Impact of Intrafractional Prostate Motion on the Accuracy and Efficiency of Prostate Cancer Treatment on CyberKnife Radiotherapy

by

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Abstract

One of the most common treatments for men with localized prostate cancer is radiation therapy, which involves delivering small doses of radiation to the prostate for an extended period of time. Stereotactic-body radiation therapy (SBRT) is a form of radiotherapy that delivers increased dosage to the prostate with more precision. The results are shorter treatment times, increased effectiveness, and less toxicity to surrounding tissue. However, the prostate has been found to move around during treatment (intrafraction) and between treatments (interfraction). With greater precision, there is a greater risk of missing the target while the prostate is moving. This study assesses the impact of intrafractional prostate motion on the accuracy and efficiency of SBRT on CyberKnife. Prostate tracking log files were acquired from 6 patients with prostate cancer, which comprises18 SBRT fractions and 1,892 X-ray image registrations. Each image contains real-time prostate motion in 6D. The data were compared against clinically used margins to identify periods of large prostate motion during treatment. Results indicate significant periods of prostate motion, with the greatest movement occurring in anterior-posterior translation (6.2% outside margin) and pitch rotation (4.3% outside margin). The percentage of prostate motion beyond margins varied among patients, with an average of 12.8% outside clinical margins and 36.0% outside hypothetically reduced margins. The treatment time for each fraction was also recorded to quantify the efficiency of CyberKnife delivery. Because of motion-related delays, optimal setup of 5-15 minutes was seen in only 50% of the fractions, and optimal beam delivery times of 30-40 minutes in 44% of fractions. Thus, results suggest that treatment accuracy and efficiency were negatively affected by the occurrence of large prostate motion. Techniques that immobilize the prostate during treatment may be considered to reduce intrafractional prostate motion and ensure greater accuracy and efficiency of prostate cancer SBRT.

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I would like to give my biggest thanks to Dr. Hong Xiang since, without him, this thesis would not have been possible. Dr. Xiang gave me the opportunity to work on this project at Boston Medical Center, where I also learned about clinical research and medicine. As a result of this project, I became inspired to pursue a career as a Physician, with the end goal of improving the lives of patients. Dr. Xiang has served as one of my greatest mentors as I considered various career options throughout my undergrad. Thank you Dr. Xiang for helping me find my way onto this very rewarding path.

I would also like to thank the other staff members at the Boston Medical Center Radiation Oncology Clinic, particularly Mustafa and Sean Keohan. Mustafa provided immense support in the collection and analysis of patient data. Sean gave me the opportunity to observe patient treatments and learn how to operate the CyberKnife. Through them, I gained a stronger understanding of prostate cancer and how it is treated with radiation therapy.

I would like to thank the participants who agreed to share their clinical data for the advancement of this study. Their contributions have allowed us to better understand the impacts of prostate motion so that we may continue to improve treatments for patients to come.

Additionally, I would like to thank my supervisor, Dr. Barbara Hughey, who helped me improve my ability to communicate scientific data. As a student in her class, my writing and oral skills improved significantly. I am very excited to have undertaken this thesis and to have her as my supervisor.

Finally, I would like to thank both my parents and my sister for the immense support they have given me throughout my time at MIT. Their strong commitment to education inspires me to seek new academic pursuits like this one and to continually challenge myself. I am very fortunate to have their mentorship and life-long support.

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1. Introduction

Prostate cancer is the most frequently diagnosed cancer in men in the United States. Depending on the stage of the cancer, there are many treatments available for these individuals. For localized tumors that are confined within the prostate gland, radiation therapy is typically the treatment of choice. This treatment consists of directing beams of intense energy to the affected area to essentially kill the cancer cells. In the past, the most widely used form of radiation therapy was image-guided radiation therapy (IMRT), which involves exposing the patient to small doses of radiation every day for extended periods of time, oftentimes for more than eight weeks. As one would imagine, this treatment schedule imposes serious lifestyle changes on the caretakers and patients who must take time-off to receive the treatment.

Luckily, new technological advancements in radiation therapy have given rise to instruments that are able to target tumors with more precision and with larger doses. The result is a treatment that lasts only 3 – 5 days with a higher success rate and a diminished risk of cancer recurrence. One of the most popular instruments of this kind is the CyberKnife stereotactic body radiation therapy (SBRT), which allows radiation oncologists to escalate dosage to smaller margins within the prostate while avoiding nearby organs at-risk [20]. The present study focuses on the use of CyberKnife for hypofractionated treatment, meaning larger doses of radiation in a shorter period of time. In this protocol, patients with prostate cancer receive standard IMRT fractionation to at-risk organs to prevent the spread of cancer cells, followed by a hypofractionated boost of radiation to the prostate using CyberKnife.

Although this treatment has proven to be more effective at killing cancer cells than previous methods, there is a risk that comes with the precision of CyberKnife. During the planning stage, beams are aligned onto a prostate gland that is fixed in space. However, during the treatment, there

are external forces like gasses travelling through the rectum or the bladder filling that can cause the prostate to deform or move in six degrees of freedom. This motion can have serious repercussions for the patient such as missed beams that expose healthy tissue to toxic radiation and thereby, less radiation to the cancerous region. If displacements or rotations exceed the margins defined by the physician, the machine pauses and the operator must reposition the patient on the machine bed to realign the prostate. Not only does this limit the accuracy of the beams, but it also increases the treatment time given all the pauses the machine must make to reposition.

Thus, the objective of this study was to measure intrafractional prostate motion in cancer patients and to investigate its impact on the accuracy and efficiency of CyberKnife delivery. By understanding the effect of prostate motion, radiation oncologists can modify existing protocols or introduce new techniques to stabilize the prostate during treatment and ensure increased accuracy and efficiency for the patient.

2. Background Information

2.1 Prostate Cancer

The prostate is the part of the man's reproductive system that is responsible for making some of the fluid that protects and nourishes sperm cells in semen. Anatomically, the prostate is located in front of the rectum and under the bladder, and is surrounded by the urethra, which is the tube that carries urine and semen out of the body through the penis. The size of the prostate varies depending on the age and health of the individual. In a young male, a healthy prostate is about the size of walnut. However, the prostate can grow in size with age and can limit the normal flow of urine by pressing against the urethra. The growth of the prostate can be characterized as being either benign or malignant, as is the case in prostate cancer. In malignant growths, the tumor can invade healthy nearby organs and tissues, presenting increased threat to the patient's life [15].

In fact, prostate cancer is the most frequently diagnosed cancer in men in the United States. The American Cancer Society estimates that there will be approximately 220,800 new cases and about 27,540 deaths from prostate cancer in 2015. The majority of these cases occur in men aged 65 or older because of the tendency of the prostate to enlarge with age. The disease is so prevalent that about 1 in 7 men will be diagnosed with prostate cancer during his lifetime. Fortunately, the majority of these men do not die from this cancer in large part because of the numerous treatments that are available to them [21].

2.2 Staging Tests

The most popular method of detecting prostate cancer early is by testing the amount of prostate-specific antigen (PSA) in a man's blood. Before this method was developed, approximately 10-15% of prostate cancers were detected via a digital rectal exam in which the physician puts a gloved finger into the rectum to feel the prostate gland [2]. If an abnormality

appeared in this exam, further exams would be conducted to validate the risk of prostate cancer. Usually, a biopsy procedure is done to study a sample of tissue. From this, the physician can obtain a grade based on how different the tumor tissue is from normal prostate tissue. The higher the grade, the faster the tumor grows and the more likely it is to spread. The current system that is used for grading prostate cancer is called the Gleason score. The Gleason score can range anywhere from 2 through 10, where 2 is a low-grade tumor and 10 is a high-grade tumor [15].

However, the Gleason score can only identify whether or not there is prostate cancer; it does not say anything about the extent of that cancer. For that, physicians use a staging system, chiefly the TNM system design by the American Joint Committee on Cancer (AJCC). The TNM system is based on five pieces of information which include the extent of the primary tumor (T category), whether the cancer has spread to nearby lymph nodes (N category), the absence or presence of distant metastasis (M category), the PSA level at the time of diagnosis, and the Gleason score from the biopsy [21]. With this information, the prostate cancer can be categorized into one of four stages and the physician can choose a treatment accordingly (Figure 1). For a detailed view of the scoring and staging of prostate cancer, see Appendix A.

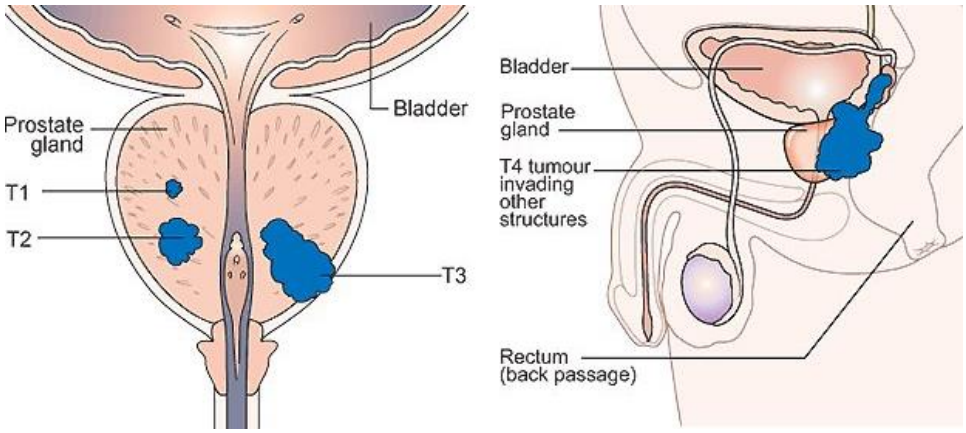

Figure 1 Clinical staging of prostate cancer. Prostate cancer is classified into four stages from a non-detectable tumor to metastatic dissemination. T1 indicates a stage 1 cancer, T2 stage 2, T3 stage 3, and T4 stage 4, as described in Appendix A [18].

2.3 Treatment of Prostate Cancer

There are many treatment options available to men with prostate cancer, some more suitable than others depending on the probability that the cancer is confined to or has spread beyond the prostate gland. Localized disease that is confined to the prostate gland is generally treated with aggressive local therapy directed at the prostate. On the other hand, advanced disease that has spread is generally treated with systemic anti-cancer agents like hormonal therapy or chemotherapy in conjunction with local therapy to prevent progression of the cancer.

This study focuses on localized cancers necessitating radiation therapy. In radiation therapy, high-energy ionizing radiation is used to kill cancer cells. For this type of prostate cancer, surgical removal of the tumor is not recommended because it usually results in some margin of the tumor left behind and therefore, it still requires post-operative radiation therapy to provide local control and overall survival [2]. Radiation therapy alone helps to reduce the size of the tumor and to provide relief from present and possible future symptoms. There are two main types of radiation therapy: external beam radiation therapy (EBRT) and brachytherapy (internal radiation) [21]. Both are effective treatment options, although there is more long-term clinical data surrounding the use of EBRT, which is the method utilized in this study.

Before starting EBRT, patient images are collected with MRI, CT, or X-ray scans to determine the location of the prostate gland in the pelvis and the location of the tumor on the prostate gland. Afterwards, a treatment plan is prepared and a machine is used to focus beams of radiation (dosage measured in gray, Gy) on the prostate gland. The most common form of EBRT for prostate cancer is image modulated radiation therapy (IMRT), which uses a computer-driven machine that moves the patient on a bed as radiation is delivered. Recent data have shown that increasing the dose in intermediate-risk prostate cancer results in reduced risk of biochemical

failure [23]. New advancements in IMRT technology have made these increased doses safer, meaning decreased tissue toxicity. On the downside, the standard dose fractionation will require patients to receive small doses of 1.8 – 2 Gy per day for a total of 8 – 8.5 weeks [2]. This has serious implications on the patient's lifestyle and any caretakers who must modify their daily schedule to accommodate the treatment.

As a result, the treatment efficacy for prostate cancer was examined and it was determined that higher fractionation sizes are "biologically potent" [2]. This called for hypofractionation of treatment, which means delivering larger doses of radiation in a shorter period of time. A more recent technique called stereotactic body radiation therapy (SBRT) is used to perform the hypofractionated treatment. This technique uses advanced image-guided technology to deliver large doses of radiation with much more precision. Today, the CyberKnife machine developed by Accuray, Inc. (Sunnyvale, CA) is one of the most widely used SBRT technologies (Figure 2) [20]. The current study examines data from patients that have received standard IMRT fractionation (1.8 Gy/Fx) to at-risk pelvis lymph nodes and organs, followed by a hypofractionated, large radiation dose (7 Gy/Fx) to the prostate using CyberKnife.

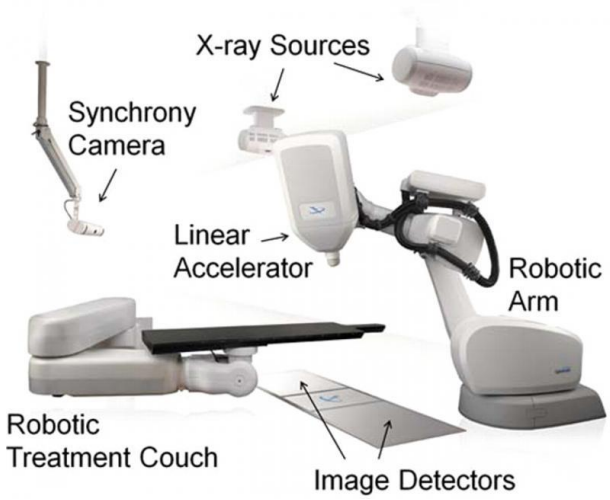

Figure 2 CyberKnife SBRT system. CyberKnife is an advanced image-guided technology that is used to deliver large doses of radiation with more precision [1].

2.4 Characterization of Prostate Motion

Due to its location in the pelvis, the prostate is prone to move inside the body. As shown in Figure 3, the prostate is located just under the bladder and proximal to the rectum. Any changes in the volume of the bladder or gas passing through the rectum can induce a displacement or rotation of the prostate, resulting in the potential for movement in 6 degrees of freedom (3 translational and 3 rotational) (Figure 4).

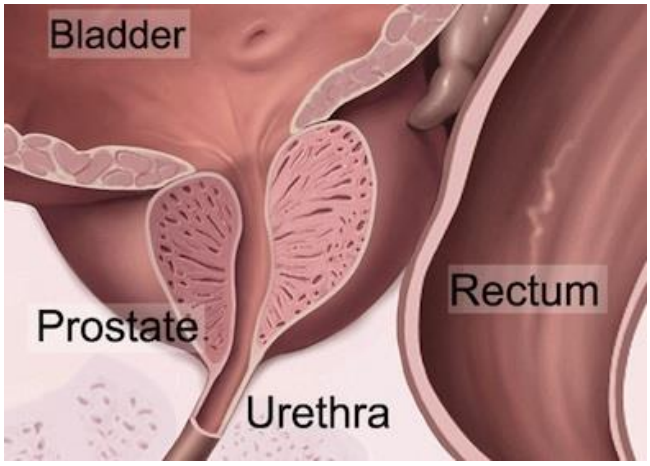

Figure 3 Location of the prostate gland in the pelvic area. The prostate is located just under the bladder and proximal to the rectum. As a result, the prostate is prone to move in response to bladder filling or rectal content. It can translate and rotate resulting in six degrees of freedom movement [7].

A group of researchers in Japan conducted an experiment to investigate the effect of rectal content on prostate motion. In the experiment, forty-seven prostate cancer patients were instructed to remove rectal gas during imaging and radiotherapy. This study concluded that there was significant prostate displacement related to the movement of gas in the rectum [12]. In another experiment, researchers studied the effects of voluntary anal contraction on the motion of the prostate. Similarly, these researchers concluded that voluntary anal contraction induces large prostate motion, mainly in the anterior and superior directions [13].

In summary, the prostate can move in six degrees of freedom during treatment: translations in the left-right, anterior-posterior, and superior-inferior directions and rotations in the pitch, roll, and yaw directions (Figure 4).

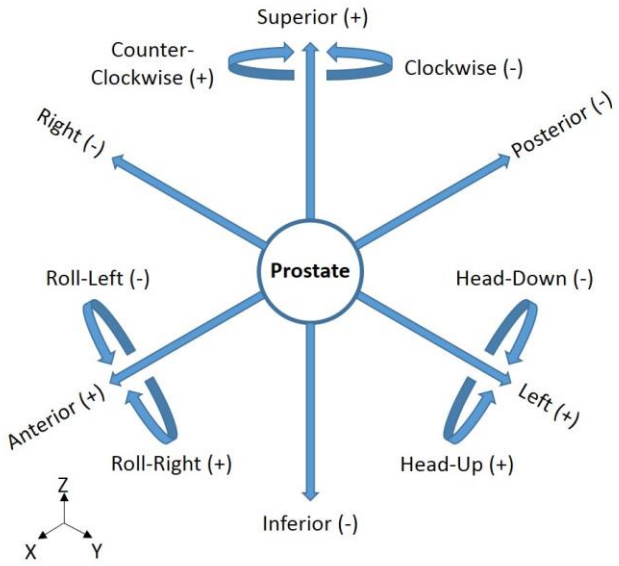

Figure 4 The six degrees of freedom of prostate motion. The prostate can translate in three directions: anterior-posterior, inferior-superior, and left right. It can also rotate in three directions: head up – head down (pitch), counterclockwise – clockwise (yaw), and roll right – roll left (roll).

Because prostate motion can occur during treatment, there is an increased risk that the radiation will miss the target and result in toxicity to nearby healthy tissue as well as decreased radiation dose to the target. Thus, the machine's ability to accurately deliver radiation to the targeted area is limited by the motion of the prostate and any errors related to patient positioning during setup.

Existing protocols that reduce errors include pelvic immobilization devices that the therapist can place on the patient or daily set-up verifications, but none of these methods will entirely eliminate errors. In fact, it has previously been shown that bladder filling and rectal content can create variation on a day-to-day basis (inter-fraction) or during treatment (intra-fraction), prompting the current study [9]. In an effort to reduce uncertainties, radiation oncologists will

generally add a 0.5 - 1.0 cm margin to the clinical treatment volume (CTV), which includes the prostate and the nearby seminal vesicles. This allows them to generate a larger planning treatment volume (PTV), which is the region that receives the dose of radiation. However, this increase in PTV must be carefully balanced with concerns about maximum acceptable dose, as a larger PTV limits the amount of dose that can be delivered safely for hypo-fractionation [11].

2.5 Detecting Motion

Knowing the extent of prostate motion during treatment is necessary in order to reduce treatment margins and ensure delivery of the desired doses to the affected area. By detecting this motion, systems can be implemented to correct prostate rotation and translation so that the radiation is delivered effectively and accurately to the tumor. Many techniques have been utilized to localize the prostate during treatment. For example, in a study of 234 prostate patients, ultrasound technique was used to show that the prostate had an average three-dimensional (3D) displacement of 7.8mm [9]. Other techniques have included an electronic portal imaging device and on-board kV X-ray imaging. One of the biggest breakthroughs was the development of a monitoring system by Calypso Medical Technologies, which provides real-time localization of the prostate based on electro-magnetic detection of implanted beacon transponders [4]. Researchers have found that the difference between using skin marks for positioning versus the Calypso system is greater than 5mm in vector length in over 75% of fractions. In the same study, Calypso helped physicians detect >3mm displacements in 41% of fractions and >5mm displacements in 15% of fractions [9].

However, the most common localization method used in prostate cancer is fiducial marker tracking. This method is used primarily for any soft tissue targets that are not fixed relative to the skull or the spine, such as the prostrate. Implantation requires that 3 – 5 cylindrical gold seeds (i.e.

fiducials) are implanted in or adjacent to the lesion on the prostate. The fiducials are small, with dimensions ranging 0.8 – 1.2 mm in diameter and 3 – 6 mm in length. During the treatment planning stage, the fiducial markers are identified on CT scans. The CyberKnife program detects the position of the fiducials by generating digitally reconstructed radiograph (DRR) images from the CT scans. During treatment, the machine can accurately position the patient by comparing the known fiducial locations on the DRR images to the real-time fiducial locations extracted from treatment X-ray images [6]. CyberKnife overlays the two images and aligns the fiducials to correct the prostate's location in six dimensions (Figure 5).

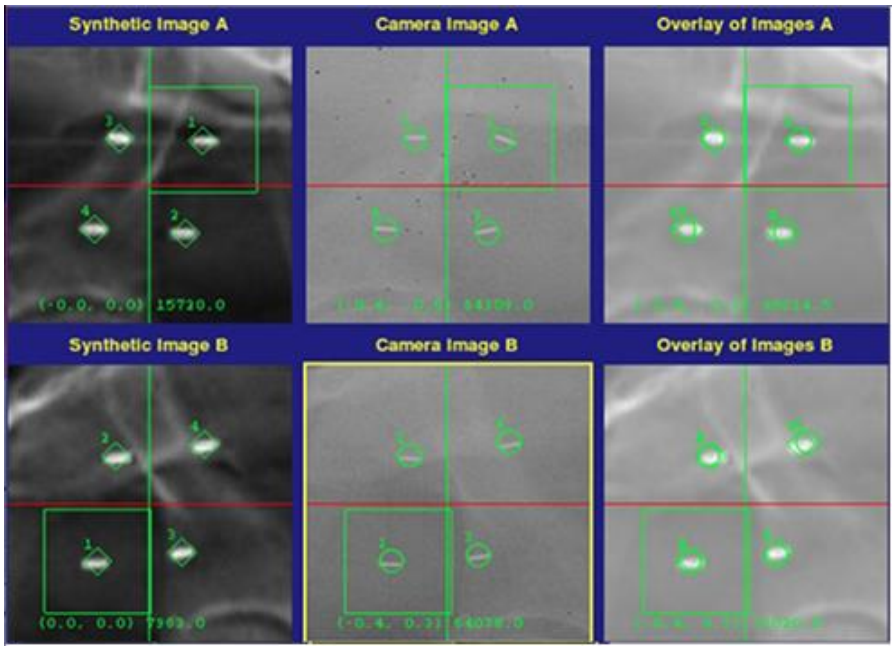

Figure 5 Auto-correction of prostate location on SBRT CyberKnife. Left: Location of fiducial markers on planning CT scan. Middle: Location of fiducial markers on real-time X-ray images captured by CyberKnife. Right: Super-positioning of CT and X-ray to align the prostate for treatment. All detected offsets are corrected by the robotic arm or by operator intervention during treatment [11].

This has been a proven method in radiation oncology with studies confirming that fiducial migration during therapy is very rare and that the prostate deforms less than 1mm due to the implantation [10]. In addition, this method is very easy to use and to reproduce from fraction to

fraction, allowing physicians to reduce PTV margins while still effectively delivering radiation [19].

2.6 CyberKnife Planning and Delivery

Treatment on CyberKnife begins by acquiring 3D images of the patient's prostate, including the tumor on the prostate as well as nearby organs. These images are transferred to the Multiplan Treatment Planning System (TPS) on CyberKnife where a 3D model is generated. Using this model, a medical physicist positions treatment beams on the tumor by specifying a source point, the machine's focal spot, and a direction point, located within the target volume as defined by the user. The user also has the ability to prevent beams from passing through any organs at risk to reduce their exposure to high levels of radiation. Finally, a set of beams are programmed such that that each beam is directed at a unique point within the target volume. These beams are optimized to have the appropriate dosage, position, orientation, field size, and settings all relative to the stereotactic coordinate system defined by the target anatomy. This program is saved as a treatment plan and transferred to the delivery system.

At the time of treatment, the beams are aligned based on automatic registration of the DRRs generated from the 3D model. Live X-ray images are captured during treatment allowing for corrections to be made throughout the course of treatment. Any translational or rotational corrections that are needed are sent to the robotic arm and used to compensate for small target movements. Image acquisition, target localization, and alignment corrections are made repeatedly every 30 – 60 seconds throughout the treatment. If there are large translations or rotations that exceed the specified margins, the machine will automatically pause and prompt the operator to reposition the patient [6]. In the case of prostate cancer, large prostate displacements due to passing gas or bladder filling will cause the treatment to stop. When this happens, the patient is generally

asked to go to the bathroom or to let time pass to stabilize the prostate. As one would imagine, these large displacements not only present a risk of targeting healthy tissue, but also generate a lot of inefficiency and wasted time when the machine is paused during treatment [5].

3. Design of the Clinical Study

3.1 Patient Selection

The patients in this study were selected from the Radiation Oncology clinic at Boston Medical Center. Pre-treatment evaluations included a complete history and physical examination, an assessment of performance status, a serum PSA, a bone scan, and a CT and/or MRI of pelvis within 90 days of registration. The CT and MRI help to identify N and M staging of prostate cancer and to estimate the total prostate volume which must be greater than 20 cc and less than 100 cc.

In order to receive treatment, these patients must have histologically proven adenocarcinoma of the prostate with high-risk disease. This means at least a Gleason score of 2 – 10 and a biopsy within six months of date of registration. By AJCC standards, these patients must also have T-stage determined by a physical exam or by MRI, N-stage determined using abdominopelvic CT scan and/or MRI, and M-stage determined by physical exam, CT and/or MRI, and bone scan. Patients are then further classified by risk level (Table 1). Only patients in the following risk groups are eligible for this study.

Table 1 Patient classification of risk level by staging tests. The risk level of prostate cancer depends on the T-stage determined by a physical exam or MRI, a Gleason score, and a PSA level. The patients in this study fall must fall under one of these categories to be considered eligible (Appendix A).

Risk Level	**Staging**
Very high risk	cT3 and Gleason 8 – 10 and PSA < 150
High risk	cT1 – cT2 and Gleason 8 – 10 and PSA < 150
Moderate high risk	cT3 and Gleason 7 and any PSA
Intermediate to high risk	cT3 and Gleason 6 and PSA ≥ 30
Intermediate to high risk	cT1 – cT2 and Gleason 7 and PSA ≥ 30

The patient must have had no prior prostate surgery or prostate cancer treatment. This includes no prior radiotherapy to the pelvis. The patient must also have had no chemotherapy for a malignancy, and no history of invasive malignancy (not including basal or squamous skin cancers) in the last 5 years. There should be no implanted hardware or other material that would prohibit appropriate treatment planning or beam delivery. On a similar note, no heart pacemaker, no metallic foreign body in the eye, or aneurysm clip in the brain that could interfere with imaging and treatment delivery. As a safety precaution, patients must have no diagnosis of inflammatory bowel disease. Once admitted for radiation therapy, the patients are planned to undergo standard androgen deprivation therapy and IMRT to the prostate and lymph nodes.

After all requirements are met, the patients are asked to complete questionnaires and to sign Institutional Review Boards (IRB) approved informed consent [2]. For a detailed view of the eligibility checklist used in this study, see Appendix B.

3.2 Clinical Protocol

The following is the schematic of the clinical procedure that was used in this experiment. The protocol begins with placement of the fiducials and image scanning for prostate localization. The first stage consists of IMRT treatment. Within one week of completion, images are taken and a final boost course is delivered with CyberKnife.

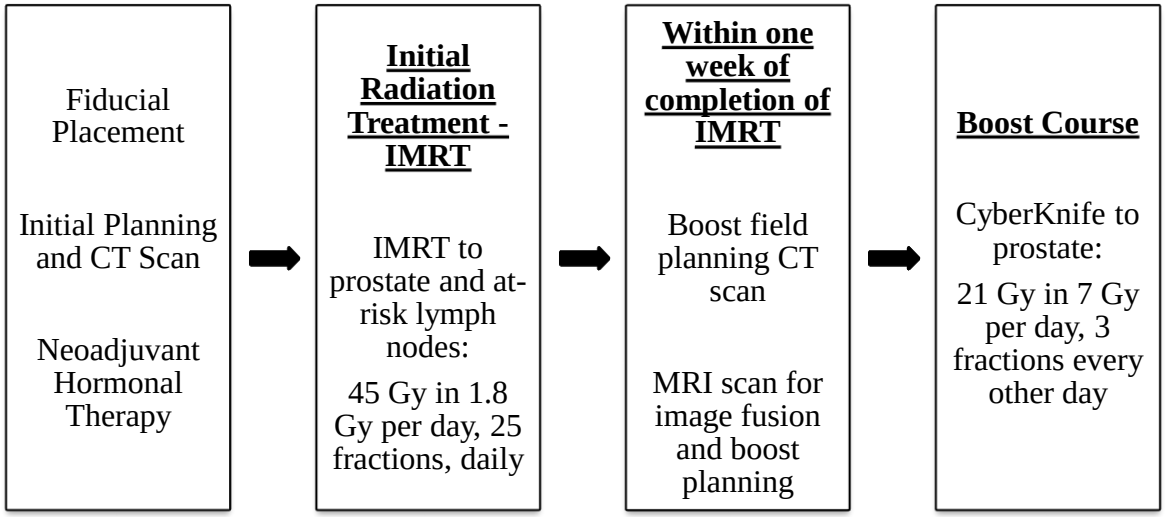

Figure 6 Schematic of prostate cancer clinical procedure. Fiducials are implanted in the prostate for tracking and CT scans are taken. Radiotherapy begins with 25 fractions of IMRT to prevent disease-spread, followed by 3 fractions boost to the prostate on SBRT CyberKnife [2].

3.2.1 Fiducial Placement

All patients had fiducials implanted in the prostate to track its location during the course of the treatment. A minimum of three fiducials are required for tracking, but four would be ideal. These were placed under transrectal ultrasound guidance by the urologist. The ideal method is to place the fiducials such that they are visible for imaging, are separated by 2cm or more, and are not collinear. Fiducial placement is typical of standard radiation therapy and therefore, it does not represent an additional procedure for the sole purpose of this study.

3.2.2 Imaging

After the fiducials were implanted, a series of images of the prostate were taken for planning. These images are the only ones used throughout the entirety of the treatment so that there is consistency across all stages. The images were taken 7 – 10 days after the fiducials had been placed to allow time for them to stabilize in place. These were taken by immobilizing the patient in the treatment position using a custom made vacuum bag. Patients were also required to perform the standard bowel preparation prior to the planning scans similar to the preparation they performed before every treatment. This means emptying the rectum and attempting to maintain as full a bladder as can be tolerated.

CT scans were taken for treatment planning (Figure 7). The slices of each scan were 1 – 1.5 mm thick, with 200 – 300 slices taken centered approximately at the prostate. These images were then sent to the MIMVista software in order to contour the prostate and other critical structures. After the organs were contoured, the image sets were exported to the Pinnacle planning system for IMRT planning and later to the CyberKnife Multiplan treatment system to construct the radiotherapy boost plan.

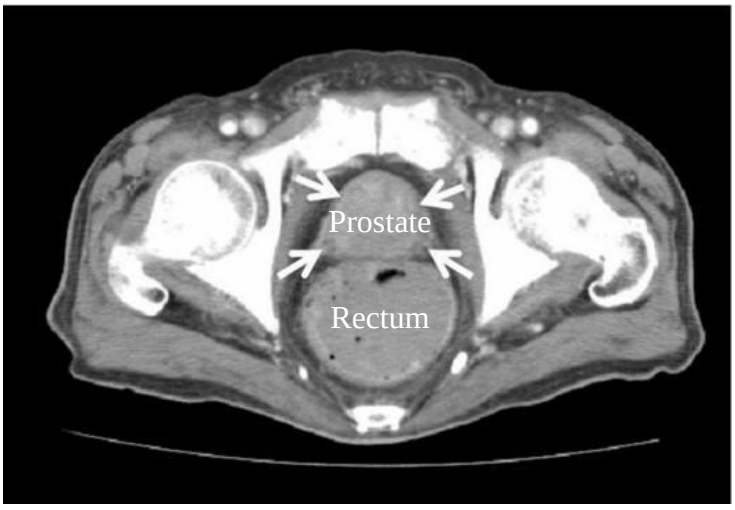

Figure 7 CT scan of prostate in pelvis. This scan shows an enlarged prostate with cancer above the rectum. These scans are used for treatment planning [14].

Furthermore, MRI images were acquired for each patient (Figure 8), which were used to identify the anatomical borders of the prostate. However, these images were not used as the image set for planning; they serve solely to identify structures with a higher contrast that is not offered by a CT scan.

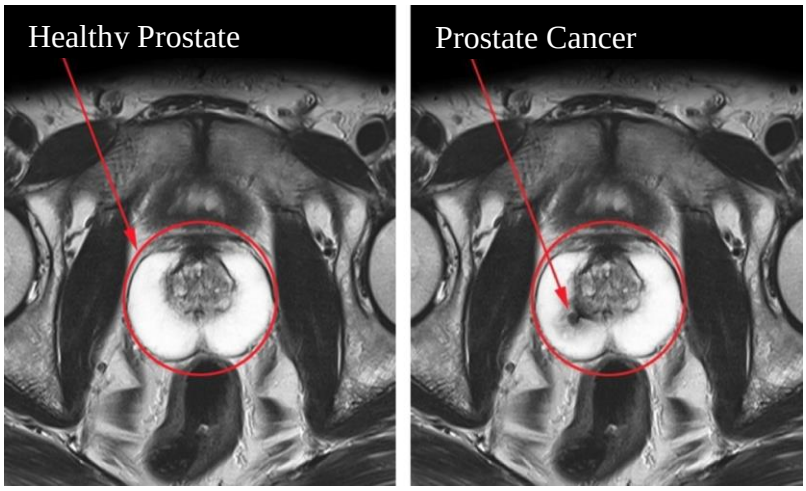

Figure 8 MRI scans of healthy prostate (left) and prostate cancer (right). MRI scans provide higher contrast than CT scans, making it easier to identify anatomical borders for contouring [16].

3.2.3 Target Volumes

The images that were taken were used to define the volumes that will receive radiation. There are three main types of volumes used in radiation therapy (Figure 9). The first is called the gross tumor volume (GTV), which defines the position and the extent of the gross tumor. This is everything that can be seen or imaged. The GTV in this study is the prostate alone. The second is called the clinical target volume (CTV), which includes the GTV plus a margin for disease spread. This is the most difficult in planning because it cannot be accurately defined for an individual patient. The CTV in this study is the prostate, seminal vesicles, and at-risk pelvic lymph node groups. The third and final volume is called the planning target volume, which allows for uncertainties in planning or treatment delivery. This is used to ensure that the CTV dosage is actually delivered as planned. In this case, it is important that the PTV include uncertainty for the

at-risk structures but does not include the bowel, bladder, and rectum. The ability to accurately define the volumes is limited by the quality of the images. That is another reason why the MRI scans are used to supplement the original CT scans [3].

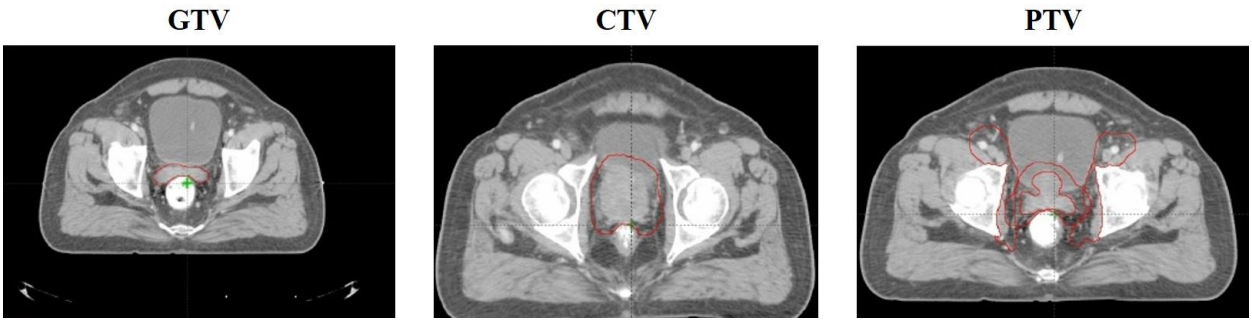

Figure 9 Three types of volumes used in radiation therapy. GTV (gross tumor volume) is the contour of the prostate alone. CTV (clinical target volume) includes the GTV plus seminal vesicles and at-risk lymph nodes. The PTV (planning target volume) includes the GTV and CTV plus room for uncertainty. The PTV is the volume used for treatment [8].

Table 2 provides the margins used in this protocol to compensate for variability in treatment set up and intrafractional motion. As can be seen, the margins are tighter in the anterior-posterior direction, given the close proximity of the rectum. The actual dimensions of each treatment volume vary on a patient-by-patient basis, but these margins remain the same.

Table 2 Clinically used PTV margins for prostate cancer radiotherapy. Depending on the direction of motion, the margin varies. This study focuses on intrafractional prostate motion on CyberKnife. The margins for translation are ±3 mm for anterior-posterior motion, and ±5 mm in all other directions. The margins for rotation are ±2º for roll, ±5º for pitch, and ±3º for yaw.

Stage	Translational Margins	Rotational Margins
IMRT Initial Course	±10 mm (Sup/Inf, Left/Right) ±5 mm (Ant/Post)	±2° Roll (RRoll/LRoll) ±5° Pitch (H-UP/H-DN) ±3° Yaw (CCW/CW)
SBRT CyberKnife Boost Course	±5 mm (Sup/Inf, Left/Right) ±3 mm (Ant/Post)	±2° Roll (RRoll/LRoll) ±5° Pitch (H-UP/H-DN) ±3° Yaw (CCW/CW)

3.2.4 IMRT Treatment Planning and Delivery

After fiducials are placed and images are taken, the first treatment stage is IMRT. The treatment plan for each patient depends on the volume of the prostate and the corresponding volumetric-dose based on the PTV and critical normal structures. The total dose of radiation during this stage is 45 Gy, which is spread out as 1.8 Gy per fraction over 25 fractions. This stage is especially important for treatment of the regional lymph nodes and the nearby seminal vesicles to prevent the spread of cancer. Again, this is standard procedure for prostate cancers that are treated using radiotherapy.

During treatment, the goal is to deliver dose in as short an elapsed time as possible. This means over consecutive days, but not including weekends. Patient preparation involves the routine protocol mentioned earlier. They are also seen weekly by the radiation oncologist to assess their progress and any side effects due to treatment.

3.2.5 CyberKnife Treatment Planning and Delivery

The path trajectory and the number of beams used in CyberKnife treatment must be determined for each patient. No more than 250 beams should be delivered; however, it is recommended that there be only 150 – 200 beams in order to reduce the overall treatment time.

The volume used for treatment is the PTV. The final dosage should cover at least 95% of the defined PTV volume and no point outside of the PTV should receive greater than 105% of the prescription dose. Finally, no point 2 cm or greater from the PTV should receive more than 50% of the prescription dose. The total dosage on CyberKnife is 21 Gy, which is spread out as 7 Gy per fraction over 3 fractions. The treatments are to be completed within one week on an every-other day basis (i.e. treatment on Monday, Wednesday, and then Friday).

On the day of the treatment, the patient is positioned on the CyberKnife couch and immobilization devices are set up. The CyberKnife system takes X-ray scans of the tumor in order to confirm that the tumor is aligned in the same orientation as in the treatment plan. If deviations are detected, the couch moves to realign the patient. These X-rays are taken during the course of the treatment to ensure that the beams are targeting the desired volume. For small rotational and translational deviations, corrections are made on the spot by automatic movement of the couch. For rotations and translations that exceed the PTV margins, the machine stops and the therapist must reposition the patient. For example, if the prostate moves more than 3 mm anterior outside the PTV margin, the machine will stop automatically. The treatment will not continue until the CyberKnife system confirms that the prostate has realigned with the original planning scans [3].

3.3 CyberKnife Data Acquisition

The CyberKnife system records data during treatment. For every fraction that is delivered, the system records the set-up time required, the number of nodes treated, the number of nodes treated with rotational corrections, the number of nodes imaged, and the total treatment time. The data in this study were recorded every 15-seconds so that the motion data has adequate time resolution, unlike typical CyberKnife treatments, which record data every 30-60 seconds. After every treatment, the data were analyzed to study the impact that intrafractional prostate motion has on the accuracy and efficiency of CyberKnife treatment.

4. Results and Discussion

4.1 Intrafractional Prostate Motion Data Analysis

Prostate tracking log files from 18 SBRT fractions for 6 patients were collected for analysis. The data were recorded from 1,892 X-ray images that were captured over the course of treatment. Each X-ray image contains 6 data points for the 6 degrees of freedom of prostate motion (i.e. left-right, inferior-superior, anterior-posterior, pitch, roll, and yaw). Analysis of the prostate motion was used to identify extended periods of large prostate motion that caused delays in setup or interruptions during beam delivery.

The 6D prostate motion was compared to clinically used PTV margins of 3 – 5 mm (±3 mm anterior-posterior, ±5 mm all other directions) and rotation correction limits (roll ± 2˚, pitch ± 5˚, and yaw ± 3˚) of the CyberKnife to quantify the accuracy of beam delivery. Another point of discussion in current radiotherapy is the desire to reduce PTV margins to 2 – 3 mm to achieve higher dosage in a more precise area. A hypothetical PTV margin of 2 – 3 mm (±2 mm anterior-posterior, ±3 mm all other directions) was also studied to examine the feasibility of reducing margins in clinical practice.

Figure 10 presents data on prostate movement as a function of time for a case with small prostate motion (A, B) and a case with large prostate motion (C, D). Here, the translation shown is in the anterior-posterior direction, and the rotation is in the pitch direction. Any time the prostate moved outside the clinically used PTV margins of ±3 mm in the Ant/Post direction and ±5º in the H-UP/H-DN (pitch) rotation, the treatment was interrupted, as indicated.

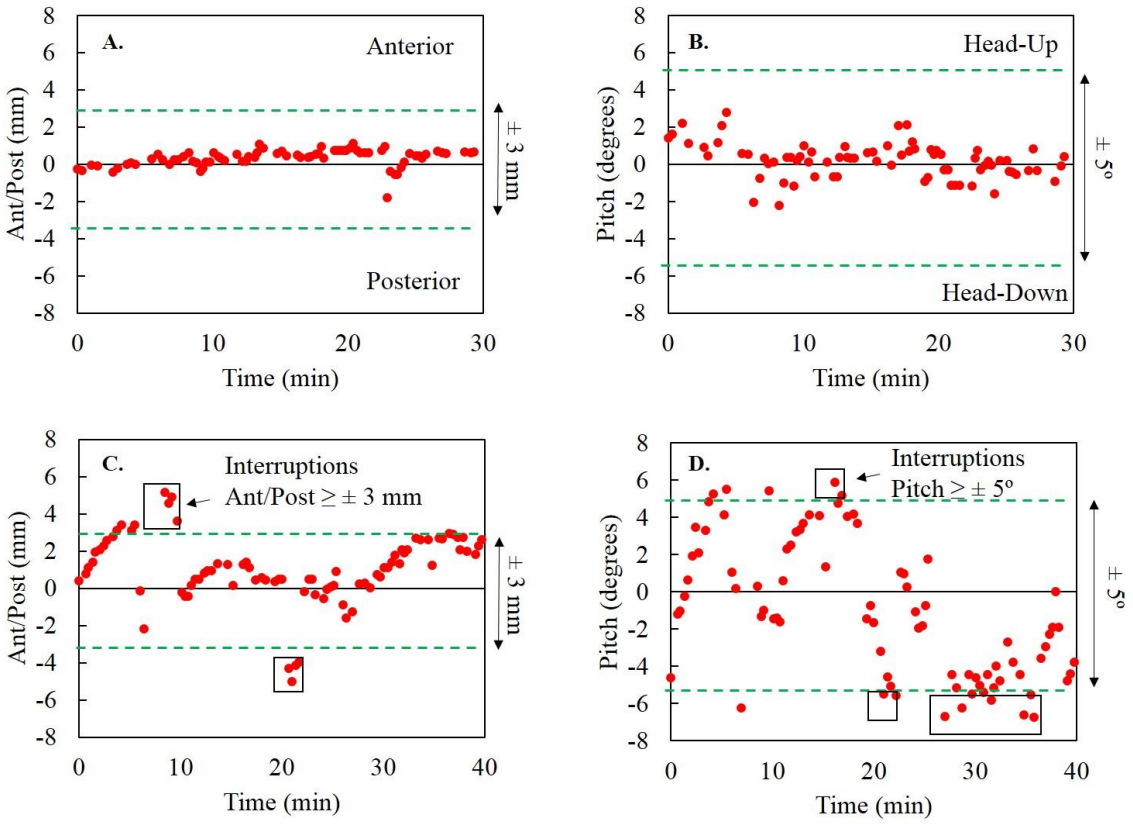

Figure 10 Examples of cases with small and large prostate motion. Anterior/posterior translation and pitch rotation for a case with small prostate motion (A, B). Anterior/posterior translation and pitch rotation for a case with large prostate motion (C, D). The thresholds indicated by the dashed horizontal lines are clinically used PTV margins of ±3 mm in the Ant/Post direction and ±5º in the pitch direction. The boxed regions indicate treatment interruptions caused by prostate motion outside of margin.

As can be seen, large prostate motion leads to various interruptions over the course of treatment. In cases with small prostate motion, the translations and rotations average to approximately zero with little variability. In cases with large prostate motion, the translations and rotations may exceed PTV margins unpredictably during the treatment.

The 6D translation and rotation data were analyzed to identify periods when the prostate moved outside the PTV margin. Figures 11 – 13 illustrate the frequency of prostate motion outside of PTV margins for the case of 3 – 5 mm margins, hypothetical 2 – 3 mm margins, and rotational limits.

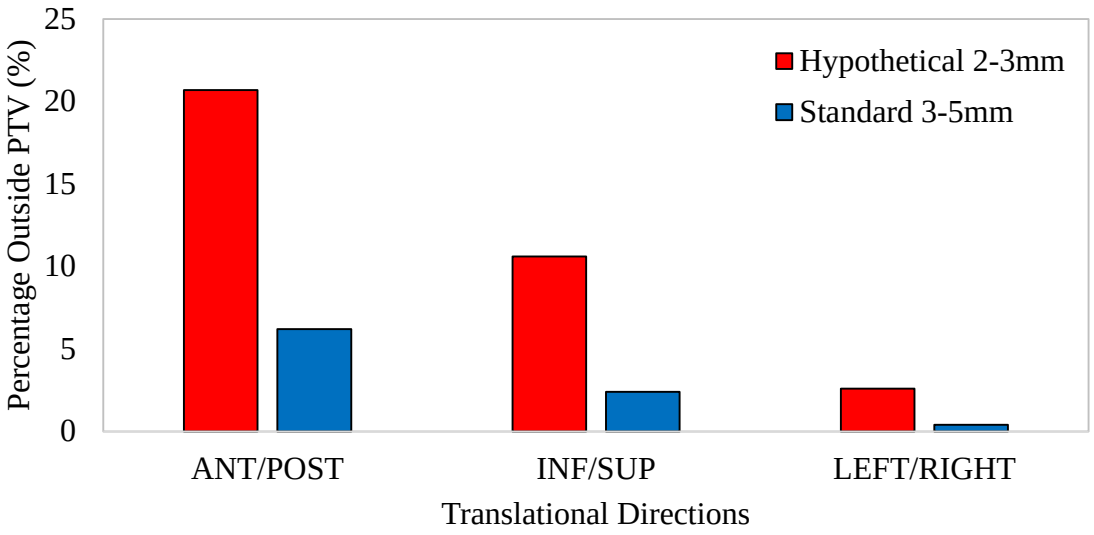

Figure 11 Results for standard 3-5mm and hypothetical 2-3 mm PTV margins. Prostate motion data collected from 1,892 registered X-ray images of prostate tracking for 6 patients. For standard margins, the greatest movement occurs in the ANT/POST direction, with 6.2% of prostate motion outside margin, followed by 2.4% (INF/SUP) and 0.4% (LEFT/RIGHT). Hypothetical margins are also analyzed to examine feasibility of reducing margins. The frequency of motion outside margin increases with 20.7% (ANT/POST), 10.6% (INF/SUP), and 2.6% (LEFT/RIGHT) outside margin.

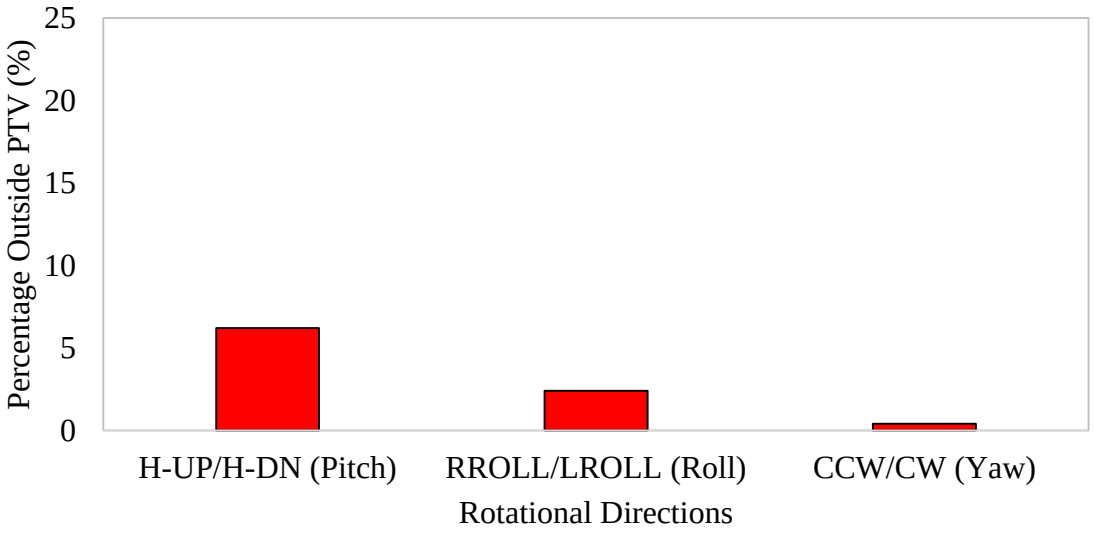

Figure 12 Results for rotational PTV margins. Prostate motion data collected from 1,892 registered X-ray images of prostate tracking for 6 patients. The prostate experiences the greatest rotation in the pitch and roll direction, with 4.3% and 4.2% outside margin. Yaw direction is negligible, with 0.4% outside margin.

The largest prostate motion occurs in the anterior-posterior and pitch directions (Table 3). The prostate exceeds PTV margins 6.2% of the time in the anterior-posterior direction, and 4.3% of the time in the pitch direction. Motion in the other directions, especially left-right translation and yaw rotations, are negligible. The average translation of the prostate is statistically indistinguishable from zero with a variability of 1 – 2 mm and up to 3º. Reducing the PTV margins to a hypothetical 2 – 3 mm results in much greater frequency of interruptions. Again, the anterior-posterior direction has the largest prostate motion, with 20.7% of motion outside margins.

Table 3 Average prostate motion in 6D. The average is calculated from 1,892 X-ray images of prostate tracking for 6 patients. The percentage of motion outside PTV margin is also measured. Any time the prostate exceeds PTV margin, treatment is interrupted for correction by robotic arm or by operator intervention.

Direction	Average	% Outside 3-5mm PTV Margin	% Outside 2-3mm Hypothetical PTV Margin
Ant/Post	(0.5 ± 1.6) mm	6.2 %	20.7 %
Inf/Sup	(-0.2 ± 1.9) mm	2.4 %	10.6 %
Left/Right	(-0.1 ± 1.1) mm	0.4 %	2.6 %
H-UP/H-DN (Pitch)	(-0.3 ± 2.5) deg	4.3 %	
CCW/CW (Yaw)	(-0.03 ± 0.74) deg	0.4 %	
RRoll/LRoll (Roll)	(0 ± 1) deg	4.2 %	

It is also worth noting that prostate motion varies significantly from patient to patient. For the 6 patients that were treated in this study, the percentage of prostate motion that is outside margin is shown in Table 4.

Table 4 Prostate Motion Outside PTV Margin by Patient. Prostate motion depends on various factors, and can occur in some patients more than others. The percentage of prostate motion outside margin is measured for each patient to compare variability. The mean is 12.8% and 36.0% outside margin for 3-5mm and 2-3mm margins respectively.

Patient	% outside 3-5 mm PTV margin	% outside 2-3 mm PTV margin
1	3.0%	4.9%
2	13.4%	36.8%
3	31.1%	65.3%
4	26.0%	83.1%
5	3.3%	3.3%
6	0%	22.4%
Mean	12.8%	36.0%

As shown in Table 4, for the 3 – 5 mm margins, the average percentage outside margin was 12.8% with a range of 0.0% - 31.1%. For the 2 – 3 mm margins, the average percentage outside of margin was 36.0% with a range of 3.3% - 83.1%. Thus, interruptions can be more prevalent in some patients than others.

4.2 Treatment Time Data Analysis

CyberKnife therapy is broken down into two time components: the setup time and the treatment time. The setup time starts when the first CyberKnife image is acquired and ends when the first beam is delivered. During this time, the patient is placed on the CyberKnife couch which then moves to align the prostate in preparation for the first beam. The treatment time is everything after that, from the time the first beam is delivered until the very last beam. In an optimal scenario where the patient receives treatment without interruption, the setup time lasts 5 – 15 minutes and the treatment time lasts 30 – 40 minutes. This means that a treatment can be completed in less than an hour and that the setup time should only account for 15 – 25% of the total treatment time. However, as was demonstrated in the previous section, large rotational and translational motion of the prostate can cause the machine to stop frequently throughout the treatment. The machine will

not continue until the patient is realigned and ready to receive the next beam. As a result, a lot of time is wasted during the treatment and there are even cases when treatment must be discontinued and repeated at a later time when bowel movements have subsided. Thus, intrafractional prostate motion can have a direct impact on the efficiency of CyberKnife radiation therapy.

The setup time and the treatment time were determined for the 18 fractions studied for 6 patients, as shown in Figures 14-15. The total treatment time (i.e. the sum of the setup plus the treatment time) and the fraction of setup time (i.e. percent of total treatment time that is dedicated to setup) were also measured (Figures 16-17). (*Note: from this point forward, all values are reported as mean ± sample standard deviation)*

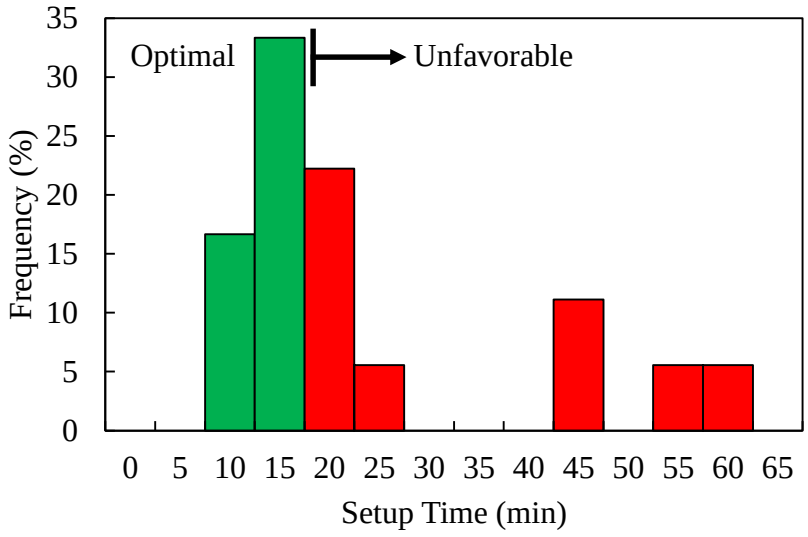

Figure 13 Setup time for CyberKnife radiation therapy. The setup time is the time it takes between the first image and the first beam. Images are taken throughout this period to align the patient for treatment. An optimal time is 5-15 min (green), although significant prostate motion can lengthen this time. 18 fractions were collected from 6 patients; the average time is (21 ± 16) min and only 50% of fractions were within the optimal range. (*Note: values are reported as mean ± sample standard deviation).*

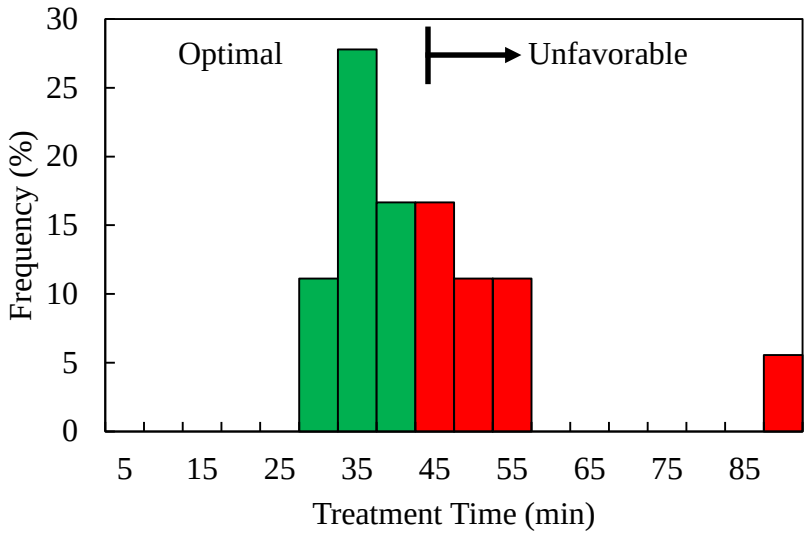

Figure 14 Treatment time (excluding setup) for CyberKnife radiation therapy. The treatment time is the time it takes between the first and the last beam. An optimal time is 30-40 min (green), although significant prostate motion can cause treatment to stop for repositioning. 18 fractions were collected from 6 patients; the average time is (42 ± 13) min and only 44% of fractions were within the optimal range.

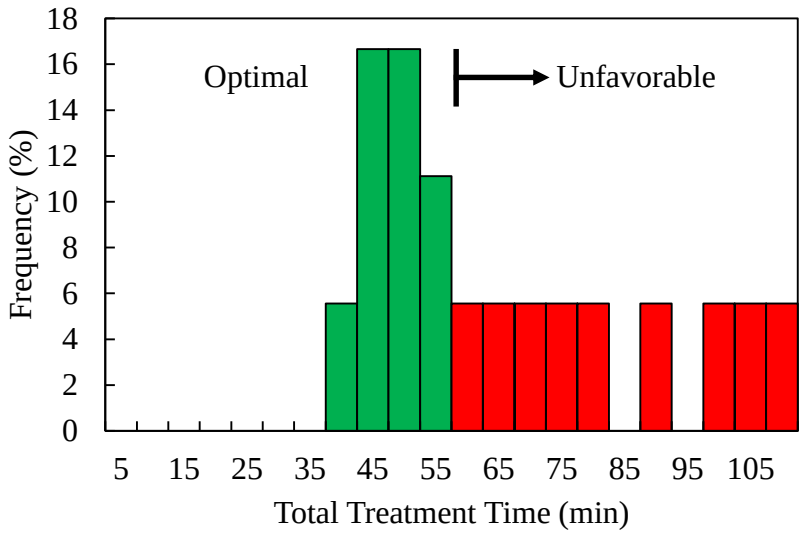

Figure 15 Treatment time (including setup) for CyberKnife radiation therapy. The total treatment time is the time between the first image and the last beam. An optimal time is 35-55 min (green), although significant prostate motion can cause treatment to stop for repositioning. 18 fractions were collected from 6 patients; the average time is (63 ± 22) min and only 50% of fractions were within the optimal range.

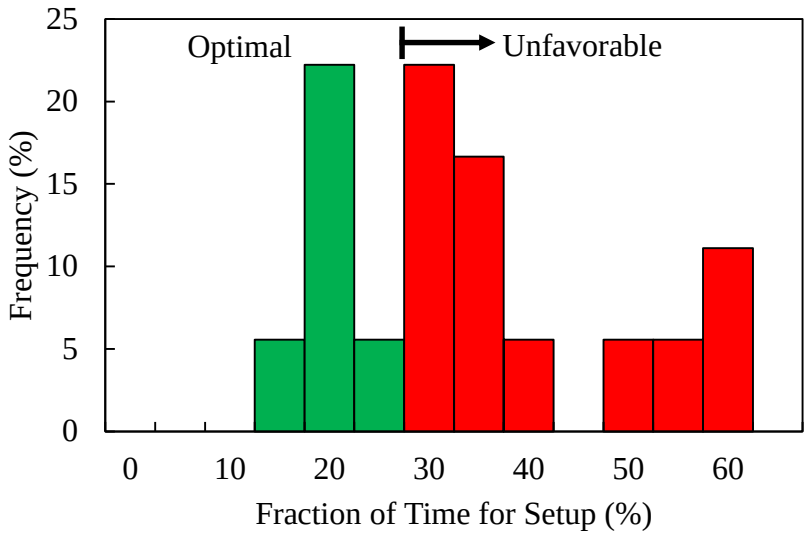

Figure 16 Fraction of time for setup for CyberKnife radiation therapy. This represents the percent of treatment time that is dedicated to setting up the patient. An optimal range is 15-25% of treatment (green), although significant prostate motion before the first beam can cause delays. 18 fractions were collected from 6 patients; the average percent is (31 ± 14) % and only 28% of fractions were within the optimal range.

The average times of the 6 patients were (21 ± 16) min for setup, (42 ± 13) min for treatment time excluding setup, and (63 ± 22) min for treatment time including setup. The average of setup time over total treatment time was (31 ± 13) %. From the 18 fractions that were collected, few were within the range of optimal values. Only 50% of fractions had an optimal setup time, 44% of fractions had an optimal treatment time (excluding setup), 50% of fractions had an optimal total treatment time (including setup), and only 28% of fractions had an optimal fractional setup time.

The large standard deviations in these measurements reflect the variability of time in radiation therapy due to intrafractional prostate motion. Patients that experienced significant bowel movements before and during treatment had difficulty stabilizing the prostate for CyberKnife delivery. As a result, treatment was inefficient since it needed to be continuously interrupted to re-align the prostate.

5. Conclusion

5.1 Impact of Intrafractional Prostate Motion

Prostate motion was collected from 6 patients (3 fractions each) comprising a total of 1.892 X-ray images of prostate tracking data. For each X-ray image, the real-time location of the prostate was recorded for 6 degrees of freedom (anterior-posterior, inferior-superior, left-right, pitch, roll, and yaw directions). The X-ray images were captured every 15 seconds for highly time-resolved data. The 6D prostate motion was compared to clinically used PTV margins of 3 – 5 mm (±3 mm anterior-posterior, ±5 mm all other directions) and rotation correction limits (roll ± 2˚, pitch ± 5˚, and yaw ± 3˚) of CyberKnife to quantify the accuracy of beam delivery. A proposed hypothetical margin of 2 – 3 mm (±2 mm anterior-posterior, ±3 mm all other directions) was also compared to examine the feasibility of reducing margins for increased dosage to a more precise area. Finally, the treatment time for each fraction was collected to quantify the efficiency of CyberKnife delivery.

Prostate motion has a direct, negative impact on the accuracy of CyberKnife beam delivery. Prostate motion was analyzed on a direction-by-direction basis to identify the directions with the greatest movement. Measurements indicate that 6.2% of prostate motion is outside 3 – 5 mm PTV margins for anterior-posterior, 2.4% for inferior-superior, 0.4% for left-right, 4.3% for pitch, 4.2% for roll, and 0.4% for yaw. Thus, the greatest motion occurs in the anterior-posterior direction, probably because of the proximity to the rectum and the tighter margins. For hypothetical margins of 2 – 3 mm, the frequency of prostate motion outside PTV margins also increased. Measurements indicate that 21% of prostate motion was outside these margins for anterior-posterior, 11% for inferior-superior, and 2.6% for left-right. Although hypothetical margins are feasible, the reduced margins would create significantly more interruptions that reduce the accuracy and efficiency of

CyberKnife delivery. These data are useful in identifying the directions with the greatest movement, but they are not indicative of how prostate motion varies from patient to patient.

The data were analyzed for each patient to measure differences in prostate motion from one patient to the next. The data indicate that prostate motion is highly patient-dependent and that it is more prevalent in some patients than others. This makes sense given the fact that some patients experience more bowel movements on the day of treatment. Measurements indicate that on average, 12.8% of total prostate motion (i.e. 6D motion) was outside 3 – 5 mm margins (range 0.0% - 31.1%) and 36.0% of total prostate motion was outside 2 – 3 mm margins (range 3.3% - 83.1%). Prostate motion outside the PTV results in periods of time that treatment is interrupted for correction by the robotic arm or by operator intervention. Thus, data analysis on a patient-by-patient basis is more indicative of the extent to which treatments are affected by prostate motion. Given the variability between patients, some patients will require more intervention than others.

In addition to the impact that prostate motion has on accuracy, it also directly affects treatment efficiency. As was observed, large prostate motion creates several interruptions throughout treatment that result in wasted time. From the 18 fractions studied, an average of (21 ± 16) min was spent on setup and (42 ± 13) min on delivering treatment. On average, (31 ± 14)% of treatment time was spent on setup. Because of interruptions due to prostate motion, only 50% of fractions had an optimal setup time, 44.4% of fractions had an optimal treatment time, and only 27.8% of fractions had an optimal percentage of treatment dedicated to setup.

The accuracy and efficiency of CyberKnife beam delivery are directly affected by the occurrence of large prostate motion. Data also suggest that lower margins are feasible, but probably not advisable given the fact that interruptions are nearly tripled. These interruptions depend heavily on the patient and on the occurrence of large bowel movements on the day of treatment. Although

in the standard protocol, X-ray images are typically captured every 30 – 60 seconds, frequent imaging of <30 second intervals would be required for these patients who experience more significant bowel movements during treatment.

5.2 Future Work

In order to verify these results for a larger patient population, more prostate motion data are required from a larger cohort. More data would help to reduce errors that arise during treatment. Some of these errors may include treatment interruptions caused by operator intervention, interruptions caused by the patients needing to use the bathroom or getting up during treatment, or patients moving on the couch. Because of these factors, it is difficult to isolate prostate motion from external motions like body movement.

Another way to reduce error is to pay more attention to pre-operation routines such as diet and bowel movement. By adhering to a clear liquid diet the night before treatment, the patient is less susceptible to large intrafractional prostate motion. This preparation is similar to the pre-operative bowel preparation for colonoscopies, which allow physicians to examine the large intestine and rectum without interference. Even though the current protocol suggests preoperative preparation, a stronger emphasis needs to be placed for patients undergoing prostate cancer radiotherapy, especially on CyberKnife.

Additionally, there are various techniques that can be used to stabilize the prostate during treatment. One technique that has been investigated is the use of an endo-rectal balloon (ERB). The ERB is inflated inside the rectum to immobilize the prostate and as a result, reduce intrafractional prostate motion (Figure 15). A study by Xiang at Boston Medical Center investigated the dosimetric impact on the rectum when using ERB as part of the SBRT protocol [22]. The study compared the dosimetry on two patient groups: a group with ERB and a group

without. Results indicate that there are consistent rectal dose-volume reductions with the use of ERB in the treatment planning stage. However, additional cases are needed to investigate the impact of ERB on minimizing acute and long-term rectal toxicity.

Figure 17 Endo-rectal balloon (ERB) for prostate immobilization. The balloon is inflated inside the rectum to stabilize the prostate and reduce motion [17].

Understanding the impact of intrafractional prostate motion will be helpful in determining safest and most effective treatments for patients with prostate cancer. For example, the methods used in the current study could be adapted for patients with ERB to compare the accuracy and efficiency of beam delivery on patients with prostate immobilization and patients without. The current research can be used to determine ways in which current clinical protocols can be altered to improve SBRT beam delivery and ensure more effective treatment for patients with prostate cancer.

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7. Appendices

Appendix A: Prostate Cancer Staging System (AJCC)

The following is the clinical staging system for prostate cancer developed by the American Joint Committee on Cancer (AJCC) 7th edition. This is the system used to classify patients for this study.

Primary Tumor (T)	Definition
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor neither palpable nor visible by imaging
T1a	Tumor incidental histological finding in 5% or less of tissue resected
T1b	Tumor incidental histological finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy
T2	Tumor confined within prostate
T2a	Tumor involves one-half of one lobe or less
T2b	Tumor involves more than one-half of one lobe but not both lobes
T2c	Tumor involves both lobes
T3	Tumor extends through prostate capsule
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than the seminal vesicles, such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall.

Regional Lymph Nodes (N)	Definition
NX	Regional lymph nodes were not assessed
N0	No regional lymph nodes metastasis
N1	Metastasis in regional lymph nodes

Distant Metastasis (M)	Definition
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph nodes
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

ANATOMIC STAGE/PROGNOSTIC GROUPS[6]

Group	T	N	M	PSA	Gleason
I	T1a–c	N0	M0	PSA <10	Gleason ≤6
	T2a	N0	M0	PSA <10	Gleason ≤6
	T1–2a	N0	M0	PSA X	Gleason X
IIA	T1a–c	N0	M0	PSA <20	Gleason 7
	T1a–c	N0	M0	PSA ≥10<20	Gleason ≤6
	T2a	N0	M0	PSA ≥10<20	Gleason ≤6
	T2a	N0	M0	PSA <20	Gleason 7
	T2b	N0	M0	PSA <20	Gleason ≤7
	T2b	N0	M0	PSA X	Gleason X
IIB	T2c	N0	M0	Any PSA	Any Gleason
	T1–2	N0	M0	PSA ≥20	Any Gleason
	T1–2	N0	M0	Any PSA	Gleason ≥8
III	T3a–b	N0	M0	Any PSA	Any Gleason
IV	T4	N0	M0	Any PSA	Any Gleason
	Any T	N1	M0	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

Appendix B: Patient Eligibility Checklist

The following checklist was adapted from the protocol used at Boston Medical Center.

Inclusion (all answers must be "yes")

Yes	No	
☐	☐	Is there histologically proven prostate adenocarcinoma (biopsy must be within 6 months of study registration date)
☐	☐	Has the patient had a full staging workup in the past three months including digital rectal exam (DRE), nuclear bone scan and CT A/P and/or MRI?
☐	☐	Is the patient age $\geq$ 18?
☐	☐	Is the patient N0, and M0?
☐	☐	Was N-stage determined using abdominopelvic CT scan?
☐	☐	Was M-stage determined by physical exam, CT and/or MRI, and bone scan?
☐	☐	Is the Gleason Score 2-10? What is the Gleason Score? _____
☐	☐	Does the patient's cancer fall into one of the high-risk groups below?

- Very high risk: cT3 and Gleason 8-10 and PSA < 150
- High risk: cT1-T2 and Gleason 8-10 and PSA < 150
- Moderate high risk: cT3 and Gleason 7 and any PSA
- Intermediate to high risk (a) cT3 and Gleason 6 and PSA $\geq$ 30
- Intermediate to high risk (b): cT1-T2 and Gleason 7 and PSA $\geq$ 30

What is the patient's PSA (must be within the past three months)? _____

What is the clinical T-stage? (AJCC 7th Edition) _____

☐	☐	Was M Stage determined by PE, CT or MRI and bone scan?
☐	☐	Is the prostate volume $\leq$ 100 cc by TRUS?
☐	☐	Is the ECOG performance status 0-1?
☐	☐	Is the patient planning to undergo standard androgen deprivation therapy and initial IMRT to the prostate and at-risk lymph nodes?
☐	☐	Does the patient agree to complete the EPIC and EQ5D questionnaires?

If no, patient will still be eligible for trial, pending reason. Please specify the reason from the following:

1. patient refused due to illness
2. patient refused for other reason: specify
3. tool not available in patient's language
4. other reason: specify

Exclusion (all answers must be “no”)

Yes	No	
☐	☐	Has the patient undergone any prior prostate surgery (including TURP)?
☐	☐	Has the patient had any prior prostate cancer treatment?
☐	☐	Has the patient had a prior invasive malignancy (other than basal or squamous skin cancers within the past 5 years?
☐	☐	Has the patient had chemotherapy for a malignancy in the past 5 years?
☐	☐	Does the patient have any metal prostheses or implants in his pelvis?
☐	☐	Has the patient had any prior pelvic radiation therapy?
☐	☐	Does the patient have a pelvic or horseshoe kidney?
☐	☐	Does the patient have inflammatory bowel disease?
☐	☐	Is patient eligible to have an MRI? (ie, no heart pacemaker, no metallic foreign body (metal sliver) in the eye, no aneurysm clip in the brain, able to tolerate the confinement of an MRI procedure)