Abbreviated Title: IMRT for Prostate Ca and nodes
CC Protocol #: 05-C-0241M
Version Date: May 16, 2017
NCT Number: NCT00214422

Title: A Pilot Study of Image Guided Prostate and Pelvic Nodal Irradiation with Intensity Modulated Radiation Therapy (IMRT) in Prostate Cancer

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Roles

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B. *Obtaining identifiable private information about living individuals*
C. *Obtaining the voluntary informed consent of individuals to be subjects*
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PRÉCIS

BACKGROUND

- This study represents a progression from findings in four previous NCI ROB protocols (02-C-0167A, 02-C-0207E, 03-C-0190B, 04-C-0171). In these previous works we have begun to develop techniques to obtain Magnetic Resonance (MR) biological images and co-register tissue in prostate cancer patients.

OBJECTIVES

- The primary objective of the first portion of this study is to assess the feasibility of using IMRT to treat the at-risk lymph nodes in prostate cancer. Also, if feasible, we hope optimize this technique with experience.

ELIGIBILITY

- This is a study of image guided, targeted radiation therapy in patients with high risk of nodal metastases from prostate cancer.
- Patients with prostate cancer who have more than 15% risk of lymph node (as defined by the Partin tables) metastasis will be eligible for this study.

DESIGN

- On the first 10 patients, we will perform approximately 5 CT simulations throughout the course of their therapy. On each simulation, the initial treatment plan will be re-run. The dose-volume data from target and normal tissues will then be re-analyzed. From this analysis we will be better able to determine the size of margins needed to account for organ motion and changes such as varying amounts of gas in the bowel and fluid in the bladder. To the best of our knowledge, no such analyses have been published.
- If the initial part of this trial is feasible, we will proceed to a phase I dose escalation trial of radiation to the at-risk lymph nodes. The primary statistical objective of the phase I portion of this study is to estimate the Maximum Tolerated Dose (MTD) of external beam radiation based on evaluating acute toxicity. The study will be conducted with a dose-escalation design with 3 patients in each dose cohort. If fewer than 2 of 3 patients experience an acute DLT than patients will be accrued to the next dose cohort. If 2 or more of 3 patients experience a DLT then the MTD will be exceeded and the prior, lower dose cohort will be considered the MTD. Secondary objectives of this study are to relate patterns in gene and protein expression to response and toxicity and to evaluate the frequency of late term toxicity.
- Specific procedures and risks will be described in a separate consent to be obtained at the time of biopsy. Tissue samples will be processed for cDNA microarray testing and stored for future analysis in the Radiation Oncology Branch, NCI.
- Anatomic Magnetic Resonance Imaging (MRI) and MR biological images of the prostate and pelvis will be obtained and tissue will be acquired with biopsy locations precisely translated (co-registered) to an MR image of reference. A fiducial marker (gold seed) will be left at the biopsy site as a fiducial marker to direct future radiation therapy to the prostate. If necessary, additional fiducial markers will be placed for prostate localization during treatment.

SCHEMA

Pathologic Diagnosis of Prostate Cancer

INELIGIBLE
Those who require radiation therapy to the prostate gland alone.

REGISTER:
Patients who require whole pelvis radiation therapy.

Perform MRI guided biopsies of areas suspicious for cancer. Leave fiducial markers at these locations.

Treatment

First 10 Patients (Feasibility Testing Period)

- The MRI of the prostate and pelvis will be registered to the treatment planning CT scan.
- The prostate will be treated to 7560 cGy in 180 cGy daily fractions (42 fractions.)
  - The maximum dose 7 mm or more beyond the prostate will be no more than 7560 cGy.
  - No More than 25% percent of the rectal volume shall receive more than 70 Gy.
  - The maximum dose to the prostatic urethra, bladder, and rectum will be limited to 78 Gy.
- For the first 25 fractions, in addition to the prostate, the high risk lymph node bearing regions of the pelvis will also be treated with IMRT to a total dose of 4500 cGy.
- The maximum dose 7 mm beyond the lymph node regions will be no more than 5040 cGy.
  - No more than 10cc of the small bowel will receive more than 55 Gy.
- There will be daily localization of the prostate and fiducial markers using portal imaging.
- All patients will receive 5 further CT simulation studies during the course of therapy
  - We will again run the initial plan on these subsequent CT simulations.
  - We will compare the dosimetry parameters above across the CT simulations
    - This analysis will allow us to determine what margins are truly appropriate to provide adequate coverage of the target volumes
- All patients will receive neoadjuvant, concurrent, and adjuvant hormone therapy.

Treatment

After the First 10 Patients (Phase I Dose Escalation)

- The MRI of the prostate and pelvis will be registered to the treatment planning CT scan.
- The prostate will be treated to 7560 cGy in 180 cGy daily fractions (42 fractions.)
- The maximum dose 7 mm or more beyond the prostate will be no more than 100% of the prescription dose of 7560 cGy.
  - No More than 25% percent of the rectal volume shall receive more than 70 Gy.
  - The maximum dose to the urethra, rectum and bladder will be limited to 78 Gy.
- In addition to the prostate, the high risk lymph node bearing regions of the pelvis will also be treated with IMRT in 180 cGy daily fractions. Total dose will be determined by dose cohort.
- The maximum dose 7 mm beyond the lymph node regions will be no more than 5040 cGy.
  - No more than 10cc of the small bowel will receive more than 55 Gy.
- There will be daily localization of the prostate and fiducial markers using portal imaging.
- All patients will receive neoadjuvant, concurrent, and adjuvant hormone therapy.

Follow Up:

- Toxicity
- MRI to evaluate for changes in imaging.
- Genomic and proteomic study of biopsied tissue

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1.0 INTRODUCTION

1.1 STUDY OBJECTIVES

Primary:

1. (First 10 patients) To determine the feasibility of treating the pelvic lymph nodes with IMRT.
2. (After the first 10 patients) To determine the maximum tolerated dose (MTD) of external beam radiation to pelvic lymph nodes of interest in patients receiving radiation therapy for prostate cancer.

Secondary:

1. To evaluate long-term effects and toxicity following IMRT dose escalation to the pelvic nodes.

1.2 BACKGROUND AND RATIONALE

1.2.1 Intensity modulated radiation therapy (IMRT)

Standard treatment of high risk prostate cancer patients, with a greater than 15% percent risk of lymph node metastases, for many years has included whole pelvis radiation therapy (WPRT). Separately, in low risk prostate cancer patients, several studies have established that escalating doses of external beam radiation therapy improve biochemical disease free survival. [1-3]

However, the benefits of escalating dose have not been applied to high risk patients because, with standard technique, dose escalation to the pelvic lymph nodes would necessitate exceeding the tolerance of the small bowel within the radiation field.

Intensity modulated radiation therapy (IMRT) is a newer form of radiation dose delivery that allows for delivery of high doses of radiation with rapid drop off of dose beyond the target. This combination of factors allows targeted dose escalation while decreasing or maintaining the amount of dose to a given volume of normal tissue.

In IMRT the physician defines the target volume as well as the dose constraints on normal tissue. The treatment planning computer then does “inverse planning” to generate an acceptable plan that meets the target coverage and normal tissue dose constraints. If the physician remains unsatisfied with the plan, the priorities of tumor coverage and normal tissue limits can be adjusted and the plan re-generated.

Thus, IMRT provides a unique opportunity to safely attempt dose escalation to the pelvic lymph nodes in prostate cancer.

Evolving research initiatives in the Radiation Oncology Branch (ROB) and the Radiation Oncology Sciences Program (ROSP), NCI, depend upon the availability of tissue samples from patients receiving radiotherapy. The tissue acquired in this preliminary effort is critical to the expansion of our knowledge of radiation induced gene and protein expression profiles, and will potentially generate novel hypotheses for molecular therapeutic strategies.

1.2.2 Dose Escalation In Prostate Cancer

In a study of 301 patients, Pollack et al demonstrated that doses of 7800 versus 7000 cGy produced significantly improved failure free survival in intermediate to high risk patients (70 versus 64%, p=0.03).[1]

Zietman et al have recently reported on a trial comparing 7920 versus 70.2 cGy (actually cobalt Gray Equivalent dose) in patients with prostate cancer treated with a proton boost. The five-year biochemical failure rates were 37.3% for the conventional dose group and 19.1% for the high dose group (p=0.00001).[2]

Increased toxicity accompanied dose escalation in Pollack's experience. This toxicity was reduced if less than 25% of the rectal volume was irradiated to 70 Gy.[1] Neither Zietman nor Pollack used IMRT.

1.2.3 Use of Whole Pelvis Radiation Therapy In Prostate Cancer

Whole pelvis radiation therapy (WPRT) has long been standard in the treatment of high risk prostate cancer patients.[3-5] Bowel toxicity thwarting dose escalation, investigators have focused on combining whole pelvis radiation therapy and hormone therapy.

Between 1987 and 1995, the EORTC performed a phase III trial with 415 high risk prostate cancer patients. They compared external irradiation alone and external irradiation combined with an analog of luteinising-hormone releasing hormone (LHRH). Hormone therapy was continued for at least 3 years or indefinitely. In both treatment groups, 50 Gy radiation was delivered to the pelvis over 5 weeks, and 20 Gy over 2 weeks as a prostatic boost. With a median follow-up of 66 months, 5-year clinical disease-free survival was 40% in the radiotherapy-alone group and 74% in the combined-treatment group (p=0.0001). 5-year overall survival was 62% and 78%, respectively (p=0.0002).[6]

RTOG trial 9413 tested the hypothesis that combined androgen suppression (CAS) and WPRT followed by a boost to the prostate improves progression-free survival compared with CAS and prostate-only RT (PORT). Between 1995 and 1999, 1323 high risk prostate cancer patients were accrued. With a median follow-up of 59.5 months, in an unplanned subset analysis, WPRT was associated with a 4-year PFS of 54% compared with 47% in patients treated with PORT (P =.022).[4]

As in the EORTC study, concurrent hormone therapy with at least 3 years or indefinite adjuvant hormone therapy will be required on this protocol.

1.2.4 MRI and the Detection of Prostate Cancer

At present there are no imaging techniques that can accurately delineate tumors within the prostate gland. Transrectal ultrasound, although in wide use for guiding biopsies, is not sensitive for the detection of prostate cancer despite the advent of color Doppler and ultrasound contrast agents.[7, 8] Computed tomography is also insensitive for localized prostate cancer.[9] PET scanning with Fluorodeoxyglucose (FDG) is limited by artifacts related to the urinary bladder and by relatively low avidity of FDG for prostate cancer.[10, 11] While other PET agents are under investigation, none has yet emerged as clearly superior to any other.[12]

MRI offers a 3D dataset, multiple imaging planes, and unparalleled soft tissue resolution, making it the modality of choice for imaging the prostate gland. MRI has been shown to provide better visualization of the prostate and surrounding structures than either ultrasound or CT.[13] T2-weighted scans depict the normal peripheral zone as high in signal and tumors are depicted as relatively low in signal, a characteristic appearance that can detect 60 to 80% of prostate cancers, but that is limited by non-specificity, with prostatitis and hyperplasia mimicking tumor. Evidence of extraprostatic spread of tumor includes hypointense stranding in the periprostatic fat, obliteration of the rectoprostatic angle, or clear-cut extracapsular extension. Staging accuracies of extracapsular extension for high field strength MR images are as high as 82% to 88% in single institutional series.[14-16]

In patients with known prostate cancer, based on our experience with ongoing protocol NCI #02-C-0207E, we have been able to identify and biopsy regions of signal abnormality by MRI. In 50% of patients these biopsies have yielded specimens containing prostate cancer.

Harisinghani et al have demonstrated that small iron particles can be used in combination with MRI to detect small metastases to the pelvic lymph nodes in patients with clinically localized prostate cancer.[17] From this original data set, Shih et al have published an abstract defining a template, based on vascular anatomy, that identifies the at risk target volume. Nearly 90% of all positive lymph nodes were within 2.5 cm of a major vessel. Therefore, a 2.5 cm expansion upon the major vessels would capture the vast majority of positive lymph nodes.[18]

Use of such a template would allow the sparing of a significant volume of small bowel while allowing treatment of upper pelvic nodes that are currently untreated by standard whole pelvis radiation therapy.

1.2.5 The 'APT-MRI' system

In collaboration with Department of Biomedical Engineering at Johns Hopkins we have developed a system that provides transrectal needle access to the prostate while a patient is imaged inside of a 'closed' scanner. This system, called the APT-MRI system (Access to Prostate Tissue under MRI-guidance), will be utilized in this study to acquire needle biopsy tissue in accurate reference to DCE-MRI images. The device has recently been reviewed by the FDA and determined to be a non-significant risk device.

The method is very similar to transrectal ultrasound guided biopsy of the prostate, except that it is applicable within a closed high-field MRI scanner. In canine studies, accurate needle placement in a variety of clinical applications (e.g. biopsy, injections, and seed placement) were demonstrated.[19] This system was adapted to clinical use and investigated for feasibility, tolerability, and needle targeting accuracy under protocols 03-C-0190 and 02-C-0167.

Clinical results to date show that the APT-MRI system is safe, well tolerated, and can target prostatic sites with millimeter accuracy (see Figures 1-3).[20] Five gold fiducial markers were placed within the prostate gland in each of five patients with localized prostate cancer. By depositing fiducial markers within the gland, we were able to assess not only needle placement

accuracy, but also the accuracy with which the tissue itself was targeted (i.e. leaving a permanent marker allows for measurement of the impact of tissue deformation, produced during needle insertion, on targeting accuracy). Subsequently, the system was also used for four 1.5T MRI-guided prostate biopsy procedures in three patients.

The mean MR procedure duration was 72 minutes; all patients tolerated the intervention well and no unexpected toxicities occurred. Using axial MR images, needle and marker placement errors were assessed. The mean needle placement accuracy was 1.9 mm for the fiducial marker placement studies and 1.8 mm for the biopsy procedures. The mean fiducial marker placement accuracy was 4.8 mm and the mean transverse fiducial marker placement accuracy was 2.6 mm. The gold fiducial markers were subsequently used to assess daily setup errors and off-line organ motion during a standard course of external beam radiation therapy for prostate cancer.

We continue to modify and improve this system to yield progressively better results.

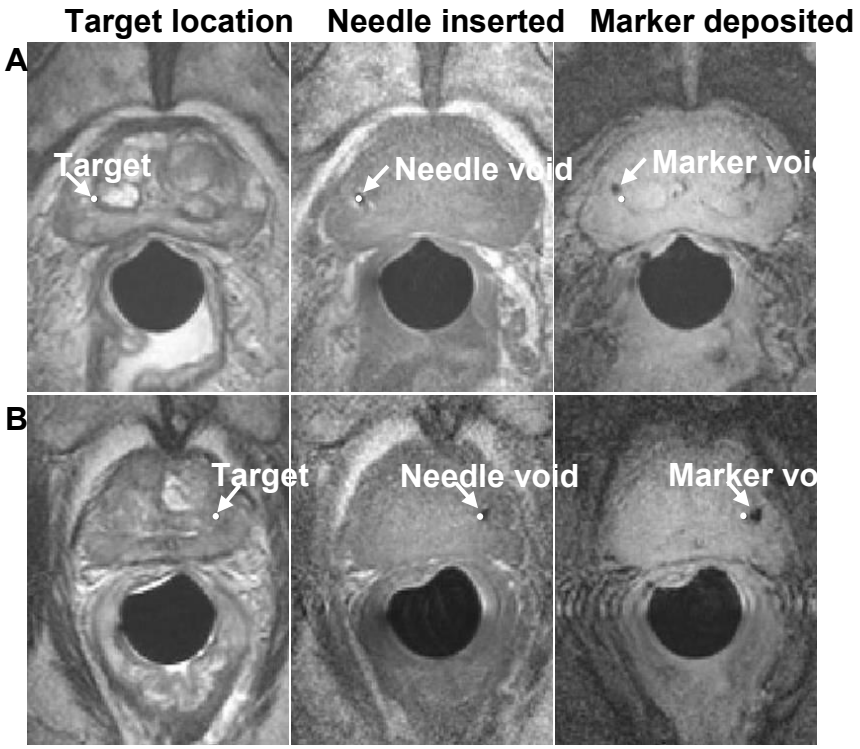

Figure 1: Targeting, needle, and fiducial-marker visualization images. Images from two patients (**Rows A and B, respectively**), show images acquired during the fiducial-marker placement procedure. **Column 1**: Targets are selected on axial, T2-weighted fast spin-echo images. The site pre-selected for targeting is represented by a white dot in all images. **Column 2**: The needle tip void is visualized in axial, T1-weighted fast spin-echo images. **Column 3**: The marker void is visualized on axial, T2*-weighted gradient-echo images. Note that there is minimal tissue motion throughout each procedure.

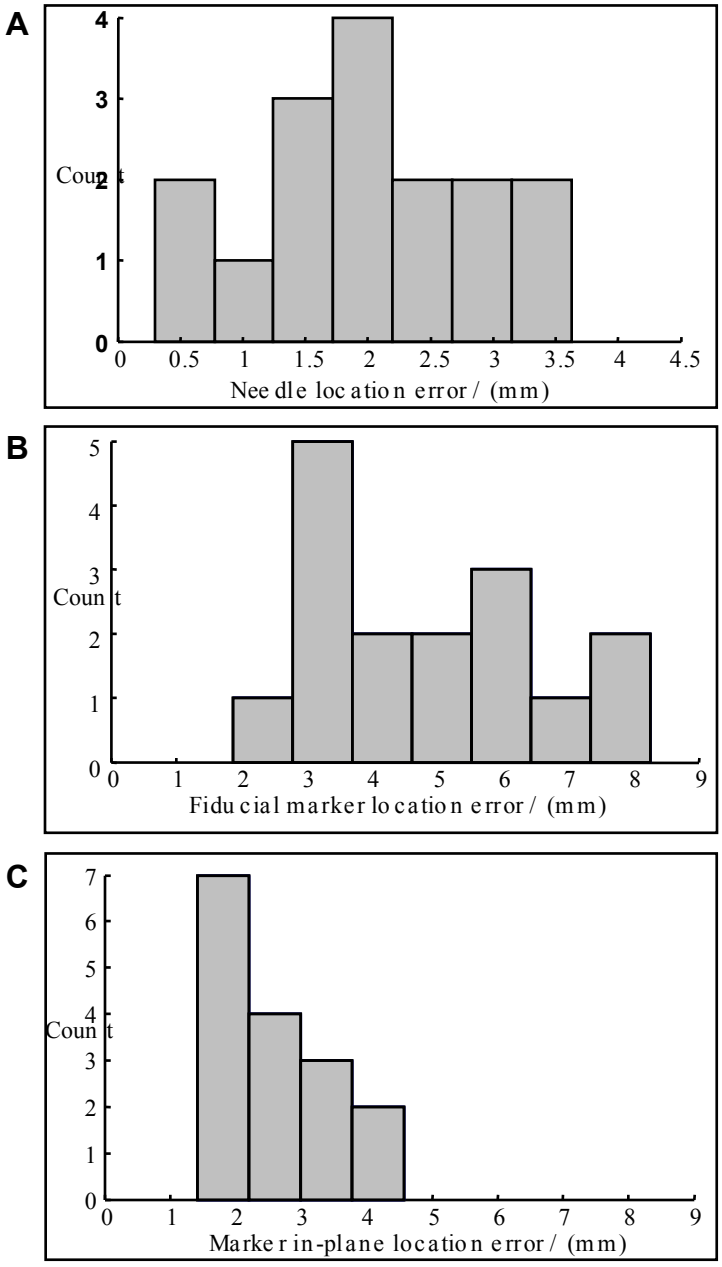

Figure 2: Needle and fiducial-marker placement accuracy. Error histograms show needle tip location errors (**Panel A**), fiducial marker location errors (**Panel B**), and fiducial marker in-plane location errors (**Panel C**) for all 16 gold fiducial markers placed. Mean placement errors for each are 1.9 mm, 4.8 mm, and 2.6 mm, respectively. Because tissue core biopsies are typically 1.5 cm long, the last measure, fiducial marker in-plane placement error, is the best predictor of tissue acquisition accuracy.

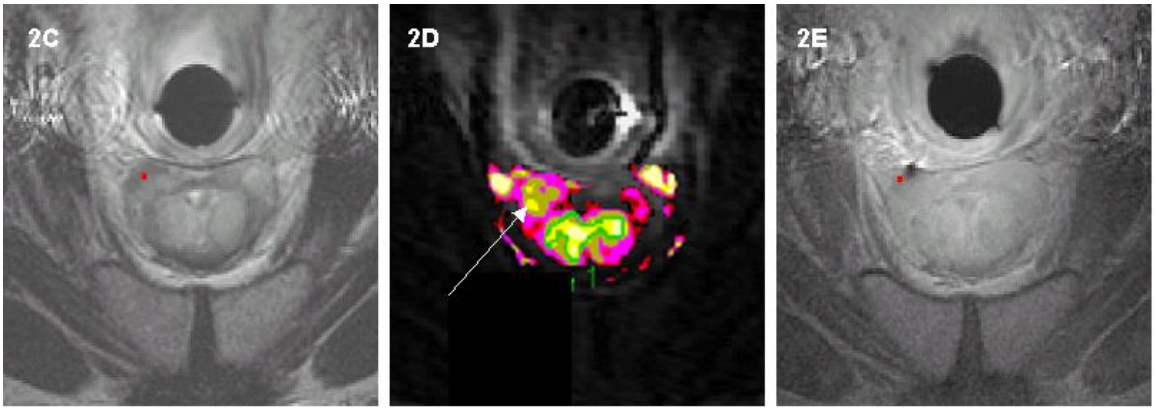

Figure 3: A case example whereby T2W FSE images (2C) shows a suspicious lesions in the peripheral zone which was targeted for biopsy (red dot). Dynamic contrast MRI color-coded for contrast kinetics (2D) shows normal activity in the central gland and neurovascular bundles, and activity suspicious of malignancy in the peripheral zone (arrow) corresponding to the targeted site. The biopsy needle can be visualized on axial images (2E - signal void) prior to tissue acquisition in close proximity to the intended target (red dot).

1.2.6 Fiducial Markers

Using MRI for anatomic guidance and visualization, between 2 and 6 gold fiducial markers will be placed within the prostate of patients with cancer prior to external beam radiotherapy. Our experience with ongoing protocol 03-C-0190C has demonstrated that these fiducial markers can be accurately placed using MRI guidance.

While placement of the gold markers per se has no direct therapeutic benefit for the patient, intraprostatic fiducial markers (placed under ultrasound) have shown value in assessing daily setup errors and off-line organ motion during external beam radiation therapy for prostate cancer.[21-23] These markers can also be utilized to aid in CT-MRI fusion[24] and result in better target delineation for treatment planning as well as daily localization.

IMRT with its very tight margins is at high risk of missing tumor beam as a result of organ motion and inaccurate patient positioning. Current measures, such as patient immobilization devices and laser-tattoo alignments, do not address prostatic motion relative to bony landmarks. Variations in bladder and rectal filling have been shown to affect prostate position within the pelvis, to an extent which may require field adjustments during the course of radiotherapy.[25] Since the rectum tends to become progressively less distended during a course of pelvic radiotherapy (mean decrease in diameter 1.5cm), the predominant prostatic motion is in the posterior and inferior direction. In one study 11% of patients showed an inferior shift of the prostate of more than 1cm and 30% showed a posterior shift of more than 1cm.[22]

Portal x-ray imaging is a technique used to monitor the accuracy of beam isocenter positioning relative to bony landmarks during radiotherapy. Since the prostate is not

visible on portal imaging, radiopaque fiducial markers are surrogates for organ localization in portal images.[26] Studies show that the degree of possible migration of the fiducial markers is negligible and within the limits of accuracy of CT measurements (2mm).[27]

As prostate motion is the major source of error in radiation treatment delivery[21], some investigators have recommended that radio-opaque markers be placed in the prostate prior to the start of radiotherapy.

The relative movement of the prostate to the target volumes delineated by Shih et al has not been evaluated. We hope that our experience with the first 10 patients treated will address this issue.

1.2.7 Toxicity Assessment

Radiation side effects will be assessed using the RTOG acute toxicity grading GI & GU (Appendix IIA). In addition, we will use several patient-based self assessment questionnaires, including: 1) The Expanded Prostate Cancer Index Composite (EPIC), a robust prostate cancer health-related quality of life instrument that measures a broad spectrum of bowel symptoms, and has been validated in patients receiving radiotherapy [29]; 2) The American Urological Association Symptom Score (AUA) to further assess patient urological functioning; and 3) the Sexual Health Inventory For Men (SHIM) to assess patient and Erectile Dysfunction (ED).

1.2.8 Genomic Analysis

Serum and tissue will be stored in the Radiation Oncology branch. Future genomic and proteomic analysis may be performed as in 3.2.3.

2.0 Eligibility Assessment and Enrollment

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 ECOG performance status of 0,1, or 2

2.1.1.2 Pathology report confirming adenocarcinoma of the prostate

2.1.1.3 Risk of lymph node metastasis greater than or equal to15% as defined by the Partin tables (see appendix I) or biopsy proven positive lymph nodes

2.1.1.4 Tumor visible on MRI

2.1.1.5 No prior surgery, radiation, or chemotherapy for prostate cancer, with the exception of hormone therapy which may be given neoadjuvantly for up to four (4) months.

2.1.1.6 Age greater than 18 y/o and less than 90 years old.

2.1.2 *Exclusion Criteria*

2.1.2.1 Cognitively impaired patients who cannot give informed consent. 2.1.2.2 Patients with metastatic disease beyond the pelvis.

2.1.2.3 Contraindication to biopsy:

- Bleeding disorder

- PT/PTT ≥ 1.5 times the upper limit of normal
- Platelets ≤ 50K
- Artificial heart valve

2.1.2.4 Contraindication to MRI:

- Patients weighing >136 kgs (weight limit for the scanner tables)
- Allergy to MR contrast agent
- Patients with pacemakers, cerebral aneurysm clips, shrapnel injury or implantable electronic devices.

2.1.2.5 Pre-existing and active prostatitis or proctitis

2.1.2.6 Other medical conditions deemed by the PI or associates to make the patient ineligible for protocol investigations, procedures, and high-dose external beam radiotherapy.

2.2 PRE-TREATMENT ELIGIBILITY EVALUATION

2.2.1 Clinical Evaluation

- History and Physical Examination.
- Pathology report confirming adenocarcinoma of the prostate (outside report acceptable for study entry; pathology review by NIH to be done prior to treatment initiation).

2.2.2 Laboratory Evaluation

- PSA
- PT/PTT
- CBC

2.3 PATIENT REGISTRATION

Authorized staff must register with the central registration office an eligible candidate within 24 hours of signing the consent. A registration checklist from the Web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and faxed to the Central Registrar's Office at 301-480-0757. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

3.0 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

3.1.1 Overall Trial Design

Patients with prostate cancer who have more than 15% risk of lymph node (as defined by the Partin tables) metastasis will be eligible for this study. The initial part of this trial (first 10 patients) explores the feasibility of using intensity modulated radiation therapy (IMRT) to deliver standard dose (4500 cGy) to the pelvic lymph nodes while dramatically reducing the volume of small bowel exposed. The prostate gland will receive the standard dose (7560 cGy). These first 10 patients will also undergo 3 to 5 CT simulations throughout the course of their therapy. On each simulation, the initial treatment plan will be re-run and the dose-volume data from target and normal tissues will then be re-analyzed. From this analysis we will be better able to determine the size of margins needed to account for organ motion and

changes such as varying amounts of gas in the bowel and fluid in the bladder. To the best of our knowledge, no such analyses have been published.

If the initial part of this trial is feasible, we will then proceed to a phase I dose escalation trial of radiation to the at-risk lymph nodes. The scientific objective is to determine what dose of external beam radiation is tolerable. Specifically, we will estimate the maximum tolerated dose (MTD) of external beam radiation to pelvic lymph nodes of interest in patients with prostate cancer.

Anatomic MRI and MR biological images will be obtained Tissue will be acquired from sites of interest, with biopsy locations precisely translated (co-registered) to an MR image of reference. Fiducial markers (gold seeds) may be left at the biopsy site(s) to direct future radiation therapy. The patient will undergo a standard CT simulation for radiation therapy treatment planning. The MR and CT images will be fused. Areas of image abnormality will undergo dose escalation as described below. The remainder of the prostate gland will receive standard dose (as per the Radiation Therapy Oncology Group (RTOG) 9406 study 7560 cGy in 180 cGy daily fractions.[1] Treatments will occur at the NCI, Department of Radiation Oncology on weekdays. There will be no treatments on weekends or holidays.

3.1.2 Dose Escalation
The first 10 patients will receive 4500c Gy to the prostate and pelvic nodes, followed by IMRT to prostate alone to 7560 cGy, which is standard dose to less volume than during whole pelvis radiation therapy.

The primary objective of this study to determine the MTD of radiation to pelvic lymph nodes (LNs) of interest (as determined by MRI) in patients with prostate cancer. based on evaluating acute toxicity. The study will be conducted with a dose-escalation design with 3 patients in each dose cohort.

Cohort	Prescription Dose to Lymph Node Regions	Max Dose to > 10 cc of Small Bowel	Max Dose Allowed Beyond Prostate + 7 mm
I	5040 cGy	5500cGy	7560 cGy
II	5400 cGy	5500cGy	7560 cGy
III	5900 cGy	5500cGy	7560 cGy

3.1.3 Criteria for Dose Escalation

Each dose cohort will accrue 3 patients. If there are no DLT in 3 patients then 3 patients will be accrued to the next dose level. If two or more patients experience a DLT then the MTD will be exceeded and the prior lower dose cohort will be considered the MTD. If a DLT occurs in one of three patients then an additional 3 patients will be accrued to that dose level. If fewer than 2 of 6 patients experience an acute DLT in the expanded cohort then patients will be accrued to the next dose cohort. If 2 or more of 6 patients experience a DLT then the MTD will be exceeded and the prior, lower dose cohort will be considered the MTD.

3.1.4 Definition of Dose Limiting Toxicity (DLT)

An acute DLT will be defined as RTOG grade 3 or greater, acute GI or GU toxicity (see appendix IIA) within 3 months after the completion of radiation. Thus, accrual to an escalated dose cohort may need to be delayed so that all 3 patients in the current cohort are followed for 2 months. Given that the volume of normal tissue irradiated to standard dose or higher will be substantially limited, late toxicity is less of a concern than acute toxicity.

3.1.5 Definition of Maximum Tolerated Dose (MTD)

The primary objective is to estimate the MTD of external beam radiation that results in limiting acute toxicity. The MTD is defined as the dose level immediately below the dose level at which 2 or more in a cohort of either 3 or 6 patients experienced a DLT attributed to radiation therapy. If DLT does not occur at the highest dose level the protocol will be amended to escalate by 10% in cohorts of 3 patients each with the standard 3-6 dose escalation procedure.

3.2 PROTOCOL ADMINISTRATION

3.2.1 MR Imaging Guidelines

In all patients, conventional anatomic imaging (Fast spin echo T2 weighted scans) in the axial and coronal oblique planes will be obtained for research purposes to define the extent of the tumor. An endorectal coil may be indicated for prostate exams.

Following conventional anatomic imaging, one or more of the following research biological imaging tests will be performed. Examples include but are not exclusive to:

a) MR Spectroscopic Imaging (MRSI)
Using standard FDA approved spectroscopy software (General Electric Medical Systems, Milwaukee, WI); this will be performed using multiple voxels at multiple slices ("multivoxel-multislice MR spectroscopy") which will generate a spectroscopic map of the area of interest reflecting the relative concentrations of various metabolites in the hydrogen resonance spectrum including citrate, choline, creatine, choline and lipids. This procedure may require approximately 30-45 minutes of scanning.

b) Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI)
This imaging study uses 1mmol/kg of an FDA approved Gadolinium chelate administered slowly by intravenous injection. Serial 3D dynamic enhanced MRI may be performed through the area of interest over a period of approximately 10 minutes. These data will be sent electronically to an independent workstation where a pixel by pixel time-signal intensity curve will be generated. This data will be automatically fit to a two compartment pharmacokinetic model using a custom designed image processing algorithm which will be used to generate semiquantitative parameters reflecting flow ("A") and vessel permeability (k_{ep}). These parameters will be used to create color encoded maps which reflect the vascular flow and permeability of various regions.

c) BOLD

To accomplish this, the patient will first breathe room air via a regulated and non-magnetic tank set at 10L/min for 5 minutes via a specially designed breathing apparatus designed by Hugh Preas, M.D. of the Anesthesia Department. This breathing apparatus consists of a mouth piece and a clamp is place on the nose. It is non-invasive, and the patient can let go of the mouth piece if they find it uncomfortable.

Following this baseline study, the inhaled gas will be switched to regulated medical grade carbogen (5% carbon dioxide and 95% oxygen) in non-magnetic tanks administered at 10-15L/min for 7 minutes. This will improve the oxygenation of tissue by a combination of hyperoxia due to the high oxygen content and vasodilation due to carbon dioxide. Following carbogen inhalation the patient will be switched back to the room air at prior rates for 5 minutes. Images will be analyzed by measuring the difference in signal between the room air and carbogen scans and color maps reflecting per cent change in signal intensity will be generated for comparison.

d) OTHER Sequences
Other MRI sequences may be obtained. However, these other sequences will involve novel pulse sequences or post-processing of image data that will be transparent to the patient and will not require any additional procedures to be performed.

Of note, given the time required to perform and analyze these sequences as well as the length of the biopsy procedure, patients may have the target imaging with various high resolution sequences done at a separate time from the biopsy itself.

If the pelvic lymph nodes are visualized by MRI, then this information may be used to alter the nodal target volume.

3.2.2 Tissue Collection

3.2.2.1 <u>General co-registration guidelines</u>
Co-registration of the biopsy site to an MRI image will be accomplished by one of the following options: 1) real-time MR guidance of the biopsy procedure, 2) placing fiducial markers visible on MRI to identify sites selected for future biopsy, 3) fusing images from CT or Ultrasound-guided biopsy procedures to MR images, 4) repeat MRI immediately after a biopsy procedure to identify needle tracts.

Tissue will be collected with standard biopsy procedures (outlined below). NSAIDS should be discontinued one week prior to a biopsy procedure unless it is deemed unsafe or violates with the treatment protocol. Note that a separate consent specific to each pretreatment biopsy or fiducial marker placement procedure will be obtained.

3.2.2.2 <u>Prostate biopsy</u>
Needle biopsies will be performed in collaboration with surgeons from the Urologic Oncology Branch-NCI, and Radiologists from the Clinical Center-NIH. During each procedure, 2-10 samples will be obtained using 14-18 gauge tru-cut needles.

Biopsies will be performed according to standard techniques as follows. Patients undergo antibiotic prophylaxis with a quinolone antibiotic for one or two days before biopsy and the morning of biopsy. If the patient is known to be allergic to this antibiotic, or if they experience an allergic reaction to it, a different one, such as Bactrim will be prescribed. A rectal enema is self-administered. Patients void and then are placed in the prone position or in the left- or right-lateral decubitus position. A transrectal ultrasound or MRI probe (custom designed coil, approved by NMR Center Research Safety Subcommittee) is inserted and imaging measurements of the prostate obtained. After initial imaging is obtained, transperineal (or transrectal) introduction of 10-20 cc 1% lidocaine or 10cc of 0.25% bupivacaine is administered along the paraprostatic neurovascular bundle and the tip of the seminal vesicle. After 3 minutes of dwell time, transperineal (or transrectal), targeted prostate biopsy is performed as directed by imaging and 3-D spatialization (i.e. in the x,y,z coordinates). The patient recovers in the supine position and is allowed to ambulate shortly thereafter with a normal mean blood pressure. The patient is required to void without difficulty prior to discharge. Prostate biopsy is extremely well tolerated with complications occurring in 1% due mostly to infection, which can be treated in most cases with parenteral or enteral antibiotics as adjudged by the clinician.

3.2.2.3 Tissue Handling

Dr. Kaushal should be notified prior to specimen collection. Unless otherwise directed by Dr. Kaushal, samples will be delivered to Building 10, RmB3/46, phone 496 -5457.

Samples will be divided at the time of the procedure. Half will be immediately fixed in formalin and submitted to the Laboratory of Pathology, NCI, for histopathological analysis. The remaining tissue will be placed in freezer vials and immediately frozen in liquid nitrogen.

3.2.2.4 Tissue Analysis

A diagnostic pathological evaluation will be performed on the specimens in collaboration with the laboratory of pathology – NCI. Supplementary tests, including but not exclusive to immunohistochemistry and counts of microvessel density, may be performed in a pilot exploratory fashion at the discretion of the principal investigator.

Tissue samples may then be processed for microarray testing. RNA will be isolated and pooled from the cell population of interest. Depending on the number of cells captured, amplification strategies may be explored.
Tissue specimens collected in the course of this research project may be banked and used in the future to investigate new scientific questions related to this study. However, this research may only be done if the risks of the new questions were covered in the consent document.

No germline mutation testing will be performed on any of the samples collected unless the patient gives separate informed consent. Tests will be pilot studies related to the Branch's work on such topics as molecular imaging, molecular profiling, and novel

molecular therapeutics. If any research tests are considered to be themselves of more than minimal risk to the patients, separate permission will be requested from the IRB to perform that test, and a new consent will be obtained.

At the completion of the protocol, the investigator will dispose of all specimens in accordance with the environmental protection laws, regulations and guidelines of the Federal Government and the State of Maryland.

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described below. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed. The PI will report any loss or destruction of samples to the NCI IRB as soon as he is made aware of such loss.

If the patient withdraws consent the participants data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

The PI will report destroyed samples to the IRB if samples become unsalvageable because of environmental factors (ex. broken freezer or lack of dry ice in a shipping container) or if a patient withdraws consent. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher. Freezer problems, lost samples or other problems associated with samples will also be reported to the IRB, the NCI Clinical Director, and the office of the CCR, NCI.

3.2.3 Radiation Therapy

3.2.3.1 Prostate

3.2.3.1.1 Treatment planning

Planning target volume (PTV) 1 will be defined as the great vessels and a concentric 2.5 cm margin. Specifically, the aorta 2 cm proximal to the bifurcation, the common, internal, and external illiac vessels will be contoured. This margin may be edited at the treating physician's discretion (e.g. to meet normal tissue dose constraints). PTV 1 will be treated to a total dose of 4500 cGy in 180 cGy daily fractions in the first 10 patients. Thereafter, dose escalations will occur as per protocol. Daily dose will remain 180c Gy per day.

PTV 2 will be defined as the prostate and a 3 mm uniform margin. PTV 2 will be treated to a total dose of 75.6 Gy in 180 cGy daily fractions.

If indicated, the seminal vesicles may also be contoured and treated. When indicated, the seminal vesicles may be treated to 5400 cGy in 180 cGy.

3.2.3.1.2 Summary Of Dose Constraints:

Highest Priority:

- PTV2 will be defined as the prostate with a 3 mm uniform margin. The prescription dose to PTV2 will be 7560 cGy in 180 cGy daily fractions. No volume 4 mm beyond PTV2 will be allowed to receive a dose beyond 100% of the prescription dose.
- Less than 25% of the rectal volume will be irradiated to 70 Gy.
- The maximum dose to 10cc or more of small bowel will be no more than 5500 cGy.

Secondary Priority:

- PTV1 will be taken to full dose as per protocol.
- No more than 40% of the bladder will receive more than 6500 cGy.

3.2.3.2 Pelvic Lymph Nodes
see section 3.1

3.2.3.3 Radiation Treatment
Patients should begin their radiation treatment once pathology is available and at least 2 months of neoadjuvant hormone therapy has been completed. Patients will receive external beam radiation in the NCI Radiation Oncology Clinic daily, Monday – Friday except holidays.

3.3 TREATMENT MODIFICATIONS

Modifications to the radiation treatment will be discussed with the Principal Investigator or Study Chairperson. Isocenter adjustments will be performed for prostate motion greater in each dose cohort, the attending physician may accept a final plan that delivers 107 to 93% of the prescription dose to PTV 1 or 2. Larger deviations will require prior approval of the PI.

3.4 ON-STUDY EVALUATION

3.4.1 Pre-Procedure (baseline)

- Informed consent obtained
- Clinical evaluation
  - History and physical exam
  - Vital signs
  - Pathology report confirming adenocarcinoma of the prostate
- EPIC
- AUA Symptom Score (Appendix IV)
- Sexual Health Inventory For Men (SHIM) (Appendix V)

- Laboratory evaluation
  - PSA
  - PT/PTT
  - CBC

3.4.2 Biopsy & Fiducial Marker Placement

- See Appendix III for MRI- Guided biopsy and FM data form
- Post fiducial marker placement MRI's may be performed to evaluate for marker migration
- No more than 12 biopsies will be performed.

3.4.3 Radiation Treatment Phase

- Weekly AP (or PA) and lateral port films
- The following acute rectal toxicity endpoints will be measured
    - RTOG acute toxicity grading- GI & GU (Appendix IIA) weekly and at the completion of treatment

3.4.4 Post Active Treatment Evaluation (follow- up)

- *Upon completion of therapy, patients will be evaluated at 2, 4, 8 and 12 weeks for acute effects of radiation therapy. Patients will be evaluated at 6, 9, 12, 18 and every 6 months afterward for late effects until 36 months.*

- Follow-up visits will include:
    - A directed history and physical examination,
    - PSA evaluation
    - Rectal toxicity assessment including:
        - RTOG acute toxicity grading- GI & GU (Appendix IIA)
        - RTOG Late toxicity grading- GI & GU (Appendix IIB)
        - EPIC (Appendix IIIC).
        - AUA Symptom Score (Appendix IV)
        - Sexual Health Inventory For Men (Appendix V)

- Follow-up MRI may be obtained after completion of therapy to better delineate the time of course of signal change after radiation therapy.

3.5 CONCURRENT THERAPIES

This study allows imaging and tissue procurement in high risk prostate cancer patients with risk of lymph node metastasis of at least 15% (as defined by 15% being included within the 90% confidence intervals of the Partin tables).

Such patients do require hormone therapy. Patients should receive at least neoadjuvant and concurrent hormone therapy. Higher risk patients may also receive indefinite adjuvant hormone therapy. Neoadjuvant hormone therapy usually consists of a non-steroidal anti-androgen (such as flutamide, an oral medication) and a gonadotropin releasing hormone agonist (such as leuprolide, an injectable medication). The non-steroidal anti-androgen is usually given for approximately 6-8 weeks. Concurrent and adjuvant hormone therapy usually consists of a gonadotropin releasing hormone agonist only.

3.6 SURGICAL GUIDELINES
None other than those required for standard biopsy procedures. Where clinically indicated, biopsies will be performed under appropriate analgesia, local/systemic anesthesia and/or conscious sedation with patient monitoring in compliance with hospital standards, no general anesthesia will be administered for research purposes only. Only biopsies that are "minimal risk" and do not require general anesthesia will be performed for research purposes only. Please refer to section3.2.2. for details on the biopsy procedures.

3.7 RADIATION THERAPY GUIDELINES
Radiation Therapy is part of the primary protocol treatment and is therefore included in section 3.2.3

3.8 OFF STUDY CRITERIA

3.8.1 Patients may be taken off study for the following non-medical or administrative reasons:

- Patient refuses the procedure or further treatment
- It is deemed in the patient's best interest as determined by the PI.
- Serious protocol violation as determined by the PI.

3.8.2 *Development of a concurrent serious medical condition that precludes the completion of fiducial marker placement, radiation therapy or follow- up.*

3.8.3 Tumor progression (if occurs during treatment, at the end of radiation therapy unless the completion of local therapy is not indicated)

3.8.4 Initiation of cytotoxic chemotherapy (if occurs during treatment, at the end of radiation therapy unless the completion of local therapy is not indicated)

3.8.5 Development of a concurrent serious medical condition during active treatment and not attributable to therapy that precludes the completion of active treatment.

3.8.6 The completion of 36 months (3 years) follow-up.

3.9 POST-STUDY EVALUATION

- At the time a patient comes off study the reason for withdrawal should be documented.

- The patient should be registered off- protocol by completing the Off Study/ Death Notification Form available from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) and faxing it to the Central Registration Office at 301-480-0757.

4.0 SUPPORTIVE CARE
These procedures may require supportive care including nursing care, local anesthetic, analgesics, anti-emetics, and antibiotic prophylaxis. Please refer to section 3.2.2.2 – 3.2.2.3 for details. In the event that a patient has a reaction (allergic) to the contrast agent or medications, all appropriate medical measures will be taken.

The most common acute side effects of radiation therapy for prostate cancer, urethritis, cystitis and proctitis, may be treated with medications consistent with the standard of practice in the radiation oncology community. It is anticipated that a minority of patients may require short-term in-patient care for problems related to this protocol, namely an inability to void immediately post-op. In such circumstances, patients will be admitted to the Clinical Center under the care of the Urologic Oncologist. Medications should be listed in the patient's records.

5.0 DATA COLLECTION AND EVALUATION

5.1 DATA COLLECTION

- Clinical data and acquired samples/images will be recorded in a NCI CCR database (C3D)**.**

- Clinical data collection will include: demographic information, pathologic diagnosis, clinical stage, PSA values, history including concurrent therapies, time of biopsy, locations of biopsies, pathology repots of biopsies, dose of radiation delivered, and toxicity assessment.

- Tissue experiments to be performed are pilot and preliminary in nature. Data from assays run at the NIH will be collected in laboratory notebooks, and the NCI online microarray database.

- MRSI and dynamic MRI measurement along with corresponding sites of tissue acquisition will be digitally archived and processed using computer software in the Radiology department of the Clinical Center, NIH, and the Radiation Oncology Branch, NCI.

  End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

  Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

5.2 RESPONSE CRITERIA

Response of tumor will be determined by tracking serum PSA levels. Three consecutive rises of the PSA post-treatment will define disease recurrence. The time of disease recurrence will be back dated to the first rise in PSA. This methodology is as prescribed by the American Society of Therapeutic Radiation Oncology (ASTRO.)

5.3 TOXICITY CRITERIA

- Acute toxicities will be evaluated by the CTC, Version 3.0. (http://ctep.info.nih.gov).
- We will also utilize the RTOG acute and Late toxicity GI/ GU scales as in appendices II A & B.

5.4 STATISTICAL SECTION
This is a phase I study to determine the maximum tolerated dose (MTD) with MRI-guided radiation dose escalation to regions of interest within the prostate gland. The dose cohorts and MTD are defined in Section 3.1.1. With this design, the probabilities of dose escalation are 0.91, 0.49, 0.17, and 0.03 if the probabilities of a DLT are 0.1, 0.3, 0.5, and 0.7, respectively

Secondary analysis includes evaluating the frequency of late term toxicities. We will tabulate the frequency of late term toxicities. All secondary analyses will be reported as exploratory.

The maximum number of patients accrued to this trial will be 19 patients. We anticipate accruing these patients within 2 years.

6.0 HUMAN SUBJECTS PROTECTIONS

6.1 RATIONALE FOR SUBJECT SELECTION
This is a study for patients with prostate cancer. The patient population in whom this disease occurs is older adult males. This disease does not occur in children; therefore, children will not be part of this study. All ethnic groups/ race categories would be represented as they are represented in the disease as a whole. Decisionally impaired individuals will not be included in this study, if they are unable to sign informed consent. Physically impaired persons who otherwise satisfy eligibility criteria will be included in this study.

6.2 PARTICIPATION OF CHILDREN
Adenocarcinoma of the prostate is not a disease of children, therefore, children will not be considered as research subjects for this study.

6.3 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS
The medical risks associated with this study are those normally expected risks associated with external beam radiotherapy and high dose rate brachytherapy for prostate cancer. Common acute and temporary side effects include fatigue, urethritis, cystitis and proctitis. Uncommon long-term side effects may include urinary frequency, urgency, incontinence, rectal bleeding, perineal pain, tenesmus, erectile dysfunction, bowel adhesions causing obstruction and infertility. Very rare long-term complications may include lymphedema, pathologic femoral neck fractures, and a second primary malignancy.

Patients on this study will be receiving treatment for their prostate cancer. Other potential benefits of participation may include fewer side effects of radiation treatment due to a better visualization of the anatomy and sparing of normal structures. The information learned from this study may also benefit other patients with prostate cancer in the future.

6.4 CONSENT AND ASSENT PROCESSES AND DOCUMENTS
The Principal Investigator and associates will recruit patients. The investigational nature and objectives of this study, the procedures involved and their attendant risks and discomforts, will

be carefully explained to the patient, and a signed informed consent document will be obtained. It is our goal to be as explicit as possible in verbal and written consent procedures to insure that all participants are joining the study without coercion.

Patients who meet study eligibility criteria, and who are willing to participate in the study, will be consented by the PI or associates. The consent form will be discussed with the patient in person. Informed consent will involve careful explanation of all items outlined in the consent form. This discussion includes the investigational nature of this study, and the possibility of lack of direct benefit to the research subject. All information will be reported in summary fashion only. A separate anesthetic/operative consent will be obtained at the time of the procedure

6.5 PATIENT ADVOCATE

The patient's rights representative is available to patients on this protocol at (301) 496-2626 in Building 10, Room 1C132, NIH. Patients may ask any questions about the study and may withdraw their consent at any time without compromising their medical care.

7.0 DATA REPORTING

7.1 PATIENT REGISTRATION FORM

Demographic information and results of pretreatment studies should be entered and reported to Harris Technical Information Services at the time of patient entry onto the trial (see section 2.3).

7.2 DATA SUBMISSION

- Summary information will be submitted to the IRB annually for continuing review and at the completion of the study.

- Data may be reported in laboratory publications as derived from pilot studies. Patients will not be indicated by name.

7.3 DEFINITIONS

7.3.1 Adverse Events

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form unless otherwise noted above in Section 5.1.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution. AEs should be reported up to 30 days following the last dose of study drug.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

7.3.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.3.3. Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.3.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

7.3.5 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.3.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

7.3.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

7.3.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

7.3.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

7.3.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

(a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

(b) the characteristics of the subject population being studied; **AND**

- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.4 NCI-IRB AND CLINICAL DIRECTOR REPORTING

7.4.1 NCI-IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report in the NIH Problem Form to the NCI-IRB and NCI Clinical Director:

- All deaths, except deaths due to progressive disease

- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

7.4.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
   - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
   - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
   - All Grade 5 events regardless of attribution;
   - All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

7.5 DATA AND SAFETY MONITORING PLAN

7.5.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis weekly when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8.0 PHARMACEUTICAL INFORMATION

8.1. Levofloxacin:

Manufacturer: Ortho-McNeil

Commercial Name: Levaquin®

Description: Levofloxacin is a synthetic broad spectrum antibacterial agent in the family of fluoroquinolones for oral administration.

Form: Levofloxacin is available as (-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyridol[1,2,3-del]-1,4-benzoxazine-6-carboxylic acid hemihydrate. It is available in 250, 500 and 750 mg film-coated tablets. The inactive ingredients are starch, microcrystalline cellulose, crospovidone, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, polysorbate 80 and synthetic red and yellow iron oxides.

Supply: Levofloxacin is commercially available and will be supplied by the Clinical Center pharmacy.

Toxicities: Nausea, diarrhea, vomiting, and abdominal pain are the most frequent side effects of levofloxacin. Bad taste in the mouth, restlessness, rash, sensitivity to sunlight and seizures are other possible side effects. Levaquin may cause dizziness or lightheadedness.

Levofloxacin should be administered at least 2 hours before or 6 hours after magnesium/aluminum antacids, or sucralfate, Videx® (didanosine) chewable/buffered tablets or pediatric powder for oral solution, or other products containing calcium, iron or zinc.

8.2 Bupivacaine:
Manufacturer: Abbott Pharmaceutical

Commercial Name: Marcaine®

Description: Bupivacaine is a long-acting local anesthetic administered by parenteral injection. It is a homologue of

mepivacaine and is chemically related to lidocaine in the class of depolarizing local anesthetics.

Form: Bupivacaine is available as 2-piperidinecarboxamide,1-butyl-N-(2,6-dimethylphenyl)-, monohydrochloride, monohydrate. It is available as a sterile injectable liquid in 0.25, 0.5, and 0.75% concentrations packaged in single use ampules ranging from 10 to 50 ml. The inactive ingredients are sodium chloride and hydrochloric acid.

Supply: Bupivacaine is commercially available and will be supplied by the Clinical Center pharmacy.

Toxicities: Adverse reactions and systemic toxicities are predominantly related to the dosage and of route injection. Maximal dosage is 150 mg in adult patients. A 10 ml dose of 0.25% contains 25 mg of bupivacaine. Central nervous system toxicities include restlessness, anxiety, dizziness, tinnitus, blurred vision and tremors. Convulsions and seizures can result from excessive plasma levels. Cardiovascular toxicities from high doses or unintentional intravascular injection may lead to high plasma levels and related depression of the myocardium, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation, and cardiac arrest. The use of low dosages of bupivacaine for regional blockade in peripheral sites not including the head and neck or obstetrical applications has a less than 0.01% chance of adverse reaction. Severe cardiac or neurologic toxicity with its use in prostate biopsy has not been reported.

8.3 MRI CONTRAST AGENT – Gadopentate dimeglumine
Manufacturer: Berlex Laboratories, Wayne NJ

Commercial name: Magnevist

Description: This is an FDA approved contrast agent in widespread use. Gadolinium produces MR contrast by altering the relaxivity of neighboring water protons. Experience at NIH has been obtained with over 30,000 intravenous injections.

Form: Gadopentate dimeglumine is available as Gd-DTPA. It is available as a sterile injectable liquid in single use ampules of 20 ml. The inactive ingredients are meglumine and diethylenetriamine pentaacetic acid.

Supply: Magnevist is commercially available and will be supplied by the Clinical Center Department of Radiology

Toxicities: The serious reaction rate (asthma, hives, seizures, hypotension) is less than 0.5%. The dose is 0.1 mmol/kg BW administered IV bolus via mechanical injector. There are no contraindications for its use. Gd-DTPA can be used in patients with elevated Cr. Levels and does not have known nephrotoxicity. Possible complications relate to extravasation of contrast in which localized swelling and pain may develop but because of the small volume (20cc) this does not lead to skin necrosis. There may be headache, nausea, vomiting, and transient sensations of heat or cold or taste disturbances following injection of gadopentetate.

8.4 Fleet Phospho-soda® enema
Manufacturer: C.B. Fleet Co. Inc., Lynchburg, VA

Description: A sodium phosphate solution for cleansing of the rectal mucosa prior to invasive procedures.

Form: Each 118 ml delivered dose includes 19g of monobasic sodium phosphate and 7 g of dibasic sodium phosphate. Latex-free application bottles contain 133 ml of solution.

Supply: Fleet® enema is commercially available and will be supplied by the Clinical Center pharmacy.

Toxicities: Fleet® enema cannot be used in patients with congenital megacolon, bowel obstruction, imperforate anus, or congestive heart failure. It must be used with caution in patient with impaired renal function, pre-existing electrolyte disturbances or a coloastomy, or in patients on diuretics or other medications that may affect electrolyte levels. Hypocalcemia, hyperphosphatemia, hypernatremia, or acidosis may occur.

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Apendix IV

AUA SYMPTOM SCORE

Last Name	**First Name**	**Date**

Highlight or bold or change font color of the response correct for you and type in your score in the far right box for all SEVEN questions.

1. **Incomplete emptying:** Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?

Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your Score
0	1	2	3	4	5	

2. **Frequency:** Over the past month, how often have you had to urinate again less than 2 hours after you finished urinating?

Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your Score
0	1	2	3	4	5	

3. **Intermittency:** Over the past month, how often have you found that you stopped and started again several times when you urinated?

Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your Score
0	1	2	3	4	5	

4. **Urgency:** Over the past month, how often have you found it difficult to postpone urination?

Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your Score
0	1	2	3	4	5	

5. **Weak-stream:** Over the past month, how often have you had a weak stream?

Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your Score
0	1	2	3	4	5	

6. **Straining:** Over the past month, how often have you had to push or strain to begin urination?

Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your Score
0	1	2	3	4	5	

7. **Nocturia:** Over the past month or so, how many times did you get up to urinate from the time you went to bed until the time you got up in the morning?

None	1 time	2 times	3 times	4 times	5 or more times	Your Score
0	1	2	3	4	5	

Add up your scores for total AUA score = _____

Quality of Life Due to Urinary Symptoms: If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that? (Bold, Highlight or Underline)

Delighted Pleased Mostly satisfied Mixed Mostly dissatisfied Unhappy Terrible

Physician Signature _____ Date _____

SEXUAL HEALTH INVENTORY FOR MEN (SHIM)

PATIENT NAME: _____ **TODAY'S DATE:** _____

PATIENT INSTRUCTIONS

Sexual health is an important part of an individual's overall physical and emotional well-being. Erectile dysfunction, also known as impotence, is one type of very common medical condition affecting sexual health. Fortunately, there are many different treatment options for erectile dysfunction. This questionnaire is designed to help you and your doctor identify if you may be experiencing erectile dysfunction. If you are, you may choose to discuss treatment options with your doctor.

Each question has several possible responses. Circle the number of the response that **best describes** your own situation. Please be sure that you select one and only one response for **each question**.

OVER THE PAST 6 MONTHS:

1. How do you rate your confidence that you could get and keep an erection?		Very Low	Low	Moderate	High	Very High
		1	2	3	4	5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?	No Sexual Activity	Almost Never or Never	A Few Times (much less than half the time)	Sometimes (about half the time)	Most Times (much more than, half the time)	Almost Always or Always
	0	1	2	3	4	5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Did Not Attempt Intercourse	Almost Never or Never	A Few Times (much less than half the time)	Sometimes (about half the time)	Most Times (much more than, half the time)	Almost Always or Always
	0	1	2	3	4	5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Did Not Attempt Intercourse	Extremely Difficult	Very Difficult	Difficult	Slightly Difficult	Not Difficult
	0	1	2	3	4	5
5. When you attempted sexual intercourse, how often was it satisfactory for you?	Did Not Attempt Intercourse	Almost Never or Never	A Few Times (much less than half the time)	Sometimes (about half the time)	Most Times (much more than, half the time)	Almost Always or Always
	0	1	2	3	4	5

Add the numbers corresponding to questions 1-5. **TOTAL:** _____

The Sexual Health Inventory for Men further classifies ED severity with the following breakpoints:

1-7 Severe ED **8-11 Moderate ED** **12-16 Mild to Moderate ED** **17-21 Mild ED**

Physician Signature _____ Date _____