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

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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.