PROTOCOL TITLE: Incorporating MR Imaging into Prostate Radiotherapy Treatment Planning: A Pilot Study to Quantitate the Potential to Limit Radiation Dose to Normal Tissues.

SHORT TITLE: MRI-based Prostate Radiotherapy Planning

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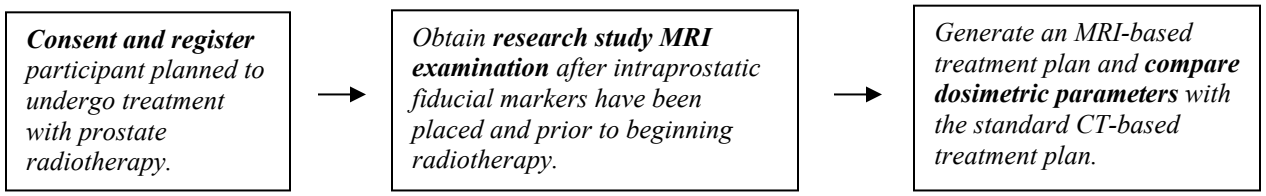
Consent and register *participant planned to undergo treatment with prostate radiotherapy.*
Obtain ***research study MRI examination*** *after intraprostatic fiducial markers have been placed and prior to beginning radiotherapy.*
Generate an MRI-based treatment plan and ***compare dosimetric parameters*** *with the standard CT-based treatment plan.*

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1.0 INTRODUCTION

1.1 Overview

This pilot study will enroll 15 men with adenocarcinoma of the prostate who are planned to undergo treatment with radiotherapy at DFCI/BWH. For this study an MRI examination will be done at the time of radiation treatment planning. In parallel to the routine CT-based plan, an MRI based-plan will be generated from which dose to pelvic organs will be calculated. We will then compare the results between the CT- and MRI-based plans and evaluate in the setting of equivalent prostate coverage to what degree our normal tissue dose constraints are met. Based on the findings of this study, the feasibility of future studies involving MRI-based prostate radiotherapy planning will be determined, including the use of new MRI methods for tumor imaging, such as diffusion weighted imaging and tumor hypoxia imaging.

1.2 Background

Prostate cancer is the most common cancer in men in the United States. Approximately 240,000 men are diagnosed annually with prostate cancer. The majority of men with newly diagnosed prostate cancer have clinically localized disease, for which external beam radiotherapy is one of the principle treatment options. Men with low-risk prostate cancer are treated with prostate radiotherapy alone, while those with intermediate-risk or high-risk disease are generally receive hormonal therapy in addition to radiotherapy. Modern radiotherapy techniques allow high doses (>75 Gy) of radiation to be administered safely. Randomized controlled trials have shown that higher doses of radiotherapy result in superior long-term prostate cancer control for men with clinically localized disease.[1-2] The major acute toxicities of prostate radiotherapy are temporary bladder and bowel symptoms, such as urinary frequency or obstruction and rectal urgency.[3] Long-term side effects include erectile dysfunction and rectal bleeding. Both acute and long-term toxicity can be minimized by limiting radiation dose to rectum, bladder, and penile bulb. Specifically, it has been shown that limiting the volume of the anterior rectal wall that receives 70 Gy or more to less than 10 cubic centimeters, decreases the risk of developing rectal adverse events.[1]

1.3 Rational

Radiation treatment planning for prostate cancer routinely involves delineation of pelvic organs on a pre-treatment computed tomography (CT) scan followed by calculation and optimization of radiation dose to the target (prostate and seminal vesicles) and organs at risk (e.g. rectum and bladder). Magnetic resonance imaging (MRI) provides a distinct advantage in delineation of the prostate and adjacent organs due to the known superior soft tissue image quality relative to CT. The improved anatomic resolution of soft tissue on MRI is particularly important at the prostatic apex where up to 40% of prostate cancer is present and where the juxtaposed neurovascular bundles, penile bulb and anterior rectal wall are within close proximity.

Several studies have shown the CT-defined prostate to be larger than the MR-defined prostate by a mean ratio of 1.2 to 1.4.[4-6] The posterior and apical margins were most likely to be over estimated to avoid missing the target due to poor resolution on CT at the prostatic rectal

interface. This resulted in increased dose to the rectum, urogenital diaphragm and penile bulb. It has also been shown that there is less inter-observer variation between prostate volumes contoured on MRI compared to volumes contoured on CT, with the greatest gains in consistency at the posterior apical prostate border.[7] An additional advantage to MRI is the ability to identify dominant lesions within the prostate as well as areas of extracapsular extension or neurovascular bundle involvement and ensure that they are encompassed by adequate margins.

For the reasons outlined above, MRI-based treatment planning has been used in several high volume cancer centers for the treatment of prostate cancer. The process typically involves five steps 1) obtain both CT and MRI images 2) outline soft tissues and bony structures on MRI 3) co-register CT and MRI images 4) transfer of soft tissue outlines to CT image 5) calculate dose to outlined structures on CT image. These steps are necessary since dose calculations depend on electron density data obtained from the CT image.

A downside of this approach is the potential to introduce error during the image co-registration process, which is based largely on bony anatomy. At our institution radio-opaque gold fiducial markers are implanted in the prostate for use on daily imaging during treatment to reduce uncertainty associated with patient setup and prostate motion between delivered fractions of radiation each day. These fiducials markers are placed after radiation therapy has been chosen as the appropriate treatment and prior to obtaining the planning CT. The routine management of patients receiving radiotherapy currently does not include MR imaging after fiducials are placed. We have determined that the fiducials are easily identified on both CT and MRI and can be used for image co-registration, obviating the need to rely on structures outside the prostate during image co-registration, thereby increasing the accuracy of prostate alignment between CT and MRI and reducing the chance for error during co-registration of the CT and MRI image data sets.

2.0 OBJECTIVES

To test the feasibility of MRI-based prostate radiotherapy planning and compare radiation dose-volume parameters for the prostate, rectum, penile bulb, and bladder using standard CT-based versus MRI-based plans with specific attention to the Rectal V70 metric which has been shown to correlate with late rectal toxicity.

3.0 RESEARCH SUBJECT SELECTION

Participants must be men with newly diagnosed stage I-III prostate adenocarcinoma who are planned to undergo external beam prostate radiotherapy, and must fit the eligibility and exclusion criteria outlined below. Men of all races and ethnic groups are eligible for this trial.

3.1 Eligibility Criteria

3.1.1 Participants must have histologically confirmed prostate cancer.

3.1.2 Prostate biopsy must be reviewed at Brigham and Women's Hospital or the Dana Farber Cancer Institute and should support a diagnosis of stage I-III prostate adenocarcinoma.

3.1.3 Candidates with PSA greater than 20, digital rectal exam consistent with disease outside the prostate (clinical T3/T4 disease), or Gleason score 8 or greater, should have a bone scan and diagnostic pelvic CT or MRI to exclude metastatic disease. These must be performed within 90 days of registration.

3.1.4 Participants should not have had prior curative local treatment for prostate cancer, including no radiotherapy or prostatectomy. A maximum 90 days of systemic androgen deprivation therapy prior to registration is allowed.

3.1.5 Participation is limited to adult patients, age 18 years or older.

3.1.6 Able to tolerate an MRI examination.

3.1.7 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Participants with known metastatic (stage IV) prostate cancer.

3.2.2 Participants with an implanted device, prosthesis, or any other foreign body with ferromagnetic properties that would make them ineligible to undergo MRI examination.

4.0 REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system.

An investigator will confirm eligibility criteria and a member of the study team will complete the QACT protocol-specific eligibility checklist.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time.

The registration procedures are as follows:

- Obtain written informed consent from the participant prior to the performance of any

protocol specific procedures or assessments. A member of the study team will meet with eligible participants to review the consent form. Ample time will be allotted to read the consent form in full and address any questions regarding participation in the trial. Eligible participants who decide to participate will be consented by a member of the study team who has completed their Human Subject Training. A copy of the informed consent form will be given to the patient.

- Complete the QACT protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. To be eligible for registration to the protocol, the participant must meet all inclusion and exclusion criterion as described in the protocol and reflected on the eligibility checklist.

- Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295. For Phase I protocols, attach participant dose level assignment confirmation from the sponsor.

- The QACT Registrar will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant when applicable.

- An email confirmation of the registration and/or randomization will be sent to the Overall PI, study coordinator(s) from the Lead Site, treating investigator and registering person immediately following the registration and/or randomization.

4.3 General Guidelines for Other Investigative Sites

N/A

4.4 Registration Process for Other Investigative Sites

N/A

NOTE: Registration and randomization with the QACT can only be conducted during the business hours of 8:00 AM and 5:00 PM Eastern Standard Time Monday through Friday. Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC Lead Institution.

5.0 STUDY DESIGN AND METHODS

5.1 Design/Study Type

With this pilot study we aim to test the hypothesis that MRI-based treatment planning combined with fiducial-based image co-registration (as described below) could enhance the therapeutic ratio of prostate radiotherapy by increasing the accuracy of target delineation while safely minimizing the dose to the anterior rectum, neurovascular bundles, penile bulb, and bladder without compromising target coverage. The study will not change patient staging or treatment. The maximum total accrual will be 15 participants.

5.2 Imaging Plan

The standard workflow for patients preparing to undergoing prostate radiation therapy at BWH/DFCI involves placement of intraprostatic fiducial markers (i.e. three gold seeds) followed by a non-diagnostic planning CT scan, typically 1-3 weeks after placement of fiducial markers. The MRI examination described below will be done after the intraprostatic fiducial markers have been placed and around the same time that the standard planning CT scan is done.

Prior to performing the MRI examination, source data will be collected for each participant. This will include the prostate biopsy report, PSA level, and other information needed to document eligibility. The procedure note from intraprostatic fiducial placement will be reviewed and the date documented in the medical record. MRI examination will be performed no earlier than 3 days after fiducial placement. The MRI examination will be performed prior to starting radiotherapy. Ideally, the MRI examination will be performed within 1 week of (either before or after) the radiotherapy planning CT examination.

Participants will have one prostate MRI examination for this study that will take approximately 60 minutes and will be supervised by an MRI technologist. The prostate MRI examination for this study will be done without endorectal coil. The MRI examination will not require any additional contrast, interventions, hospitalizations, or blood tests. Subjects will be positioned lying on their back within the MRI magnet which is a large cylindrical tube that allows strong magnetic fields to pass through the body. The whole body coil within the MRI will be used for image acquisition. Ear plugs and a padded table will be provided for the subject's comfort. A radio frequency receiver coil encased in a plastic mold called a phased-array coil will be positioned around the subject's pelvis. The imaging protocol will include fast spin echo (FSE) for T2WI and fast spoiled gradient (FSPGR) for T1WI. Following the MRI exam, the imaging data will be collected and archived. A safety read will be performed in a timely fashion and the study PI will be informed of unexpected or clinically relevant findings.

5.3 Data Collection Plan

In addition to the MRI examination described above, all radiographic images associated with the standard processes of staging, planning and delivery of radiation therapy will be collected.

5.4 Data Processing Plan

Data processing and analysis will commence as soon as evaluable data from MRI and CT imaging is obtained. The target (i.e. the prostate gland and seminal vesicles) and normal tissues (i.e. bladder, rectum, and penile bulb) will be outlined independently on both CT and MR images by the same physician. The MRI will be co-registered with the standard planning CT scan by aligning intraprostatic fiducial markers. MRI-based contours will be transferred to the CT scan and a mock radiotherapy plan will be generated from these contours. As is conventional for a standard CT-based plan, dose volume histogram (DVH) analyses will be done for each contoured structure. Using DVH data, MRI-based and CT-based plans will be normalized to produce

equivalent target coverage. It will then be determined to what degree normal tissue dose constraints are met.

5.5 Publication Plan

The end of the study is the time point at which data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. The results will be made public within 12 months of reaching the end of the study. At that time a manuscript will be prepared for publication in a peer-reviewed journal.

5.6 Compensation Plan

Participants will not receive compensation for this study.

5.7 Criteria for Taking a Participant Off Study

Participants will complete MRI examination and will be included in the analysis as per protocol unless one of the following criteria applies:

- Metastatic disease progression prior to MRI
- Intercurrent illness that prevents MRI examination
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with MRI examination and/or documentation requirements
- Participant decides to withdraw from the study
- General or specific changes in the participant's condition render the participant unacceptable for MRI examination or ability to proceed with prostate radiation treatment planning in the judgment of the treating investigator

Participants will be removed from the protocol when any of these criteria apply. The reason for removal from protocol, and the date the participant was removed, will be documented in the medical record.

5.8 Adverse Reactions and Their Management

5.8.1 Reporting Adverse or Unanticipated Events

Investigators must report to the Overall PI any serious adverse event (SAE) that occurs at the time of MRI examination on the local institutional SAE form. Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

5.8.2 Anticipated Reactions
Anxiety, claustrophobia, and other related symptoms may occur in some patients prior to or during MRI examination.

5.8.3 Reaction Management
Participants will be asked about history of difficulty/inability to tolerate MRI examination, panic attacks, claustrophobia, or other symptoms that would increase the likelihood of inability to tolerate an MRI examination. A low dose of lorazepam will be prescribed for patients who may benefit from mild sedation during the examination. All participants will be encouraged to promptly report adverse or unanticipated reactions. They will be provided with contact information for the principle investigator and study nurse, as well as a 24-hour contact number.

6.0 STATISTICAL ANALYSIS

6.1 Statistical and Analytical Plan

Standard dose constraint metrics, specifically the rectal V70 (volume of the rectum receiving at least 70 Gy), penile bulb V70 and V50, and bladder V80, V75, V70 and V65 will be calculated and compared between MRI-based and CT-based plans. The primary comparison is rectal V70, and analysis of other dose constraint metrics will use the same approach. There will be no adjustment for multiple testing given the pilot nature of the study.

The quantitative level (volume in cc) of each metrics will be summarized as mean (standard deviation, SD) or median (range). Change in levels from CT- to MRI-based plan will be analyzed using the paired t-test (or Wilcoxon signed rank test, if appropriate). Percent reduction from CT- to MRI-based plan will be reported descriptively as mean with two-sided 90% confidence interval (CI). The proportion of participants who achieve reduction of 10% or more in each metrics will also be provided with the exact binomial two-sided 90% CI.

6.2 Sample Size, Accrual Rate and Study Duration

A total of 15 evaluable participants will be accrued within one year. With 15 subjects, the estimated width of 90% CI on an observed mean percent decline of a dose constraint marker from CT to MRI would be +/-8.5% and +/-17%, assuming that the SD is 20% and 40% respectively. There is 80% power to detect an 0.68SD change corresponding to mean decline of 14% and 27% using a one-sample paired t-test (two-sided alpha=0.10), assuming SD is 20% and 40% respectively. The maximum width from the exact binomial 90% CI for the proportion of participants with reduction of 10% or more is 46% (+/-23%).

The study will terminate when all required imaging data from the last participant is obtained. It is hoped that accrual targets will resemble the ethnic and racial composition of the U.S. population as closely as possible. Given the small sample size for this pilot study, no pre-specified accrual targets by racial or ethnic category will be defined.

7.0 REFERENCES

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