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Treatment planning study of cyberKnife prostate SBRT (stereotactic body radiation therapy) using CT-based vs MRI-based prostate volumes

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TREATMENT PLANNING STUDY OF CYBERKNIFE PROSTATE SBRT
(STEREOTACTIC BODY RADIATION THERAPY) USING
CT-BASED VS. MRI-BASED PROSTATE VOLUMES

by

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DEDICATION

I would like to dedicate this work to my parents, and all my brothers and sisters who have been constantly supporting and motivating me during the challenge of graduate school and life. I am truly thankful to god for having them in life.
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ABSTRACT

This study has been conducted for the purpose of investigating the systematic
dose reduction of rectum and neurovascular bundles (NVBs) during treatment
planning of the CyberKnife™ prostate SBRT using CT-Based volumes versus
MRI-based volumes. Three prostate cancer patients were planned for the
CyberKnife™ prostate SBRT and they underwent computed tomography (CT)
and magnetic resonance imaging (MRI) preplanning exams. The patients were
positioned during both exams using an immobilizing device. A radiation
oncologist and a radiologist delineated the prostate gland, intra-prostatic and
peri-prostatic structures, and pelvic organs of interest in both CT and MRI
images. The CT and MRI images were fused based on fiducial markers to
accurately align the prostate. Radiation Therapy Oncology protocol RTOG 0938
was followed to meet the target volume (prostate plus margin) dose coverage
requirement, and dose-volume constraints for organs at risk, including rectum,
bladder, femoral heads, penile bulb, urethra, skin and NVBs. Radiation dose
volume parameters were recorded for both volumes and compared. The
preliminary result shows that the CT-based volumes were generally larger than
MRI-based volumes of the prostate. Therefore, the CT-based volumes resulted in
less accurate treatment planning and dose delivery to radiosensitive structures.
# TABLE OF CONTENTS

**TITLE** ........................................................................................................................................ i

**APPROVAL PAGE** .......................................................................................................................... iii

**DEDICATION** ................................................................................................................................ iv

**ACKNOWLEDGMENTS** .................................................................................................................. v

**ABSTRACT** .................................................................................................................................... vii

**LIST OF TABLES** .......................................................................................................................... xii

**LIST OF FIGURES** ........................................................................................................................ xiii

**LIST OF ABBREVIATIONS** ........................................................................................................... xiv

Chapter I: Introduction ....................................................................................................................... 1

Chapter II: Background ...................................................................................................................... 2

2.1. Prostate Anatomy ................................................................................................................... 2

2.1.1 Prostate Zones and Function ............................................................................................... 4

2.2 Prostate Cancer .......................................................................................................................... 5

2.3 Prostate Cancer Treatment Options .......................................................................................... 6

2.3.1 Prostate Cancer Active Surveillance .................................................................................... 6

2.3.2 Radiation Therapy ............................................................................................................... 6

2.3.3 Prostate Cancer Surgery .................................................................................................... 7

2.4 Prostate Cancer Imaging ............................................................................................................ 7

2.4.1 The Role of Trans-rectal Ultrasound (TRUS) ..................................................................... 7
Bibliography.................................................................................................................................32

Curriculum Vitae ..........................................................................................................................36
LIST OF TABLES

Table 1: CT-based volumes values and dose constraints........................................27

Table 2: MRI-based volumes and dose constraints. .................................................28
LIST OF FIGURES

Figure 1: Anatomy of the prostate. ................................................................. 3
Figure 2: Prostate Location ................................................................. 3
Figure 3: Prostate on three-plane MRI images ........................................ 3
Figure 4 & Figure 5: The three prostate zones ........................................ 4
Figure 6: Prostate contours and surrounding structures ......................... 10
Figure 7: The CyberKnife™ room ........................................................... 12
Figure 8: The CyberKnife™ technical components ................................... 13
Figure 9: CT volume treatment planning ............................................... 21
Figure 10: MR volumes treatment planning ........................................... 22
Figure 11: CT and MR volumes .............................................................. 24
LIST OF ABBREVIATIONS

BMC ........................................................................................................ Boston Medical Center
CRT ........................................................................................................... Conformal Radiation Therapy
CT ............................................................................................................. Computed Tomography
CTV .......................................................................................................... Clinical Target Volume
CZ ............................................................................................................... Central Zone
DCE ........................................................................................................... Dynamic Contrast Enhancement
DRE ........................................................................................................... Digital Rectal Exam
DVH .......................................................................................................... Dose-Volume Histogram
GTV ........................................................................................................... Gross Tumor Volume
IMRT .......................................................................................................... Intensity Modulated Radiation Therapy
LINAC ....................................................................................................... Linear Accelerator
MRI ........................................................................................................... Magnetic Resonance Imaging
MSD .......................................................................................................... Medical Science Direct
NCI ........................................................................................................... National Cancer Institute
OAR ........................................................................................................... Organ At Risk
PTV ........................................................................................................... Planning Target Volume
PSA ........................................................................................................... Prostate Specific Antigen
PZ ............................................................................................................... Peripheral Zone
QA ........................................................................................................... Quality Assurance
RT ............................................................................................................ Radiation Therapy
RTOG ......................................................................................................... Radiation Therapy Oncology Group
SBRT .......................................................... Stereotactic Body Radiation Therapy
TRUS .................................................................. Trans-rectal Ultrasound
UCSF ................................................................. University of California San Francisco
Chapter I: Introduction

Prostate cancer has become a leading cause of death and the most commonly seen in men. In 2012, there was an estimated report for 2,795,592 men who have had prostate cancer in the United States. In 2015, the estimated number people with prostate cancer became 220,800 (Seer: Prostate Cancer). "In the United States, men currently have the risk of prostate cancer diagnosis is a 17.3%, while the risk of prostate cancer death is 3% (Thompson, 2005)."

Prostate cancer treatment decisions are based on the size of cancer and its aggressiveness. Some prostate cancers grow slowly and don’t need immediate treatment, and the patient may choose active surveillance. Other cancers, larger or more aggressive need surgical treatment or radiation treatment. Once the cancer is not gland confined, radiation therapy is the therapy of choice. Over the last decade, MRI has become the preferred imaging modality to detect and stage the prostate cancer, while CT is the standard tool to perform the treatment planning. For prostate cancer radiotherapy treatment, the CyberKnife™ can be used in conjunction with Stereotactic Body Radiation Therapy (SBRT). SBRT is a new emerging technique, which delivers a single high radiation dose or multiple fractionated doses to the prostate gland. Also, the CyberKnife™ SBRT of prostate cancer uses an X-ray beam accelerator equipped with a robotic arm, which allows tracking the prostate motion and delivering non-coplanar beams precisely. This study focuses on the systematic dose reduction to the rectum and neurovascular bundles in treatment planning of the Cyberknife™ prostate SBRT
using CT-based vs. MRI-based prostate volumes.

Chapter II: Background

2.1. Prostate Anatomy

The prostatic gland is located in the male pelvic region, and it is about the size of a chestnut. The prostate gland is anatomically formed of an apex, a base, and four surfaces. It can be seen underneath the urinary bladder and in front of the rectum. The main function of the prostate is producing a thin protein fluid that also contains minerals. This prostatic fluid nourishes and transports sperms during orgasm. The prostate gland base is situated close to the inferior part of the urinary bladder, while the prostate gland apex is situated near the top surface of the urogenital diaphragm. The anterior prostatic lobe is known as the anterior part of the gland located in front of the urethra. The median prostatic lobe is about the shape of a cone, and it is the part of the gland located between the urethra and the ejaculatory ducts. The left and right prostatic lobes make the gland main part, and both lobes are divided by the prostatic urethra. The posterior prostatic lobe is located in the posterior and medial part of the prostate gland. (NCI Seer training, 2015) (See figures 1, 2 & 3).
Figure 1: Anatomy of the prostate gland (NCI, 2015).

Figure 2: The prostate gland is highlighted in blue (MSD, 2012).

Figure 3: The Prostate gland on three-plane MRI images (Kressel, 2014).
2.1.1 Prostate Zones and Function

The prostate gland is separated into 3 zones: peripheral zone (PZ), transition zone (TZ), and central zone (CZ) (See figure 4 and 5). The peripheral zone is the biggest zone in the prostate that is located closest to the rectum and the doctor can easily feel it during a digital rectal examination (DRE). 75% of prostate tumors are found in the prostatic peripheral zone. The transitional zone is the area located in the middle of the prostate gland, between the two other zones. This zone surrounds the urethra and passes through the prostate and it builds up about 20% of the prostate gland until the age of 40. When men get older, the transitional zone starts to become larger, until it turns to be the largest area of the prostate. When the transitional zone enlarges, it starts pushing the peripheral zone of the prostate all the way towards the rectum. The central zone is in front of the transitional zone and it is the part of the prostate located far from the rectum (Canadian Cancer Society, 2016).

Figure 4 & Figure 5 The three prostate zones (NCI, 2015) (Vilanova, 2012).
2.2 Prostate Cancer

“Prostate cancer has the highest prevalence of any non-skin cancer in the human body, with similar likelihood of neoplastic foci found within the prostates of men around the world regardless of diet, occupation, lifestyle, or other factors. Essentially all men with circulating androgens will develop microscopic prostate cancer if they live long enough (Bostwick, 2004).” Prostate cancer grows slowly and usually becomes constricted to the prostate gland where it might not be harmful. Some types of prostate cancer may require no treatment, while other types can aggressively spread. In the early prostate cancer stages, cancer may not necessarily cause symptoms or signs. In contrast, advanced-stage prostate cancer might cause symptoms. For instance, it may cause urination difficulties, bloody semen, and painful pelvic region, erection dysfunctions. In most of the cases, prostate cancer is detected incidentally; during routine yearly Digital Rectal Exam (DRE) performed by the urologist. During a DRE, the physician uses lubricated gloves to cover his finger and he/she inserts the finger into the patient’s rectum to palpate the prostate gland. If any abnormalities in the prostate gland are detected, the patient might need further tests. Also, prostate cancer can be detected by a Prostate-specific antigen (PSA) test. In PSA test, the physician draws a sample of blood from a vein to check natural substance, which is produced by the patient’s prostate gland (Hoffman, 2016). However, these tests do not determine the extent and the stages of this cancer. For this reason, doctors who think that cancer has spread beyond prostate request advanced
imaging exams such as CT and MRI.

2.3 Prostate Cancer Treatment Options

The prostate cancer treatment depends on some factors. The first factor is how fast the prostate cancer grows, the second one is how much cancer has spread, and the last factor is the benefits and the complications of the prostate cancer treatment. For early-stage prostate cancers, instant treatment might not be necessary. Otherwise, physicians recommend:

2.3.1 Prostate Cancer Active Surveillance

For active-surveillance patients, blood tests (follow-up tests), DRE and prostate biopsies might be needed to check the prostate gland cancer progression. If the tests demonstrated any cancer progressions, the patient might undergo a treatment such as surgery or radiotherapy. The active surveillance can be an available option for those who have prostate cancer with no expected-growing symptoms (Johnson, 2014).

2.3.2 Radiation Therapy

There are two ways to deliver the prostate cancer radiation therapy. The first way is using external beam radiation in which high-energy X-rays are sent to the prostate cancer to kill the cancerous cells. The second way is the radiation brachytherapy, which involves inserting some radioactive seeds into the prostate gland. The seeds deliver radiation with small dose over an extended period, and they are implanted into the prostate using a needle for guidance by ultrasound.
images (Greenfield, 2011).

2.3.3 Prostate Cancer Surgery

The prostate gland cancer can be removed by three different ways. First, through making an incision in the patient’s lower abdomen and this surgery may cause nerve damage leading to bladder health issues as well as erection difficulties. Second, through making a surgical opening between the patient’s scrotum and anus. This surgery may allow for faster recovery, but it can be more difficult for doctors to avoid the nerves while removing the surrounding lymph (Comploj, 2012). Lastly, laparoscopic radical prostatectomy and it can be done through a small incision in the patient’s abdomen and a laparoscope is used (small tracking camera). This surgery may carry risks to the nearby structures. For this reason, it is not commonly requested for prostate cancer treatment (Finkelstein, 2010).

2.4 Prostate Cancer Imaging

2.4.1 The Role of Trans-rectal Ultrasound (TRUS)

TRUS is a common clinical imaging technique used in clinical sites. It is important for prostatic cancer biopsy. In case the prostate gland cancer is suspected, the proper diagnostic exam is the biopsy in conjunction with US. Prior to biopsy, the patient is injected with an enema to clean up the rectum. Afterwards, TRUS probe is inserted in the patient’s rectum. After visualizing the prostate and seminal vesicles, the US images are obtained in axial and sagittal views. Then, a needle guide is used to perform prostatic biopsy, which help doctors to make the pathologic interpretation (Hricak, 2007).
2.4.2 The Role of CT Scan

Since the soft tissue contrast of CT is so low, sometimes it is hard to visualize the intra-prostatic and peri-prostatic structure. However, the major role of CT is in the prostate cancer staging. In some cases, CT visualizing ability is limited. If the patient’s PSA level is > 20 ng/mL, his Gleason score is > 7, and the clinical tumor stage is 3 or higher, CT should be considered (Hricak, 2007).

2.4.3 The Role of MRI

2.4.3.1 T2-Weighted Imaging

T2W imaging is mainly used to visualize anatomy and to assess the seminal vesicles and the prostate capsule. Also, it is used to assess the prostate cancer stage. T2W imaging has a high spatial resolution, superior soft tissue contrast, and a large FOV. On T2W imaging, the tumor appears hypo-intense in the peripheral zone while the normal peripheral zone appears hyper-intense. For this reason, the tumor is easily identified. However, changes of signal intensity on T2W images within the prostate region must be interpreted carefully. Some other pathologies may appear similar to cancer on T2W images. After the prostate cancer biopsy is done, it is highly recommended to wait 8–12 weeks to perform T2W-MRI exam. This way the image misinterpretation can be avoided (Gillian Murphy, 2013).

2.4.3.2 Dynamic Contrast Enhanced T1-W MRI (DCE MRI)

The angiogenesis and vessels permeability in cancerous cells make DCE-MRI
the best technique of choice for imaging cancerous tissues. DCE-MRI provides a high quality visualization of prostatic-tumor vascularity. Also, using DCE-MRI allows visualizing tissue perfusion and cellular leakage. In DCE-MRI of prostate, a series of fast gradient-echo T1W images are acquired immediately prior, during, and after gadolinium-based contrast injection. This is because the onset time to enhancement, time to enhancement peak, during the enhancement peak, and washout time of DCE-MRI can differentiate cancerous tissues from normal tissues (Murphy, 2013).

2.5 CT Versus MRI In Prostate Treatment Planning

CT and MRI contoured prostate gland volumes were compared and significant differences between both volumes were shown. The CT-contoured prostate volume was 2-7 mm larger than the MRI-contoured prostate volume (See figure 6). The MRI contoured volume was superior to CT regarding the visualization of the prostate apex (Tiina Seppälä, 2015). Also, it has been confirmed that MRI contouring enables radiation dose reduction to the rectum during the prostate treatment. The rectum volume received 80% of the prescribed dose when MRI-based volumes were used compared to CT volumes (Debois, 2013). “The average dose delivered to the rectum might be reduced from 74.9% to 64.2% of the prescribed dose by applying MRI contouring instead of CT contouring of the prostate. For this reason, MRI-based volumes were more accurate than CT in terms of precise delineation of the prostate and its surrounding structures and organs (Buch, 2015)”.
2.6 The CyberKnife™ Prostate Stereotactic Body Radiation Therapy

Radiation therapy scan can be performed using some technologies such as Intensity-Modulated Radiation Therapy (IMRT) or 3D-Conformal Radiation Therapy (CRT). Over the years, newer and more precise methods such as the CyberKnife™ or linear accelerator (LINAC) have been developed and are used routinely in specialized centers. The CyberKnife™ developed in the 1990s, and it is known as a Stereotactic Body Radiation Therapy (SBRT) system, which is made to perform very precise radiosurgeries in different areas in the human body (Katz, 2010). The CyberKnife™ SBRT system is able to produce three-dimensional tumor localization and release multiple direction radiation beams for the purpose of destroying the tumor (See figure 7). The CyberKnife™ SBRT
allows the delivery of very high-radiation dose with high precision to the target with negligible damage to the healthy tissues surrounding the targeted organ. The CyberKnife™ has proven its effectiveness as an alternative technique that can be used for treating small tumors. A high performance linear accelerator combined with a robotic arm makes treatment more precise. The standard linear accelerator has only a single rotational movement in one plane. The robotic arm in the CyberKnife™ has six degrees of moving freedom. Because the radiation treatment beams in the CyberKnife™ can be directed from various angles, the Cyberknife™ can be called the non iso-centeric radiation therapeutic modality (Gopalakrishna, 2010). The CyberKnife™ system has sub-millimeter accuracy, which is suitable for treating respiration-related movement targets and central nervous system targets. Since the prostate gland constantly moves during the delivery of radiation therapy, the Cyberknife™ treatment system accounts for those movements during the treatment. Considerable intra-fractional prostatic motion was recorded with a range up to 3 mm, 6 mm and 8 mm in both vertical and horizontal directions, roughly (Siyuan Lei, 2011). Also, it was reported that intra-fractional prostatic motion could be similar or greater than 1 cm over a period of 8 minutes (Armas, 2015). The superior advantage of the CyberKnife™ system is that it requires no anesthesia and patients can resume daily-life activities immediately after the fractionated treatment. Also, it has been invented to minimize the geometrical limitations of conventional treatment modalities and to reduce the invasive doses of SBRT systems (Katz, 2013).
6.2.1 The CyberKnife™ System

The CyberKnife™ system is composed of two diagnostic X-ray sources and digital X-ray detectors. A constant update of the patient’s and target position is provided. This system permits the robotic arm to compensate for any minor changes in patient position at the same time of treatment delivery. A flexible positioning table allows an automatic patient re-positioning before and during beam delivery. The CyberKnife™ system contains some very sensitive optical tracking sensors that are used for tumor movement compensation, which may result from respiration during treatment delivery. Planning and procedure monitoring screens are located outside the CyberKnife™ shielded room to assist radiotherapists monitoring the patients during the hypo-fractionated treatment (Smith, 2007) (See figure 8).
2.6.2 The CyberKnife™ Prostate SBRT Treatment Workflow

The CyberKnife™-based prostate SBRT is carried out by a multidisciplinary clinical team involving a radiologist, a radiation oncologist, a medical physicist and a radiation therapist. Before the radiotherapy treatment begins, the workflow starts with the first step, which is the patient preparation. At least one week prior to acquiring the CT scan for SBRT treatment planning, radiopaque fiducial markers are implanted by an ultrasound trans-rectal special exam to place the markers inside the prostate gland. Then at the CT scan for treatment planning, the patient is placed in a customized cast body support for immobilizing him on the treatment table. Additional imaging scans of MRI are also acquired for better visualization of soft tissue organs including prostate, intra-prostatic lesions, urethra, penile bulb, and neurovascular bundles. These imaging examinations
are employed as inputs for contouring both the volumes of disease (GTV and CTV) and the sensitive normal tissues close to the target volumes. In the normal workflow, the oncologist and radiologist work closely to delineate GTV and CTV, as well as the surrounding organs at risk (OARs) as mentioned. Next, plan optimization is carried out to achieve the clinical treatment goal of adequate target volume coverage by prescription dose, and at the same time making sure that the radiation dose to the surrounding organs at risk are all within tolerance based on prostate SBRT dosimetry guidelines (such as RTOG 0938) for OAR dose-volume constraints. The optimization process will select and optimize the number, orientation and MU (monitor unit) of beams for treatment. Upon completion of the treatment plan optimization, radiation oncologist will review and approve the plan for treatment, and the plan will then go through a quality assurance (QA) check by a second physicist and peer review at chart round before delivering the treatment. During the treatment, the patient remains immobilized to minimize movements while keeping the patient in a comfortable position. Next, real-time X-ray projections are required to determine the prostate position and orientation, which are compared to the planned prostate position and orientation. Any detected deviations in the real time data from plan are corrected before (if larger than a set of pre-selected tolerance) or during beam delivery. After computing the data the system can approximately align the patient’s real position with the planned position. The system continues maneuvering until a certain alignment threshold is met. Finally, accurate
alignment is then accomplished by using the robotic manipulator. The robotic arm moves around the patient and treatment beam delivery can begin in a continuous manner. The CyberKnife™ beam gantry follows a certain path around the patient as optimized by the treatment plan. During treatment delivery, the imaging system makes frequent check for the patient’s alignment and calculates the prostate position. Prostate displacement information is used to allow the robotic arm to automatically modify its delivery and compensate for prostate movement. However, when the prostate movement level is minimized, the operator can control the imaging frequency reduction for the sake of expediting the treatment. Also, when the prostate motion exceeds an acceptable displacement limit, the beam delivery is stopped and the prostate can be re-aligned. The same workflow can be repeated by the clinical team for any radio-therapeutic treatments that require more than one fraction.

2.6.3 Subsystem As Used in the CyberKnife™ Prostate SBRT Treatment

All Individual elements, which the CyberKnife™ radiotherapy systems rely on, are described and how they contribute to enhance the clinical workflow. Accuray (the vendor) has equipped the CyberKnife™ system with software known as the Accuray CyberKnife™ MultiPlan. This software enables clinical teams to achieve the step of visualizing and contouring anatomical structures in an accurate manner. These essential procedures may be done remotely from clinicians practice office or hospitals via computer network connections and it can increase clinical efficiency. A series of medical images (CT, MRI) is imported to the
CyberKnife™ Multiplan software. The multi-modality image fusion methods are incorporated into the treatment planning system to enable the optimal use of the possibility of different imaging modality. Sophisticated-built in drawing tools allow the clinical team to contour the target and other related anatomical regions on any of the fused images, giving the required number of structures for dose planning. 3D visualization features make an efficient viewing of anatomical regions and proper dose calculation of the target volume and neighboring healthy tissues.

Chapter III: Methods and Materials

3.1 Patient Selection and Preparation
A number of 3 prostatic cancer patients were scanned in the treatment position with both MRI and CT. Four fiducial markers were implanted into the prostate. The actual RT was planned and delivered according to the current CT-based clinical protocol, and based on target volumes drawn by the physician responsible for treatment of the patients. Two days prior to the CyberKnife™ treatment planning, patients were asked to follow the low residual and low gas diet to remove the amount of gas produced in the bowls. Also, they were asked to eat light dinner prior to 5:00 pm the night before the scans. At 5:00 pm the night before the scans, then they had to take 2 Dulcolax (Bisacodyl) 5 mg tablets by mouth and they also had to take 2 Gas-X (Simethicone) 80 mg tablets to decrease gas production. During the day of the treatment planning scans, the patients were asked to take 1 fleet Enema 2 hours prior to their appointment
3.2 MRI and CT Scans

MRI was performed using a 1.5T MRI scanner Philips Achieva. The prostate patient imaging included non-contrast T2-weighted (coronal, axial views) images and BLISS (axial view) images for the diagnostics of prostate (Philips Healthcare; matrix 200 X 200; field of view, 200 X 200mm; slice thickness 3mm, XL Torso coil placed over a flat board for immobilization purposes. The images covered the whole penile bulb and seminal vesicle. All markers were visible in BLISS images as hyper-intense dots and their location was confirmed. CT scan images were obtained using the CT scanner (Philips Healthcare, CT Brilliance Big Bore). The imaging volume (slice thickness 1.5 mm, matrix 512 X 512, FOV 500 mm, 120 KV, 50 MA) covered the area of the T2 and BLISS images. The filling state of the bladder and rectum were controlled with written instructions. All patients emptied their rectum with 1 (Fleet Enema) 2 hours before imaging. Also, they were guided to empty their bladder and then drink two glasses of water 1 h before the first imaging procedure. During the exams, they were lying in a supine RT treatment position on a rigid flat and indexed table top, immobilized using the Securevac cushion (Bionix) for both MRI and CT, which were carried out on the same day.

3.3 The CyberKnife™ Prostate Treatment Planning

3.3.1 MRI/CT Image Fusion

Rigid co-registration of the CT and T2W-MRI images was performed using the
RT image processing software, which is equipped with a high-quality monitor (MIM 5.4, MIM Software Inc., Cleveland, OH, USA). The CT and the T2W-MRI images were fused based on the middle point of the fiducial markers. The prostatic borders and capsule were compared in three views, to confirm precise anatomical alignments. The T2W-MRI sequence gives optimal visualization of the urethra and prostate; the BLISS-MRI sequence helps identifying the fiducial markers, which provide a low signal in the T2-W-MRI images. Minor adjustments of co-registration were made if the borders of the prostate in both images did not become superimposed. Overlapping issues can be due to possible marker displacements. The angle rotation and the image co-registration, as well as the displacement of the central point of the fiducial markers in both images were accurately measured.

3.3.2 The CyberKnife™ Prostate SBRT Contouring and Planning

A radiologist and a radiation oncologist and both are first-hand experienced and specialized in prostate. They delineated the prostate capsule in CT and T2W-MRI images in an independent way. The images were drawn randomly and separately. At this stage, the MRI and CT images were not fused. The prostate and radiosensitive structures in CT and MRI were defined by the radiation oncologist and the radiologist (See figure 8).
Figure 8: Three plane CT images (at the top) and three plane MRI images (at the bottom) after drawing and before registration. OARs including prostate are delineated. Red=prostate, green=rectum, light red within the prostate=urethra, pink=femoral heads, orange=bladder, yellow under prostate=LT NVB, purple=RT NVB (BMC, 2016).

The oncologist set up the volumetric center of the delineated prostate based on the iso-center of the plan. The anterior, posterior, right, and left directions were planned based on the prostate chestnut shape and dimensions in order to give geometrical variations. Those variation of the prostate contours had to be towards both the balder and rectum. Based on RTOG 0938 protocols, the GTV (Gross Tumor Volume) was prescribed by the physician along with the CT and MR clinical planning information. The GTV based on the protocol was the prostate only. The CTV (Clinical Target Volume) was as the same as the GTV;
however, it included only the prostate without including the seminal vesicles as described in a routine-axial CT scan. The PTV (Planning Target Volume) was defined exactly as the CTV plus a margin of 3 mm posteriorly and a margin of 5 mm in all other dimensions. For the purpose of meeting, meet RTOG0938 dose constraints and requirements, the anterior margin had to be reduced to 3 mm. For all cases, the prescription iso-dose line successfully encompassed a minimum of 95% of the PTV. For the CyberKnife™ patients, the maximum dose permitted within the PTV was 20% over the prescribed dose. Efforts were done to keep the maximum dose within the PTV close to the maximum dose for (IMRT) and proton treatments. The prescribed doses of the required arm of this study were inside of the PTV. Planning hotspots were adjusted to avoid the prostatic-rectal and prostatic-bladder anatomical regions. The prostate treatment planning was performed using the Accuray CyberKnife™ Multiplan treatment planning system (Sunnyvale, CA, USA). The normal tissues contoured in this study were bladder, rectum, both femoral heads (at the ischial tubercles level), seminal vesicles, penile bulb, skin, neurovascular bundles and urethra. For the CyberKnife™ treatment, the visualization of the urethra was required with a maximum point dose of 0.03 cc, which exceeded 38.78 Gy (5 fractionated arm). All contoured organs were planned on both CT and MRI except urethra and neurovascular bundles (more clear in MR volumes than CT volumes). The bladder had to be contoured from the base to its apex. Also, the rectum had to be contoured from the anus (at the ischial tubercles level) for a length of 15 cm. All
tissues within or surround the skin and PTVs were labeled as undetermined tissues. The treatment delivery doses that did not follow these given limits were constituted as a variation acceptable or deviation unacceptable protocol violation (RTOG0938, 2011). The contours were measured horizontally and vertically. Horizontal measures were done in left, right, anterior and posterior directions of the prostate. Vertical measures were done in the base and apex of the prostate (See figure 9 & 10).

Figure 9: includes the CT volume treatment planning, which was completed through the CyberKnife™ Multiplan system, and it is showing the prostate PTV and other dose constraints before the optimization step (BMC, 2016).
Figure 10: includes MR volumes treatment planning, which was completed through the CyberKnife treatment system, and it is showing the prostate PTV and all other dose constraints before the optimization step (BMC, 2016).

3.3.3 Treatment Planning Optimization and Evaluation

This optimization method enables solving planning problems and optimizes multiple treatment planning doses. During the treatment planning, the possibility of optimizing the radiation doses is retained or relaxed after each step by applying a specific user-defined value. This value can improve the planning quality and enable meeting the dose constraints and limits. In this study, the implementation of the CyberKnife™ sequential optimization was achieved in the
same day of the target planning. It was run to meet the RTOG 0938 dose constraint requirements and to achieve the following clinical goals: First, to cover at least 95% of PTV with 100% of the prescription dose (3625 cGy). Second, to meet all dose requirements for OARs; 1) It should keep the volume of urethra, which received (3878 cGy) 107% of the prescription dose; 2) to minimize the volume of rectum received 3806 cGy of the prescription dose below 1 cc, volume received 3440 cGy below 3 cc, volume receiving 90%, 80% and 50% of the prescription dose below 10%; 3) Bladder volume received 3806 cGy below 1 cc, volume receiving 90% and 50% of the prescription dose below 10% and 50%; 4) Penile bulb maximum dose below 3625 cGy and volume receiving greater or equal to 20 cGy below 3 cc; 5) Left and right femoral heads, volume receiving 20 cGy below 10 cc. 6) Skin: no area of skin receiving dose above 3000 cGy. Finally, to obtain a high conformal dose distribution (conformity index below 1.2 or below 1-2-1.5) around the target with no hot spots over 107% beyond prescription dose in normal tissue. After having an acceptable quality plan, the beam reduction tools were used to make the best compromise between treatment efficiency and dosimetric quality (See figure 11).
Figure 11: includes the both CT an MR volumes after the step of fusion and contouring, the DVH histogram at the right top corner shows the estimated dose spread for all included organs and at this optimization step, medical physicist can manipulate the max dose and the beam to meet the RTOG 0938 criteria (BMC, 2016).
Chapter IV: Result

4.1 Prostate Doses

Based on the RTOG 0938 guideline for the CyberKnife™ prostate SBRT planning, this study has shown that comparable prostate dose coverage can be achieved for both CT-based volumes and MRI-based volumes, that is to have at least 95% of the PTV covered by the prescription dose of 725x5 (3625 cGy). The minimum dose received by the entire PTV was between 31.0 Gy and 34.0 Gy) for both CT and MR based plans. The maximum point doses were all within 120-125% of the prescription dose. The volumes of PTV receiving 4350 cGy or higher were all approximately meeting the requirement of the RTOG 0938.

4.2 Rectum Dose-Volume Profile Comparison

For rectum volumes that receive 3806 cGy (105% of the prescription dose) were all below 1.0 cc for both CT-based and MR-based plans, rectum volumes that receive 3440 cGy (95% of the prescription dose) were all in the order of 3.0 cc, all approximately meeting the RTOG 0938 requirements (2011).

For MR-based plans, volume of rectum receiving 3263 cGy (90% of the prescription dose) were between 96.4% and 97.5%, volume of rectum receiving 2900 cGy (80% of the prescription dose) were between 92.3% and 94.5%, volume of rectum receiving 1813 cGy (50% of the prescription dose) were between 75.3% and 88.0%.
For CT-based plans, volume of rectum receiving 3263 cGy (90% of the prescription dose) were between 90.4% and 91.6%, volume of rectum receiving 2900 cGy (80% of the prescription dose) were between 83.1% and 85.3%, volume of rectum receiving 1813 cGy (50% of the prescription dose) were between 64.9% and 66.4%.

4.3 NVBs Doses

The doses delivered to the right and left neurovascular bundles were recorded on the MRI-based volumes but not on the CT-based volumes. In MRI, The maximum dose to the NVBs were between 41590 cGy to 4420 cGy for the MR based plans.
Table 1: CT-based volumes values and dose constraints based on RTOG 0938.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Volume Constraints (September 2011)</th>
<th>Volume Constraints (December 2014)</th>
<th>Dose (Gy) CK (RTOG 0938)</th>
<th>CT#1</th>
<th>CT#2</th>
<th>CT#3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>Max point dose: 1 cc</td>
<td>Max point dose: (0.03 cc)</td>
<td>≤ 38.06 Gy (105% of prescription dose)</td>
<td>0.0 cc, max 34.7 Gy</td>
<td>0.2 cc, max 44.2 Gy</td>
<td>12.1 cc, max 45.9 Gy</td>
</tr>
<tr>
<td></td>
<td>Min dose received by 95% of PTV</td>
<td>Min dose received by 95% of PTV</td>
<td>≥ 36.25 Gy (100% of prescription dose)</td>
<td>≤ 34.4 Gy (95% of prescription dose)</td>
<td>33.2 Gy</td>
<td>33.0 Gy</td>
</tr>
<tr>
<td>Rectum</td>
<td>Max point dose: 1 cc</td>
<td>Max point dose: (0.03 cc)</td>
<td>≤ 38.06 Gy (105% of prescription dose)</td>
<td>0.0 cc, max 34.7 Gy</td>
<td>0.2 cc, max 44.2 Gy</td>
<td>12.1 cc, max 45.9 Gy</td>
</tr>
<tr>
<td></td>
<td>Less than 3 cc</td>
<td>Less than 3 cc</td>
<td>&lt; 34.4 Gy (95% of prescription dose)</td>
<td>≤ 32.6 Gy (90% of prescription dose)</td>
<td>1.8 cc</td>
<td>5.4 cc</td>
</tr>
<tr>
<td></td>
<td>90% rectum</td>
<td>90% rectum</td>
<td>≤ 32.6 Gy (90% of prescription dose)</td>
<td>91.6%</td>
<td>90.4%</td>
<td>90.4%</td>
</tr>
<tr>
<td></td>
<td>80% rectum</td>
<td>80% rectum</td>
<td>≤ 29 Gy (80% of prescription dose)</td>
<td>≤ 29 Gy (80% of prescription dose)</td>
<td>85.3%</td>
<td>83.1%</td>
</tr>
<tr>
<td></td>
<td>50% rectum</td>
<td>50% rectum</td>
<td>≤ 18.125 Gy (50% of prescription dose)</td>
<td>≤ 18.125 Gy (50% of prescription dose)</td>
<td>66.4%</td>
<td>64.9%</td>
</tr>
<tr>
<td>Bladder</td>
<td>Max point dose: 1 cc</td>
<td>Max point dose: (0.03 cc)</td>
<td>≤ 38.06 Gy (105% of prescription dose)</td>
<td>0.0 cc, max 34.7 Gy</td>
<td>0.2 cc, max 44.2 Gy</td>
<td>12.1 cc, max 45.9 Gy</td>
</tr>
<tr>
<td></td>
<td>90% bladder</td>
<td>90% bladder</td>
<td>≤ 32.6 Gy (90% of prescription dose)</td>
<td>≤ 32.6 Gy (90% of prescription dose)</td>
<td>82.7%</td>
<td>62.1%</td>
</tr>
<tr>
<td></td>
<td>50% bladder</td>
<td>50% bladder</td>
<td>≤ 18.125 Gy (50% of prescription dose)</td>
<td>≤ 18.125 Gy (50% of prescription dose)</td>
<td>30.6%</td>
<td>16.9%</td>
</tr>
<tr>
<td>Penile bulb (recommended)</td>
<td>Max point dose</td>
<td>Max point dose</td>
<td>No more than 100% of prescription dose</td>
<td>max 27.1 Gy</td>
<td>max 33.0 Gy</td>
<td>max 24.8 Gy</td>
</tr>
<tr>
<td></td>
<td>Less than 3 cc</td>
<td>Less than 3 cc</td>
<td>≤ 20 Gy (54% of prescription dose)</td>
<td>≤ 20 Gy (54% of prescription dose)</td>
<td>0.7 cc</td>
<td>2.4 cc</td>
</tr>
<tr>
<td>Femoral heads</td>
<td>≤ 10 cc cumulative (both sides)</td>
<td>≤ 10 cc cumulative (both sides)</td>
<td>20 Gy (54% of prescription dose)</td>
<td>20 Gy (54% of prescription dose)</td>
<td>both 0.0 cc</td>
<td>0.5 cc</td>
</tr>
<tr>
<td>Skin</td>
<td>Max point dose</td>
<td>Max point dose</td>
<td>30 Gy (81% of prescription dose)</td>
<td>≤ 30 Gy</td>
<td>≤ 30 Gy</td>
<td>≤ 30 Gy</td>
</tr>
<tr>
<td>Urethra Dose</td>
<td>Max point dose</td>
<td>Max point dose</td>
<td>≤ 38.78 Gy (107% of prescription dose)</td>
<td>max 37.4 Gy</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>NVBs; LT/RT</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Table 2: MRI-based volumes and dose constraints based on RTOG0938.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Volume Constraints (September 2011)</th>
<th>Volume Constraints (December 2014)</th>
<th>Dose (Gy) CK (RTOG_0938)</th>
<th>1: CBUMT03_ML</th>
<th>2: HBUG98_O_ML</th>
<th>3: PBUK085_ML</th>
</tr>
</thead>
</table>
| Prostate       | Max point dose: 1 cc
               | Min dose received by 95% of PTV    | ≤ 43.5 Gy (120% of prescription dose) | 2.8 cc, max 44.8 Gy   | 0.3 cc, max 45.3 Gy | 4.5 cc, max 45.9 Gy |
|                | Min dose received by 99% of PTV    | ≥ 54.25 Gy (100% of prescription dose) | 96.4%                  | 95.6%         | 94.8%         |
|                | Min dose received by PTV           | ≥ 34.4 Gy (50% of prescription dose) | 31.1 Gy                 | 33.4 Gy       | 32.0 Gy       |
| Rectum         | Max point dose: 1 cc
               | Less than 3 cc
               | ≤ 38.0 Gy (100% of prescription dose) | 0.02 cc                 | 0.2 cc        | 0.04 cc       |
|                | Less than 3 cc
               | < 44.4 Gy (95% of prescription dose) | 0.6 cc                  | 1.1 cc        | 3.2 cc        |
|                | 90% rectum
               | ≤ 32.625 Gy (90% of prescription dose) | 97.5%                   | 96.6%         | 96.4%         |
|                | 80% rectum
               | < 28 Gy (80% of prescription dose) | 94.5%                   | 94.8%         | 92.3%         |
|                | 50% rectum
               | ≤ 18.125 Gy (50% of prescription dose) | 77.8%                   | 88.0%         | 75.3%         |
| Bladder        | Max point dose: 1 cc
               | 90% bladder
               | ≤ 38.06 Gy (100% of prescription dose) | 0.4 cc                 | 0.9 cc        | 0.4 cc        |
|                | 90% bladder
               | ≤ 32.625 Gy (90% of prescription dose) | 90.4%                   | 91.9%         | 94.4%         |
|                | 50% bladder
               | ≤ 18.125 Gy (50% of prescription dose) | 59.6%                   | 91.0%         | 65.9%         |
| Penile bulb    | Max point dose
               | Less than 3 cc
               | ≤ 38.06 Gy (100% of prescription dose) | max 28.5 Gy            | max 12.4 Gy   | max 17.6 Gy   |
| (recommended)  | Max point dose
               | Less than 3 cc
               | ≤ 32.625 Gy (90% of prescription dose) | max 20.0 Gy            | max 12.0 Gy   | max 17.6 Gy   |
|                | ≤ 10 cc cumulative
               | ≤ 10 cc cumulative
               | 20 Gy (54% of prescription dose) | 0.9 cc                | 0.0 cc        | 0.0 cc        |
| Femoral heads  | (both sides)                      | (both sides)                      | both 0.0 cc            | both 0.0 cc   | both 0.0 cc   |
| Skin           | Max point dose
               | Max point dose
               | ≤ 38.78 Gy (100% of prescription dose) | max 40.0 Gy            | max 40.0 P    | max 38.3 M, 39.9 P |
| Urethra Dose   |                                   |                                   | max 43.6 Gy            | max 42.3 LT, 44.2RT | max 42.6 LT, 41.5 RT |
| NVBs: LT/RT    |                                   |                                   |                         |               |                |
Chapter V: Discussion

5.1 Inter-modality Differences and Organs at Risk Doses

This study has investigated the systemic doses of prostate and some of the other surrounding healthy tissues; specifically, the rectum and NVBs, which may be highly affected during the CyberKnife™ prostate SBRT treatment. Based on the data collected at Boston Medical Center, the prostate doses in CT and MRI volumes are meeting the RTOG0938 dose constraints, however, the MRI prostate dose was much smaller and accurate than the CT prostate dose. To illustrate that, the minimum dose received by 95% of the prostate PTV must be above 95%. Therefore, the MRI minimum dose received by 95 % of the prostate was 95.6% unlike CT minimum dose, which was around 95.4%. Regarding the rectum dose delivery, the MR-based volumes well met the RTOG0938 protocol requirements comparing to the CT-based volumes. In other words, 90%, 80% and 50% of the prescription doses in the rectum CT-based volumes were larger than the same prescription doses in the rectum MRI-based volumes, which make the MRI modality more accurate than the CT modality. For the bladder doses, MRI modality volumes met the dose requirements and constraints and the CT volumes did not meet at some points. However, the bladder MRI-based volume doses were smaller than the bladder CT-based volumes. The average maximum point dose in CT volumes exceeded 1 cc, which means that the patient will be exposed to unnecessary treatment doses. Also, the bladder CT-based volumes met the required prescription doses and the bladder MRI-based volumes
sufficiently met the required prescription doses. This means that MRI is still superior to CT in terms of rectum doses delivery. The penile bulb dose in both CT and MRI-based volumes were less than 3 cc (RTOG0938 protocol). However, the penile bulb dose based on the MRI volume was much smaller than the CT volumes, and this shows that the MRI soft tissue superiority over CT. In skin and urethra, both volumes have similar values; however, the urethra dose delivery based on the MRI volume perfectly met the requirements and showed larger value than 38.78 Gy compared to the urethra CT volumes, which was 37.4 Gy. Overall, MRI-based volumes are much accurate than CT based volumes particularly for the Cyberknife™ prostate SBRT treatment planning.

5.2 Study Limitations and Future Directions
Since this study primarily focuses on the Cyberknife™ as a radiation therapy treatment technique, meeting the RTOG0938 dose constraints was quite challenging and the reason is that the Cyberknife™ technique used for treating small tumors and reducing the dose shells is hard to medical physicists and dosimetrist. In addition, the dataset collected lacks the CT-based contouring of NVBs. For this reason, the NVBs dose comparison was not included in this work. Further cases and additional modifications needed to answer the other half of the study empirical question.
Chapter VI: Conclusion

In conclusion, this study has demonstrated through real patient cases that the soft tissue contrast of MRI-based volumes is more accurate for the CyberKnife™ prostate SBRT compared to the CT-based volumes. For CT-based and MR-based SBRT plans, the PTV dose coverage per RTOG 0938 can be achieved, as well as the dose-volume constraints for the rectum volumes. However, a preliminary dose-volume profile comparison between the two set of plans revealed noticeable differences in DVHs for the rectum, with the CT-based plans showing a generally higher DVH than the MR-based plans. This potentially could be significant for dose reduction to the rectum for the CyberKnife™ prostate SBRT leading to lower rectum toxicity. In addition, we also recorded dose to the NVBs for the MR-based plans, which have not been available for CT-based plans. In summary, using MRI-only-based volumes for the CyberKnife™ prostate SBRT can provide higher accuracy treatment of prostate target volumes while better preserving normal tissues such as rectum.
Bibliography


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English tutoring volunteer at International Learning Center 2015
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