria were indistinguishable between proton and photons.

<table>
<thead>
<tr>
<th>4D-3D Mean</th>
<th>Lung V5</th>
<th>Heart V5</th>
<th>Cord 1% Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMRT</td>
<td>+0.4%</td>
<td>-0.6%</td>
<td>-23 cGy</td>
</tr>
<tr>
<td>PSPT</td>
<td>+1.0%</td>
<td>+0.4%</td>
<td>+127 cGy</td>
</tr>
<tr>
<td>p-value</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
</tr>
</tbody>
</table>

A secondary goal of this chapter was to determine if the 4D vs. 3D differences could be predicted by the extent of tumor motion. For each DV index, Pearson correlation coefficients were calculated between the 4D-3D difference and the extent of respiratory motion. An example plot of 4D-3D vs. tumor motion for MLD is shown in Figure 2-28. The Pearson correlation coefficient was found to be significant (p<0.05) for two metrics: the extent of tumor motion was positively correlated to 95% PTV dose coverage and negatively correlated to the heterogeneity index. No significant correlation coefficients were found between any normal tissue DV index and the tumor motion.
Figure 2-28: The difference between 4D and 3D dose plotted against the extent of tumor motion for PSPT (right) and IMRT (left). The value of $\Delta(4D-3D)$ represents the 4D minus 3D MLD.

Figure 2-29: 4D-3D dose vs. tumor motion for PSPT (right) and IMRT (left) for PTV D95 (top) and H.I. (bottom). The Pearson correlation coefficient ($r$) was given along with the 95% confidence interval (CI) for each correlation. A linear regression line was fit to the data to judge if the data follow a linear trend.
Figure 2-30: Important dose-volume criteria for normal tissue structures such as lung, heart, esophagus and spine dose-volume criteria were denoted in the same fashion as Figure 2-28. Pearson correlation coefficients for all normal tissue DV indices were not significant.
2.3.1 Weekly 4D Dose Accumulation Example

The weekly 4D dose was calculated for an example patient with 9 mm of tumor motion. To compute the final accumulated weekly 4D dose, 70 deformations were calculated. For each weekly 4D dose, the plan dose was recalculated 10 times on the 10 phases of the weekly 4DCT. The dose to each phase was deformed to the weekly T50 phase, necessitating the calculation of 9 deformable vector fields per week. The 4D dose during weeks 1-7 for the PSPT plan is shown in Figure 2-31. The weekly 4D doses were deformed to the week 0 T50.

The PSPT accumulated 4D dose over all seven weeks is compared to the week 0 4D dose in Figure 2-32. For IMRT, the calculated dose delivered during weeks 1 through 7 are shown in Figure 2-33. The normal tissue doses are observed to vary more than in the PSPT case. However, the accumulated IMRT dose over all weeks, shown in Figure 2-34, is very consistent with the 4D dose from the original plan. For a patient with a mobile lung tumor, this result has demonstrated that the 4D calculation technique can be used to estimate the dose delivered over all weeks of treatment.
Figure 2-31: Weekly 4D dose for the PSPT plan for the example patient. The normal tissue doses showed variation from week to week, but the lung and tumor target coverage was consistent from week to week for this patient.

Figure 2-32: Accumulated PSPT weekly 4D dose (dotted) was compared to the original PSPT plan 4D dose (solid) on the simulation 4DCT. The overall esophagus, heart and spine dose was increased over the weeks of treatment. The target and lung dose as calculated in the original 4D dose was very close to that of the weekly 4D accumulation.
Figure 2-33: Weekly 4D doses for the IMRT plan for the example patient. In some structures, the normal tissue doses experienced greater dose variation than the PSPT plan for this example patient.

Figure 2-34: Accumulated IMRT weekly 4D dose (dotted) was compared to the original IMRT plan 4D dose (solid) on the simulation 4DCT. The accumulated dose over all weeks was well represented by the 4D as calculated on the simulation week 0 4DCT.
2.4 Discussion

In the results it can be observed that changes due to respiratory motion are present in both proton and photon planning. Neither modality was immune to the effects of respiratory motion on the planned dose. Interestingly, 4D dose assessment showed a slight improvement of PTV coverage compared to 3D dose for both PSPT and IMRT. Regions of high dose were reduced in 4D dose calculation, and dose was increased to under-dosed regions of the tumor target compared to 3D dose calculation methods. This result may be attributed to the hot spots of dose in the 3D calculation were smeared out due to motion of anatomy in the 4D calculation. We found that the effects of respiratory motion on DV indices were comparable between PSPT and IMRT in terms of target coverage for this cohort. The margin formalisms (and smearing radii for protons) used during plan creation were sufficiently large to maintain tumor coverage over all phases of respiration; however, this does not take into account other uncertainties such as interfractional setup and anatomical variations.

Only 3 of the 27 DV indices observed demonstrated a significant difference in the mean values of 4D-3D between PSPT and IMRT cohort. This was contrary to the commonly echoed caution that proton therapy is more sensitive to the anatomical changes during
respiration. The low dose (Lung V5 and Heart V5) DV indices, on average, demonstrated a larger difference 4D-3D change in PSPT. This increase of volumes receiving low dose in proton therapy could signify that the protons range deeper into tissue than currently calculated using 3D dose calculation methods.

For 3 patients with fields directed towards the spinal cord, the PSPT 4D cord maximum dose increased from 3D by more than 5 Gy. Again, these results signify that the PSPT fields typically ranged deeper into the lung than current 3D calculation methods predicted. If possible, most PSPT fields are designed to avoid directions towards the spinal cord. From this study, we confirm that such practice should be continued and encouraged during PSPT field angle selection.

For one patient, this aim demonstrated the potential to calculate 4D dose delivered for each week during the course of radiotherapy. We were limited to one patient for this study due to the large time constraints to recalculate 70 plan doses and perform 70 dose deformations over the seven weeks of treatment. However, automation of the dose calculation and DIR software has the potential to greatly reduce the user’s workload. The results show that the weekly 4D dose delivered may vary in both modalities. However, the accumulated dose over all weeks of treatment was well approximated by the original 4D
dose as calculated on the simulation 4DCT. For this patient, we demonstrated that the 4D dose originally planned was representative of the dose that could be delivered over the entire course of radiotherapy. Our results have assumed volumetric alignment to setup to the GTV, and that the respiratory motion represented on the weekly 4DCT is accurate. For patient treatment, the variation of respiratory motion is a large uncertainty that remains unsolved. We anticipate that this uncertainty is patient-dependent and must be monitored on an individual basis. We feel that results from our single patient show that the 4D dose calculation methods outlined in this chapter can represent the true dose delivered to the patient over the course of treatment.

It should be cautioned in cases where a tumor shrinks or a patient loses weight, there will be increased uncertainty in calculating the deformable vector field. The patient selected for weekly 4D analysis demonstrated minimal tumor shrinkage over the course of treatment. The primary GTV volume was measured to be 63.6 cc during week 0. The CAT software was used to deform the original contour onto the week 7. The resulting primary GTV volume was measured to be 55.3 cc. We caution that our results are for this specific patient only. However, this aim has demonstrated that it is feasible to estimate the dose delivered over the course of treatment using the 4D dose calculation methods outlined above. Weekly
4D dose analysis could be a useful tool in future studies to assess the need for adaptive re-planning efforts for lung cancer patients.

Due to the lack of strong correlations, our results also indicate that the extent of tumor motion does not predict the 4D vs. 3D dose differences. Since we cannot currently predict conditions that respiratory motion would alter the planned dose distribution, this result suggests that use of 4D calculation methods may be appropriate in the analysis of lung cancer patients. It should be noted that the method of 4D dose calculation outlined in this work used only the simulation 4DCT dataset and does not account for any intrafractional or interfractional variation of respiratory motion.

It was observed that the patients with the largest changes in lung DV indices for both the PSPT and IMRT modalities had relatively small (3-6 mm) tumor motion. While these patients’ tumors were relatively immobile, upon further review, it was revealed that the patient diaphragms moved over 10-20 mm during respiration. Therefore, in some patients there exist tissues with respiratory motion larger than the measured tumor motion. This observation suggests that the current definition of tumor motion might be a poor metric to quantify the magnitude of the complex process of the effect of respiration on dose distribution. Since we have yet to determine predictors to estimate the 4D vs. 3D variation,
this suggests that 4D dose calculation might be beneficial to all lung patients.

This project has outlined a method for calculating 4D dose using the simulation 4DCT dataset. Many lung patients currently receive 4DCT as a clinical standard. Thus, the calculation of 4D dose is a possibility for a large group of lung cancer patients. Future work will be directed towards automating the process of 4D dose calculation. Currently, an in-house solution is being developed by the computational scientist group by Dr. Jinzhong Yang. Currently, batch processing of 4DCT dose data is being tested by the author. Such automation of the dose accumulation process will enable future researchers to complete the 4D dose calculations in far less time. The commercial treatment planning systems currently are a bottleneck in the workflow of 4D dose calculation. In this work, the treatment plan was manually copied and recalculated on all ten phases of the 4DCT dataset. The potential to automate the dose calculation would speed the process greatly. Future work will be directed towards automating the 4D dose calculation process. This may require the use of dose calculation tools outside of the Eclipse or Pinnacle TPS. It is our hope to develop clinically useful tools to calculate the effect of respiratory motion on a plan without time consuming demands from the user. Based on the current processing time to calculate dose and accumulate the 4D dose, we estimate an automated system could process 4D dose
calculation for the simulation 4DCT in less than 30 minutes.

2.5 Conclusion

In this chapter, we have calculated the 4D dose for paired PSPT and IMRT treatment plans for 20 lung patients enrolled on a randomized clinical trial. Our results demonstrated that target coverage was maintained in both PSPT and IMRT. Only three of the mean 4D-3D DVH indices (lung V5, heart V5 and spinal cord max) were statistically distinguishable between PSPT and IMRT, which is contrary to the widely held belief that proton therapy was more susceptible to respiratory motion. For all normal tissue DVH indices, no correlation was found between the change in dose due to respiration and the extent of tumor motion. The magnitude of tumor motion was not correlated to the potential dosimetric variation caused by respiratory motion. Therefore, the extent of tumor motion is not a predictor of the effect of respiration on the planned dose distribution.
CHAPTER 3: ESTIMATING THE BENEFIT OF RESPIRATORY GATED MOTION MANAGEMENT IN PROTON AND PHOTON RADIOTHERAPY

Chapter 3 is based on material that was presented at the annual meeting of the American Association of Physicists in Medicine at Indianapolis, IN [Abstract ID: 22114, AAPM Meeting 2013] and Vancouver, Canada [Abstract ID: 14998, AAPM Meeting 2011] by the author of this dissertation.

3.1 Introduction

We have demonstrated in the previous chapter that respiratory motion can affect the planned dose distribution of both passively scattered proton therapy (PSPT) and intensity modulated photon therapy (IMRT) for late stage lung tumors. If a patient demonstrates dosimetric deviations due to respiration, the next step is to effectively and accurately treat the patient. To mitigate or reduce the impact of respiratory motion, this chapter estimated the dosimetric benefits of respiratory motion management to determine whether proton or photon therapy would demonstrate a greater benefit.

3.1.1 Respiratory Gating

In the first chapter, we listed proposed methods of respiratory motion management:
Respiratory gating, breath hold, and tumor tracking. In this chapter, we focused on respiratory gating at the full-exhale position of the free-breathing respiratory cycle. It is possible that patients with compromised lung function due to their disease would not be able to comply with breath hold techniques. Tumor tracking techniques would require additional hardware and introduce additional uncertainty in treatment delivery. Any method of mitigating the respiratory motion with compression devices was deemed unsuitable for consideration in this study. Therefore, respiratory gating during free-breathing was selected as it should allow the most patients to comply.

Gating at full-exhale was chosen for this work because the exhale phase, as previously mentioned, has been considered to be the most stable and repeatable in this phase of the respiratory cycle. Also, it has been reported that for typical patient respiration, a larger amount of the respiratory cycle is spent at positions near full-exhale. Thus, the selection of an end-exhale phase to gate would theoretically allow for a higher duty cycle than any other respiratory phase.

### 3.1.2 Uncertainties in Respiratory Gating

When considering the implication of end-exhale respiratory gating, one of the largest
sources of uncertainty is the non-repeatability in respiratory motion characteristics. Patients’ respiratory patterns can vary in magnitude, period, and reproducibility between the original imaging and treatment delivery. Variation in respiration may occur within a treatment session (intrafraction), such as the patient’s abdominal muscles relaxing on the treatment couch over time. Variations can also occur between fractions (interfraction) such as changes to the lung motion after radiation damage or tumor growth/shrinkage. If a patient demonstrates variable respiratory patterns, audio-visual feedback has been demonstrated to improve reproducibility in respiratory patterns. As the tumor position changes from respiratory cycle to cycle, margin must be added to account for the uncertainty of the target position. Image guidance is key to verifying and monitoring the tumor position during respiration.

Also of importance during respiratory gating is to understand the errors associated when gating the beam off and on according to the patient’s respiratory state. In general, when the patient’s respiratory pattern enters/matches a predetermined level, a signal is sent from the respiratory monitoring device to the treatment machine. Then, depending on modality, the accelerator’s treatment beam is then signaled to turn on the beam to deliver treatment. This communication between devices results in a slight delay between the exact
moment the patient anatomy is within limits and the actual delivery of the radiation dose. When the patient respiratory state falls outside of the predetermined level, any delay when gating the treatment beam off results in small dose delivery uncertainties. The subsequent effect of the beam on/off delay on dose delivery has been studied for both proton\textsuperscript{107} and photon\textsuperscript{105} radiotherapy. During clinical treatment, it is important that such lag times be quantified and accounted for. In order to estimate the gated plan dose, we considered the delay to have negligible impact on the calculated dose.

When delivering therapy during a finite gating window, the patient anatomy may still move while the beam is enabled. Motion during the gated delivery is referred to as residual motion\textsuperscript{149}. This motion will be a fraction of the total respiratory motion, however it must be considered in the formulation of the planning margins\textsuperscript{150}. The extent of the residual motion also is dependent on the type of respiratory gating, length of gate, duty cycle, target position and patient respiratory characteristics.

Most implementations of respiratory gating do not directly observe the tumor motion. Some systems intermittently image the tumor, such as the ExactTrac gating system\textsuperscript{97} (Brainlab, Westchester, IL) and Cyberknife Synchrony Respiratory Tracking System\textsuperscript{151} (Accuray, Sunnyvale, CA). Few reports have described systems that gate by monitoring
implanted fiducials near the tumor using continuous fluoroscopy\textsuperscript{66}. Most internal tumor tracking systems require implanted fiducials to serve as a surrogate for the tumor tissue, however the fiducial implantation process is not without risks\textsuperscript{152}. The most common methods monitor the external respiratory characteristics of the patient. Examples of commercial external patient monitoring systems include the RPM system\textsuperscript{153} (Varian, Palo Alto, CA) and the Align RT system\textsuperscript{154} (Vision RT, London, UK). These methods assume correlation between external and internal motion. However, this assumption of correlation between internal and external anatomy also carries uncertainties\textsuperscript{62, 88, 155}.

Most issues present in non-gated radiotherapy are still present in respiratory gated therapy. Sources of error include, but are not limited to:

- Geometrical variation of the patient anatomy due to weight loss, organ deformation, bowel gas, tissue swelling, etc.
- Tumor growth/shrinkage from time of simulation to treatment, as well as change in tumor size during treatment in response to therapy
- Artifacts on the simulation 4DCT data
- Delineation error in the contours for treatment
- Inaccuracies of the treatment planning system dose calculation and modeling for modality specific hardware

- Daily patient setup uncertainties such as variation in patient positioning, mechanical uncertainties of equipment, transfer of setup error from CT simulator to treatment couch, and mechanical uncertainties in the delivery system

Radiotherapy delivery during target motion can present unique challenges. During modulated treatment delivery, such as IMRT, the changes between modulation (e.g. leaf sequence) and target motion can result in uncertainty in the dose distribution. This effect should be reduced during respiratory gating, however as previously mentioned, residual motion will still be present during gating. Bortfeld et al. reported that the interplay effect between IMRT and residual motion should be negligible during highly fractionated delivery\textsuperscript{77}.

The interplay effect can also appear in scanned beam proton therapy. The use of PSPT avoids this issue by using a scattering system and by delivering multiple Bragg peaks “quasi-simultaneously” to the entire target with a rapidly spinning range modulator wheel. In effect, this is analogous to rapid “repainting” methods proposed for scanned beam proton therapy\textsuperscript{156}.
3.2 Methods and Materials

It was the goal of this chapter to determine if proton or photon radiotherapy would benefit more from respiratory gated techniques. In this chapter, we estimated the benefit of respiratory gating for a patient cohort by creating and comparing a gated treatment plan to the non-gated, nominal plan. The overall benefit of respiratory gating for each modality was then compared to determine if proton therapy demonstrated a larger reduction in normal tissue dose as originally hypothesized.

3.2.1 Patient Selection

The cohort of locally advanced NSCLC lung cancer patients selected for this aim was the same cohort from the randomized clinical lung trial as defined in chapter 2. Table 2-2 summarizes the tumor motion, prescription dose, tumor location, and histology for each patient in this cohort. We defined motion in the same fashion as the previous chapter: the centroid excursion of the GTV from inhale to exhale phases of the simulation 4DCT. For this cohort, prescription dose levels were determined using current clinical standards (60, 66, or 74 Gy) and fraction size was constant at 2 Gy per fraction.
3.2.2 Nominal Planning

For the cohort of patients from the randomized clinical trial, the proton and photon plans were originally designed using non-gated methods. The previous chapter details the creation of the nominal treatment plans in both PSPT and IMRT. The 4D dose as calculated in the previous chapter was considered to be a more accurate representation of dose actually delivered compared to the 3D dose calculation. For comparison to the gated plan, the 4D dose was considered to be the dose delivered to the patient for the non-gated technique.

3.2.3 Gated Planning

In general, our method of free-breathing exhale-gated planning involved designing a gated treatment plan on the T50 dataset following the standard planning formalisms. Our method of estimating the gated plan dose does not explicitly account for effects of intrafractional and interfractional respiratory irregularities. However, the margins added to the plan implicitly account for such variations. The effects of such irregularity are highly patient-specific, but are important to consider in the design of treatment plans.

For each patient in this study, the number of fields and angles from the non-gated plan were maintained when creating the gated plan. It was assumed that the contours on the
T50 represent the patient anatomy during the exhale gated delivery. Using the anatomical structures as delineated on the T50 phase, the gated treatment fields were redesigned following the planning methodology discussed in previous chapter. Essentially, respiratory gating reduced the target size by limiting tumor motion during treatment delivery. Any effects of residual motion during the gating window was considered negligible due to the selection of a narrow gating window (10%).

For each plan, the primary and nodal gross tumor volumes were used to define the gated GTV for the gated plan. The gated CTV was given by a standard 8 mm expansion of the gated GTV. The setup margin required for gated therapy is an important and controversial topic. We decided that it would be a reasonable starting point to assume the same required setup margin (5mm) as in the non-gated techniques.
Figure 3-1: Figure from Nelson, et al demonstrating the necessary margin to completely encompass the CTV and GTV over all weeks of treatment. It can be seen that when considering volumetric alignment (Tumor COV alignment), the required setup margin is the minimum. For gated planning, we considered setup margin for gated therapy delivered with 10% duty cycle to be 5 mm. This figure is reprinted from reference 157 with permission from Elsevier.

Using Figure 3-1, we justified our selection of a 5 mm setup margin. Nelson et al estimated the margin needed to encompass the tumor during gating for various scenarios of image-guided setup. Nelson’s work determined that volumetric alignment was the most accurate method of alignment compared to skin mark, vertebral body, and implanted fiducial alignments. With repeated 4DCT imaging over the course of treatment, the necessary setup margin to cover the CTV was estimated. Nelson reported that for the narrowest duty cycle (10%) with volumetric target alignment, that the mean setup margin would be less than 5
mm. The report concluded with the recommendation that respiratory gating should be considered in conjunction with image guided setup to ensure proper patient alignment. However, by comparing 100% duty cycle to 10-50% duty cycle, it is clear from the figure that gating theoretically reduces margins for all cases.

For this work, we simulated gating with a (minimum) 10% duty cycle. Also, setup margin assumed the use of volumetric imaging to align patient to the tumor center of volume. The MDACC PTC does not currently have the ability to perform volumetric imaging (e.g. cone beam CT). However, results from this study were useful to suggest implementation of volumetric imaging hardware at the MDACC PTC.

### 3.2.4 IMRT Gated Planning

To create the gated IMRT plan for our cohort, it was necessary to alter the plan to treat the gated target volumes. Therefore, it was necessary to re-optimize the field modulation and multileaf collimator subfield shapes for each field in the gated plan. As discussed in the previous chapter, each patient IMRT plan has a set of objective functions used to calculate sub-scores which sum to yield a composite score. The IMRT optimization algorithm attempts to minimize the composite score when selecting beamlet intensities. As an initial
step to re-optimize, the objectives associated with structures in the nominal anatomy delineated on the average CT were substituted with corresponding structures in the end-exhale anatomy. For example, in Figure 3-2, the lung avoidance structures and PTV ring structures used during IMRT optimization were replaced with corresponding volumes created from the T50 image of the patient. After each structure was replaced, IMRT optimization was run for the same number of iterations as in the non-gated plan. An example of the objective functions used is shown in Figure 3-3. All objective weights and constraints were kept constant between the non-gated and gated plan.

Figure 3-2: An example of the structural changes between the gated plan (left) and non-gated plan (right). The IMRT optimization process of the original, non-gated plan included constraints for the PTV (light blue), a 1 cm ring around the PTV (yellow colorwash), a 2 cm ring around the PTV (purple), contralateral lung (green) and ipsilateral lung (red). The structures from the original IMRT optimization were changed to the corresponding volume as delineated on the T50 phase of respiration to simulate IMRT gating at full-exhale.
After the optimizer had completed the specified number of iterations, a final plan dose was calculated in the same fashion as for the non-gated plan. The final dose for the gated plan was normalized to match the target coverage as in the non-gated plan: 95% dose coverage to 95% of the PTV volume.

3.2.5 PSPT Gated Planning

To create the gated PSPT plan, the same methodology was followed as outlined in the PSPT planning section in the previous chapter. Essentially, the only difference was the use of the T50 phase CT and structures as the calculation datasets. The gated CTV was treated the same way as the ITV in non-gated methods for the purposes of creating aperture
blocks, compensators, proximal and distal margins. Each field was assigned beam-specific margins in order to cover the CTV as delineated on the T50 image. Each gated field retained the same weighting factor as in the non-gated PSPT plan. Once all fields were designed, the total dose was normalized to achieve the same target coverage as in the non-gated plan: 95% dose coverage to 95% of the PTV volume.

Figure 3-4: Coronal view of gated (left) and non-gated plan (right) with the gated target outlined in blue, and the non-gated target outlined in red. For comparison, the nominal plan displays both gated and non-gated target volume. By gating at exhale, we reduce the internal target volume margin needed, thus we spare dose to normal tissue regions (arrow) inferior to the target that would have been irradiated during respiratory motion when not using respiratory gating.

3.2.6 Plan Analysis

To estimate the benefit of gating, this chapter compared the gated plan DV indices to those of the non-gated plan. For each non-gated plan, we assumed that the 4D DV indices calculated in the previous chapter were a more accurate representation of non-gated plan dose. Therefore, we compared the gated plan DV indices to the non-gated 4D DV indices calculated in the previous chapter. The dose-volume parameters analyzed were the same as
the normal tissue indices listed in Table 2-3. The dosimetric benefit of gating was determined for each DV index by subtracting the gated from the non-gated value. In this definition, a positive value denotes an increase in the DV index when gating and a negative value denotes a decrease in the DV index when gating.

Our comparison for this study was to determine if proton or photon gating demonstrates a larger dosimetric reduction in normal tissue DV indices. To determine if PSPT or IMRT showed greater reduction in DV indices for the cohort, we compared the mean change in DV indices for the cohort between the gated and non-gated plans. Paired t-tests were used to calculate if one modality demonstrated a statistically significant difference in the mean benefit of gating across the cohort.

3.2.7 Gated Dose Accumulation Example

The process of gated planning made many idealized assumptions. In terms of respiratory motion, our method has assumed the constancy of the patient respiratory cycle and repeatable positioning of the target during the gated beam delivery. To validate our estimation of the gated dose, it would be useful to estimate the variation of gated plan dose over the course of radiotherapy.
In the previous chapter, we demonstrated an example of weekly dose accumulation for proton and photon therapy. For the estimation of the gated accumulated dose, we examine the same patient as evaluated in the last chapter. This patient was treated for seven weeks with 37 fractions. As in the previous chapter, this patient received weekly 4DCT imaging and we assumed volumetric alignment to setup to the GTV target for each image. The workflow to estimate the gated accumulated dose over seven weeks of treatment is shown in Figure 3-5. The weekly T50 image of the patient at exhale was used to estimate the dose delivered by the gated plan during each week of treatment. During weekly 4DCT imaging sessions, the patient may be setup on the couch in a different spatial location. Therefore, we needed to align the weekly isocenter to the original planned isocenter location. To calculate the shift for our example patient, the CAT software was used to rigidly align the primary GTV to the corresponding tumor volume on the weeks 1 through 7 T50 image. On the weekly images, the planned isocenter was shifted from the original location in the treatment plan according to the rigid alignment results. The gated plan fields were recreated at this weekly isocenter. The plan dose was recalculated for each weekly T50 image. The resulting recalculated doses were considered to be the dose delivered during each week of the gated treatment.
After the weekly gated dose was calculated, we wanted to compare the accumulated
dose over weeks 1-7 to the original (week 0) gated plan dose. The CAT software was used to
deform the weekly dose back to the simulation T50 image. The resulting accumulated dose
over the seven weeks of treatment was calculated. The accumulated dose was compared to
the originally calculated dose to estimate the robustness of the gated plan to weekly changes
in anatomy at the exhale phase of respiration.
Figure 3-5: Proposed workflow to estimate the accumulated dose across all weeks of treatment for the gated plan. The CAT software was used to rigidly align the isocenter in the gated plan to the weekly T50 image. The gated plan isocenter was shifted to the new weekly isocenter, and dose was calculated on the weekly T50 image. The recalculated dose was then exported to the CAT software. All seven weekly doses were deformed to the original week 0 T50 image. The doses were weighted and accumulated for weeks 1-7. The accumulated gated dose was exported back to the TPS to compare against the original gated dose.
3.3 Results

For the cohort of 20 patients, the gated plan dose has been calculated for both PSPT and IMRT. In general, it was found that both PSPT and IMRT gating reduced the normal tissue DV index values for at least three-fourths of the plans, depending on the index. The values of the MLD, MED, and MHD for the nominal and gated plan are given in Figure 3-6. In Figure 3-7, the mean lung, esophagus and heart dose changes between the gated and nominal plan are displayed. Respiratory gating for proton therapy reduced the MLD for 19/20 plans, MED for 16/20 plans, and MHD for 19/20 plans. Respiratory gating for photon therapy reduced the MLD for 17/20 plans, MED for 16/20 plans, and 18/20 patients. In Table 3-1, a paired t-test determined that respiratory gating showed a significantly larger mean benefit for PSPT than IMRT in terms of mean lung and esophagus dose. The average benefit of gating in terms of mean heart dose was not statistically different between the two modalities.
Figure 3-6: “Before and after” plot of DVH values for 20 PSPT (red, left) and IMRT (blue, right) for the nominal and gated plan mean lung dose (top), mean esophageal dose (middle) and mean heart dose (bottom).
Figure 3-7: Scattered dot plots showing the change in mean structural doses (ΔDose) of gated minus nominal plan. The change between gated and nominal plan is plotted for mean lung dose (MLD), mean esophagus dose (MED) and mean heart dose (MHD). The mean value for the benefit of gating for each DV index over the cohort of 20 patients is displayed as black line.

Table 3-1: Mean change in MLD, MED and MHD for the cohort of 20 patients. The mean and standard error of the mean are given for both modalities. A paired t-test was used to determine if the mean was significantly different between the two modalities. The MLD and MED were improved by ~2 Gray and ~1 Gray for PSPT and IMRT, respectively, in the gated plan.

<table>
<thead>
<tr>
<th>Index</th>
<th>PSPT [cGy]</th>
<th>IMRT [cGy]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLD</td>
<td>-203±25</td>
<td>-101±27</td>
<td>0.001</td>
</tr>
<tr>
<td>MED</td>
<td>-196±48</td>
<td>-98±28</td>
<td>0.04</td>
</tr>
<tr>
<td>MHD</td>
<td>-191±37</td>
<td>-191±57</td>
<td>0.41</td>
</tr>
</tbody>
</table>
Figure 3-8: A scattered-dot plot showing the benefit of respiratory gating for the PSPT (red, left) and IMRT (blue, right) plans in terms of the gated reduction in lung DV indices. The values are given in terms of the gated minus nominal DV index. A negative value means that gating reduced the DV index. The black line denotes the mean change in each DV index for the plan cohort. For 90+ percent of the PSPT plans, lung DV values improved with respiratory gating.

Table 3-2: The mean change in important lung DV indices between the gated and nominal plans is shown below. For the cohort of 20 patients, respiratory gating reduced lung DVH values on average for both modalities. However, PSPT gating demonstrated a larger mean benefit in terms of lung DV index reduction for the cohort compared to IMRT gating.

<table>
<thead>
<tr>
<th>ΔDVH Index</th>
<th>PSPT [%]</th>
<th>IMRT [%]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung V5</td>
<td>-3.9%</td>
<td>-1.1%</td>
<td>0.002</td>
</tr>
<tr>
<td>Lung V10</td>
<td>-3.4%</td>
<td>-1.3%</td>
<td>0.024</td>
</tr>
<tr>
<td>Lung V20</td>
<td>-3.1%</td>
<td>-1.2%</td>
<td>0.009</td>
</tr>
<tr>
<td>Lung V30</td>
<td>-3.0%</td>
<td>-1.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lung V40</td>
<td>-2.7%</td>
<td>-1.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lung V50</td>
<td>-2.4%</td>
<td>-1.3%</td>
<td>0.002</td>
</tr>
<tr>
<td>Lung V60</td>
<td>-2.1%</td>
<td>-1.7%</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Figure 3-9: A scattered-dot plot showing the benefit of respiratory gating for the PSPT (left) and IMRT (right) plans in terms of the reduction in esophagus dose-volume indices.

Table 3-3: The mean change in important esophagus DV index between the gated plan and nominal plan is shown below. For the 20 patient cohort, the simulation of respiratory gating reduced esophagus DVH values on average for both modalities. PSPT gating demonstrated a significantly larger mean reduction for intermediate esophagus DVH values (Eso V40, V50 and V55). For other DV indices, there was no statistical difference in the mean benefit of gating between PSPT and IMRT.

<table>
<thead>
<tr>
<th>ΔDVH Index</th>
<th>PSPT [%]</th>
<th>IMRT [%]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eso V20</td>
<td>-3.4%</td>
<td>-2.2%</td>
<td>0.297</td>
</tr>
<tr>
<td>Eso V30</td>
<td>-3.5%</td>
<td>-2.0%</td>
<td>0.165</td>
</tr>
<tr>
<td>Eso V40</td>
<td>-3.4%</td>
<td>-1.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Eso V50</td>
<td>-2.7%</td>
<td>-0.6%</td>
<td>0.002</td>
</tr>
<tr>
<td>Eso V55</td>
<td>-2.0%</td>
<td>-0.2%</td>
<td>0.027</td>
</tr>
<tr>
<td>Eso V60</td>
<td>-1.7%</td>
<td>-1.1%</td>
<td>0.063</td>
</tr>
<tr>
<td>Eso V65</td>
<td>-0.5%</td>
<td>-1.0%</td>
<td>0.746</td>
</tr>
</tbody>
</table>
Figure 3-10: A scattered-dot plot showing the benefit of respiratory gating for the PSPT (left) and IMRT (right) plans in terms of the reduction in heart dose-volume indices.

Table 3-4: The mean change in important heart DV index between the gated and nominal plan is shown below. For the 20 patient cohort, the simulation of respiratory gating reduced heart DV indices on average for both modalities. There was no statistical difference between the mean PSPT and IMRT gated reduction for any heart DV index.

<table>
<thead>
<tr>
<th>∆DVH Index</th>
<th>PSPT [%]</th>
<th>IMRT [%]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart V5</td>
<td>-4.9%</td>
<td>-5.8%</td>
<td>0.613</td>
</tr>
<tr>
<td>Heart V30</td>
<td>-2.8%</td>
<td>-2.9%</td>
<td>0.868</td>
</tr>
<tr>
<td>Heart V45</td>
<td>-1.9%</td>
<td>-2.1%</td>
<td>0.670</td>
</tr>
<tr>
<td>Heart V60</td>
<td>-1.2%</td>
<td>-1.1%</td>
<td>0.623</td>
</tr>
</tbody>
</table>
Figure 3-11: Plot of nominal and gated plan maximum to 1% of cord volume (Cord 1%). In general, IMRT spinal cord maximum dose was more consistent over the patient plans. Depending on the tumor location, proton therapy varied more than for photons. In some plans, gating demonstrated an increase in the cord dose value; however this can be attributed to the target proximity to the cord and dosimetrists’ manual modifications in the aperture shape for the nominal plan that was not duplicated in the gated plan.

Figure 3-12: A scattered-dot plot showing the benefit of respiratory gating for the PSPT (left) and IMRT (right) plans in terms of the reduction in maximum cord dose (Cord 1%). While the variation in cord dose was greater in proton therapy, a paired t-test found the mean between PSPT and IMRT to be indistinguishable (p = 0.8).
Important ΔDV indices are reported in the preceding plots for lung, esophagus, and heart. Each plot shows the change between gated and nominal plan for a variety of DV indices. A negative value represents an estimated reduction in dose with respiratory gating, while a positive value means that gating increased the DV index.

One of the most important organs at risk for our patient cohort was the normal lung. Figure 3-8 demonstrates the change in lung DV indices between the gated and nominal plan. The mean benefit of gating was taken to be the average benefit of gating in terms of DV index reduction (gating – nominal) over all 20 plans. Table 3-2 displays the mean benefit of gating over the 20 plan cohort for PSPT and IMRT. For all lung DV indices observed, a paired t-test calculated that the mean dose reduction during respiratory gating was statistically greater for PSPT than for IMRT.

Figure 3-9 shows the esophagus DV index differences when gating the plan cohort for both PSPT and IMRT. The mean benefit of gating is summarized in Table 3-3 for esophagus V20 through V65. It was calculated that for low (V20, V30) and high doses (V60, 65), the mean benefit of gating was indistinguishable. Only at intermediate doses (V40, V50, and V55) was the mean benefit of gating between PSPT and IMRT distinguishable by a paired t-test.
For the heart DV indices, PSPT and IMRT gating demonstrated a benefit in a majority of cases, as shown in Figure 3-10. However, the mean benefit of gating was not distinguishable between the two modalities in terms of any heart DVH indices. In Figure 3-11 and Figure 3-12, it was observed that the maximum spinal cord dose varied more in proton therapy. In terms of the maximum spinal cord dose, a paired t-test showed that the mean benefit of gating was statistically indistinguishable between PSPT and IMRT.

3.3.1 Gated Dose Accumulation Example

For a sample patient, the weekly dose delivered by the gated plan was estimated using the weekly repeat 4DCT imaging. The calculated doses delivered during weeks 1-7 were deformed back to the simulation week T50 image. The structures as delineated on the simulation CT were used to calculate DVH curves for each week of treatment. Dose volume histogram curves created from the weekly gated plan dose delivered each week is shown in Figure 3-13 for PSPT and Figure 3-14 for IMRT.

The weekly doses deformed to the simulation T50 image were weighted by 1/7th and summed to estimate the accumulated dose over the seven weeks of treatment. The final accumulated PSPT and IMRT dose was exported back to the treatment planning system for
comparison to the original gated plan dose. The estimate of accumulated dose delivered over
the multiple weeks of treatment is shown in Figure 3-15 for PSPT and Figure 3-16 for
IMRT.

From our estimate of the weekly accumulated dose using volumetric setup to align to
the tumor target, the originally planned and weekly accumulated doses matched closely for
PSPT and IMRT. Target coverage was maintained in both PSPT and IMRT over multiple
weeks of treatment. Small deviations were noted between planned dose and weekly
accumulated dose to normal tissues, but no normal tissue constraints were violated. From
this example patient, we can infer that the estimation of the gated plan dose was a reasonable
approximation to the delivered dose accumulated over multiple weeks of treatment.
However, these results may not be generalizable to all patients.
Figure 3-13: Weekly estimate of dose delivered with the gated PSPT plan. The weekly variation in the PTV, CTV, and total lung volume was relatively low. Larger variations were observed in the esophagus, and heart. However, no weekly structural dose violated normal tissue constraints.

Figure 3-14: Weekly estimate of dose delivered with the gated IMRT plan. The weekly variation in the PTV, CTV, and total lung volume was relatively low. Larger variations were observed in the spinal cord, esophagus, and heart. However, no weekly structural dose violated normal tissue constraints.
Figure 3-15: Comparison of original PSPT gated plan dose (solid line) and PSPT gated plan dose accumulated over seven weeks of radiotherapy (dotted line). The weekly accumulated dose matches closely with the original plan DVH, especially for the lung and tumor target. The heart displays a modest increase in dose during treatment, but is still within tolerance criteria.

Figure 3-16: Comparison of original IMRT gated plan dose (solid line) and IMRT gated plan dose accumulated over seven weeks of radiotherapy (dotted line). The weekly accumulated dose matches closely with the original plan DVH, especially for the lung and tumor target. The accumulated esophagus and heart doses display small variations from the planned dose.
3.4 Discussion

This chapter has estimated the benefit of gating at end-exhale for both proton and photon lung radiotherapy. For a majority of patients, our estimated benefit of respiratory gating showed a decrease in normal tissue dose relative to the nominal, non-gated plan dose. The results demonstrate that the benefit varies from patient to patient, but on average, respiratory gating reduced the planned dose to normal tissues. However, the goal of this chapter was to determine if proton or photon therapy demonstrated a greater benefit from respiratory gating.

The results demonstrate that respiratory gating significantly reduced the lung DV indices for PSPT by a larger amount compared to IMRT. Also, intermediate esophageal dose (V40-V55) was reduced by a larger amount during PSPT gating. The remainder of heart and esophagus DV criteria was improved with respiratory gating, but the average benefit of gating was statistically indistinguishable between PSPT and IMRT.

We have estimated the benefit of respiratory gating based on several idealizing assumptions. This work assumed that patient respiratory variations were negligible; however, this is a simplification. The variability of the patient anatomy during the gate is a complex and patient-specific issue that needs to be investigated for any patient considered
for respiratory gating techniques. By making these same assumptions in creating the gated PSPT and IMRT plan, these assumptions should affect both modalities equally.

In some cases, respiratory gating did not demonstrate a benefit to the patient. This could be attributed to several factors, depending on the patient. Separation between the target and organ-at-risk may be reduced during exhale. Also, changes in structure size may affect the calculated DV index. For example, if the lung volume decreases during exhale but the volume receiving dose is constant, the resulting DV indices will be increased. Also, if a structural volume such as the spinal cord receives too much dose, a dosimetrist may alter the margins. To maintain consistency in plan design, such alterations were not done during the gated planning; it can be difficult to detect these manual changes in the original, non-gated plan. The instances of gating with increased cord maximum dose can be attributed to manual aperture changes when creating the original treatment plan. In these scenarios, it is possible for a structure to have received increased dose during gating at exhale compared to non-gated delivery during free-breathing.

This work has only estimated the benefit of respiratory gating. The actual dose delivered to the patient over a series of respiratory cycles over multiple fractions is a much more complex issue and is beyond the scope of this work. For one example patient, the dose
delivered by the gated plan was recalculated using weekly imaging over the seven weeks of
treatment. The variation of estimated weekly dose was found to be reasonably low. The
accumulated dose over all weeks of treatment was found to be very near that of the original
plan dose. Target coverage was maintained over the course of therapy for this patient. From
the example case, this work assumed that the initial estimation of gating could be reasonably
approximate the dose delivered over multiple fractions of a gated plan for both PSPT and
IMRT.

This chapter assumed the setup margins for gated therapy to be 5 mm. Our results
suggest that PSPT and IMRT gating may demonstrate a benefit for a majority of locally
advanced NSCLC cancer patients if the required margins to account for setup uncertainty
and intra/interfractional respiratory variations are 5 mm or less. Further investigation is
required to determine the necessary margins to account for all uncertainties for gated therapy
in either modality.

We have shown that protons, compared to photons, could achieve a greater dosimetric
advantage through respiratory gating techniques for the treatment of locally advanced
NSCLC patients. However, to realize the estimated benefit of gated therapy, it is important
to understand, quantify and manage all of the uncertainties that arise in gated radiotherapy.
The next chapter focuses on predicting the estimated benefit of gated therapy in order to determine when respiratory gating techniques can improve a patient’s treatment plan.

3.5 Conclusion

In this work, we have demonstrated that respiratory gating at end-exhale showed a benefit in terms of normal tissue dose reduction for a majority of proton and photon treatment plans. On average, respiratory gating lowered the dose for lung, heart and esophagus for both modalities as compared to non-gated techniques. On average, PSPT gated therapy demonstrated a statistically greater reduction for all lung DV indices than IMRT. If the variations of respiratory motion and setup uncertainties are properly managed, this work has demonstrated that proton therapy, compared to photon therapy, can potentially achieve larger benefits from respiratory gated motion management.
CHAPTER 4: DETERMINING THE THRESHOLD OF TUMOR MOTION

NECESSITATING RESPIRATORY GATING FOR PROTON AND PHOTON RADIOTHERAPY

Chapter 4 is based on material that was presented at the annual meeting of the American Association of Physicists in Medicine at Indianapolis, IN [Abstract ID: 20913, AAPM Meeting 2013] by the author of this dissertation.

4.1 Introduction

In previous chapters, the benefit of respiratory gating in terms of normal tissue dose reduction was compared between proton and photon therapy. We demonstrated that respiratory gating produced a reduction in dose to normal tissues for a large majority of cohort patients. However, some treatment plans had an increase of normal tissue dose-volume indices during respiratory gating. The results demonstrated variations in the benefit of gating across the patient cohort for both PSPT and IMRT.

There are additional issues to consider before treating with respiratory gated methods. The efficacy of respiratory gating techniques must be justified before respiratory gating can be implemented clinically\textsuperscript{158}. Proper application of respiratory gating requires additional
staff demands on the physicians, physicists, and the therapist staff. The delivery of respiratory gated therapy can result in elongated treatment time. Fox et al. reported that free-breathing gated photon therapy treatment time was, on average, 5.5 times greater than non-gated therapy. Tsunashima et al. estimated that during respiratory gating of PSPT using protons accelerated by a synchrotron, one could expect a factor of 2-5 increase in the overall treatment time. This may mean that PSPT gating is comparable, or even more efficient, in terms of treatment time elongation when compared to photon gating. Any increases in treatment time, such as gating, leads to decreased patient throughput. Decreases in patient throughput may be an issue for proton therapy centers as operating costs can be more expensive than for photon therapy. All of these factors should be considered along with the potential normal tissue dose reduction possible when determining if respiratory gating is appropriate. In short, respiratory gating may not be necessary or advantageous for all lung patients.

Therefore, it is important to determine for each patient if or when the normal tissue dose benefit of gating outweighs the potential challenges of respiratory gating. Historically, the extent of tumor motion has been associated with the need for respiratory motion management in proton and photon therapy. Most published reports of respiratory
motion management contain only large (>10 mm) motion patients\textsuperscript{92, 93, 162}, which do not represent the general population of patients with lung cancer\textsuperscript{74}. An expert task group has suggested that some form of respiratory motion management be considered for tumor motion above 5 mm\textsuperscript{63}. However, the recommendation of 5 mm was not evidence-based and was made only for photon therapy. To date, no published data has demonstrated evidence of a threshold, or cutoff criterion, of respiratory motion above which respiratory motion management should be considered. The goal of this chapter was to predict the benefit of respiratory gating based on tumor motion metrics and to determine if there is a threshold of tumor motion above which PSPT or IMRT gating should be considered.

4.2 Methods and Materials

In the previous chapter, we have outlined a method of gated planning in order to estimate the benefit of gated proton and photon radiotherapy. Our methodology involved creating a plan on the full-exhale phase of the simulation 4DCT. The gated plan assumed setup margins were equal to that of the non-gated, nominal plan. The definition of tumor motion for this work was the same as in the previous chapter: centroid displacement of the gross tumor volume between inhale and exhale phase of the simulation 4DCT.
To predict the benefit of gating, this work first determined the correlation between respiratory tumor motion and the computed normal tissue dose reduction in gated therapy. The Pearson correlation coefficient was calculated to find the relationship between two quantities\textsuperscript{163}. Specifically, the benefit of PSPT or IMRT gating, defined as the dose difference between the gated plan and the nominal plan, was correlated against the extent of tumor motion. For each normal tissue dose-volume index listed in Table 2-3, Pearson correlation coefficients were calculated between the estimated benefit of gating and the tumor motion.

It would be advantageous to determine if a metric was not only highly correlated to the benefit of gating, but that the metric could be used to predict the benefit. Linear regression analysis was performed to determine a linear fit could model the relationship between the tumor motion and the benefit of gating. The coefficient of determination, denoted by $R^2$, indicates how well data points fit a line or curve\textsuperscript{163}. The $R^2$ value was calculated for each linear fit determined by a linear regression of the benefit of gating plotted against the extent of tumor motion. In the case of linear regression, $R^2$ is the squared value of correlation between the value of outcome (gated benefit) and the values of the predictive variable (tumor motion).
4.2.1 Investigation of Additional Metrics

Along with tumor motion, this chapter explored additional metrics to correlate with the benefit of respiratory gated therapy. During treatment planning using 4DCT datasets, the lung volume can be delineated at the full-inhale (T0) and full-exhale (T50) phases of respiration. In chapter 2, some patients with small tumor motion exhibited large diaphragm motions. Even if the tumor was relatively immobile, the lung tissues could still be moving considerably during respiration. As a surrogate for lung motion, we propose measuring the ratio of the lung volume change between inhale and exhale phases of respiration. This value should yield a simple metric to quantify how much the anatomy in the lung expands during respiration.

Another metric that may predict the benefit of gating is the overall tumor size. The attending physician delineated, for each patient, the total GTV size as observed on the T50 phase (GTV_T50) and the volume of excursion of the GTV during respiratory motion (iGTV). Correlation coefficients were calculated between the benefit of gating and the tumor size (GTV_T50) to determine if the overall tumor size can predict the benefit of respiratory gating.

It is also possible that the ratio of the target volumes between the nominal and gated
plans could serve as a predictor for the benefit of respiratory gating. One proposed metric was to determine the ratio of the volume encompassing the tumor motion, iGTV, to the size of the tumor, GTV_T50. Also, the volume of the PTV on the nominal plan was measured and compared with the volume of the PTV in the gated plan (PTV_T50). Ratios were calculated of the iGTV to GTV_T50 and also PTV to PTV_T50. These ratios represent a potential metric to describe the relative target volume differences between the gated and the nominal treatment.

All of these structure volumes can be measured from the 4DCT simulation full-exhale and full-inhale phase datasets. This work also calculated the Pearson correlation coefficients between the benefit of respiratory gating and the additional metrics described in this section. A linear regression fit and $R^2$ value was calculated between the benefit of gating and motion metrics for both PSPT and IMRT.

### 4.3 Results

#### 4.3.1 PSPT Gating and Tumor Motion

The difference of the gated minus nominal MLD is plotted against the tumor motion for PSPT in Figure 4-1. The PSPT change in mean lung dose ($\Delta$MLD) during gating was
correlated against the extent of tumor motion. It was calculated to not to have a statistically significant (p = 0.46) Pearson r value of -0.18 with a 95% confidence interval of [-0.58, 0.28]. A linear regression fit to the data is shown; however the R² value of 0.03 shows a poor fit to the data. The value of R² can be interpreted as the proportion of response variation (e.g. benefit of gating) “explained” by the regressor (e.g. tumor motion) in the model. Thus, R² = 1 indicates that the predictor variable explains all variability in the predicted variable. Since the R² value is nearly zero, no linear relationship was found. The result shows that the change in MLD between gated and nominal PSPT could not be explained by the range of tumor motion in the patient cohort.

In Figure 4-2, the gated reduction in mean heart dose (MHD) and mean esophagus dose (MED) versus tumor motion are shown in the same fashion as the previous graph. The same trends as seen for MLD were continued: No significant correlation (p = 0.42 and 0.43, respectively) was found between the gated dose differences for MHD or MED and tumor motion. Linear regression fit to the change in MHD and MED and tumor motion yielded a poor fit (R² = 0.04 and 0.03, respectively).

Clinically important lung dose-volume (DV) metrics were examined in Figure 4-3. No significant correlations were found and any linear regression fit to the data yielded poor fits
to the lung DV data. For important esophagus (Eso), heart and spinal cord (Spine) DV indices in Figure 4-4, no significant correlation coefficients were found between the benefit of respiratory gating and the tumor motion for any proton therapy plan. Once again, linear regression fit of the benefit of gating versus tumor motion yielded poor fits for every normal tissue DV index analyzed.

Figure 4-1: The change in MLD between the nominal and gated plan (gated-nominal) was plotted against the extent of tumor motion for PSPT. The Pearson correlation coefficient was not significant (r = -0.17, p = 0.46), and a linear fit (black line) to the data demonstrated a poor fit with the data ($R^2 = 0.03$).
The change in mean esophagus dose (MED) and mean heart dose (MHD) between gating and nominal methods was plotted against the extent of tumor motion for PSPT. No significant Pearson correlation coefficients were found, and linear regression fits to the data yielded poor fits to the line ($R^2<0.04$).

Figure 4-2: The change in mean esophagus dose (MED) and mean heart dose (MHD) between gating and nominal methods was plotted against the extent of tumor motion for PSPT. No significant Pearson correlation coefficients were found, and linear regression fits to the data yielded poor fits to the line ($R^2<0.04$).
Figure 4-3: For PSPT, the change in lung dose-volume indices from Lung V5 to V50 were plotted versus tumor motion. No significant Pearson correlation coefficients were found for any indices and a linear regression to the data (black line) demonstrated a poor fit to the data, the highest R squared value was 0.20 for Lung V50 data.
Figure 4-4: Additional important esophagus, heart and spinal cord DV index changes between gating and nominal methods plotted against the extent of tumor motion. No significant correlation Pearson correlation coefficients were found for any DV index. Linear regression fits to the data were also observed to be very poor fits to the data.
4.3.2 IMRT Gating and Tumor Motion

For IMRT, the gated dose differences were plotted against tumor motion in the same fashion as for the PSPT plans in the previous section. Shown in Figure 4-5, the IMRT ∆MLD motion was found not to have statistical significant (p = 0.11) correlation (r = -0.36, CI = [-0.69, 0.09]) to tumor motion. A linear regression line fit to this data calculated a $R^2$ value of 0.13. For other structural mean doses, such as MED and MHD, the data was poorly fit with a linear regression and no significant correlations were found. It can be seen in Figure 4-6 that a linear fit to the data was poor. The tumor motion has no significant correlation with the benefit of respiratory gating in terms of MHD and MED plans for the patient cohort. For these observed lung, esophagus and heart ∆DV indices, no significant correlation was found between the benefit of gating and the tumor motion.
Figure 4-5: The change in IMRT MLD between the nominal and gated plan (gated-nominal) was plotted against tumor motion for PSPT. The Pearson correlation coefficient was not significant ($r = -0.37, p = 0.11$), and a linear fit to the data demonstrated a poor fit with the data ($R^2 = 0.13$).

Figure 4-6: The difference in mean esophagus dose (MED) and mean heart dose (MHD) was plotted against tumor motion for IMRT. No significant Pearson correlation coefficient was found, and a linear regression to the data demonstrated very weak fit of $R^2$ less than 0.01 for both MED and MHD.
Figure 4-7: For IMRT, the change in gated minus nominal lung dose-volume indices from Lung V5 to V50 were plotted against tumor motion. No significant Pearson correlation coefficients were found for any indices and a linear regression to the data (black line) showed a poor fit to the data, the highest R squared value was 0.15 for Lung V10 data.
Figure 4-8: Additional important esophagus, heart and spinal cord DV metric changes between gating and nominal methods plotted against the extent of tumor motion. No significant correlation Pearson correlation coefficients were found for any DV index. Linear regression fits to the data were also observed to be very poor fits to the data.
In Figure 4-7, no correlations were found between the tumor motion and the benefit of IMRT gating in terms of the lung DV indices. A linear fit to the benefit of gating for each ∆DV had a poor linear relationship with tumor motion: $R^2 < 0.15$ for all lung indices. All regression line slopes were not significantly different from zero, so we cannot detect any relationship between the benefit of IMRT gating and the extent of tumor motion. The results are similar for all esophagus, heart and spine DV indices as shown in Figure 4-8. Linear regression fits to the data were still poor ($R^2 \leq 0.21$). Only one DV index, Esophagus V40, demonstrated a linear fit to tumor motion that had significantly non-zero slope. However, if we removed an outlier for the esophagus V40 (patient #2, -6.8%), the significance of the slope disappears.

For IMRT, as with PSPT, results have shown that the magnitude of tumor motion is not related to the benefit of respiratory gating as observed by lack of significant correlation. The lack of strong $R^2$ values indicates the benefit of IMRT respiratory gating could not be predicted by a linear model based on the extent of tumor motion.

4.3.3 Additional Metrics

For each patient in this study, the T0 and T50 lung volumes were recorded from the TPS
for the each patient plan. Table 4-1 lists the extent of tumor motion (“Motion”) and the TPS measured volumes of the T0 and T50 total lung contours. The tumor motion is given in millimeters and the change in lung volume between inhale and exhale is given in cubic centimeters. The volumetric change in lung between exhale and inhale (“ΔVolume”) expressed as a percentage of the exhale lung volume (“Volume [%]”) is also given for the cohort.

Table 4-1: The total lung volume was measured in the T0 and T50 phases of the simulation 4DCT. The lung volume difference in between inhale and exhale is shown in “ΔVolume” and the difference is expressed as a percentage of the T50 volume in the last column “Volume [%]”. For reference, the tumor motion between exhale and inhale is given in the “Motion [mm]” column.

<table>
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<th>Patient #</th>
<th>Motion [mm]</th>
<th>T50 [cm³]</th>
<th>T0 [cm³]</th>
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<th>Volume [%]</th>
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As an example, in Figure 4-9, the MLD reduction of gating is shown plotted against the volumetric reduction of lung from inhale to exhale. The use of this lung volume metric was not significantly correlated to the any ∆DV indices during respiratory gating. We might have expected a patient with a large variation in lung volume (-53%) between inhale and exhale to demonstrate a larger benefit of gating, however this was not the case. To the contrary, this was one of the patients with smaller respiratory motion (6 mm) and with normal tissue DV metrics that actually increased during respiratory gating. For the remainder of the cohort, the change in lung volume metric shows no trends that could be used to predict the estimated benefit of gating. The proposed metric of the T50 vs. T0 volumetric lung variation was not useful to predict the benefit of respiratory gating.
Table 4-2 Comparison of the iGTV and PTV used to design the nominal plan and GTV_T50 and PTV_T50 as used to design the gated plan. All volumes are given in cubic centimeters.

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In Table 4-2, the GTV_T50 and iGTV size measured by the TPS in cubic centimeters are given along with the ratio of iGTV/ GTV_T50 volumes. Similarly, the volumes of the PTV and PTV_T50 are given along with a ratio of PTV/PTV_T50. The benefit of PSPT and IMRT gating in terms of MLD was plotted against the GTV size (Figure 4-10), the iGTV/GTV_T50 ratio (Figure 4-11) and PTV/PTV_T50 ratio (Figure 4-12). The benefit of gating in terms of MLD was not significantly correlated to any of the three metrics. A linear fit to each target size metric provided a very poor fit of $R^2<0.1$. All other normal tissue DV indices had no significant correlation to the additional metrics. Therefore, we have omitted
displaying data for any additional DV indices beyond MLD due to lack of correlations. These additional metrics failed to provide any useful predictors to determine when respiratory gating might benefit a patient.

Figure 4-10: The MLD benefit of respiratory gating is plotted against the size of the GTV for the patient cohort for protons (left) and photons (right). The results show that the patient with the largest GTV (474 cc) did not benefit from gating in either modality. While a trend might be visually observed, the benefit of gating in both modalities was not significantly correlated with the GTV size. Linear regression fit to the data provided a poor fit to the data in both modalities ($R^2 < 0.1$). Results are similar for the iGTV size data as well (not shown).

Figure 4-11: The MLD benefit of respiratory gating is plotted against the ratio of iGTV to GTV_T50 for the patient cohort for protons (left) and photons (right). Neither modality had significant Pearson correlation coefficients. Linear regression analysis showed a poor linear fit ($R^2 < 0.1$) to the data for all other DV indices as well.
Figure 4-12: The MLD reduction during respiratory gating is plotted against the ratio of PTV to PTV_T50 for the patient cohort for protons (left) and photons (right). Neither PSPT (left) nor IMRT (right) demonstrate significant Pearson correlation coefficients or strong linear regression fit ($R^2 < 0.1$) to the data for all other DV indices as well.

4.4 Discussion

In this chapter, we have demonstrated that the benefit of respiratory gating, as estimated in the previous chapter, was not correlated to the extent of tumor motion. This was an unexpected result as we initially expected that the benefit of respiratory gating would correspond to the tumor motion. As respiratory motion increased in the cohort, the benefit of gating showed large variation. A linear regression of the respiratory motion to the benefit of gating showed a poor fit to the data for all observed DV indices. With 20 patients, we have $\geq 80\%$ power to detect $r \geq 0.6$ as different from zero with significance level of 5%. Our results were not able to predict the benefit of respiratory gating using tumor motion in either modality, thus we are not able to determine if a threshold of tumor motion exists to indicate
gated therapy for either modality.

We proposed a metric to quantify the lung volume change between inhale and exhale. This change in lung volume metric was of no value to predict the benefit of respiratory gating. Next, we calculated ratios of target sizes of the non-gated plan to the gated plan. As with tumor motion, the ratios of non-gated vs. gated target sizes provided no significant correlations to the benefit of respiratory gating. The results indicated that the use of these lung and tumor volume metrics provided little useful information in terms of predicting the benefit of respiratory gating.

It is evident from our results that considering the tumor motion alone is not the best method to predict the impact of gating on the complex process of respiration. We investigated other metrics to quantify respiratory motion, but these metrics also were related to target volume motion (PTV or GTV ratio), or simplistic quantifications of the lung volume changes (Lung T50 vs. T0 volume). We believe that all of these factors may be related to the benefit of respiratory gating in some way, however, we have yet to find a predictive metric that incorporates the many complex variables associated with respiratory motion. Multiple linear regression analysis was attempted but yielded no meaningful improvements to predict the benefit of respiratory gating.
We propose that additional metrics be considered that quantify the motion of all irradiated anatomy. After demonstrating the weakness of using tumor volume motion alone, we should seek other ways to quantify respiratory motion. In both proton and photon therapy, the dose delivered to the target can be affected by the anatomy proximal to the target. This effect is greater for proton therapy; any anatomical variation along the field path will lead to variations in the delivered dose from the originally planned dose. We have stated earlier that proton therapy beam range is dependent on the density of the material traversed. To further investigate new metrics to quantify respiratory motion, we discuss in the next chapter a novel method to quantify respiratory motion in the delivery of proton therapy.
4.5 Conclusion

In this work, we have determined that the extent of tumor motion was not able to predict the benefit of respiratory gating for PSPT and IMRT. Thus, we were not able to determine a threshold of respiratory motion to determine when respiratory gating would benefit the normal tissue dose-volume indices. Additional simple lung and target metrics were also unable to provide any correlation with the benefit of respiratory gating.

Tumor motion quantifies how one sub-region of the patient anatomy moves during respiration. The process of respiration and the anatomical variation during the respiratory cycle are too complex to be adequately modeled by a single sub-region of the lung, such as the tumor volume. Our results show that it is not adequate to quantify respiratory motion using the only the tumor volume, which has historically been the common method in radiation oncology. From our results, we have concluded that the current methods to assess the impact of respiratory motion are inadequate to predict the dosimetric changes due to respiration and inadequate to predict the benefit of respiratory gating.
CHAPTER 5: THE USE OF WATER EQUIVALENT PATH LENGTH TO PREDICT
THE EFFECT OF RESPIRATORY MOTION ON PLANNED DOSE IN PROTON
THERAPY

Chapter 5 is based on material that is prepared for submission to Medical Physics by the
author of this dissertation.

5.1 Introduction

Previously, we have demonstrated that respiratory motion can cause deviations in
calculated proton dose distributions. Also, we have shown that the variations in dose due to
respiratory motion were not predicted by the extent of tumor motion. Our results have also
shown that the benefit of respiratory gating was not predicted by the extent of tumor motion.
Figure 2-13 demonstrates that variations in anatomy along the field path can alter the planned
dose distribution in proton therapy. This chapter outlines a novel method to describe
anatomical variation in density along a proton beam path to predict the dosimetric changes
in proton therapy due to respiration.

As outlined in Chapter 1, the proton range in a medium is finite due to multiple
Coulombic interactions. PSPT planning requires that the maximum incident proton energy
is sufficient to penetrate to the distal depth of the target. As in photon therapy\textsuperscript{164}, quality assurance and beam commissioning data for proton therapy are commonly measured in water\textsuperscript{165}. For convenience of relating proton ranges in different materials, the proton energy can be described by the water equivalent path length (WEPL) or water equivalent thickness (WET). For example, if we consider two monoenergetic proton beams of identical initial energy incident upon two materials of different proton relative stopping power (e.g. Lucite or water), each beam would penetrate to different physical depth. However, the water equivalent thickness of the material traversed will be essentially the same for the two proton beams of identical initial energy. Therefore, we have the ability to describe the range of the proton beam not only with a physical depth of penetration in a given medium, but with WET that the beam would penetrate.

In order to calculate WET, we need to know the relative stopping power (RSP) for each material traversed by the proton beam. The International Commission on Radiation Units and Measurements (ICRU) has issued extensive data tables on the stopping power values for protons\textsuperscript{166, 167} Accurate knowledge of the patient anatomy as well as all beam modifying materials such as any range modulator wheel, compensator, scattering system, and energy absorbers are required to calculate the physical proton range. The WET along a straight line
(z) between the proton source and a specific depth in a heterogeneous medium can be calculated using a line integral of relative stopping power (RSP) of the form:

$$WET = \int_{source}^{depth} RSP(x, y, z)dz$$

Where the relative stopping power is given by

$$RSP(x, y, z) = \frac{\rho_m \bar{S}_m}{\rho_w \bar{S}_w}$$

Where $\rho_m$ and $\rho_w$ are the mass density of the material and water, respectively, and $\bar{S}_m$ and $\bar{S}_w$ are the mean proton mass stopping powers for the material and water, respectively. Therefore, to determine the RSP value for a given medium for a particular point, it is necessary to determine the mean proton mass stopping power ($\bar{S}$). Theoretically, the Bethe equation (Equation 1) can be used to calculate the stopping power given that the ionization potential, electron density, and elemental compositions of the medium are known. However, these values may not be known for a given composite material. Therefore, an empirical relationship is used to estimate the RSP.

For the purpose of treatment planning, the RSP of the patient anatomy is approximated by a one-to-one function between CT Hounsfield (HU) units and the RSP. The Hounsfield number as defined in computed tomography is given by
\[ HU = 1000 \frac{\mu_m - \mu_w}{\mu_w} \]  

(17)

where \( \mu_m \) and \( \mu_w \) are the mean linear attenuation coefficients for the material and water, respectively, averaged over the x-ray spectrum. For polyenergetic photon beams less than 1.02 MeV, such as those used in CT imaging, the attenuation coefficient for a material can be written in the form

\[ \mu = \rho N_g(Z, A)(\sigma^{ph} + \sigma^{coh} + \sigma^{inc}) \]  

(18)

where the quantity \( \rho N_g \) is the electron density, and \( \sigma^{ph}, \sigma^{coh} \) and \( \sigma^{inc} \) are the cross sections for the photoelectric effect, coherent scattering and incoherent scattering, respectively. The electron density \( (\rho_e) \) for a material is given by the product of the density \( \rho \) and electrons per gram \( (N_g) \) which in turn is dependent on the atomic number \( (Z) \) and the atomic mass \( (A) \) of the material. Rutherford et al\(^{169}\) provided a parameterization of these cross-sections to yield:

\[ \mu = \rho_e * (K^{ph}Z^{3.62} + K^{coh}Z^{1.86} + K^{KN}) \]  

(19)

where \( K^{ph}, K^{coh} \) and \( K^{KN} \) are constants which characterize the photoelectric, coherent scattering, and Klein-Nishina cross sections for an element of a material mixture.

The most common method to model the HU to RSP conversion is referred to as the “stoichiometric method” proposed by Schneider et al.\(^{170}\) In Schneider’s method, the HU numbers of selected tissues encountered in a human body were calculated based on
modeling parameters from a CT system. By making measurement of HU values for different tissues substitutes of known chemical composition, Schneider estimated the relationship between HU and measured and calculated RSP values. An example of the calibration curve to convert HU into RSP is shown in Figure 5-1.

Figure 5-1: An example of the calibration curve that maps Hounsfield units from computed tomography to the relative stopping power ratio used in proton therapy range calculation.

The calculation of WET takes into account all anatomy along the proton range. As previously mentioned, we have determined that tumor motion magnitude was a poor metric to estimate the effects of respiration motion and to estimate the benefit of gating for proton
therapy. Characterizing the tumor motion only describes anatomical displacements in one small sub-region of the patient anatomy. It would be useful to determine a metric that quantifies the changes of all anatomical changes that affect the calculated proton dose distribution. In 2007, Mori et al. reported that the WET fluctuations during cardiac motion could be used to assess potential heavy charged particle range fluctuations\textsuperscript{171}. In a follow-up study, Mori suggested the use of WET analysis of 4DCT data to quantify changes in lung tissue to optimize planning and delivery of lung tumors\textsuperscript{172}. This chapter proposes to use WET analysis as a novel metric to quantify for respiratory motion of all patient anatomy along the proton path length.

5.2 Methods and Materials

In this chapter, we explored the relation between $\Delta$WET, or change in water equivalent thickness, and the change in PSPT dose during respiration. The relative stopping power has been introduced as a method to calculate the water equivalent penetration depth for a proton beam. Any variation in the WET during respiration would result in variation of the proton beam range during respiration. In this chapter, we designed a program to calculate the WET to the distal depth of the target volume in the exhale and inhale 4DCT phases. The T50 and
T0 phases were selected for analysis as they represent the extreme phases of respiration. Secondly, the change in WET (ΔWET) was calculated between the inhale and exhale phases of respiration and analyzed. We determined metrics that represented the change in calculated dose (ΔDose) between the T0 and T50 phases of respiration. Pearson correlation coefficients were calculated between the ΔWET and ΔDose values. Lastly, a method of ΔWET planning was outlined to demonstrate one of the many potential uses of ΔWET-based analysis in proton therapy.

5.2.1 Patient Selection

For this work, we analyzed patient data from 29 PSPT plans from patients enrolled in an institutional review board approved trial randomizing treatment between PSPT and IMRT for locally advanced stage II-IIIB lung cancer. Patient information is given in Table 5-1. Each patient on the trial had PSPT plan approved for treatment by a physician. This cohort consisted of the twenty patients from the cohort used in previous chapters with an additional nine patients treated after the selection of the original cohort (January 2012). The cohort was expanded to include recent patients on the clinical protocol and to increase the overall number of treatment fields to analyze. A total number of 87 fields were used for the 29 PSPT
plans, averaging 3 fields per patient. The internal tumor volume for this expanded cohort ranged from 41 to 1205 cm$^3$.

Table 5-1: Data from twenty nine patients was used in this project to correlate WET to the dosimetric effects of respiratory motion. The original twenty patients from the first three aims were included in this study and an additional nine patients were added from the clinical protocol. A total of 87 fields angles were used over the 29 PSPT plans for an average of 3 fields per plan.

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<th>Motion [mm]</th>
<th>Rx [Gy]</th>
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<th>ITV [cc]</th>
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<th>Fields/Plan</th>
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<td>74</td>
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</table>

*Abbreviations: Rx = prescription dose, ITV = internal target volume, RLL = right lower lobe, RUL = right upper lobe, LLL = left lower lobe, LUL = left upper lobe, Squamous = Squamous-cell carcinoma, Adeno = adenocarcinoma, Large Cell = large cell carcinoma, NOS = not otherwise specified*
5.2.2 ΔWET Analysis

An in-house program was designed using Matlab (Mathworks, Natick, MA) to analyze the WET variance during respiration. The program works by processing patient information stored in a standardized format: the Digital Imaging and Communication in Medicine format (DICOM). The interface as seen by the program user is shown in Figure 5-2. First, the software imports the T50 and T0 DICOM CT image. The software reads a conversion table of CT number to RSP values plotted in Figure 5-1. The HU values of the voxels of each CT image are then converted into the corresponding values of RSP. The program reads a file containing the anatomical structures exported from the Eclipse or Pinnacle TPS. The software then prompts the user to identify the target volume from the contoured structures in the treatment plan. For analysis in this chapter, we selected the ITV to encompass the tumor motion throughout respiration. To perform WET analysis as a function of field angle, the software prompts the user to input the desired field angle spacing and, optionally, input the field angles selected for treatment.
Figure 5-2: Example of the user input to the WET program. After selecting the location of the plan data, the user is prompted (left) to enter a field angle interval and, if treatment field angles are known, the user can enter the values. The target structure is also defined by the user before WET calculation (right).

A series of rays, shown in Figure 5-3, is created along the beam’s eye view (BEV) ranging to the distal end of the target volume at the selected angles. The software then calculates the T50 and T0 “WET matrix”. Each element (or pixel) of the WET matrix represents the required proton WET in a grid equal to the projected CT voxel size (1x1x2.5 mm) perpendicular to the field direction. A schematic illustration of the WET matrix for a single slice of the patient anatomy is shown in Figure 5-4. The WET matrix value for each pixel \((i, j)\) for each angular projection is calculated using the equation:

\[
WET_{i,j} = \int_0^d RSP(i, j, z) \, dz
\]  

(20)

where \(d\) represents the distance to the distal surface of the selected target along the ray at \((i, j)\) parallel to the field axis, and \(RSP(i, j, z)\) is the relative stopping power at each voxel encountered along the line segment in the mapped CT HU-to-RSP dataset. The change in
water equivalent thickness during respiration (ΔWET) along each ray to the distal side of the target was defined as the difference between the T50 and T0 WET matrices. This process was repeated for a series of co-planar fields specified by the user-defined angular spacing over a 360 degree arc around the patient. In the program, we analyze only co-planar field angles normal to the central axis of the patient. This was done to limit the calculation time and simplify the resulting summary; no proton plans in our patient cohort used non-coplanar field arrangements. However, the software could easily be extended in the future to calculate ΔWET for a range of non-coplanar fields.

Statistical analysis values (mean, median, 5th and 95th percentiles, etc.) of the ΔWET matrix were calculated for each field angle. Images of the T50 WET, T0 WET and ΔWET matrices were saved to a summary report. An example of the ΔWET analysis program output for a single field angle is shown in Figure 5-5. Once the ΔWET calculation was done for all angles, the ΔWET for each field is plotted as a function of angle around the patient.

For each analyzed angle and corresponding ΔWET matrix, the software also calculates the numbers of pixels (rays) that changed by less than 5 mm in WET between the T50 and T0 image. This value divided by the total number of rays yielding a percentage which represents the percentage of the distal surface area of the target as seen from the BEV which
changes less than 5 mm in WET during respiration (ΔWET<5mm). This work considered a change of WET less than 5 mm to be an acceptable deviation or “passing”, while ΔWET over 5 mm was considered “failing”. The 5 mm level was selected based on historical recommendations, as respiratory motion less than 5 mm have generally been considered negligible in radiation therapy. The above calculations were also repeated for the series of co-planar fields specified by the user.

Figure 5-3: For an example patient, an image of the 250 degree BEV (left) on T50 CT image of patient with a tumor target (light blue) surrounded by the aperture block (red shaded region). Also shown is esophagus (green), heart (purple) and spinal cord (red). For a series of rays (yellow) in the BEV of anatomy shown on the left, the rays are shown on the right for an axial slice of the patient anatomy. Each ray traces to the distal surface of the target volume.
Figure 5-4: A schematic illustration of the method used to calculate the required range or WET of the proton field to cover the target for a single coronal slice. First, the voxels of the CT were converted into relative proton stopping power values using Figure 5-1. To calculate the pixel values (red or blue square) of the WET matrix, the value of each voxel was summed along the ray (red and blue lines) until reaching the distal edge of the target volume (yellow). This process was repeated for all pixels to create WET matrix containing the WET values for each field direction.
Figure 5-5: Example output from the ∆WET analysis software for a sample field at a gantry angle of 250 degrees. On the top row is the beam’s eye view WET matrix of depth to the distal side of the target for T50 (a) and T0 (b). The ∆WET matrix (c) is calculated from the difference of the first two images. To visually assess the ∆WET per field, a boxplot (d) and histograms are shown of ∆WET (e) and the absolute value of ∆WET (f). All reported values in millimeters.
Figure 5-6: Left: WET analysis output example of the mean, median and 95th percentile of the absolute value of every 10 degrees in a coplanar arrangement around the patient. Green lines are added to illustrate the field angles selected for the PSPT clinical plan. Right: For each field angle, the program calculated “ΔWET<5mm”, or the percentage of rays for which the ΔWET to the target’s distal surface changed by less than 5 mm. Thus, the percentage of surface below 5 mm ΔWET is inversely proportional to the change in WET during respiration.

After ΔWET data were calculated at each potential angle, an angular summary was plotted by the software. In Figure 5-6, the mean, median and 95th percentile of the absolute ΔWET values were plotted on the left for hypothetical fields spaced every 10 degrees around the patient. Since an approved clinical plan was already created for this patient, the clinical field angles are denoted by green lines in Figure 5-6. On the right hand side of Figure 5-6, the ΔWET<5mm pass rate was plotted for hypothetical fields spaced every 10 degrees.
around the patient. In the plot, the surface % pass rate signifies the dWET<5mm. In Figure 5-6, a higher pass rate denotes a smaller ΔWET variation across the field.

Analysis was completed for all patients listed in Table 5-1. Each set of patient structure file and image sets were analyzed with the ΔWET program. Three metrics were recorded for each planned field: the ΔWET median, 95th percentile and ΔWET<5mm pass rate.

5.2.3 ΔDose Analysis

The planned dose as calculated by the treatment planning system can be described either as a 3D matrix of voxels or a 3D “cloud” of dose. The purpose of this step was to quantify how the delivered PSPT dose cloud changes between inhale and exhale phase of respiration.

To test whether ΔWET can predict dosimetric changes due to respiration, we need to correlate the ΔWET to a respiratory-induced deviation in calculated dose. Such a comparison would require calculation of dose deviation on a field-by-field basis. The dose distributions for each field from the cohort of clinically approved, non-gated PSPT plans was recalculated on the patient’s T50 and T0 4DCT dataset. The resulting T50 and T0 dose matrices for each individual field were exported for analysis.
The patient T50, T0, structure, and field-specific dose DICOM files were imported into the Computational Environment for Radiotherapy Research (CERR) software platform. CERR is a Matlab-based software platform for development of visualization and analysis tools for radiotherapy plan comparisons. The use of CERR allowed (1) the dose matrix to be matched to the spatial coordinates of the CT image and structure files, (2) normalization by dividing the dose per voxel by the field weighting factor, (3) saving the normalized dose and (4) the results to be analyzed and visualized in the MATLAB environment.

Multiple fields were used in a plan and the field weighting factors were not necessarily equal. Some fields, at the discretion of the treatment planner, were weighted more or less to achieve a desired composite dose. To compare the changes in dose between fields with different weighting, it was necessary to normalize each field dose. The calculated dose for each field was divided by the field’s weighting factor. Essentially, the dose was normalized such that the dose delivered by each field achieved the full prescription dose. The normalized dose differences between the T50 and T0 phases of respiration were calculated for all planned treatment fields.

In earlier chapters, the changes in the calculated dose were given by reporting the changes in dose-volume (DV) indices. One weakness of this method is that changes in dose
that occur outside the region of interest structures would not be reflected in any DV indices. In a complex 3D dose distribution, it can be challenging to find a single metric to quantify the differences between two distributions. Four methods were identified to compare the change each field’s dose during respiration (ΔDose) values: (1) Root mean square deviation (RMSD), (2) Histogram ±3% dose pass rate, (3) 3D gamma analysis and (4) differential area under the DVH curve.

The first method was to calculate the root mean square deviation of the dose difference. For all voxels within the external body contour of the patient, a MATLAB routine was written to read the normalized T50 and T0 field dose, ignore any voxels outside the patient body (e.g. dose calculated within the treatment couch), and calculate the RMSD using the equation:

\[
RMSD = \sqrt{\frac{\sum_{i=1}^{n} (D_{T50} - D_{T0})^2}{n}}
\]  

(21)

where \(D_{T50}\) and \(D_{T0}\) represent the field dose calculated at corresponding voxels in the T50 and T0 image, respectively, for each of the \(n\) voxels in the patient anatomy. The RMSD was recorded for all treatment fields, and an example of one field’s dose difference is shown in Figure 5-7.
Figure 5-7: An example of the normalized dose difference in Grays for a 165 degree treatment field. The dose difference was calculated by subtracting the T0 from the T50 normalized beam-specific dose. The root mean square deviation was calculated for the voxels within the patient anatomy for each treatment field. The PTV is shown outlined in light blue.

The next method was a histogram analysis of the dose difference between the T50 and T0 dose cloud (Histogram ±3% dose pass rate). A dose difference tolerance of 3% of prescription was selected arbitrarily selected as the passing criteria. After calculating the change in dose between exhale and inhale (T50-T0), depending on the field size and angle, large unirradiated areas of the patient have zero dose difference. To compare the changes in only the irradiated volumes of the patient, we excluded all voxels that received less than 3% of the prescription dose. Figure 5-8 shows an axial, sagittal, and coronal view of the dose cloud differences for a 250 degree treatment field. After removing the uninvolved voxels, if the change in voxel dose between the T50 and T0 dose was ±3% of the prescription dose,
the voxel was considered “passing”. To calculate a passing rate, the number of passing voxels was divided by the total number of irradiated voxels. A histogram of the dose difference in the involved volumes is shown in Figure 5-9.

Figure 5-8: For a 250 degree field angle from a sample cohort patient, an axial (left), coronal (upper right) and sagittal slice (lower right) of the absolute value of T50-T0 calculated dose difference. After removing the regions receiving less than 3% of the prescription dose (74 Gy), the differences between T50 and T0 dose clouds are shown on the T50 CT image for reference. All doses are given in Gray.
The third $\Delta$Dose metric was a gamma analysis\textsuperscript{174} applied in three dimensions to quantify the differences in the T50 and T0 dose cloud\textsuperscript{175}. Perturbations between these two dose distributions were scored by calculating the percentage of voxels for which the gamma value was greater than or less than 1. This value was defined as the 3D Gamma pass rate. We chose a 3\% dose difference and 3 mm distance to agreement criteria following the original 3D gamma analysis report by Wendling et al.\textsuperscript{175} The previous histogram analysis method is identical to a 3D gamma analysis with 3\% dose difference and 0 mm distance to agreement criteria. While the original intent of gamma analysis was to compare measured 2D data with planar calculated data, literature has reported on the use of 3D gamma analysis.
as a metric to compare between calculated 3D dose distributions\textsuperscript{176,177}. We believe the use of 3D gamma analysis in this fashion, while different than the original intention of Low et al., was useful for comparing the relative changes between 3D dose distributions.

The last method to quantify the change in dose between inhale and exhale was to calculate the differential area under the cumulative T0 and T50 DVH curves (dAUC)\textsuperscript{178}. When dose delivered to a structure is altered, such as during respiration, the dose-volume histogram curves may reflect this change. To calculate the DVH curves, the original planning structures were used as delineated by the dosimetrists for the clinical plan. An illustrative example of the dAUC method is shown in Figure 5-10. Hypothetical differences in the T50 PTV curve and T0 curve are shaded red or blue, respectively. The dAUC is the sum of the red and blue shaded areas and can be expressed by the equation:

$$dAUC = \sum_D (|DVH_{T50}(D) - DVH_{T0}(D)| * d)$$ (22)

Where $DVH_{T50}(D)$ and $DVH_{T0}(D)$ represent the value of the cumulative DVH for T50 and T0, respectively, for a given dose bin D with width d. As the dose differences between the T50 and T0 calculation increase, so does the dAUC for the T50 and T0 DVH curves. This metric could be a potential way to quantify the “robustness” of a field to the effects of respiration motion.
For each field, the PTV, total lung, esophagus, heart and spinal cord dAUC values were calculated between the T50 and T0 normalized field doses. To compare the changes in T50 vs. T0 DVH curves for a combination of important structures, this chapter proposed the use of a “total dAUC” metric defined as the sum of the dAUC values for PTV, total lung, esophagus, heart and spinal cord. An example of the DVH curves is shown for an example patient in Figure 5-11. In this example, it is shown that the field at 165 degrees demonstrated minimal dose difference between the exhale and inhale dose calculation. However, the field at 250 degrees demonstrated large deviations in the esophagus and heart dose between
inhale and exhale. Table 5-2 gives the calculated dAUC values for the PTV, esophagus, heart, total lung and spinal cord DVH curves for the example fields in Figure 5-11. The total dAUC values provided a single metric to quantify the change in dose between the inhale and exhale phases of respiration.

Table 5-2: This table gives the values of dAUC analysis for the example patient in Figure 5-10. For the two treatment fields selected for this patient, one field at 250° demonstrates a larger variation of dose due to respiratory motion, as seen on the comparison of T50 and T0 DVH curves in the previous figure. The sum of the individual dAUC values provided a single metric (Total dAUC) to quantify the magnitude of change between the T50 and T0 calculated doses.

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Figure 5-11: An example of the DVH curves for T0 (solid) and T50 (dotted) for the two fields selected for this patient’s plan. The heart (pink), total lung (orange), spinal cord (red), esophagus (green) and PTV (light blue) are shown. The field at angle 165 (left) shows very little change between the dose calculated on the T50 and T0 phases. For the field at 250 degrees (right), large changes are observed in the heart and esophagus dose between the T50 and T0 phases. It should be noted the spinal cord received no dose from the 250 degree field.
5.2.4 Correlation of ∆WET to ∆Dose

First, three metrics were outlined to quantify the change in water equivalent thickness (ΔWET) to the distal surface of the tumor target. Next, we outlined four metrics to quantify change in the calculated dose cloud between the T50 and T0 phase of respiration (ΔDose). Pearson correlation coefficients were calculated and linear regression fits to the data were calculated between the various ΔWET and ΔDose metrics. To reduce type I error rate inflation due to multiple hypothesis testing, we conservatively adjusted our significant p-value with a Bonferroni correction by the number of hypothesis (12) to \( p = \frac{0.05}{12} \approx 0.004 \).

5.2.5 ΔWET Reduction Treatment Planning

During treatment planning, it is important to determine if the resulting plan would be affect by respiratory motion. In Figure 5-6, it was observed that the angles selected for treatment (green lines) could be altered to reduce the values of ΔWET. This aim anticipated that WET analysis could be a useful method to select field angles that would reduce the impact of respiratory motion on the PSPT plan. The current clinical method to assess the effect of respiratory motion on the plan involves a qualitative assessment of the original plan...
dose recalculated and compared between the T50 and T0 phases. The original dose is calculated on the average CT dataset, and is compared to the dose as calculated on the T0 and T50 phase. If dose deviations are observed between the T50 and T0 dose, the plan may or may not be altered. There are currently no quantitative measurements for passing or failing a particular plan. The dosimetry team attempts to create a plan that is robust in the presence of respiratory motion. However, the selection of field angles is currently through a process of trial and error and reliant on the planner’s experience. The assessment of the effect of respiratory motion on a proton plan is only conducted after the treatment plan field angles have been selected.

As a demonstration of the potential of the use of ∆WET in PSPT planning, this work has identified three proton plans from our cohort with the largest variations between T0 and T50 calculated dose. This work sought to minimize the effect of respiratory motion on the planned dose by using the ∆WET analysis program.

In Figure 5-12, we revisited Figure 5-6 and attempted to select new field angles using the ∆WET analysis results as guidance. It can be observed that the 165 degree treatment field is near the global minimum of the median ∆WET value (left), and near the maximum ∆WET<5mm surface pass rate (right). The normalized field specific DVH curves for this
example patient were shown in Figure 5-11. In this figure, we observe that the 250 degree field shows much greater deviation in the normal tissue structures are compared to the 165 degree field. Therefore, we hypothesized that if we were to replan this patient and move the treatment fields to improve the ∆WET values (Figure 5-12), we would create a plan that was more robust to respiratory motion.

![Figure 5-12: An example of a plan where the chosen field angles for treatment do not correspond to the best angles to optimize the ∆WET values. The 250 degree field was noted to be particularly affected by respiratory motion (Figure 5-11). New field angles of 155 and 350 degrees (gold lines) were chosen to design a new treatment ∆WET optimized treatment plan.](image-url)
The fields that were selected to optimize the \( \Delta WET \) values for this particular patient were 155 and 350 degrees, as denoted by the gold lines in Figure 5-12. The redesign of the treatment fields including proximal and distal margins, aperture, compensator, and proton beam line followed the same design methodology as in the original plan, which was discussed in Chapter 2. Once the new “\( \Delta WET \) reduced plan” was completed, the plan dose was recalculated on the T0 and T50 datasets. For comparison, dAUC analysis was used to quantify the changes in T50 and T0 DVH curves between the original plan and the dWET analysis replan.

5.3 Results

The \( \Delta WET \) and \( \Delta \)Dose metrics have been calculated and compared for 87 fields over 29 PSPT plans. In this chapter, we have outlined four methods of quantifying the change in the dose distributions between the exhale and inhale phase of respiration: RMSD, Histogram \( \pm 3\% \) dose pass rate, 3D Gamma analysis and Total dAUC. First, we present the \( \Delta \)Dose metrics for 87 fields over 29 patients plotted against patient tumor centroid motion in Figure 5-13.

It was observed that for the four \( \Delta \)Dose metrics demonstrated no significant correlation
(Pearson’s r) to the tumor motion. A linear fit to the data showed that $R^2$ value was near zero in all cases, with the largest $R^2$ value being 0.04. This reaffirms our previous conclusions on a field-by-field basis: the extent of motion is not correlated to the change in dose due to respiration. The weak linear fit to the data reaffirms that the tumor motion cannot predict the effects of respiratory motion on the calculated dose.

Figure 5-13: Plots of $\Delta$Dose for the 87 normalized field doses were plotted against the tumor centroid motion observed for each patient. Pearson correlation coefficients ($r$) were calculated between $\Delta$Dose metrics and the tumor motion. The four $\Delta$Dose metrics were root mean square deviation (RMSD), total area under the DVH curves (dAUC), the percent of body voxels within 3% dose agreement (Pass Rate < 3% $\Delta$Dose), and the 3D gamma analysis with a pass criterion of 3%, 3 mm. No significant correlation was observed between the $\Delta$Dose metrics and tumor motion. The $R^2$ values were near zero for the linear fit of tumor motion versus the four $\Delta$Dose metrics.
First, correlations for the median ∆WET values versus the multiple ∆Dose metrics were calculated. Even after the conservative use of a Bonferroni correction to the p-value from 0.05 to 0.004, a significant correlation was found between median ∆WET values and all four ∆Dose metrics, as shown in Figure 5-14 through Figure 5-17. As the ∆WET metric increased, the RMSD (Figure 5-14) and the dAUC (Figure 5-17) changes between the inhale and exhale dose increased. We expected that as the respiratory motion increases, the RMSD value and total differential area under the DVH curves would also increase. In Figure 5-16, the percentage of irradiated volumes within ±3% dose agreement and 3D gamma pass rate in Figure 5-15 decreased as the median ∆WET increased. Again, we expect as respiratory motion increases, the percentage of voxels within 3% dose agreement should decrease between the T0 vs. T50 doses. Figure 5-18 shows linear fits to the previous four figures. The linear fits to the ∆WET data were still weak, with an $R^2$ value between 0.17 and 0.27. However, this was an improvement to the fit compared when using tumor motion alone (Figure 5-13).
Figure 5-14: Plot of median of ∆WET for each field versus the root mean square deviation of dose between the T50 and T0 full body dose. Significant positive correlation (p<0.0001) was found with Pearson correlation coefficient of 0.45.

Figure 5-15: Plot of median of ∆WET for each field versus the 3D Gamma pass rate with 3%/3mm tolerance between the T50 and T0 full body dose. Significant negative correlation (p<0.0001) was found with Pearson correlation coefficient of -0.51.
Figure 5-16: Plot of median of ΔWET for each field versus the percentage of irradiated patient volume within ±3% of prescription dose between the inhale and exhale. Significant negative correlation (p<0.0001) was found with Pearson correlation coefficient of -0.41.

Figure 5-17: Plot of median of ΔWET for each field versus the total differential area under the DVH curves (dAUC) between the inhale and exhale dose. Significant positive correlation (p<0.0001) was found with Pearson correlation coefficient of 0.42.
Figure 5-18: Least squares linear fit to the data for the last four figures. The $R^2$ values were given as a measure of the goodness of fit. While values of $R^2$ ranged from 0.17 to 0.27, the slope of the linear regression line was significantly ($p < 0.0001$) non-zero, which was not observed for the tumor motion vs. $\Delta$Dose metrics.

In Figure 5-19, the $\Delta$WET 95th percentile values were compared against the four $\Delta$Dose metrics for each treatment field in the cohort. The Pearson correlation coefficient, 95% confidence interval, $p$-value and the $R^2$ value of the least squares linear fit to the data was included for each metric. Each $\Delta$WET was significantly ($p < 0.0001$) correlated to each $\Delta$Dose metric analyzed. Figure 5-20 gives a comparison similar to Figure 5-19, but for the $\Delta$WET<5mm surface pass rate. The $\Delta$WET<5mm metric was also significantly correlated to
each ΔDose metric analyzed.

Figure 5-19: ΔWET 95th percentile was plotted against ΔDose metrics for RMSD (top left), total dAUC (top right), histogram ±3% dose pass rate (bottom left) and a 3D gamma pass rate with 3%, 3mm criteria (bottom right). Pearson correlation coefficients (r) are given along with 95% confidence interval, and p-value for significance. A least square linear fit to the data is given with $R^2$ value for goodness of fit.
All three ∆WET metrics were found to have moderate (0.31<|r|<0.56), but significant (p≤0.0005) correlation to the four ∆Dose metrics. The results indicated that ∆WET is correlated to the difference between the calculated dose differences between the inhale and exhale phases. The results for ∆WET is in contrast to the demonstration that the extent of tumor motion is not significantly correlated to any metric quantifying the dose difference between the inhale and exhale phase of respiration.
5.3.1 ΔWET Reduction Treatment Planning

Three patients were identified for re-planning efforts using the ΔWET analysis to select new field angles. The first patient was previously described and two additional patients have been re-planned using dWET analysis to guide field angle selection, as shown in Figure 5-22 and Figure 5-23. For the first patient (Figure 5-12), the T50 vs. T0 recalculated dose for the two new field angles (bottom, 155 and 350 degrees) is compared to the original angles (top, 165 and 250 degrees) in Figure 5-21.

![Figure 5-21: An example of the ΔWET guided plan (bottom) compared to the original, clinical plan (top). An axial slice plan dose is shown on the top for T50 (left) and T0 (right) image set. The ΔWET guided plan has new field angles of 155 and 350 degrees which were determined using the ΔWET analysis program.](image-url)
Figure 5-22: Angular WET analysis of the second patient that was re-planned to improve ∆WET values. The original treatment field angles were 205° and 290° (green lines). In the new plan, the original 205° field was maintained and the 290° treatment field was moved to 350° degrees (gold line) and a new field was designed.

Figure 5-23: Angular WET analysis of the third patient that was re-planned to improve ∆WET values. The original treatment field angles are 215°, 270°, and 315° (green lines). The new field angles (gold lines) chosen based on the ∆WET metrics were shifted by 30-35 degrees to 185°, 235°, and 280°.
In one case shown in Figure 5-24, the re-planned dose to the spinal cord dose was increased from that of the original plan (patient #2). The solid lines show the original plan’s DVH curves for T50 and T0, while the dotted lines shown the ∆WET reduction plan T50 and T0 DVH curves. The goal of ∆WET reduction planning was not necessarily to reduce the normal tissue dose, but to reduce the variation in dose delivered between exhale and inhale respiratory phases. While the cord dose was increased in this patient, the variation of dose between the T50 and T0 phase of respiration was reduced for the lung, spine, heart and esophagus.

Figure 5-24: For patient #2, the original plan T50 and T0 DVH curves (solid lines) are shown in comparison to the WET reduced plan T50 and T0 (dotted lines). The WET replan demonstrated higher spinal cord dose, but the variation between the T50 and T0 curves was reduced.
Table 5-3: Three PSPT plans were redesigned using field angles that improved upon the ∆WET metrics are compared to the original plan (Original). Between the T0 and T50 dose clouds for both plans, the root mean square deviation (RMSD) was calculated. For both the original and dWET plan, the T50 and T0 DVH curves were compared for each plan using differential area under the curve analysis. The plan created to reduce ∆WET variation demonstrated lower RMSD and reduced total dAUC values for all three patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Plan</th>
<th>RMSD</th>
<th>PTV dAUC</th>
<th>Lung dAUC</th>
<th>Eso dAUC</th>
<th>Heart dAUC</th>
<th>Spine dAUC</th>
<th>Total dAUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>0.34</td>
<td>0.47</td>
<td>3.11</td>
<td>3.59</td>
<td>0.00</td>
<td>7.50</td>
</tr>
<tr>
<td>1</td>
<td>∆WET</td>
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<td>0.18</td>
<td>1.06</td>
<td>0.13</td>
<td>0.02</td>
<td>0.04</td>
<td>1.43</td>
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<tr>
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<td>0.25</td>
<td>1.62</td>
<td>1.93</td>
<td>1.55</td>
<td>2.22</td>
<td>7.57</td>
</tr>
<tr>
<td>2</td>
<td>∆WET</td>
<td>1.45</td>
<td>0.06</td>
<td>1.49</td>
<td>0.61</td>
<td>0.15</td>
<td>0.59</td>
<td>2.90</td>
</tr>
<tr>
<td>3</td>
<td>Original</td>
<td>2.23</td>
<td>0.17</td>
<td>1.91</td>
<td>1.17</td>
<td>1.61</td>
<td>2.25</td>
<td>7.11</td>
</tr>
<tr>
<td>3</td>
<td>∆WET</td>
<td>1.91</td>
<td>0.08</td>
<td>0.70</td>
<td>0.10</td>
<td>1.51</td>
<td>0.26</td>
<td>2.65</td>
</tr>
</tbody>
</table>

For the three sets of original and ∆WET reduction plans, the variation between T50 and T0 plan dose was compared using dAUC and RMSD metrics.

Table 5-3 lists the results for the comparison between the original plan and the ∆WET reduction plan. For the three plans that were redesigned using ∆WET analysis, the RMSD between the T50 and T0 dose cloud within the patient anatomy was calculated. Dose-volume histogram curves were constructed for PTV, Total lung (Lung) esophagus (Eso), heart, spinal cord (Spine). The differential area under the DVH was compared and a total sum of the dAUC is shown in

Table 5-3. For each plan, the RMSD between the calculated T50 and T0 dose was reduced by ~15-35% for the three ∆WET reduction plans. The dAUC values were reduced
by more than 60% in the ∆WET reduction plan compared to the original plans. By reducing
the calculated dose differences delivered during the inhale and exhale phases of respiration,
these results demonstrate that the ∆WET reduction plans are more robust to the effects of
respiratory motion compared to the original treatment plan.

5.4 Discussion

We have introduced the use of a new metric to quantify the impact of respiratory motion
in proton therapy: the change in water equivalent thickness during respiration or ∆WET. The
∆WET metrics quantify the anatomical density variations along the field path due to
respiratory motion. Instead of measuring the respiratory motion of the tumor volume, ∆WET
allows us to quantify the variation of all anatomical structures that can affect the planned
proton dose. It should be noted that by combining all 87 field for analysis, we assumed the
results from different fields within the same patient are statistically independent. This should
be reasonable to assume because current treatment planning methods prohibit fields within
40 degrees of another field. The tumor motion was not correlated to the effect of respiratory
motion on the planned dose in chapter 2. In this chapter, we reaffirmed this finding by
demonstrating the lack of correlation between tumor motion and the ∆Dose metrics. Next,
the ΔWET metric was shown to be significantly correlated to the change in dose due to respiration for 87 fields over 29 patient plans. This new metric provides information on the movement of all anatomy that affects the delivered dose in proton therapy.

The effect of respiratory motion was determined on a plan-by-plan basis in previous chapters. However, the WET metric in this chapter was measured on a field-by-field basis. Our results suggest that the effects of respiratory motion in PSPT should be considered on a field-specific basis. In the current methodology of PSPT planning, treatment fields are designed by assigning margins on a field-by-field basis. If we account for uncertainties on a field-specific basis, it would follow that we should assess uncertainties such as dose variation due to respiration motion on a field-specific basis. If a particular field is the cause of large dose variations during respiration, it would be advantageous to select a different angle, or reduce the offending field’s weight.

The calculation of WET thickness as outlined above is a relatively fast process, taking <5 seconds per field angle on a 3.3 GHz Intel Xeon processor. An entire patient can be analyzed with a fine angular interval (10 degrees) in under 3 minutes. There is even potential to speed up the calculation by excluding unusable fields, such as angles incident upon contralateral lung. However, we feel the current version is fast enough to provide clinically
useful data to the treatment planning team.

This chapter has also demonstrated that ΔWET is a useful metric to reduce the effect of respiratory motion in proton therapy. By selecting field angles that minimize ΔWET, we can reduce the impact of respiratory motion without the need of any form of respiratory gating. We propose that before a plan is considered for respiratory motion management such as with gating, ΔWET analysis should be performed to determine if the optimum field angles are being considered. If ΔWET reduction plan can improve the robustness of the non-gated plan dose to respiratory motion, the need for respiratory gating may be reduced or eliminated. Future work could identify patients to investigate these potential uses of ΔWET analysis.

It should be noted that the dose-volume indices in the ΔWET reduced plans were not always improved compared to the original plan. However, the variation in planned dose between the T50 and T0 respiratory phase was reduced in all three cases. Our intention was not necessarily to create a superior plan compared to the original, but to create a plan that was more robust to the effects of respiratory motion. It was observed that the ΔWET re-planned dose had smaller variations due to respiration compared to the original plan dose. However, it is important to note that there are many factors that are considered when
selecting field angles for PSPT. Respiratory motion is only one factor among factors many to consider. Commonly, at least one field per PSPT plan is designed to not be directed towards the cord ("off-cord"). This is done to limit potential dose to the cord if proton range uncertainty is present. In the first patient re-plan (Figure 5-12), the fields with the lowest $\Delta$WET values were near an anterior-posterior and posterior-anterior field setup configuration. This configuration has no off-cord fields. Such a selection of field angles may not be considered for patient treatment under current planning guidelines. However, as we reduce the range uncertainty in proton therapy, such restrictions may be relaxed. The $\Delta$WET analysis was useful in the example of patient #1 because large $\Delta$WET variations were observed for one of the treatment fields. The WET variations proximal to the target were caused by very large diaphragm motion affecting fields near a 270 degree angle. For this plan, the use of $\Delta$WET analysis would have quickly alerted the planning team that respiratory motion would greatly impact the calculated dose distribution of the initially chosen field angles.

In Figure 5-11, the 250 degree field dose was greatly affected by respiratory motion, but the 165 degree field dose was relatively stable over the respiratory cycle. We hypothesize it would be possible to selectively gate the field angles that demonstrate
anatomical density variation along the proton beam path. The ∆WET analysis could potentially be used to identify which field angles would be optimal for respiratory gating. If one of the treatment field angles was robust to the effects of respiratory motion, then gating that particular field may not improve the calculated dose’s robustness to respiratory motion and would prolong the treatment time. In this example, we could potentially gate the 250 degree field based on the ∆WET analysis, and treat the 165 degree field without gating. This use of ∆WET analysis could be investigated in the future.

In this chapter, we defined ΔDose as the difference between the T50 and T0 dose clouds. This definition was based on the current clinical practice of evaluating the effect of respiratory motion on a plan by examining recalculated dose cloud differences between the T50 and T0 phases. The comparison of the dose clouds is different than comparing the dose delivered to each voxel of patient anatomy. The latter comparison would require the additional use of deformable image registration. For this aim, the simplification of comparing the T50 vs. T0 dose clouds followed clinical practice, shortened computational time and removed any uncertainty associated with deformable image registration. We anticipate that it may be more accurate to use deformable image registration software to compare the change in calculated dose to each voxel. If we had deformed the calculated
dose before comparison, we anticipate the calculated dose differences between inhale and exhale would increase for each field. This would increase the slope of the linear fit between \( \Delta \text{WET} \) and \( \Delta \text{Dose} \), but the Pearson’s correlation coefficient between the two metrics should remain significant. For the first patient in Table 5-3, the RMSD between the composite T50 and T0 dose was 2.24. If the dose from T0 was deformed onto the T50 coordinate system, the resulting RMSD between the composite T50 and T0 doses would increase to 3.45. Our current method of dose cloud comparison was able to demonstrate significant correlation between \( \Delta \text{WET} \) and \( \Delta \text{Dose} \). If we had used deformable image registration to calculate \( \Delta \text{Dose} \) for 87 fields, we anticipate the results would serve to strengthen our prior conclusions.

It was our intent to create a useful clinical tool that could be applied before any fields were chosen for a plan. The current \( \Delta \text{WET} \) analysis program only requires 4DCT data and structural information on the treatment target. Delineation of target volumes by the physician is one of the first steps in creating the treatment plan. Therefore, \( \Delta \text{WET} \) analysis can be completed early in the treatment planning process. The use of \( \Delta \text{WET} \) analysis could be used to quickly identify patients where respiratory motion causes variation in anatomy along the field path.
We envision that the ΔWET analysis program could provide a useful addition to any field angle selection tools for proton therapy planning. One potential improvement to the program is to use the anatomical structure data to help ignore or suggest certain field angles. For example, the program could ignore field angles that encounter critical structures (e.g. incidence on contralateral lung) or to suggest at least one field that is “off cord” to limit potential spinal cord dose. Use of ΔWET angular analysis could compliment the method of field angle selection through minimizing beam-specific PTV outlined by Park et al\textsuperscript{179}. The ΔWET analysis program has already been used to provide useful feedback to clinicians considering a patient for proton therapy.

5.5 Conclusion

In this aim, we have investigated a new metric to quantify the impact of respiratory motion that incorporates global tissue variation during respiration: ΔWET. This metric is of particular interest in proton therapy, where the range of the proton can be defined in terms of water equivalent thickness. This work has led to the development of a program that can analyze the WET between the inhale and exhale phase of respiration, and report ΔWET for a series of angles around the patient. In the first step of this project, we demonstrated that the
ΔWET metric was significantly correlated to various metrics that quantified that change in calculated dose between exhale and inhale phases of respiration. In the second step, we demonstrated that ΔWET analysis can be useful in suggesting proton field angles that are robust to respiratory motion. Three PSPT plans were re-planned with new field angles to reduce the observed ΔWET metrics. Of these three ΔWET reduced plans, each new plan was more robust to respiratory motion than the original plan. Minimizing the variation in dose due to respiration is just one of many considerations in proton field selection. To aid in this selection, we have developed a tool which can quickly provide feedback early in the treatment planning process. The ΔWET analysis program can be used to suggest optimum field angles that limit the effects of respiratory motion without the need for gating or other forms of respiratory motion management.
CHAPTER 6: CONCLUSIONS OF DISSERTATION

6.1 Restatement of Hypothesis

We hypothesized that proton therapy planned dose (1) would be more affected by respiratory motion, (2) would demonstrate a larger dosimetric benefit when implementing gated motion management, and (3) that the magnitude of respiratory motion to demonstrate a benefit from gated motion management would be smaller compared to photon therapy.

6.2 Specific Aims

6.2.1 Specific Aim 1

We have quantified the effect of respiratory motion by outlining a method to calculate 4D dose. In this aim, the calculated dose delivered to each phase of respiration was registered to a reference phase at full-exhale. Deformable image registration software was used to accumulate the dose to each voxel over the entire respiratory cycle. The accumulated 4D dose distributions were calculated for 20 patients with physician-approved plans for both passively scattered proton therapy and intensity modulated photon therapy. Our results demonstrated that, for the margins used in the current practice, target coverage was
maintained in both modalities. The mean change between 4D vs. 3D calculated dose was statistically distinguishable for only three indices between proton and photon modalities: Lung V5, Heart V5 and spinal cord maximum dose. The results were contrary to the commonly held assumption that proton therapy will be more susceptible to respiratory motion compared to photon therapy. In both proton and photon therapy, for all normal tissue dose-volume indices observed, no significant correlation was found between tumor motion and the effect of respiratory motion on the calculated dose.

6.2.2 Specific Aim 2

The second aim of the research was to estimate the benefit of respiratory gating by simulating a free-breathing respiratory gated radiotherapy treatment to be delivered at full-exhale. The patient cohort from the previous aim was considered for respiratory gating. For proton and photon therapy, the differences in dose-volume indices were examined between the gated and non-gated plans. Our results demonstrate that respiratory gating can, in theory, reduce normal tissue dose-volume indices for a majority of patients in our cohort. Compared to IMRT, PSPT gating demonstrated a statistically larger mean reduction for all lung (V5-V60) and intermediate (V40-V55) esophagus dose-volume indices. If the variations of
respiratory motion and setup uncertainties are properly managed, the results demonstrated that proton therapy, compared to photon therapy, can lead to larger lung dose reductions from exhale-gated techniques of respiratory motion management.

6.2.3 Specific Aim 3

The benefit of respiratory gating was compared against the measured extent of tumor motion between the inhale and exhale phases of respiration. The results demonstrated that, for our cohort, the benefit of respiratory gating cannot be predicted by the extent of tumor motion alone. This result is contrary to the commonly held belief that protons are more affected by respiratory motion, and thus will demonstrate a benefit of respiratory gating for smaller respiratory motion magnitudes.

Due to the lack of significant correlations between tumor motion and the benefit of gating, we are not able to predict the benefit of gating from the extent of tumor motion. Other simple metrics were investigated such as lung volume and target volume changes during gated delivery. These simple metrics were not able to provide a useful model to predict the benefit of respiratory gating. Therefore, this work was not able to determine a threshold of tumor motion above which to consider respiratory gating. Our results indicate
that respiratory gating can benefit a majority of patients, but short of trial-and-error, we currently lack methods to identify such patients.

The results highlight that the dosimetric consequences of respiration and anatomical variations during the respiratory cycle are too complex to be accurately predicted by the motion of only a single sub-region of the anatomy, namely the tumor volume. We concluded that the current methods to quantify respiratory motion are inadequate. The weakness of tumor motion as a predictor for the benefit of respiratory gating suggests that we need to quantify ‘global’ respiratory motion of the involved patient anatomy, not just of the tumor volume. We hypothesized that the total variations of anatomical densities along the beam path may be a useful metric to quantify respiratory motion.

6.2.4 Specific Aim 4

After demonstrating the weakness of tumor motion to predict variations in planned proton dose due to respiration, we proposed a metric to quantify the density along the beam path to the target: the water equivalent thickness (WET). The WET is the sum of the relative proton stopping power of voxels along the patient anatomy traversed by a proton beam. We demonstrated that the difference in WET between the inhale and exhale phases of respiration
(ΔWET) was significantly correlated to the change in dose (ΔDose) during respiration. In a ΔWET analysis over 87 treatment fields for a 29 patient cohort, we demonstrated ΔWET was significantly correlated to variations in planned dose between the inhale and exhale.

Currently, the predictive power of ΔWET metrics alone is weak. However, we demonstrated the usefulness of ΔWET analysis by improving the robustness of patient plan doses to the effects of respiratory motion. Three patients with the largest dose deviations due to respiratory motion were identified using observed ΔDose metrics. The WET analysis program demonstrated that the original treatment field ΔWET values could be minimized by selecting new field angles. This project created plans that were more robust in the presence of respiratory motion by selecting new field angles with improved values of ΔWET. The use of ΔWET analysis gives a powerful new tool in proton therapy to quantify the anatomical variations of all irradiated tissue along the proton beam path.

6.3 Response to Hypothesis

For the cohort of locally advanced lung cancer patients in this study, the effect of respiration motion was relatively indistinguishable between proton and photon therapy. It was determined that the calculated dose could be affected by respiratory motion in both
modalities. Four dimensional dose calculations showed that low dose spread to the lung and heart was increased in proton therapy compared to the current method of dose calculation using the average 4DCT. The effects of respiratory motion on the PSPT and IMRT calculated dose were not predicted by the extent of tumor motion.

The estimated respiratory gated plan dose was found to show significant reduction in both PSPT and IMRT normal tissue dose-volume indices. The estimated mean benefit of PSPT gating, compared to IMRT gating, was shown to be greater in terms of a greater reduction in all lung dose volume indices (V5-V60) and intermediate esophagus DV indices (V40-V55). However, the extent of tumor motion was not correlated to the benefit of respiratory gating. Due to the lack of significant correlation, we cannot currently determine a model to predict the benefit of respiratory gating. Thus, we have been unable to determine a threshold of motion to indicate gated therapy in either modality. Therefore, it is necessary to evaluate each and every patient for the potential effects of respiratory motion on the calculated dose and the potential benefits of respiratory gated radiotherapy.
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VITA

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