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Re-optimization of Radiation Therapy Dose to the Prostate Using CBCT: Reducing Dose to Organs at Risk

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Abstract

Cancer of the prostate is the second most common cancer among American males. The prostate is small gland, located in the pelvis, posterior to the bladder and anterior/inferior to the rectum. Due to this location when irradiating the prostate the normal tissue organs at risk are the bladder and rectum. Negative effects seen when these structures are irradiated can include; bladder stricture, dysuria, hematuria, diarrhea, rectal bleeding, and proctitis.

In order to eliminate or reduce these negative effects more precise and accurate treatment techniques have been employed. Intensity Modulated Radiation Therapy (IMRT) has been successful in achieving greater precision when irradiating the prostate. IMRT has increased precision while sparing dose to the organs at risk (OAR) of the bladder and rectum allowing for current dose recommendations to be in excess of 75 Gray (Gy). Improvements in accuracy have been most notably achieved with the use of computerized tomography (CT) for treatment planning as well as treatment machine base cone beam CT (CBCT) used for alignment.

The function of the bladder and rectum can cause either to be more or less full, thus changing these structures volume. Improvements have been made in both precision and accuracy however, volume based adjustments to daily treatments have not been evaluated. This project aims to use a paired sample case control study design to link daily changes in volumes to the need for re-optimization for that patient's treatment. Daily volumes to the target (prostate and/or seminal vessels and/or lymph nodes) and the organs at risk (OAR) of the bladder and rectum will be compared to those from planning. Using the current location, volume, and density of these organs, a more accurate estimation of absorbed daily dose by treatment planning software may result.

The results illustrate re-contouring of the bladder and rectum, using daily CBCT, will indicate a change in volume, thus suggesting a change in the dose delivered to these OAR. While, re-optimization was indicated to account for dose changes in OAR, of larger concern, re-optimization was also indicated to account for dose changes in the PTV.

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I. Introduction

Introduction

Prostate cancer is the second most common cancer among American males, behind skin cancer with over 180,000 new cases estimated to be diagnosed this year (American Cancer Society, 2016). The use of ionizing radiation is one of the main treatment modalities for this disease. According to the National Comprehensive Cancer Network (NCCN), depending on the extent of the cancer, this treatment may include the prostate as well as pelvic lymph nodes and seminal vesicles in the planning target volume (PTV). Optimal dosing should be between 75.6 to 79.2 Gray (Gy) in standard 1.8 Gy per fraction (NCCN, 2016). As the target area for treatment becomes larger, so does the area of nearby normal tissues, placing these structures at risk for increased acute and chronic side effects.

The prostate is located in the pelvis posterior to the bladder and anterior/inferior to the rectum. Due to this location when irradiating the prostate the normal tissue organs at risk are the bladder and rectum. The negative effects of ionizing radiation to these structures can include bladder stricture, dysuria, hematuria, diarrhea, rectal bleeding, and proctitis (Chennupati, Pelizzari, Kunnavakkam, & Liauw, 2014). In order to eliminate or reduce these negative effects more precise and accurate treatment techniques have been employed.

Intensity Modulated Radiation Therapy (IMRT) has been successful in achieving greater precision when irradiating the prostate. IMRT has increased precision while sparing dose to the normal tissues of the bladder and rectum allowing for current dose recommendations to be in excess of 75 Gy (Cahlon, Hunt, & Zelefsky, 2008). The modulation of dose, or intensity, across a volume in IMRT is achieved by planning with multiple beams from different directions

(Siebers, 2006). Optimal intensity is calculated by the treatment planning software using the beam angles and treatment objectives defined by the planner on a computed tomography scan (CT). The densities of structures in this scan are defined by the Hounsfield Units (HU). These variations in HU, seen as white to black gray scale, allow for the planning software to estimate the dose delivered to structures in the path of the radiation beams (Siebers, 2006). The assumption is that the path of the radiation beam will intersect the same density on a daily basis allowing this estimate to hold true for each treatment. This estimate fails to be accurate when low density tissue, i.e. gas in the rectum, is absent in the planning CT but present during the delivery of this treatment, or vice versa.

The function of the bladder and rectum can cause either to be more or less full when compared to the planning CT. This change in volume can affect the precision of the dose calculation, as described above, as well as the position of prostate affecting treatment accuracy. A study by Hatton et al. (2011) identified that the daily variation in prostate volume contributes to a significant increase in dose to both the bladder and rectum. To combat this issue multiple imaging modalities have been implemented. One such modality is the use of linear accelerator mounted CT, coined cone beam CT (CBCT), based on the x-ray beam used in the process. Petitto and Pingitore (2008) demonstrated that CBCT provided quick, clear, and accurate images of the prostate as well as the bladder and rectum for daily alignment.

When treating the prostate with ionizing radiation, both accuracy and precision must be employed. The neglect of one or both of these can lead to improper dosing to the target as well as dose to nearby normal structures resulting in disease progression and/or negative effects to the normal surrounding tissues. Accounting for the daily uncertainties of location, volume and density should be considered.

Purpose

The purpose of this project is to determine whether contouring daily CBCT data would illustrate significant changes in volumes of the PTV, bladder, and rectum, suggesting the need for re-optimization of prostate treatment plans.

Scope

This project will use a paired sample case control study design to link daily CBCT images to the original optimized plan used for that patient's treatment. Daily volumes of the target (prostate and/or seminal vessels and lymph nodes) and the organs at risk (OAR) of the bladder and rectum will be compared to those from planning. The patient population for this study would be those diagnosed with prostate cancer who received at least 75.6 Gy in 42 to 46 daily fractions, five times per week.

Assumptions

This project assumes that changes in volumes of the PTV and OAR will cause changes in dose to these structures. With re-optimization based off of daily imaging, one can account for changes in position and volume. Using the current location, volume, and density of these organs, a more accurate estimation of absorbed daily dose by treatment planning software will result. This estimation will equate to a modulated dose that will better achieve the goal of higher dose to target while reducing dose to normal structures.

Hypothesis

Null hypothesis (Ho): re-contouring of the bladder and rectum, using daily CBCT, will not indicate a significant change in volume, thus no change in the dose delivered to these OAR.

Alternative hypothesis (Ha): re-contouring of the bladder and rectum, using daily CBCT, will indicate a significant change in volume, thus suggesting a change in the dose delivered to these OAR.

Significance

Accuracy and precision are of the utmost importance when treating prostate cancer with radiation therapy. The daily uncertainty of the OAR can result in an increased daily dose to these organs. Increased dose to these organs can result in negative outcomes in the form of short or long term side effects. Re-optimization may give more accurate and precise treatments to patients with prostate cancer while reducing the negative side effects seen in these OAR.

II. Literature Review

Prostate Cancer

The prostate is a small, walnut sized, gland in the male pelvis located between the bladder and the rectum. The urethra carries urine from the bladder through the prostate as it travels out of the body through the penis. The prostate is responsible for creating fluid that acts as a source of nourishment and protection for sperm in semen. As men age the prostate can grow in size normally or due to the growth of malignant cells. These malignant cells are most commonly glandular in origin and therefore classified as adenocarcinomas (American Cancer Society, 2016).

According to the American Cancer Society (2016), prostate cancer is the second most common cancer in American men. In 2016, there will be an estimated 180,890 new cases of prostate cancer diagnosed. This relates to a 1:7 chance of prostate cancer diagnosis during a man's lifetime (American Cancer Society, 2016). As a part of the diagnosis process, prostate cancer is given a grade (Gleason score) based on cellular features and also staged based on the extent of the disease including tumor size, lymph node involvement, and the presence of metastatic disease (TNM). The stage and grade are used in identifying prognosis and possible treatment options (American Cancer Society, 2016).

Radiation therapy is an option for men with any stage prostate cancer as a first line or adjuvant treatment. The National Comprehensive Cancer Network (NCCN) uses TNM staging and Gleason score to rank men as either very low, low, intermediate, high, or very high risk prostate cancer. According to the NCCN, their recommendation is watchful waiting for very low and low risk patients. Intermediate risk patients may undergo watchful waiting, surgery, or

radiation therapy, while high risk to very high risk patients need to receive treatment. This treatment may include pelvic lymph nodes and seminal vesicles in the gross tumor volume (GTV) depending on the extent of the cancer (NCCN, 2016). With the adding of more structures to the treatment field, size is added to the GTV. A larger GTV increases dose to surrounding normal tissue structures placing these organs at risk (OAR) for increased acute and chronic side effects which include bladder stricture, dysuria, hematuria, diarrhea, rectal bleeding, and proctitis (Chennupati et al., 2014). Given the serious nature of these acute and chronic side effects, can daily imaging paired with dose recalculation to reduce the absorbed dose in OAR for the treatment of prostate cancer with radiation therapy?

Radiation Therapy

Since the early 1900s, radiation therapy has been successfully used to treat prostate cancer (Tewari, Whelan, & Graham, 2014). As the equipment, computers, and other technological advances have improved, so too has the treatment of prostate cancer with radiation. In the beginning, low voltage x-rays were used with dramatic negative effects to the patient's skin, such as moist desquamation (Tewari et al., 2014). With the advent of Computerized Technology (CT), advanced treatment planning software, and more accurate dose calculation algorithms, megavoltage x-rays at doses in excess of 64 Gray (Gy) have been used to successfully treat prostate cancer with reduced recurrence and disease progression (Tewari et al., 2014). According to the NCCN, dosing between 75.6 to 79.2 Gy in standard 1.8 Gy per fraction is considered the appropriate dose to treat very low and low risk patients. This recommendation includes dose escalation to 81 Gy as risk increases to the intermediate, high, and very high risk groups (NCCN, 2016). The successes in high dose prostate treatment are not without negative effects. Zelefsky et al. (2008) found that as many as 13% of patients treated at high doses (>70

Gy) would have acute effects to their rectum such as bleeding or diarrhea. Of these 13%, 42% continued complaining of these same effects to the rectum over a 10 year span classifying these as late side effects (Zelefsky et al., 2008). Late effects are not necessarily those that present after a certain amount of time but rather, are long term in nature and do not resolve on their own once radiation treatments are stopped, like an acute reaction would. In this same sample, researchers found the incidence of bladder side effects, such as dysuria, to be as high as 20% and concluded that as dose increased the incidence of rectal and bladder toxicities also increased (Zelefsky et al., 2008). While all effects of radiation are considered to be random in occurrence over time, as defined by the stochastic nature of these late side effects, the increase in dose does not increase the probability of late side effects but rather the additional treatments (increased fractionation) increase the probability that these effects will occur (Brodsky, 2012). The study by Zelefsky et al. (2008) does highlight that with increased treatment dose, and thus increased fractionation, the precision in radiation therapy becomes increasingly important to reduce the effects seen on the OAR.

Precision

To address the issues of precision when treating with radiation therapy, conformal treatment planning techniques have been investigated. Conformal radiation therapy (CRT) is one technique utilized to account for daily patient specific variation throughout treatment while reducing the inclusion of normal tissue (Ghilezan, Yan, & Martinez, 2010). To account for target (GTV) and OAR variation in position, shape, and size, a 3-dimensional margin can be added to the GTV creating a planning target volume (PTV). The question becomes how much margin should be added. Over expansion could lead to more dose to normal tissue while under expansion could lead to inadequate coverage of the target. A study by Dearnaley et al. (2005)

investigated the appropriate size margin in all dimensions to achieve CRT and found 10 mm to be satisfactory to account for GTV variation while minimizing excessive inclusion of normal tissues. While improvements are seen in precision with 3-D CRT, areas of dose above tolerable levels within the defined OAR are still present (De Meerleer et al., 2000).

Tolerable dose (TD) levels have been studied for years and are given in terms of dose that would equate to a certain effect in 5% of the population after 5 years; referred to as organs TD 5/5. It is generally accepted that these doses are the dose limit allowed for OAR. The rectum and bladder have been found to have TD 5/5's at 60 Gy and 65 Gy, respectively (Emami et al., 1991). Looking at the previous section, the NCCN recommends treatment doses of 75.6 to 81 Gy to the PTV. As 3-D CRT improves precision, the presence of treatment doses above the TD 5/5 necessitates an even more precise treatment planning method.

IMRT treatment planning

Intensity Modulated Radiation Therapy (IMRT) has been successful in achieving further precision with high doses to the prostate, while sparing dose to the normal tissues of the bladder and rectum (Cahlon et al., 2008). The process of planning IMRT treatment is both technical and labor intensive taking about a week to complete, from starting in simulation with a stable and reproducible patient setup to the first day of treatment. The process of simulation varies with the clinical site, however; all prostate IMRT simulation contains an element of image acquisition through CT for targeting and daily treatment replication. To achieve this, most patients lay supine, arms on their chest, with a cushion under their knees. Patients are also asked to fill their bladder as best they can and clear their rectum. This strategy is used to reduce the daily uncertainty in the position of the prostate due to changes in the volume of the rectum and bladder

(Munck af Rosenschöld et al., 2014). This is important, as most patients will be receiving 42 to 45 days' worth of treatments. Scout films, which are orthogonal x-rays on CT, are used to verify patient compliance prior to the CT study being completed. Once the CT and positioning of the patient are created, the treatment planning process continues by defining the target volume (GTV) and normal tissue structures including OAR (Ghilezan et al., 2010). As previously described, the target volume will be the prostate and may or may not include the seminal vesicles and/or pelvic lymph nodes depending on the extent of disease. Normal tissue structures will include the bladder, rectum, bowel, colon, and femurs. Using radiation therapy treatment planning software, contours are created to define each of these structures. Once these structures have been identified from the planning CT, radiation therapy treatment beams can be added. These beams will number as few as five to as many as nine non-coplanar beams (Siebers, 2006). This arrangement will depend on the preference of the dosimetrist and physician in order to achieve conformity.

A conformal treatment is one that achieves the goal of delivering the prescribed dose to the PTV while sparing dose to OAR, mainly the rectum and bladder (Martin & D'Amico, 2014). The use of the conformity index can quantify this measure. The successful conformity found in this type of treatment is due to the ability of the planner and planning software to adjust the dose across normal tissue through the optimization process, thus reducing dose to the OAR. The work done by Viani and his colleagues was able to use IMRT to deliver conformal doses >70 Gy to the prostate with minimal dose to the OAR (Viani, Stefano, & Afonso, 2009). The use of IMRT has since been the gold standard for achieving high doses to the target volume while sparing dose to the OAR.

Optimization

The modulation of dose across a volume in IMRT is achieved by planning with multiple beams from different directions, where each beam delivers a non-uniform dose to the target (Siebers, 2006). The end result is a conformal plan which delivers a high dose to the target with a steep fall off protecting OAR. The non-uniform dose, or modulation of intensity, is achieved through the movement of a multi-leaf collimator (MLC). MLC's are small, 0.4 cm to 1 cm in width, metal projections that can move independently to block out photons from the linear accelerator. The optimal intensity (fluence) is then calculated by the planning software using an optimization algorithm (Siebers, 2006). The algorithm is given specific treatment objectives to achieve from the planner and physician. These objectives include the prescribed dose to the target as well as the desired limits to normal tissue.

Optimal intensity is calculated from the beam angles and treatment objectives using the simulation CT. The densities of structures, as shown by the Hounsfield Units (HU), allows for the planning software to estimate the dose delivered to structures in the path of the radiation beams. These doses are the result of the incident photons as well as their resultant electron scatter being absorbed by tissue (Siebers, 2006). The more dense tissues, seen as bright white on CT, will absorb more dose, while the darker, less dense tissues, will allow dose to more easily pass through as it is not being absorbed. This becomes a specific issue when low density tissue, i.e. an air cavity in the rectum, is present in the planning of treatment but absent during the delivery of this treatment, or vice versa. In order to achieve optimal intensity, one must take into account the heterogeneity of the tissues that the beams will be passing through (Siebers, 2006).

Specific objectives include maximum dose desired at the target as well as minimum dose desired to OAR to reduce the incidence of organ toxicity. As discussed above, doses to target can be as high as 81 Gy to achieve optimal disease control. As for the dose to OAR, studies have

shown that late morbidity to the bladder, specifically dysuria and hematuria, occurred in 4% and 9% of patients, respectively, when treating the prostate with a dose of 74 Gy with less than 15% of the bladder receiving greater than 70 Gy (De Meerler et al., 2007). Late rectal toxicity was identified as hemorrhage, proctitis, and diarrhea. As discussed earlier, late effects do not necessarily always present at the end of treatment but rather, are chronic in nature and do not resolve without some intervention. Late effects present in 86% of men after two years from treating their prostate with a dose of 74 Gy with 10% of the rectum receiving less than 70 Gy (Chennupati et al., 2014). These negative effects, if seen earlier, can impact a patient's treatment by causing delays, which affects the efficacy of the treatment itself.

Accuracy

While IMRT can be used to help improve precision in delivering high doses of radiation to the prostate while sparing OAR, the problem becomes the transient nature of the prostate due to its anatomical relationship to the bladder and rectum. Due to their functions, both the bladder and rectum can be either more full or more empty than they were during the acquisition of the planning CT. When using the planning CT to identify the GTV and OAR, one is limiting the planning and daily alignment to this single snapshot or moment in time. One is assuming that these structures will be in a similar position at the time of treatment. Hatton et al., (2011) have shown that the daily variation in prostate location contributes to a significant shift in target volume coverage and an increased dose to both the bladder and rectum. This increase in dose can result in both the chronic and acute effects seen in the above mentioned studies by De Meerleer et al., (2007) and Chennupati et al., (2014), respectively. In order to account for this daily variation, a variety of imaging techniques have been utilized to clearly and accurately

delineate the target and normal tissue volumes. The use of imaging for daily shifts to improve accuracy of dose delivery has been coined image guidance (IG).

Daily Imaging

Daily Imaging has been studied as the solution to verifying location of GTV and OAR prior to treatment, thus improving accuracy of treatment. A study by Ghadjar et al., (2010) demonstrated a significant reduction in acute and late effects of both the rectum and bladder in a group of daily imaged patients compared to those imaged weekly. A popular daily imaging technique for IG-IMRT is CT imaging with a cone beam CT (CBCT) unit that is integrated into the linear accelerator. This technology has been demonstrated to provide quick, clear, and accurate images of the prostate as well as the bladder and rectum for daily alignment (Petitto & Pingitore, 2008). These images can be compared to the planning CT and then aligned using a X, Y, & Z coordinate system. The coordinate system can be translated into lateral, vertical, and longitudinal shifts, giving the treatment team the ability to adjust the patient so that current location of structures match the location during planning (Mestrovic, Milette, Nichol, Clark, & Otto, 2007).

Dose Calculations with CBCT

As identified by Petitto and Pingitore (2008), CBCT data can improve the accuracy of prostate irradiation by representing the position of the prostate, rectum, and bladder allowing for daily corrections prior to treatment. These images can also be used to improve treatment precision by allowing for calculations of dose to the PTV and OAR from their real time position. As discussed earlier, the process of treatment planning and optimization can be repeated using CBCT data in place of the simulation CT data. Hüttenrauch et al. (2014) have

shown that HU can be accurately calibrated from electron densities seen in the CBCT and then used by the treatment planning software to accurately estimate the dose to these structures based on their real time CBCT position. Taking this one step further, once the dose to these structures has been estimated, re-optimization of the fluence can be conducted to maximize dose to the prostate and limit dose to the bladder and rectum based on their relatively current location and size (Li et al., 2013).

Some would argue, the re-optimization process is very time and labor intensive thus, a frivolous act as the size and location of the target and OAR could be different once the re-optimization is completed (Li et al., 2010). A suggested solution to the problem of identifying when re-optimization should take place was proposed by Oates et al. (2015). They used rectal diameter as a predictor of need to re-optimize the treatment plan from CBCT data. The researchers determined that a rectal diameter >3.5 cm would indicate a significant risk for displacement of the prostate by as much as 4 mm which could correlate to a significant dose variation (Oates et al., 2015). This study was able to quickly identify patients that might need to be re-optimized but did not complete this re-optimization process to see if any benefit exists. The intent of this research is to take the study by Oates et al. (2015) one step further and examine if contours on daily CBCT images would produce changes in volumes that would suggest re-optimization of prostate treatment plans, thus reducing dose to OAR.

Summary

In the treatment of prostate cancer with radiation therapy, accuracy and precision are of the utmost importance. Not only for the eradication of cancerous cells but also for the sparing of normal cells reducing the incidence of acute and chronic side effects, specifically to the OAR of

the bladder and rectum. Through multiple studies, motion of OAR and the treatment target have been shown to affect both accuracy and precision in prostate treatment. Accounting for this motion both daily shifts and beam intensity should be considered. Oates et al., (2015) identified daily volume changes in the bladder and rectum. The aim of this study is to further assess what the volumetric difference is to the primary target, rectum, and bladder between the CT planned IMRT treatment and the treatment that was delivered. A volumetric difference would suggest a dose difference could exist. Therefore, necessitating daily re-optimization of plans in an effort to provide a more accurate and precise treatment to the prostate while improving the sparing of OAR through a reduction in their dose.

III. Methods

A retrospective analysis of previously treated prostate patients will be used to compare the volumes of the PTV and OAR in planned and delivered treatment to volumes of these structures identified from a daily, 80 slice CBCT. The daily CBCT images will be used to delineate target and OAR location and size for the evaluation process. The source of this data will come from six male patients treated for prostate cancer at a single West Michigan outpatient cancer center from 2015-2016.

Inclusion and Exclusion Criteria

A convenience sample of six prostate patients will be randomly selected from the cancer center's electronic medical record. These patients all have received at least 75.6 Gy via external beam IMRT to the prostate over a period of about six weeks, equal to 42-46 treatment days between January 1, 2015 and June 30, 2016. This will total 252 - 276 days' worth of patient CBCT data to be contoured and then re-optimized. Therefore, included in the patient treatment record must be daily imaging in the form of CBCT images. As various stages of disease can influence the target volume, special attention will be made to identify which structures comprised this target (PTV) for each patient. Included in the earlier discussion, the PTV can be defined as; the prostate alone, the prostate and seminal vessels, or the prostate, seminal vessels, and various pelvic lymph nodes, all including an added margin. Any stage disease, and thus any size PTV, will be included in this study. Men are to be excluded if they did not complete the full course of treatment, the PTV was not defined, and/or CBCT data was missing for any one day during the full course of treatment.

Study Design

A paired case control study design will be used to compare the volumes used in planning to the volumes seen daily over the course of treatment for these six patients. This study design allows for comparisons to be made between the planning volumes as the control, to the re-contoured daily volumes as the cases. Using a paired case control design, each patient is both the case and the control. This design helps to limit variability of the internal anatomy between different patients and control other confounding variables (Hosmer & Lemeshow, 2000). As all patients have already received treatment, comparing this "exposure" as the control to the cases of re-contoured daily treatments, is additional rationale for this design. Patient data will be de-identified once their daily CBCT's are matched or "fused" to the planning CT during each day of treatment as shown in figure 1.

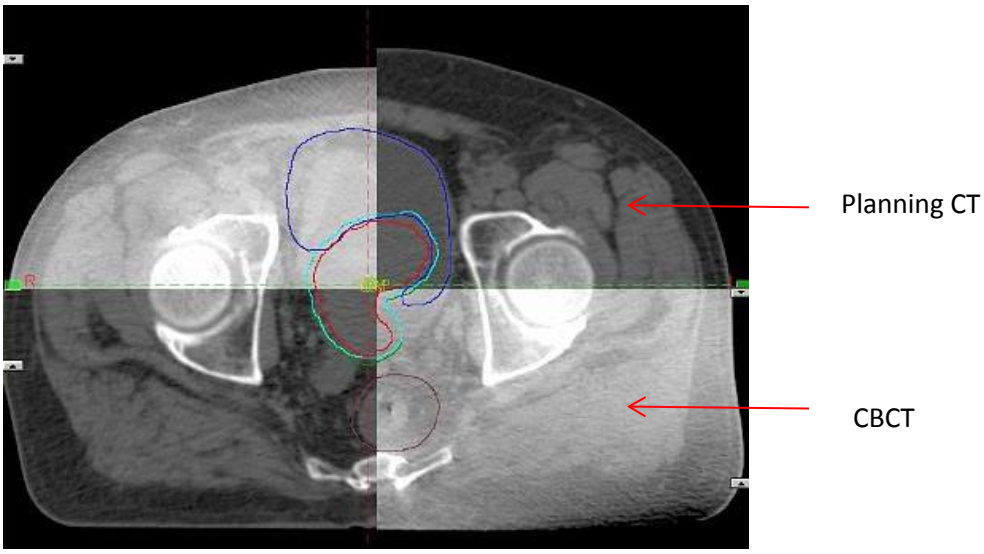

Figure 1. Cone beam computed tomography and planning computed tomography fusion and alignment. An overlay technique can be used to verify patient's alignment compared to plan. Adapted from Google Images (2016a).

Once selected to be included in the study, the patient's daily CBCT, which has been matched to the planning CT to correct for motion, will be uploaded into the treatment planning system. Once in the software, identification of the target as well as the OAR can be done on the CBCT data. The identification and outline, also known as contouring, of the PTV, bladder, and rectum will need to be done. The contouring process uses the planning software to draw and label structures on each slice of the 2-dimensional images, creating 3-dimensional structures. Images are just pictures, without proper delineation and labeling of the structures, the target and the OAR, identifying the dose associated to each will be impossible. For optimization, it is important to identify these structures correctly so that proper dose limits and objectives can be assigned and used by the planning system. This identification is achieved via contouring, done by the dosimetrist. As seen in figure 2, different colors are used to denote various structures.

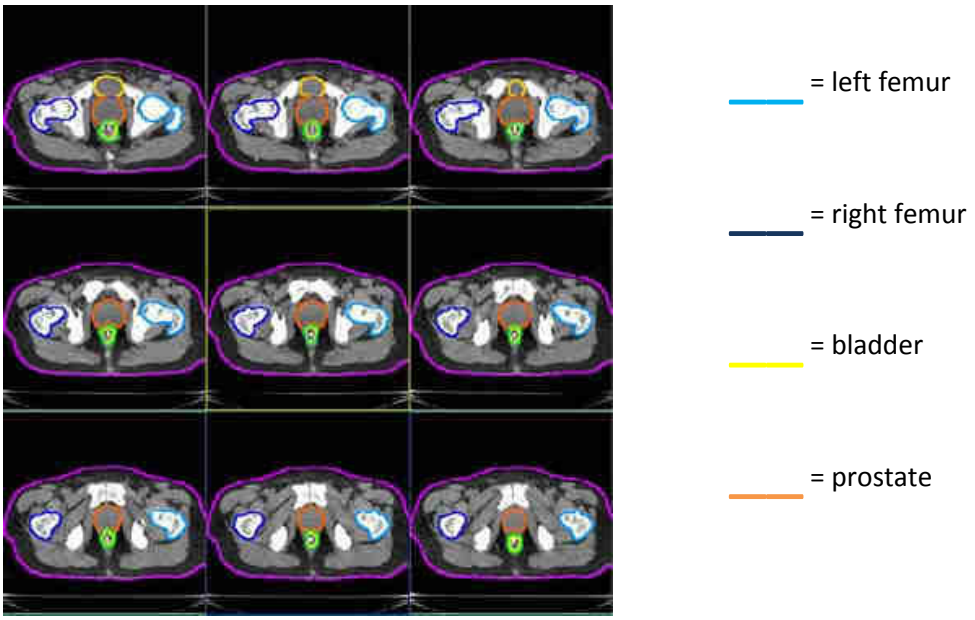

Figure 2. Contours of axial slices through a patient's pelvis. Colors are assigned to each structure to make them more easily distinguishable. Adapted from Google Images (2016b).

planning to predict radiation interactions with matter (Zurl, Tiefling, Winkler, Kindl, & Kapp, 2014). These variations in HU, or gray color, are also used to differentiate between anatomical structures. When viewing a CT data set, one can adjust these values to aide in the identification of normal tissues. The bladder and rectum will follow traditional contouring rules, as the structures themselves will be contoured. The identification of the PTV will follow the treatment planning directive. For five of the six patients this included the prostate, the proximal 1cm seminal vesicles, and a 0.5cm margin to these. To create this structure, the use of Eclipse's bouillon operations was implemented. First the prostate and seminal vesicles were outlined. The intersection of the prostate plus 1cm of proximal seminal vesicles was obtained via a multi-step bouillon operation. This combined structure was given a 0.5cm margin and labeled PTV.

Prior to any optimization, the HU will need to be corrected for electron density via the electron density conversion model (Guan & Dong, 2009). This conversion will allow for the treatment planning software to better anticipate the interaction of incident radiation within the patient based on the density of material it will encounter. Optimization of treatment plans from simulation CT was completed and a total dose to each of these structures was calculated using the Anisotropic Analytical Algorithm (AAA) prior to treatment day number one (Ronde & Hoffmann, 2009).

After the dose has been calculated by the planning system and a series of checks completed, treatment can begin. CBCT images collected during the treatment process will be used to compare daily volumes with those of the original plan, which was optimized using structures identified from the planning CT. During the treatment planning process dose to volume relationships are regularly checked. This comparison is done using a dose volume histogram (DVH). A DVH is generated by the planning system, and can quantify the dose

calculated to a specific volume of a structure, once the structure has been identified by the planner. As reported by Marks et al. (2010), this information can be useful in planning as it illustrates the dose-to-volume relationship for normal tissues. Certain dose-to-volume relationships, as discussed earlier, have been associated with negative side effects. To reduce the probability of these effects, certain dose-to-volume values will be used as the planning objectives for the planning systems optimization. The dose-to-volume relationships are expressed as a percentage of the tissues volume receiving a certain amount of dose. An example of this for the rectum would be, V50 Gy < 50%. This would equate to a planning objective where 50% of the volume will receive less than 50 Gy. Each OAR may have multiple dose-to-volume recommendations. For the OAR in prostate irradiation the recommendations are described as; V50 Gy < 50%, V60 Gy < 35%, V65 Gy < 25%, V70 Gy < 20%, V75 Gy < 15%, with maximum dose < the prescription for the rectum, with V65 Gy $\leq$ 50%, V70 Gy $\leq$ 35%, V75 Gy $\leq$ 25%, and V80 Gy $\leq$ 15% for the bladder (Marks et al., 2010). For this study, the above values were used as the planning objectives in the original optimization and will be used as checkpoints for the volume comparison processes.

The comparison of volumetric data from planned values to the values calculated after re-contouring will be completed. For this paired case-control study, the control will be defined as the treatment as it was planned using the original optimization from a single CT image. Each control will have multiple cases paired to it as the re-contouring will be completed for all six patients on each of their daily CBCT images. This analysis will be completed using Varian's Eclipse treatment planning system's contouring function. Varian's Eclipse treatment planning data allows for comparison of multiple plans at the multiple dose-volume checkpoints described above. After re-contouring, the total volume of these structures will be calculated and defined at

these above identified volumetric checkpoints. These data will be recorded and compared to the data from the treatment plan DVH. This comparison will result in the volume being described as higher, lower or the same as the control volume of the PTV, bladder, and the rectum.

Human Subject Protection

All patient data and images will be accessed and stored through secure network. Patient data will be de-identified through the use of anonymization software within the network. The lead investigator has completed training in ethical human based research. This study was submitted for approval to Metro Health Hospital's Institutional Review Board (IRB). Appendix 1 contains this letter of approval.

Statistical Analysis

To evaluate if re-optimization might be necessary to reduce dose to the OAR, the volumes calculated for these structures from the plan will be compared to the volume of these structures from the re-contouring, using the CBCT data. This paired case-control study will use each patient's planning CT as the control, while their daily CBCT will be used to create a re-contoured plan and be considered the case. Due to the treatments being delivered over multiple days, multiple cases will be paired to each of the six controls. As the controls will be the comparable standard, all six will have no volume change. Each case will have their volumes of OAR and PTV calculated to the tenth of a cubic centimeter (cc) by the eclipse treatment planning software. These data will be reported as structure name _ patient number, i.e. bladder_1.

For this study, having 42 treatments paired with 6 patients, yields more than 250 sets of data. This sample size was determined to be associated with a power of 0.95. Each data set will have multiple volumes for comparison. For the rectum and bladder, the total volume in each

data set will be compared to the control. Changes in these volumes will suggest change in dose to these structures and possible affects to the PTV. For the PTV volume, the total volume will be compared in relation to changes in volumes of OAR. The recommendation for optimal coverage of the PTV should be 100% of the PTV receiving greater than 95% of the prescription (Rx) but also less than 110% of the prescribed dose. Changes to the PTV size will have associated consequences to the dose coverage.

Theoretically, the PTV volumes should not change as these structures are not transitional in nature like the bladder and rectum. However, the transitional effect the bladder and rectum may have effects on the volume of the PTV. A post hoc pairwise comparison will be completed with a Bonferroni adjustment to analyze if the bladder or rectum volume changes can be related to changes in the PTV volume.

As a number of different conditions are to be measured on multiple days, a repeated measures analysis of variance (ANOVA) will be completed to evaluate if a significant difference in means exists. This also allows each matched pair to be considered a single data set. This one way repeated measures ANOVA including the post hoc pairwise comparison will be completed using SPSS Statistical software.

IV. Results

An ANOVA with repeated measures was used to evaluate statistically significant differences between the means of within-subjects factor. Time in this project will be considered the independent variable or, "within-subjects factor" as volumes were recorded from the planning CT and 42 daily CBCTs. For validity of results from ANOVA, five assumptions must be true. First, dependent variables should be measured as intervals or ratios. The volume measurements of bladder, rectum, and PTV will represent the dependent variables and each is measured as an interval. Second, the independent variable should consist of at a minimum of two categorical matched pairs. For this project the independent variable is time, and the categorical matched pairs include the first CT done in simulation matched to each treatment day. As there is only one independent variable, a one way ANOVA with repeated measures is most appropriate. The third assumption states there should be no significant outliers in any level of the within subjects factor. As represented by the boxplot in figure 3 below, the significant outlier at time 12 for Bladder 1 is noted by the asterisk.

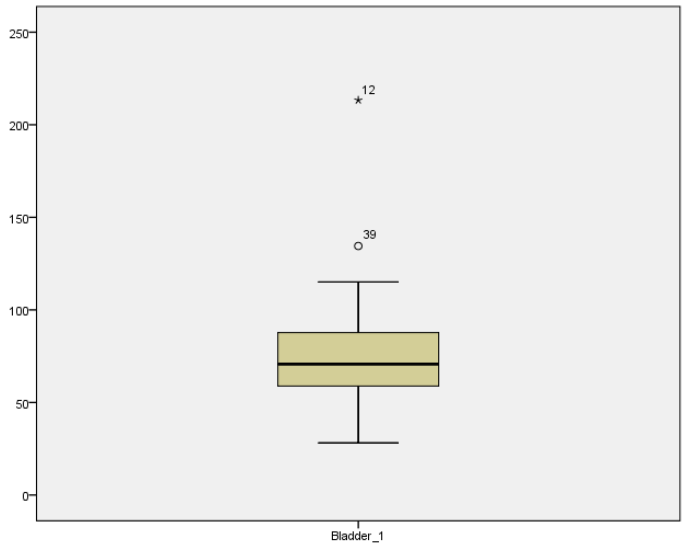

Figure 3. Boxplot of Bladder_1 volumes

Significant outliers exist for Bladder 1 time 12, Rectum 4 times 4 and 5, and Rectum 5 time 11. After further investigation, these extreme outliers are not due to data entry or measurement errors and therefore are genuinely unusual data points that should not be rejected as invalid. As this project is examining volumetric changes in living human beings it is believed that these volumes are valid and will be left in for analysis. Leaving these outliers in the analysis will require the one-way ANOVA to be ran with and without the outliers.

Assumption four requires the dependent variable to be approximately normally distributed for each level of the within-subjects factor. As this project has more than 50 participants, a normal Q-Q plot will be used to assess normality. As seen in figures 4, 5, & 6 below, the volumes of the Bladder, Rectum, and PTVs were relatively normally distributed, all with a slight positive skewness.

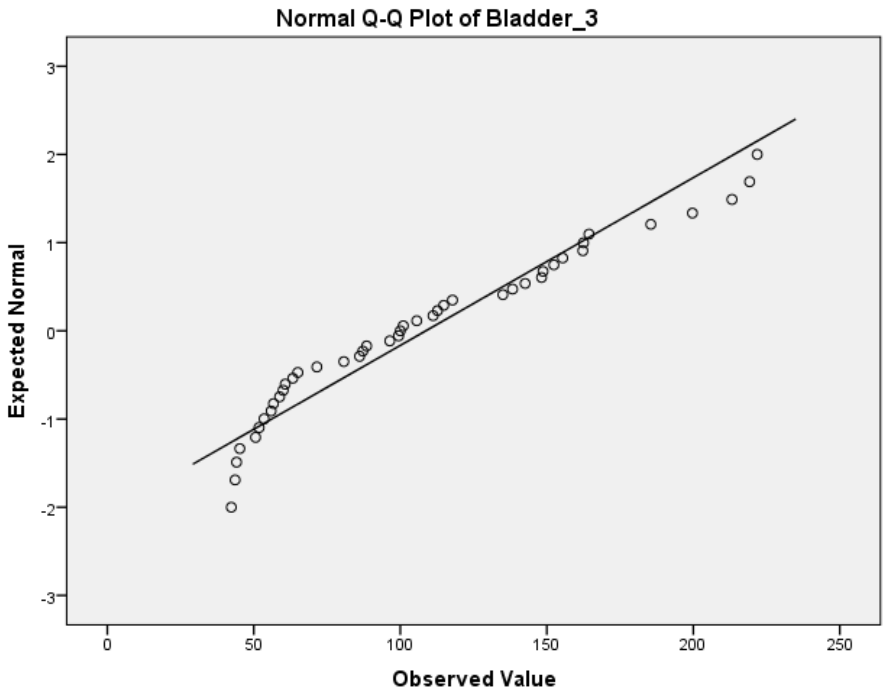

Figure 4. Example Q-Q Plot of bladder

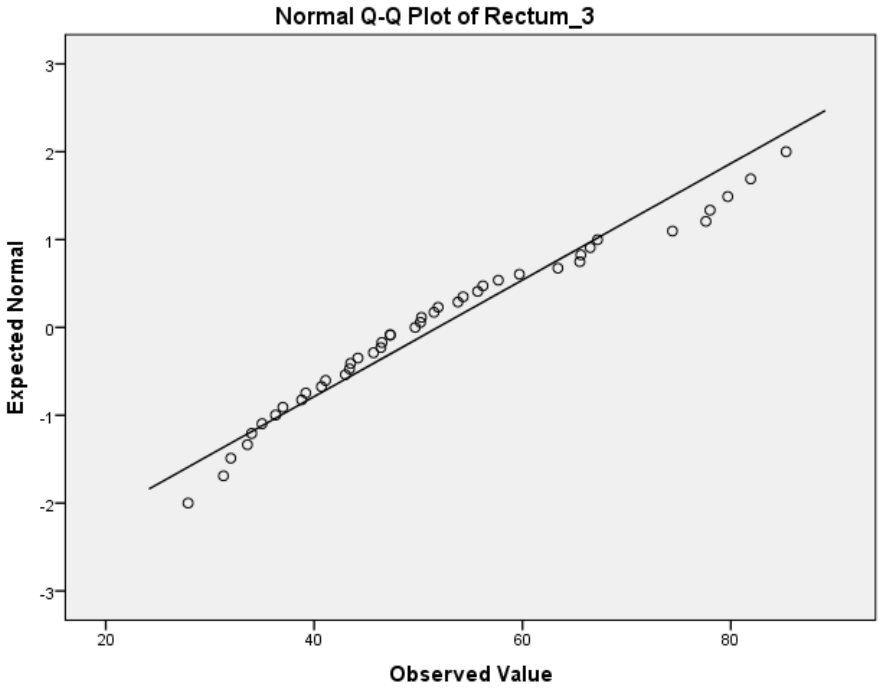

Figure 5. Example Q-Q Plot of rectum

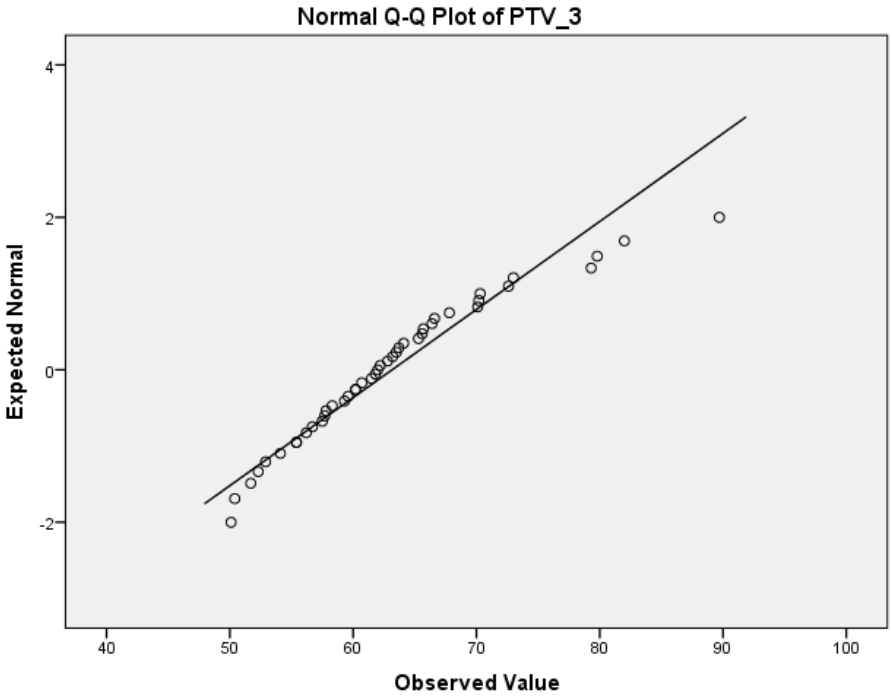

Figure 6. Example Q-Q Plot of PTV

In order to meet assumption five, the variances of differences between all combinations of levels of the within-subjects factor must be equal. This is also known as the assumption of sphericity and can be testing using Mauchly's test of sphericity. Using SPSS the Mauchly's test of sphericity was ran at the same time as the one-way ANOVA procedure. As seen in figure 7 below, Mauchly's test of sphericity indicated that the assumption of sphericity has been violated as each patient's significance level is less than .05. The highest of these was patient 1 at .43 however, still representing a $p < .05$. As the assumption of sphericity was found to be violated, a correction will have to be used to adjust for this bias when calculating the p-value of the ANOVA. As the Greenhouse-Geisser values in the epsilon portion of figure 7 are near or below the value of .75, the Greenhouse-Geisser correction will be utilized when interpreting the ANOVA results. (Maxwell & Delaney, 2004).

Mauchly's Test of Sphericity[a]

Within Subjects Effect	Measure	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[b]		
						Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Volume	Patient_1	.855	6.415	2	.040	.873	.908	.500
	Patient_2	.289	50.857	2	.000	.585	.591	.500
	Patient_4	.477	30.370	2	.000	.656	.669	.500
	Patient_5	.087	100.026	2	.000	.523	.524	.500
	Patient_3	.236	59.215	2	.000	.567	.572	.500
	Patient_6	.084	101.588	2	.000	.522	.524	.500

Figure 7. Mauchly's test of sphericity from SPSS

Using the Greenhouse-Geisser correction, statistically significant changes in volume over time where the result. Reviewing the Greenhouse-Geisser rows from appendix 2, all six

patients have significant changes in volumes with $p < .0005$. As $.0005 < .005$, one may reject the null hypothesis and accept the alternative hypothesis that re-contouring of the bladder and rectum, using daily CBCT, will indicate a change in volume, thus suggesting a change in the dose delivered to these OAR.

As the volumes of the bladder and rectum were seen to fluctuate throughout the 42 days of prostate treatment, their volume changes may also have an effect on the volume of the PTV. As there are three volumes of interest, there will be three combinations of interactions between these volumes for each patient. The post hoc Bonferroni test will examine these interactions within each patient. First, looking at the mean volumes of each structure in figure 8 below, one can compare these to the mean difference of each structure from the pairwise comparisons, appendix 3. In the pairwise comparisons show in appendix 4, within each patient the bladder is represented as 1, the PTV as 2, and the rectum as 3. In this comparison, as the rectum volume changed the associated PTV volumes decreased in five out of six patients. The average decrease in PTV volume for each patient is 4.41 cc, 3.84 cc, 2.40 cc, 3.09 cc, and 1.60 cc respectively. Patient 5 reported an increase of 3.50 cc in PTV volume as rectum volume changed. Data are mean +/- standard deviation, all significantly significant with $p < .05$.

Summary

A one-way repeated measures ANOVA was conducted to determine whether statistically significant changes in volume existed in six prostate patients over the 42 days of treatment. There were significant outliers for Bladder_1 time 12, Rectum_4 times 4 and 5, and Rectum_5 time 11. These outliers were not rejected as invalid as they represented structures whose volumes are known to fluctuate. Further normality was established with normally distributed Q-

Q plots with slight positive skewness. The assumption of sphericity was violated, as assessed by Mauchly's test of sphericity ($p < .05$). Therefore, a Greenhouse-Geisser correction was applied. Statistically significant volume changes were identified in all patient's rectum, bladder, and PTV. Post hoc analysis with a Bonferroni adjustment suggested an association between the change in volume of the rectum and change in volume of the PTV. The average decrease in PTV volume for each patient is 4.41 cc, 3.84 cc, 2.40 cc, 3.09 cc, and 1.60 cc respectively. Patient 5 reported an increase of 3.50 cc in PTV volume as rectum volume changed. Data are mean +/- standard deviation, all significantly significant with $p < .05$.

Structure	Mean Volume (cc)	N
Bladder_1	74.95	43
PTV_1	92.63	43
Rectum_1	50.15	43
Bladder_2	181.31	43
PTV_2	124.73	43
Rectum_2	48.85	43
Bladder_3	143.38	43
PTV_3	63.16	43
Rectum_3	51.87	43
Bladder_4	143.38	43
PTV_4	177.47	43
Rectum_4	52.07	43
Bladder_5	290.26	43
PTV_5	60.72	43
Rectum_5	72.43	43
Bladder_6	190.15	43
PTV_6	82.89	43
Rectum_6	47.44	43

Figure 8. Mean Volumes

V. Discussion and Conclusions

Discussion

As illustrated by the results above, one can reject the null hypothesis and therefore, accept the alternative hypothesis which states; re-contouring of the bladder and rectum, using daily CBCT, will indicate a change in volume, thus suggesting a change in the dose delivered to these OAR. This finding may be intuitive as we understand the functions of the bladder and rectum however, accounting for this dose due to volumetric change remains time consuming and elusive. In addition, the effect that this change in volume has on the doses calculated is yet to be determined. Over the course of treatment the fluctuations in size of the OAR, either larger or smaller than originally contoured, may cause a dose averaging effect. We must also consider the cause of the volume change. Is this change due to increases in fluid (more dense) or increases in air (less dense)? Each would have different effects on the incident x-rays.

Just as in the study by Oates et al., (2015) identified volume changes potentially affecting dose, this project described a pattern of volume changes throughout the course of treatment that could change the dose to OAR and the PTV. Not only volume changes to the rectum, as described by Oates et al., (2015) but also significant volumetric changes to the bladder and PTV as well. As these were most associated with changes in volume to the rectum, extra care and patient preparation to reduce changes in rectal volume should be implemented. A study by Heng and colleagues illustrated a simple protocol of daily laxative use was well tolerated by patients and lead to more consistent rectal volumes seen during treatment (Heng, Low, & Sivamany, 2015). This same study went on to establish a reasonable procedure to help reduce changes in bladder volumes. They found that if patients would consume 4-5 cups of 250 milliliters of water

one hour prior to treatment, bladder volumes remained relatively consistent (Heng, Low, & Sivamany, 2015).

Strengths & Limitations

The use of a paired case control study design was a major strength of this project. This design allows for comparisons to be made between the planning volumes and the volumes seen daily over the course of treatment for these six patients. To account for patient specific variables, a non-traditional case control study design was successfully implemented. This was helpful in evaluating multiple dependent variables within the same patient over time. As with any case control study, the advantages of looking at multiple risk factors is essential to this project. Unlike other case control studies this project did not rely on patient recall but rather the data was readily accessible. Having complete CBCT data that was workable constituted a large strength to this study.

One of the major limitations identified while completing this project was that of structure identification. As discussed earlier having contours that accurately represent their identifying structures has a major impact on dose. The best way to have accurate contours is to have clear images. Many of the CBCT images had artifacts that made structure delineation more difficult. Many times these artifacts were due to the rectum being full of air or feces interacting with the very x-rays used to obtain the image. Also, as this was a student led project one must question the accuracy of the contours as no procedure for review of these structures were implemented.

The 80 slice limit of the CBCT image set would also be a limitation. While limiting the range of the image is necessary for quality patient care, larger bladders could have a portion of their volume outside of the visible range. This was seen in one of the 252 date sets. The volume

of this bladder was incompletely calculated but still significantly greater than the volume seen in the treatment plan. So much greater that this bladder volume was identified as a significant outlier.

Recommendations for Future Research

Further research in the area of dose to OAR in prostate cancer must be considered. As proposed in the discussion section, what effect the change in volume has on dose to the OAR and the PTV is yet to be identified. Advancements in imaging will help us to eliminate or reduce many of the limitations identified in this project. However, the time required to implement any planning change will be the limiting factor.

Longitudinal research in the area of patient outcomes may be a natural progression for future research. Further investigating any association between recurrence rates of prostate cancer as well as chronic effect seen in the rectum and bladder due to noted changes in volume during treatment. These outcomes measures may be helpful in evaluating "quality" of treatment.

Conclusions

The purpose of this project was to determine whether contouring daily CBCT data would illustrate significant changes in volumes of the PTV, bladder, and rectum, suggesting the need for re-optimization of prostate treatment plans. The results suggest that re-optimization due to volume changes might be necessary to further improve the accuracy of prostate IMRT. However, from the results and discussion one must consider the time needed to complete this task. Not only consider the time necessary to position the patient and gather the CBCT image but then use these data to contour and then optimize for dose delivery. This does not include the time necessary for the physician to approve these contours and re-optimized plan as well as the

time needed to properly check this new plan prior to implementation. In our current workflow this task would not be practical, as from start to finish one could expect this process to need almost 90 to 120 min. After such a delay the re-optimization could be argued to not represent the current conditions, just as the original did not. Ghilezan et al., (2010) had a unique solution with their introduction of adaptive radiation therapy for prostate cancer. In this study, Ghilezan and colleagues relied on "off-line", or after treatment, planning and analysis. This allowed the time necessary to complete the contouring and optimization process with the patient not on the treatment table. However, this re-optimization used only the first five treatments to create their "adaptive plan" and did not reoccur at any point in treatment (Ghilezan et al., 2010).

While, re-optimization was indicated to account for dose changes in OAR, of larger concern, re-optimization was also indicated to account for dose changes in the PTV. Keeping the goal of radiation therapy in mind, (treating targets with high doses of radiation, while minimizing dose to normal tissues) as well as understanding risks associated with under dosing targets, having a heightened awareness of affect volume changes have on the accuracy of our IMRT prostate treatments is imperative.

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Appendix 1. Letter of Approval Metro Health Hospital

MetroHealth

Metro Health Institutional Review Board
Metro Health Professional Building
5900 Byron Center Ave, SW
Wyoming, MI 49519
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NON HUMAN RESEARCH DETERMINATION

July 22, 2016

R. Charles Keider, B.S., R.T. (T)
Instructor & Clinical Coordinator of Radiation Therapy
Department of Diagnostic and Treatment Sciences
CookDeVos Center for Health Sciences
301 Michigan Street NE
Grand Rapids, MI 49503-3314

PROJECT NAME: **Re-optimization of Radiation Therapy Dose to the Prostate Using CBCT: Reducing Dose to Organs at Risk**

Dear Mr. Keider:

On July 22, 2016, the above referenced project was reviewed. It was determined the proposed activity does not meet the definition of research as defined in 45 CFR 46.102(d).

Approval by Metro Health IRB is not required. This determination applies to the activities described in Protocol version date July 19, 2016. If changes are made and there are questions about whether these activities are human research, please contact the IRB office.

Your project will remain on file with the IRB office, but only for purposes of documenting this determination. If you should have questions regarding the status of your project, please contact Maureen Oostendorp at 616-252-5026 or email irb@metrogr.org.

Sincerely,

Maureen A. Oostendorp

Maureen A. Oostendorp, MM, CIP
Human Research Protection Program Officer
Metro Health IRB

Appendix 2. Greenhouse-Geisser Correction

Greenhouse-Gisser Correction

Patient	Significance (p)	Sphericity Assumed
Patient_1	.000	Yes
Patient_2	.000	Yes
Patient_3	.000	Yes
Patient_4	.000	Yes
Patient_5	.000	Yes
Patient_6	.000	Yes

Appendix 3. Bonferroni Adjustment

Bonferroni Adjustment

Patient	(I) Structure	(J) Structure	Mean Difference (cc)	Sig. (p)
Patient_1	Bladder_1	PTV_1	-17.68	.021
		Rectum_1	24.80	.000
	PTV_1	Bladder_1	17.68	.021
		Rectum_1	42.48	.000
	Rectum_1	Bladder_1	-24.80	.000
		PTV_1	-42.48	.000
Patient_2	Bladder_2	PTV_2	56.58	.000
		Rectum_2	132.46	.000
	PTV_2	Bladder_2	-56.58	.000
		Rectum_2	75.87	.000
	Rectum_2	Bladder_2	-132.46	.000
		PTV_2	-75.88	.000
Patient_3	Bladder_3	PTV_3	45.53	.000
		Rectum_3	56.82	.000
	PTV_3	Bladder_3	-45.53	.000
		Rectum_3	11.29	.000
	Rectum_3	Bladder_3	-56.82	.000
		PTV_3	-11.29	.000
Patient_4	Bladder_4	PTV_4	-34.08	.000
		Rectum_4	91.31	.000
	PTV_4	Bladder_4	34.08	.000
		Rectum_4	125.39	.000
	Rectum_4	Bladder_4	-91.31	.000
		PTV_4	-125.39	.000
Patient_5	Bladder_5	PTV_5	229.54	.000
		Rectum_5	217.83	.000
	PTV_5	Bladder_5	-229.54	.000
		Rectum_5	-11.71	.000
	Rectum_5	Bladder_5	-217.83	.000
		PTV_5	11.71	.000
Patient_6	Bladder_6	PTV_6	107.26	.000
		Rectum_6	142.71	.000
	PTV_6	Bladder_6	107.26	.000
		Rectum_6	35.45	.000
	Rectum_6	Bladder_6	-142.71	.000
		PTV_6	-35.45	.000