MEASUREMENTS AND CHARACTERIZATION OF INTRA-FRACTIONAL
PROSTATE MOTION DURING SBRT TREATMENT OF PROSTATE CANCER ON
CYBERKNIFE FOR OPTIMIZING IMAGE-GUIDED DOSE DELIVERY

By
Kathryn Olivia Harris

SUBMITTED TO THE DEPARTMENT OF NUCLEAR SCIENCE
AND ENGINEERING
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF
BACHELOR OF SCIENCE IN NUCLEAR SCIENCE AND ENGINEERING
AT THE
MASSACHUSETTS INSTITUTE OF TECHNOLOGY

June 2012

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Submitted To The Department Of Nuclear Science And Engineering on May 14, 2012
In Partial Fulfillment of The Requirements for The Degree of Bachelor of Science in Nuclear Science And Engineering

ABSTRACT

Prostate cancer is currently the most frequently diagnosed cancer among men in the United States. Due to the low $\alpha/\beta$ ratio (on the order of 1.5-2.0) compared to normal tissue, the therapeutic benefit of hypo-fractionation allows for higher cancer cell kill with a lower probability of late grade III-IV toxicity to surrounding healthy organ tissues. Such hypo-fractionated radiation treatment poses a more stringent requirement on the accuracy of target localization and dose delivery. CyberKnife is a robotic radiosurgery system that has been shown to be accurate for delivering stereotactic body radiation therapy for extra-cranial tumor targets. However, in the case of prostate SBRT, intra-fractional prostate motion presents a unique challenge for the accurate delivery of treatment. The purpose of this work is to characterize and quantify the time dependence of intra-fractional prostate motion. Results from this study will be used for optimization of the treatment planning and improvement of SBRT delivery accuracy. Retrospective imaging guidance data were studied for prostate cancer patients treated with SBRT on the CyberKnife. At the time of treatment, prostate is localized and tracked by taking stereoscopic X-ray images of implanted fiducial gold markers. For smaller movements of translations and rotations, the beams can be corrected before beam-on dose delivery. For larger magnitudes of prostate movements that exceed the limits of beam corrections, treatment was automatically halted to allow re-establishing the target alignment before resuming the delivery. Treatments were planned and optimized to have each beam with MUs not exceeding 150~160 MU, thus to allow timely monitoring the prostate position between consecutive beams. All beam corrections were recorded in the system log files, and downloaded after all planned fractions of treatment were completed. This study analyzed both rotational and translational prostate movements at an interval of 10-15 seconds compared to previously published translation data only for an interval of ~40 seconds. For the case being analyzed, it was observed that under normal conditions, the translations of intra-fraction prostate motions are generally under 3-5 mm and the rotations are generally under 2°-5°, both are within the CyberKnife beam correction range. However, it was also well observed that the gas pocket formation and passing targeted region of interest are unpredictable during treatment delivery. They can cause
much larger misalignments that are either beyond the PTV margins or beyond the beam angle correction range, leading to suspension of the treatment for extended time, typically 30-40 min per fraction. The study of time-dependence of intra-fraction prostate motion revealed significant uncertainties during treatment delivery. Timely imaging at shorter time intervals is effective for detecting such uncertainties, and helping to improve the accuracy of dose delivery. In addition, the results from this study also points to the need of finding better ways of managing intra-fraction prostate motion, such as using endo-rectal balloon to stabilize prostate position during treatment and release gas pockets from upstream before their reaching to the target region of interest. More patient data cases are needed to further support these important preliminary findings.

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Acknowledgements

I would like to thank my supervisor, Dr. Hong Xiang, for taking me on to help with his research and for the support and dedication towards the completion of my project.

I would like to thank radiation therapy technologist (RTT), Sean Keohan, for answering any and all questions I had about the operation of the CyberKnife.

I would like to thank physicists, physicians, therapists, and all staff in the radiation oncology department of Boston Medical Center for their guidance and support to me on this project as well as Macy Rupert in the Volunteer Services Office during the externship in January 2012 and the following months.

I would like to thank the MIT Externship Office and MIT Alumni Association for allowing me the opportunity to extern during the month of January at Boston Medical Center.
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1. Introduction

The National Cancer Institute estimates 192,280 new cases and 27,360 deaths from prostate cancer, the most frequently diagnosed cancer in the United States, in 2009. The prostate specific antigen (PSA) has been influential in its early detection. Development in classification of the level of disease by PSA, Gleason score and the clinical T-status allows for physicians to treat better according to risk of metastases and disease specific survival.

External beam radiation therapy (EBRT) has been considered the treatment of choice for managing locally advanced prostate cancers due to the minimal invasiveness compared to surgery. Recent randomized trials have suggested that dose escalation results in a decreased risk of biochemical failure. Therefore, higher dose is considered the standard of care for men with localized prostate cancer. The standard dose fractionation will require the patient to be treated on an outpatient basis for a duration of 8-8.5 weeks, three times a week. This schedule has proved to be an inconvenience to patients.

The low $\alpha/\beta$ ratio for prostate cancer, which corresponds with increase rate of repair of normal tissue to exposure to radiation, suggests that higher fractionation sizes are biologically potent. Accuracy, Inc.’s CyberKnife technology allows for high-dose hypo-fractionated X-rays to penetrate the localized tumor area. A new technology, studies have begun which extend for a maximum length of 5 years with positive results. Therefore, the long-term effects of the CyberKnife technology fail to be known.
2. Statement of Problem

2.1 Background Information

Recently, stereotactic body radiotherapy (SBRT) has emerged as an alternative radiation treatment that delivers hypo-fractionated dose to the prostate, comparable in many respects to HDR brachytherapy, but with a non-invasive approach [1, 2, 3]. For low-risk prostate cancer treated on CyberKnife, studies have shown that 93% of patients had no recurrence of their cancer at a median follow-up of five years, a rate that compares favorably to results obtained with other treatment modalities, including surgery and conventional radiotherapy [4].

Such hypo-fractionated radiation treatment (SBRT) delivers 3-4 times higher dose per fraction to prostate with smaller PTV margins of 3-5 mm, while the standard IMRT or 3DCRT treatments are delivered with lower dose per fraction (180-200 cGy) and larger PTV margins (5-10 mm). The greatest technical challenge in such hypo-fractionated dose escalation for prostate has been to develop and implement an accurate image-guided delivery solution for measuring and monitoring the intra-fractional prostate motions in well-resolved time scale and also be able to compensate for prostate motion in real-time.

CyberKnife Robotic Radiosurgery System offers intra-fraction imaging and real-time motion management capabilities that help to adapt the beam delivery to target motion through frequent image guidance and robotic manipulation. To date, clinical data on intra-fraction prostate motion collected from CyberKnife SBRT treatments have been reported for a time interval of ~ 40 sec (every 3 nodes on the prostate path), which span the time intervals for delivering 3-4 beams with MUs less than ~150 MU, or 1-2 beams.
of higher MUs that takes longer time to deliver [7].

However, a multi-site study of intra-fractional prostate motion using Calypso electromagnetic transponder tracking system has revealed faster and larger prostate movements during external beam radiotherapy [8]. The study reported continuous and unpredictable intra-fractional prostate motions that vary from persistent drift over time to transient erratic movements. For a cumulative duration of ~ 30 seconds, larger than 3 mm offsets are seen in over 41% of the sessions, and larger than 5mm offsets are seen in over 15% of the sessions. For individual patients, larger than 3 mm offsets were seen in 3-87% of the sessions, and larger than 5mm offsets were seen in 0- 56% of the sessions.

These results suggest that position offsets larger than PTV margins (3-5 mm) in SBRT for prostate can happen during treatment with significantly high probability (average of 41% and up to 87% for > 3mm offsets, and average of 15% and up to 56% for > 5mm offsets). The imaging time interval used in previous CK-based study (~40 seconds, or every 3 nodes) appears to be too long to inclusively capture the transient rapid prostate motion. They imply the need for image acquisition at smaller time interval that is comparable to the beam-on dose delivery time during which the prostate really needs to stay within the margins to ensure the delivery accuracy and avoid strayed beams delivered to the surrounding normal tissues of rectum, bladder and penile bulb that are right next to the prostate gland.

In this project, we acquired imaging data during prostate SBRT delivery at considerably smaller time interval of 10-15 seconds or imaging before every beam. This imaging frequency will allow the measurements of inter-fraction prostate motion at a
time scale that is comparable to the beam duration and help to significantly improve the delivery accuracy on a beam-by-beam basis, thus ensuring the over-all delivery accuracy.
3. Procedures

3.1 Patient Selection

Patients with high-risk disease (cT1-T2 and Gleason 8-10 and PSA <150) were considered for this prospective study at Boston Medical Center. Contraindications include prior prostate surgery, prior prostate cancer treatment, evidence of metastatic disease, and inflammatory bowel disease. One of six patients has thus far been evaluated and will be included in this thesis report. The patient was treated with 45 Gy in 1.8 Gy per day, 25 fractions, daily with IMRT to the prostate and at with lymph nodes, followed by boost course of a 21 Gy in 7 Gy per day, 3 fractions, every other day using CyberKnife to the prostate only. Three gold fiducials were placed non-collinearly, more than 2cm apart in the prostate under the guidance of transrectal ultrasound to be used for tracking during treatment. Standard bowel preparation beginning at 6PM on the night prior to treatment the patient was utilized which included placing the patient on a diet of clear liquids, instructing him to take a self-administered enema and, encouraging him to consume Gas-X and to defecate prior to treatment.

3.2 Treatment Planning and Optimization

The patient was imaged using both a CT and a MRI for anatomical benchmarks to be used for CyberKnife planning. The patient was immobilized in the supine position using a Vac-Loc according to protocol. Standard bowel preparation was done before image scans were taken. CT slices are 1mm thick, with 200 slices taken centered on the prostate. The CyberKnife treatment plan was made using dose volume histogram (DVH) analysis
and visualization of dose lines around the primary target volume (PTV) and organs at risk (OARs).

Figure 1. Beam Configuration and Isodose Distributions of Prostate SBRT CyberKnife Treatment Plan on MRI Image in Axial, Sagittal, and Coronal Views
3.3 Treatment Delivery

Immobilization and setup device for radiation therapy included the Vac-Loc bag. The patient was treated in the supine position. During each fraction initial positioning was determined using skin markers and lasers.

During treatment, fiducials must be rigidly fixed. The setup and treatment is diagramed in Fig. 1. Orthogonal X-rays are acquired so the absolute position of the tumor can be determined relative to the couch. The 3D rotation and translational movement is calculated, monitored, and corrected if necessary. During the treatment, the couch adjusts automatically if the offset is below the threshold for continuing, taken to be 5mm in all directions. X-ray images are acquired every node for our study, approximately every 10 seconds.
3.4 Components of System

The CyberKnife System is diagrammed below in Figure 3.

![Figure 3. The CyberKnife System](image_url)

The system is primarily composed of a robotic manipulator, a six-axis RoboCouch Patient Positioning System, LINAC hardware with fixed circular collimators, an X-ray imaging system, and a stereo camera system. The Robotic Manipulator has six degrees of freedom, Two diagnostic X-ray sources are mounted to the ceiling to detect orthogonal X-ray fields in order to continually monitor the placement of the fiducials. Optical markers are continuously measured throughout treatment.

3.5 Image Guided Data Collection

The CyberKnife system uses fiducial marker tracking Imaging System to view the fiducial markers (see Figures 4-6). The system determines the absolute position of the target volume using the image-to-digitally reconstructed radiograph. X-ray images are acquired every node when the beam fails to be blocked by the aperture.
3.6 Prostate Motion Data Analysis

After treatment, a log-file with the center of mass displacements of the fiducials in the six directions was automatically saved to the CyberKnife system encoded in UNIX. The statistical information of the first fraction was first analyzed during the data sets. This analysis provided valuable information for the time it takes the prostate to reach the current threshold. The general trend of the other fractions was also examined but has yet to be analyzed in detail. The overall patient-specific behaviors of the translational and rotational prostate displacement were investigated.
4. Results

4.1 Duration of Data Sets

For the one patient, 126 timestamps, which constitute 5 data sets, were recorded. The mean duration for each data set is 582.86s. The duration suggests the time for prostate to move more than 5mm in any direction or 3°, 5°, 2° in the roll, pitch and yaw directions respectively. A shorter duration corresponds with more movement of the prostate during treatment. The entirety of the first fraction took nearly sixty minutes due to pauses between data sets, twice the expected amount of time. Ideally, a patient should be on a table no longer than thirty to forty-five minutes.

4.2 Behavior of Intrafractional Motion

The mean shift in each translational direction averaged over the first fraction of the patient was $1.17 \pm 0.84$mm, $0.02 \pm 0.38$mm, $0.07 \pm 0.76$mm in SI, LR, AP directions, respectively. The average vector length of the shift is $1.53 \pm 0.64$mm. The mean shift in each rotational direction averaged over the first fraction of the patient was $0.41 \pm 0.65^\circ$, $0.42 \pm 1.43^\circ$, $0.31 \pm 0.7^\circ$ in yaw, pitch, and roll directions, respectively. Table 1 summarizes the statistical characterization of the data for each direction and vector length of the shift. It should be noted that these numbers reflect the threshold limits established by the therapist, and does not reflect the entire prostate motion.
Table 1. Statistical Characterization of Fraction 1 Deviations in Six Directions and the Average Shift Length (SI = Superior/Inferior, LR = Left/Right, AP = Anterior/Posterior)

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<th>LR</th>
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<th>Length</th>
<th>Yaw</th>
<th>Pitch</th>
<th>Roll</th>
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<tr>
<td>Average</td>
<td>1.17</td>
<td>-0.02</td>
<td>-0.07</td>
<td>1.53</td>
<td>0.41</td>
<td>-0.42</td>
<td>-0.31</td>
</tr>
<tr>
<td>SD (mm)</td>
<td>0.84</td>
<td>0.38</td>
<td>0.76</td>
<td>0.64</td>
<td>0.65</td>
<td>1.43</td>
<td>0.7</td>
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The motion of the fiducials serves as a model for the prostate. Figures 4, 5, 6 show raw data taken directly from the CyberKnife Imaging System. Also, figures 7 and 8 show a graphical representation of that data for each data set. Also,

Figure 4. Raw Image Data from the CyberKnife System for Fraction 1
Figure 5. Raw Image Data from the CyberKnife System for Fraction 2

Figure 6. Raw Image Data from the CyberKnife System for Fraction 3
Figure 7. Translational Prostate Movement of the Patient in Different Data Sets
Figure 8. Rotational Prostate Movement of the Patient in Different Data Sets
5. Conclusions

5.1 Discussion

The data suggests that deviations in the translational direction agree with previous studies done by Xie et al. which suggests very little or no need to increase the image time. However, the rotational deviations failed to be considered in that research. Our data is conclusive that the rotational deviations in the yaw direction reach as high as 9-15 degrees with gas passing through the rectum. The movement is not inconsequential. Relative dose to nearby organs of the penile bulb and the rectum should be investigated further with such large angular deviations.

Delays of treatment due to the prostate rotational motion tripping the CyberKnife System causes the entire duration of treatment to be one the order of an hour, almost double the ideal treatment time. These large deviations need to be controlled either with the use of a strict pre-treatment diet or use of a device to control passing of gas. Here are 4 figures showing images at time of normal treatment delivery, and 3 instances of gas pockets in rectum, forcing the suspension of the treatment delivery, on the average, by 30-40 min, to allow the patient to get off the treatment table and release gas before resumption of treatment.
Figure 9. Fraction 2, 10:12 AM, Good Alignment with Small Offsets in Translations and Rotations all Well Within the Tolerances.

Figure 10. Fraction 2, 09:55 AM, gas pocket in rectum just under the prostate, causing significant misalignment in translations (>3 mm) and rotations (>5 degree): both are out of tolerance.
Figure 11. Fraction 2 10:23 AM, Gas Pocket in Rectum Just Under the Prostate, Causing Significant Misalignment in Translations (>3 mm) and Rotations (>5 degree): Both are out of Tolerance.

Figure 12. Fraction 3, 11:15 AM, Gas Pocket in Rectum Pushing Prostate (Fiducial Markers) Outside the Tracking Search Range, Led to Low Confidence and “Blank-out” in Target Localization
5.2 Suggestions for Future Research

For future research, in order to achieve statistical significance more patients will need to be examined according to the protocol. In this patient, three fiducials were placed at >2cm distances, rectally. Ideally, four fiducials should be used to ensure that if one fiducial fails to be visible the tracking system still would be able to detect the other three fiducials. Also, considerations of linked fiducials with fixed interfiducial distance may allow for less migration in tissue. With more attention paid to the placement of the fiducial placement, the systematic error of our calculations will reduce.

In order to reduce the passage of gas in the patient during treatment, use of the endorectal balloon (ERB) is being considered. The ERB will stabilize the rectum by inflating to allow the passage of gas freely through its pores. The ERB is tolerated in 95% of patient. Attention must also be paid to the diet and preparation of the patient to ensure the patient conforming to a strict, clear fluids diet the night prior to treatment.

In the future, more statistical analysis needs to be done with a larger cohort. Other factors influencing the accuracy of the CyberKnife technology such as rigid body error (RBE) should be also statistically analyzed.
References


