CASE COMPREHENSIVE CANCER CENTER

Study Number: CASE 11813

Clinicaltrials.gov #: NCT02163317

Study Title: Magnetic Resonance Guided Focal Stereotactic Body Radiation Therapy for Localized Prostate Cancer

Principal Investigator: Elisha Fredman, MD
University Hospitals Cleveland Medical Center
Case Western Reserve University
11100 Euclid Avenue
Cleveland, OH 44106
Phone: 216-844-3061
Email: elisha.fredman@uhhospitals.org

Statistician: Pingfu Fu, Ph.D.
Case Comprehensive Cancer Center
Seidman Cancer Center
11100 Euclid Avenue
Cleveland, OH 44106
Phone: 216-844-7452
Email: pxf@bfox.EPBI.cwru.edu

Sponsor: Case Comprehensive Cancer Center

Support: Elekta SBRT Research Grant Program, Stockholm, Sweden.
Invivo, Gainsville, FL,
Philips Medical Systems, Cleveland, OH

SUMMARY OF CHANGES

Protocol Date	Section	Change
05.23.2014		Initial IRB approval
09.26.2014	Cover page	Updates to co-investigators on cover page
04.08.2015	7.3	"Concomitant medication assessment including hormone therapy" was added to all visits past 30 days
	App. 3	Updated EPIC QOL to include all pages
02.04.2016	4.3.12 7.1 7.3	Added Bone Scan
3.30.2016	4.0 4.3.1 4.3.5	Removed "within 1 year of screening"
	4.3.6	Removed hematologic and hepatic function. Updated creatinine
	7.0 7.3	Updated study procedures to better align with SOC
10.25.2016	Cover page	Removed Case Medical Center references
	4.3	Removed 12 month reference missed in 3.30.2016 amendment
12.15.2016	Cover page	Changed PI to Bryan Traughber, removed list of co-investigators
	9.2	Updates to RECIST tumor response section
5.10.2017	Cover page	Change PI from Traughber to Bryan Traughber
	7.1 and 7.3	update bullet point for screening visit #1 in section 7 on Pelvic mpMRI with contrast and multiparametric sequences to clarify timeframe within 90 days of screening, corresponding change to calendar
1.31.2018	Cover page	Change PI from Kumar back to Traughber

Protocol Date	Section	Change
1.16.2020	6.1, 7.1 and misc.	Section 7.1: bone scan only to be completed when "clinically indicated" Section 6.1.1: option for hydrogel spacer placement added during fiducial placement Stereo Tactic Targeting and Treatment: Biopsy clarification – only to be done if no biopsy exists As practice patterns have changed, many patients are now coming with "mapping" biopsies including in-gantry MRI and MR/US fusion. This does not need to be repeated for protocol, making it an unnecessary risk/procedure for the patient. Section 7.1: Pelvic mpMRI changed to within 180 days of screening visit (from 90 day) Misc. administrative updates Consent updated accordingly for spacer, MRI, bone scan and biopsy
8.4.2020	Cover Page	Change PI from Traughber to Fredman

TABLE OF CONTENTS
Table of Contents

1.0 Introduction

1.1 Study Conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board, and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB according to its policies and procedures.

1.2 Background

Despite many advances in imaging and therapy, prostate cancer remains the second most common cause of cancer-related death of men in the United States. The management approach to men diagnosed with low risk prostate cancer remains a socioeconomic dilemma with no clear consensus whether prostatectomy or whole-gland radiation therapy improves outcomes and these treatments are often associated with significant long-term morbidity negatively impacting quality of life parameters that require long-term management. Another approach has been 'active surveillance' but often these men are under staged at the time of diagnosis, and will clinically progress and ultimately receive definitive therapy to the whole gland, while more frequently many men opt for partial gland ablative therapy with surveillance.

Previous research has demonstrated the value of radiation dose escalation in patients with prostate cancer (Bolzicco 2010, Friedland 2009). However, to date, most paradigms have focused on dose escalation applied to the whole gland. It is recognized that higher doses to the whole gland are associated with higher treatment related toxicities (impotence, incontinence, rectal fissures) (Zelefsky). Now, with advanced delivery techniques such as intensity modulated radiation therapy (IMRT), proton therapy, and stereotactic body radiation therapy (SBRT) dose escalation can be achieved targeting sub-volumes of the prostate. Preliminary evidence suggests that sub-volume dose escalation based upon molecular and anatomical imaging may improve outcomes (Eggner 2007, Ellis 2010). This research will evaluate the safety and efficacy of SBRT for focal partial gland therapy in prostate cancer.

There is growing concern over the risk of over treating patients who may not be at risk of dying from the disease. Prostate cancer remains the sole malignancy where treatment is always delivered to the whole organ in routine practice. Many low risk patients therefore opt for Active Surveillance rather than immediate whole gland treatment to limit treatment related decrease in quality of life associated with either surgery or whole gland radiation. A growing body of evidence also suggests that treatment of the dominant prostatic lesion/s may be sufficient to prevent systemic disease progression, and that small lesions less than 5 mm may be indolent, thus if left untreated initially may not be likely to progress in a clinically significant manor. Additionally once a dominate lesion is treated, the patient may return to a course of active surveillance using PSA, physical examinations, and repeat MRI or biopsy as clinically indicated (Scardino 2009, Cosset 2013).

Despite early success using molecular and anatomical data to identify sub-volumes of disease for image-guided therapy, physicians remain reticent to escalate dose based upon imaging findings alone, which are inherently limited by sensitivity and specificity (Ellis 2010, Pinto 2011). Therefore, a treatment planning methodology that provided direct 3D spatial correlation of imaging sets with the gold standard of histopathology would be highly effective to exclude normal tissue (false positives by imaging) and simultaneously allow radiation dose escalation to clearly delineated "true positive" target volumes.

By using high resolution 3T MRI imaging with parametric sequencing to identify areas suspicions for harboring malignancy, we believe that focal therapy could be safely delivered to property selected patients. Biopsy confirmation of the imaging findings for both suspicious and non-suspicious regions based on MRI imaging would be used to confirm that cancer is present at the suspected locations using a patented methodology to define the treatment target volumes. Rather than treating the whole gland, therapy could then be targeted to partial prostate volumes with the goal of reducing treatment related morbidity and long term cost for treatment.

A recent systematic review of the focal therapy in localized prostate cancer evaluated 2350 cases reported in 30 studies through October 2012, mainly delivered in low and intermediate disease, and some high-risk patients where imaging suggested unilateral disease. Post therapy incontinence, and erectile function toxicities were limited, with promising short- to medium term disease free survival outcomes (Valerio 2013). In a separate critical appraisal of focal therapy for localized prostate cancer, Eggener et al. (representing an international multidisciplinary task force with expertise in prostate cancer) evaluated "the focal lesion paradigm" (Eggener 2007) and the role of focal ablative therapy. This review panel concluded with encouragement for prospective clinical research in emergent focal technologies for the treatment of unifocal and biologically unifocal prostate cancer – as needed options for men resistant to active surveillance and watchful waiting. A number of other authors from major universities, have more recently reported good outcomes with whole-gland, unilateral and focal ablative cryotherapy applications. These authors list focal ablative options to include focused ultrasound, brachytherapy, thermotherapy, photodynamic therapy, and stereotactic radiosurgery (Polascik 2008, Hou 2009, Pisters 2010, Boomers 2013). Radiation therapy is uniquely qualified for use in focal therapies as it stands alone as a standard of care for prostate cancer treatment with long term outcomes showing safety and efficacy for whole gland disease control, and growing evidence with partial gland focal therapy (Ellis 2010, Katz 2010, Cossett 2013).

Focal image-guided radiation therapy is a novel alternative that may provide a cost-effective and less morbid treatment option for men diagnosed with low-risk disease. Conceptually, focal therapy targets only diseased prostatic tissue and spares adjacent non-cancerous prostate tissue which may be as efficacious as whole-gland therapy but with less side effects. Further, clinical evidence suggests that the α/β ratio of prostate cancer is quite low providing an opportunity for greater therapeutic gain with hypofractionated courses of radiotherapy compared to traditional fractionated treatment. The hypothesis of this proposal is multiparametric MR data including T2 weighted, contrast enhanced, and diffusion weighted imaging when correlated with marked histopathology biopsy sites confirming tumor foci, will allow appropriate patient selection for focal radiation therapy with a higher sensitivity than routine MR imaging alone. Further, that using advanced imaging to guide dose modulation in focal stereotactic body radiation therapy (SBRT), also named stereotactic ablative radiotherapy, may provide equivalent outcomes to whole-gland therapy with shortened treatment courses and decreased toxicity. This prospective investigational review board (IRB) approved, single institution pilot study will be used to demonstrate clinical feasibility and may potentially lead to future federally funded Phase I/II and consortium supported multi-center clinical research trials for focal SBRT in localized low-risk prostate cancer patients.

Most recently, parametric sequencing MRI have been reported to identify prostatic regions that are highly suspicious for tumor foci (Valerio 2013). The current study will be used to help select for the proper group of patients for whom focal therapy may be appropriately offered. Men who have a diagnosis of localized prostate cancer with only moderately elevated PSA and Gleason score of 7 or lower without either a dominate pattern 4 or a tertiary pattern 5 seen on initial pathology may be

eligible for evaluation, as these patients meet the institutional clinically accepted determination making them eligible for Active Surveillance (AS). Many men meeting AS criteria, however, prefer treatment with curative potential, and opt for partial gland therapy aiming at limiting potential treatment related toxicities that may be associated with treatment to whole gland. A staging 3T MRI is our adopted standard of care evaluation for men presenting for radiation therapy planning with parametric sequences. In the current study we will use the staging and treatment planning images to evaluate regions highly suspicious for tumor foci as a screening tool for appropriateness of focal therapy and for eligible patients, for use in guided biopsy to confirm pathology on the imaging studies.

Standard radiotherapy for the treatment of prostate cancer is delivered at 1.8 to 2 Gy per fraction in a protracted course over 8 to 9 weeks to total doses in the range of 78 to 81 Gy. Following the published work of Hall and Brenner suggesting that prostate cancer may have a lower alpha beta ration describing the cell line's ability to repair damage caused by ionizing radiation; many centers have routinely adopted into clinical practice that prostate cancer may be treated using larger doses per fraction ranging in size from 3 to 19 Gy in as many as 20 or as few as a single fraction of therapy (Brenner 1999). The assumption is that the alpha beta ration of most tumors is as high as 10, while the surrounding normal tissues at risk of late radiation reactions is around 3 to 5 (Yoshioka 2013). Positive histopathology findings on co-registered diagnostic MRI data sets (T2 and parametric functional imaging) will be used to segment a dominant biologic target volume and improve disease mapping across the gland. Subjects will then be treated in a series of three SBRT (typically every other day) treatments to deliver a total dose of 29.25 Gy in 9.75 Gy fractions, yielding a total biologic equivalent dose (BED) of 273.15 allowing dose to reach the desired minimal BED of 268 with an assumed alpha beta of 1.2 for prostate cancer as suggested by Martinez (2011). A similar dose regimen has been published by Barkate et.al. using HDR brachytherapy in a three fraction dose escalation trial to deliver minimal dose of 30 Gy in 3 fractions over two days to a maximal dose of 34.5 Gy at 11.5 Gy per fraction. (Barkati 2012). While the published 3 fraction HDR regimen gave a minimal dose of 10 Gy, we feel that 9.75 Gy per fraction is effectively equivalent when taking into account the additional 12 cGy per fraction we will be giving to allow for tracking of intrafraction prostate motion with Image Guided Radiation Therapy using a series of 4 cone beam CT image sessions obtained before, during and after each fraction, thus accounting for a daily fractionated dose of 987 cGy, or 9.9 Gy. What is uniquely novel in this protocol is not the total dose of radiation delivered but rather that it is to be delivered in a non-invasive fashion using SBRT, and more importantly delivered to a novel partial prostate volume using a patented methodology to define the volume at risk to be treated using focal therapy for prostate cancer. This methodology may be adopted as a template for directing therapy to partial organ volumes using other treatment modalities based on the results of this trial if the use of tracked histopathology location is found to have significant influence on the selected treatment volumes in this study beyond what would be used based on functional and anatomic imaging studies alone.

2.0 Study Objectives

Hypothesis: Multiparametric MRI with histopathological correlation can be used to treat sub-volumes of the prostate with focal SBRT in low- and intermediate-risk patients leading to equivalent outcomes as whole-gland therapy with reduced toxicity and improved quality of life.

To validate the above hypothesis in this prospective study, the specific aims include:

1) Evaluate the correlation of histopathology findings in comparison to regions of the prostate reported to be suspicious for harboring tumor burden on multiparametric MRI report/s;
2) Demonstration of the dosimetric and radiobiological advantages of focal SBRT versus whole-gland radiation therapy;
3) Evaluation of clinical outcomes in focal SBRT for localized prostate cancer.

3.0 Study Design

3.1 General Design

This 2-year pilot study will include patients with positive diagnostic prostate biopsy, with or without positive digital rectal exam (clinical stage T2a or T1cN0M0), Gleason score ≤7(3+4), with a PSA ≤10ng/mL and routine imaging that includes bone scan and MRI of the pelvis.

Patients eligible for either whole-gland therapy or active surveillance will be evaluated by staging MRI and the scan used to screen for disease burden within the gland. Patients identified with a focal dominate lesion greater than 5 mm in size confirmed with imaging and biopsy will be eligible for this trial. Patients found to have no focal abnormalities will be offered other disease management options off study, such as active surveillance or whole gland therapy with traditional fractionated external beam radiation therapy (EBRT) and/or brachytherapy.

Eligible patients (≤6 total per year) will sign consent to enroll and be treated with focal SBRT on study at a dose of 29.25 Gy in 3 fractions (9.75 Gy per fraction) to involved sub-volume of the prostate using volumetric modulated arc therapy (VMAT) with the Synergy BMX2 with Agility collimator (Elekta, Stockholm, Sweden and Atlanta, GA).

4.0 Subject Selection and Withdrawal

4.1 General Characteristics of the Proposed Subject Population

Histologically confirmed diagnosis of adenocarcinoma of the prostate. Gleason scores ≤7(3+4); Clinical stage T1-2a; PSA ≤10 ng/mL (PSA should not be obtained within 10 days after prostate biopsy).

4.2 Anticipated Number of Research Subjects

24 screened and 12 enrolled over 2 years.

4.3 Inclusion Criteria

Patients with positive diagnostic prostate biopsy with or without positive digital rectal exam (DRE) (clinical stage </=T1-T2a or T1cN0M0), Gleason score ≤7(3+4), with a PSA ≤10ng/mL and routine staging work-up consistent with a diagnosis of localized prostate cancer. Patients eligible for either whole-gland therapy or active surveillance will use the staging MRI to screen for intraprostatic disease burden. Patients having a single focal dominate lesions greater than 5 mm in size confirmed with imaging and biopsy will be eligible for this trial. Patients (≤6 total per year) will be treated with focal SBRT delivering on study to 29.25 Gy in 3 fractions (9.75 Gy per fraction) to involved sub-volume. Eligible patients must be able to undergo an MRI with contrast.

Patient's Name _____

Medical Record # _____

Research Nurse /
Study Coordinator Signature: _____ **Date** _____

Treating Physician [Print] _____

Treating Physician Signature: _____ **Date** _____

Patients must meet all of the following inclusion criteria to be eligible for enrollment:

_____4.3.1 Patients must have a histologically confirmed diagnosis of adenocarcinoma of the prostate.

_____4.3.2 Patient must have a history/physical examination with digital rectal examination of the prostate within 90 days prior to screening

_____4.3.3 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of the study treatment in patients <18 years of age, children are excluded from this study.

_____4.3.4 ECOG Performance status must be level 0 or 1 within 60 days prior to registration [See Appendix A].

ECOG PS = _____
Date: _____

_____ 4.3.5 Patient must have a histological evaluation of the prostate biopsy with assignment of a Gleason score to the biopsy material; Gleason scores ≤7(3+4)

_____ 4.3.6 Patients must have adequate renal function as defined below:

Serum Creatinine < or = 1.5 times the ULN (Normal: ≤1.17 mL/min/1.73 m^2)
Serum Creatinine: _____
Date of Test: _____

_____ 4.3.7 Clinical stage a </=T1-T2a (AJCC 7th edition)

_____ 4.3.8 PSA ≤10 ng/mL within 90 days prior to registration. PSA should not be obtained within 10 days after prostate biopsy.

_____ 4.3.9 Subjects must have the ability to understand and the willingness to sign a written informed consent document.

_____ 4.3.10 Patient willing and able to complete the Expanded Prostate Cancer Index

Composite (EPIC) questionnaire (Baseline, 6, 12 and 24 months post end of radiation therapy)

_____4.3.11 Patients must be able to undergo an MRI with contrast

_____4.3.12 Bone scan, when clinically indicated, completed within 90 days

4.4. Exclusion Criteria

The presence of any of the following will exclude a patient from study enrollment.

_____4.4.1 Evidence of distant metastases

_____4.4.2 Regional lymph node involvement

_____4.4.3 Previous radical surgery (prostatectomy), cryosurgery, or HIFU for prostate cancer

_____4.4.4 Previous pelvic irradiation, prostate brachytherapy, or bilateral orchiectomy

_____4.4.5 Previous hormonal therapy, such as LHRH agonists (e.g., goserelin, leuprolide) or LHRH antagonists (e.g., degarelix), anti-androgens (e.g., flutamide, bicalutamide), estrogens (e.g., DES), or surgical castration (orchiectomy)

_____4.4.6 Use of finasteride within 30 days prior to registration. PSA should not be obtained prior to 30 days after stopping finasteride.

_____4.4.7 Use of dutasteride within 90 days prior to registration. PSA should not be obtained prior to 90 days after stopping dutasteride.

_____4.4.8 Previous or concurrent cytotoxic chemotherapy for prostate cancer

_____4.4.9 Severe, active co-morbidity, defined as follows:

_____4.4.10 Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months

_____4.4.11 Transmural myocardial infarction within the last 6 months

_____4.4.12 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration

_____4.4.13 Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration

_____4.4.14 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol. (Patients on Coumadin or other blood thinning agents are eligible for this study).

_____4.4.15 Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients

_____4.4.16 Patients unable to undergo an MRI with contrast.

4.5 Subject Recruitment and Screening

Subjects will be recruited from patients presenting to Urology and/or Radiation Oncology for consultation with a diagnosis of localized prostate cancer.

4.6 Inclusion of Women and Minorities

Men and members of all races and ethnic groups are eligible for this trial. Women will not be eligible for this trial.

5.0 Registration

All subjects who have been consented are to be registered in the OnCore Database. For those subjects who are consented, but not enrolled, the reason for exclusion must be recorded.

All subjects will be registered through a study coordinator and will be provided a study number by calling telephone number: 216-286-6641

5.1 Early Withdrawal of Subjects

Criteria for Removal from Study

Subjects may be removed from the study upon request or at the discretion of the Principal Investigator for safety reasons, failure of subject to adhere to protocol requirements, subject consent withdrawal, or disease progression. Withdrawn subjects may be replaced.

Follow-up for Withdrawn Subjects

Subjects may withdraw from the study at any point. If subjects withdraw prior to delivery of SBRT, they may be replaced with an additional subject(s). Follow up for withdrawn subjects will continue per standard of care for disease stage as reported through the staging biopsy, off study. All routine standard of care imaging and physical exams to monitor disease progression, may be conducted as similar to that care described on trial. Data collected following consent and registration through the screening biopsy will be reported for all subjects, including those withdrawn prior to SBRT.

6.0 Study Treatment or Procedures

- Completion of the Staging MRI with contrast is mandatory for all patients.
- Minimum and maximum (1-2) dominant intraprostatic tumor foci are suggested on MRI during screening
- Visualization of the urethra on CT scan for treatment planning will be accomplished through fusion of pelvic MRI with CT simulation images.
- Baseline testosterone

- In addition to standard of care IPSS and SHIM questionnaires, EPIC, EQ5D, and Utilization of Sexual Medications/Devices Supplement will be obtained at baseline, and 6, 12 and 24 months post end of radiation therapy.

6.1.1 Description of Radiation Therapy

Radiation treatment will be delivered using Elekta S Agility, LINAC-based technology (SBRT). Prior to SBRT 3-5 fiducial markers will be placed in the prostate for image guidance during radiation therapy. Fiducial marker placement will be conducted using standard of care FDA approved ultrasound guidance device and will incorporate findings from MRI image sets to guide the selection of biologic target volumes suggested on imaging to represent tumor burden within the prostate. If eligible, patient may also have a hydrogel spacer placed to maximally spare the rectum, as per standard of care. At least 1 week will elapse between fiducial marker and hydrogel spacer placement and treatment planning simulation to allow for fiducial settling and any potential for migration. Using a LINAC-based SBRT system, the technique of motion control will be abdominal compression and /or rectal balloon, combined with 4D CT simulation. This information related to treatment and treatment planning will be recorded and processed in the UHCMC Seidman Cancer Center Department of Radiation Oncology password protected electronic medical record per institutional policy.

Imaging the Prostate

All patients will undergo a Serum Creatinine clearance study prior to MRI exams. Patients who are unable to undergo a staging MRI scan with contrast during screening will not be eligible for the study. Prior to radiation therapy, all patients will have a staging 3T MRI (utilizing a body coil) of the pelvis to include standard (T2 weighted) and multiparametric MRI sequences (to include Dynamic Contrast Enhanced and Diffusion Weighted scans or mpMRI) with gadolinium contrast. Axial, sagittal and coronal MRI scans are required for all MRI scans.

CT and MRI Treatment Planning Simulation

Each patient will have a treatment planning simulation prior to delivery of SBRT at least 1 week following the insertion of radio-opaque fiducial markers implanted in the prostate for target localization and daily set up during fractionated dose delivery. A custom made immobilization device consisting of a whole body vac bag and vacuum wrapping (Medical Intelligence BodyFix) will be made for every patient. A CT scan with and without contrast of the pelvis will be performed with the immobilization device in place. If the patient is not a candidate for CT contrast, non-contrast CT will be performed. Treatment planning CT scans must take into account the respiratory motion. A 4DCT or combination of end-inspiration and end-expiration CT scans will be taken. A treatment planning MRI (with contrast is preferred and using standard MRI and mpMRI sequences as described above for the staging MRI) will be acquired following placement of fiducial markers and prior to delivery of SBRT. A rectal balloon may be used during simulation and treatment, as tolerated by each subject.

Dose Specifications

Radiation will be delivered in to 29.25 Gy in 3 fractions (9.75 Gy per fraction) to involved sub-volume/s of the prostate using VMAT by the Synergy S with Agility collimator (Elekta, Stockholm, Sweden and Atlanta, GA) as focal therapy. Dose escalation to organs-at risk surrounding the prostate target volume is not allowed. Dose constraints of normal tissues surrounding the target will be set to limit toxicity. Although this three fraction SBRT regimen is novel, the tolerance levels selected for the normal organs are consistent with Radiation Therapy Oncology Group (RTOG) protocol RTOG 0938

"A randomized phase II trial of hypofractionated radiotherapy for favorable risk prostate cancer" (http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0938 accessed 12/09/2013) and selected to provide the minimal Biological Equivalent Dose (BED) or Equivalent Dose in 2 Gy fractions (EQD2) felt to be required at a high dose per fraction to provide a high likelihood for tumor control as noted above in the concluding paragraph of the introduction (page 9).

This protocol requires the use of SBRT that uses inverse treatment planning (dose specifications are provided below in further detail). It is thought that SBRT treatment plans and delivery for this pilot series may be achievable without increase in normal tissue toxicity compared to whole organ treatment using either SBRT or HDR brachytherapy as defined above. If a patient is determined to have failed therapy using acceptable clinical standards, such as the Phoenix definition (a rise in PSA following nadir of 2 ng/mL) or biopsy proven locally recurrent or persistent disease, the patient may be offered other curative therapy or therapies off study, depending on the patient's clinical status and intent to treat.

Dose Coverage

The isodose line used for the prescription dose should cover a minimum of 95% of the PTV. This will be recorded in the Department electronic medical record for each patient.

Minimum Dose

The minimum dose within the PTV to a point that is 0.03 cc in size must be ≥95% of the prescribed dose. This will be recorded in the electronic medical record for each patient.

Critical Structures

Critical Organ Dose-Volume Limits

The normal tissue volume to be contoured will include bladder, rectum, bilateral femora (to the level of ischial tuberosity), seminal vesicles, penile bulb, neurovascular bundles, skin, and urethra. The normal tissues will be contoured and considered as solid organs rather than contouring the bladder and rectal walls. The bladder should be contoured from its base to the dome. The rectum should be contoured from the anus (at the level of the ischial tuberosities) for a length of 15 cm or to the rectosigmoid flexure. This generally is below the bottom of the sacroiliac joints. The tissue within the skin and outside all other critical normal structures and PTVs are designated as unspecified tissue. These data will be recorded in the electronic medical record for each patient.

Supportive Measures

Urinary

Symptomatic urinary medicines, (e.g. tamsulosin) are allowed at the discretion of the treating radiation oncologist or urologist.

Bladder

Patients will be asked to have a full urinary bladder both during simulation and treatment. Consistent bladder filling procedure should be used for an individual patient for simulation and for each treatment. Bladder filling may be achieved by asking patients to drink 16-24 oz of water or other fluid 2-3 hours prior to treatment and to not urinate between this time and treatment as they are able.

Bowel

Patients will be advised to adhere to a low gas, low motility diet commencing one day prior to the treatment. One tablespoon of Milk of Magnesia will be taken the night before the simulation and the

night before each treatment. One Fleet's enema will be administered 2-3 hours before the simulation and each treatment. Rectal balloons may be used when patients tolerate, both for simulation and during treatments at the discretion of the Radiation Oncologist.

Supportive measures will be recorded in the usual fashion in the electronic medical record.

SBRT Dose Constraints

		Dosimetry Parameters
Organ	**Volume**	**Dose (Gy)**
Prostate (PTV)	Maximum point dose (0.03cc)	≤ 31.298 Gy 107% of prescription dose *
	Minimum dose received by 95% of PTV	≥ 29.25 Gy 100% of prescription dose
	Minimum dose received by PTV	≥ 27.79 Gy 95% of prescription dose
Rectum	Maximum point dose (0.03cc)	≤ 30.71 Gy 105% of the prescription dose
	Less than 3 cc	< 27.79 Gy 95% of prescription dose
	90% rectum	≤ 26.325 Gy 90% of prescription dose
	80% rectum	≤23.40 Gy 80% of prescription dose
	50% rectum	≤14.625Gy 50% of prescription dose
Bladder	Maximum point dose (0.03cc)	≤30.71 Gy 105% of prescription dose
	90% Bladder	≤ 26.325 Gy 90% of prescription dose
	50% Bladder	≤16.5 Gy 50% of prescription dose
Penile bulb (recommended)	Maximum point dose	No more than 100% of prescription dose
	Less than 3 cc	15.795 Gy 54% of prescription dose
Femoral heads Skin (recommended)	Less than 10 cc cumulative (both sides)	15.795 Gy 54% of prescription dose
	Maximum point dose	23.69 Gy 81% of prescription dose
Urethra dose		≤ 31.298Gy * 107% of prescription dose

*Visualization of the urethra would be required to confirm urethral dose is ≤31.298 Gy – 107% of prescription dose where the max point dose (0.03cc) within the PTV exceeds 31.298 Gy – 107% of prescription dose. Prescription and treatment notes will be recorded in the electronic medical record.

Technical Factors

Stereotactic Targeting and Treatment

This protocol will require treatments to be performed with an image-guided technique with the use of a 3-D coordinate system defined by 3D sub-volume/s of the prostate using VMAT by the Synergy S Agility collimator (Elekta, Stockholm, Sweden and Atlanta, GA). A computerized method for image registration is required for determination of the patient shift information. Serial MRI images with parametric sequencing will be used both to evaluate intra fraction response and post therapy response. The intrafraction image (between the second and third fraction) will be evaluated for yield in intra-therapy response, that may be useful future in clinical applications such as in MRI-Linac based adaptive radiotherapy planning. Post therapy serial MRI will also be used to evaluate radiographic determined response to therapy, versus pre and mid treatment scans and as compared to clinical features such as PSA follow-up.

All available image sets will be co-registered using clinical software such as MIM Maestro (MIM software, Cleveland, OH) and PercuNav (Invivo, Gainsville, FL) and/or evaluated using our available in-house developed software for image registration verification, as is customary for clinical cases. Imaging data will thus be transferred to our Linac based treatment planning system Pinnacle, Philips Medical Systems (Cleveland, OH) for SBRT delivery. We will also use 3D cone-beam kV CT for alignment of *in-vivo* fiducials to track and adjust for internal target motion detection.

As previously described (6.1 Description of Radiation Therapy) a minimum of three and maximum of five radio-opaque fiducial markers will be inserted in to the prostate for use in fractionated dose target positioning during SBRT (delivered in three fractionated doses on 3 different days, typically every other day). At least one fiducial marker for treatment planning will be guided to a prostatic region reported on mpMRI to be highly suspicious for tumor burden.

For patients who have not previously received a targeted biopsy (in-gantry MRI or US-MRI fusion), during this fiducial marker placement procedure, and just prior to needle insertion to place the fiducial marker, a guided biopsy will be targeted to the location of disease suggested by mpMRI using FDA approved devices for image guided biopsy procedures. An FDA approved sterile surgical needle will be introduced either transrectally or transperineally through which the biopsy needle will pass. Following extraction of tissue sample, a fiducial marker will be placed in each of 3-5 biopsy cavities and recorded for spatial *in-vivo* orientation with to the anatomic and functional image sets (US, CT, MRI and mpMRI).

If additional mapping biopsies are necessary, other sextant regions of the prostate reported as normal by screening MRI will be biopsied as is typical for a mapping biopsy procedure to improve disease staging and localization of true positive disease during the screening procedure. Thus, a total of 12 to 15 biopsies will be obtained from each patient for screening eligibility to aid in a determination of likelihood that disease is not multifocal and to enable delivery of focal partial organ therapy. Each biopsy site will be tracked using a combination of permanent and virtual fiducial markers. Virtual markers will be electronically tracked in the regions suggested to be negative for the presence of disease on imaging at the sites of all other sextant biopsy locations using the biopsy needle tip as a temporary fiducial imaged by ultrasound at the time of biopsy and fused back to the mpMRI and planning CT scan if the patient goes on to be treated on protocol.

It should be noted that the permanent fiducial markers placed for screening would not preclude prostatectomy, or could be used for directing radiotherapy if the patient is found to be ineligible for

partial prostate treatment based on more extensive pathology being found on the screening biopsy. Conversely, should the patient elect to remain in active surveillance despite qualifying for the protocol, the fiducials would serve to help direct subsequent biopsies required for active surveillance. Inserted permanent fiducial markers will satisfy the following requirements for prostate cancer: (1) good radiographic visibility on kV imaging/diagnostic Xrays, (2) minimal distortion of delivered dose, (3) minimal artifacts on MRI and CT images used for treatment planning, and (4) minimal migration during treatment. Temporary markers (biopsy needle tip tracking) will be used to track mapping biopsy locations (≤12 additional sites) and all biopsy locations will be recorded and tracked for *in-situ* position and for subsequent correlation to pathology findings and sequential MRI scans. Individual biopsy tissue samples will be labeled and processed by the institution's clinical pathology laboratory for prostate biopsy reporting.

Three D (3D) mapping will be used with SBRT using cone beam CT (CBCT). Doses reported for kV cone beam CT on the Elekta Synergy machine are in the range of <3 cGy per image Alaei (2010). The doses for 3D imaging systems are anticipated in this study to be around 12 cGy per fraction assuming 4 CBCT's daily during treatment cGy. Thus one may assume that the total dose delivered daily may actually be at least 9.87 cGy when taking into account the prescribed dose of 9.75 Gy and the 12 cGy daily IGRT. This would yield a total BED of 273.15 for an alpha beta of 1.2 allowing us to reach the desired minimal BED of 268 suggested by Martinez (2011).

Localization

We will use a set-up CBCT, as well as repeat CBCT after every 3.25 Gy and following completion of therapy daily to assess intrafraction prostate organ motion. One goal of the project will be to use these data to assess the need for continuous IGRT such as that achievable with MRI Linac based SBRT applications. The Hexapod couch will be used to correct for rotation using the fiducial markers for each IGRT image set during treatment. A minimum of 4 IGRT CBCT's will be acquired daily as initial setup and after every 3.25 Gy has been delivered to assess intrafraction prostate motion. At the discretion of the radiation oncologist/physicist, monitoring of intrafraction motion may be required more frequently.

Imaging studies for staging, treatment planning and response to therapy monitoring

Multiparametric and Magnetic Resonance Imaging (mpMRI)

Prior to radiation therapy, all patients will have standard of care staging and treatment planning MRI's of the pelvis, with contrast unless clinically contraindicated, using standard morphologic imaging sequences, per institutional standard of care imaging protocols for anatomic detail and localization. Additional functional mpMRI sequences will also be acquired and evaluated to enable morphologic and/or quantification of various tissue parameters as are routinely ordered prior to radiation therapy. The duration of the entire mpMR imaging procedure (patient on the scanner table) will be no longer than at total of 90 minutes, which is within the range for a standard single diagnostic MRI scan. Quantitative MRI data may include analysis of some or all of the following parameters:

Diffusion weighted imaging (DWI):

- Measurement of b-value assesses different levels of diffusivity within tumor tissue and normal tissue.
- Apparent diffusion coefficient (ADC) will be calculated as a quantitative measure from multiple b-values by measurement of ROI in the target lesion.

Dynamic contrast enhanced MRI (DCE-MRI):

- Typical quantitative parameters will be obtained describing tissue enhancement pattern and perfusion, contrast agent exchange rates of tissues and distribution of contrast between the various tissue spaces using standard evaluation models.
- Quantitative assessment will be performed with post processing techniques as commercially available as well as post processing software under investigation or development to demonstrate feasibility with currently available and future techniques.

These sequences will be recorded for virtual comparison to the standard MRI sequences to determine if the investigational functional data correlates with histopathology data, and to determine if these data would have changed the radiation therapy contouring and dose delivery. Any change in treatment planning due to functional MRI versus standard sequences alone will be recorded, and evaluated for utility in the determination of tumor response to therapy.

Target Delineation

All clinically relevant radiologic images will be transferred to the Radiation Oncology Pinnacle (Philips, Cleveland, OH) treatment-planning system. Using the various MRI sequences and the CT image data sets, a composite gross tumor volume (GTV) will be generated. The focal GTV will be contoured and approved by the attending radiation oncologist and urologist. The 4D CT will be fused with the treatment planning CT and an internal target volume (ITV) will be generated. The location of tumor foci from each positive biopsy core will also be segmented and expanded by 5mm to add to the PTV along with imaging data sets. An additional 0.3-0.5 cm margin will be placed around the image data set ITV to generate a final PTV to account for set-up variation. The use of abdominal compression may be used to decrease the volume of ITV since there is no real-time target tracking. Surrounding normal structures, including the rectum, small bowel, bladder, femora, seminal vesicles, penile bulb, and skin will be contoured. Skin is defined as a 0.5 cm concentric ring beneath the skin.

Mid Treatment and Post SBRT (MRI) with multiparametric sequences (mpMRI)

Each subject will be offered up to 4 additional MRI scans: 1 during therapy (between the 2nd and 3rd fractionated treatments), at 6 months following the end of radiation therapy, and again at 12 and 24 months. All mpMRI will be requisitioned in the same manner as described above (Staging MRI) as described above at page 16 (6.1 Imaging the Prostate), with the exception that contrast with gadolinium is preferred. If patients are unwilling or clinically unable to undergo contrast or have all follow-up MRI scans, the patient will remain on study and followed for PSA response and toxicity outcomes.

Computed Tomography (CT)

CT will be fused with MRI scans and used as a primary image platform for treatment planning. It is preferred that CT with contrast be acquired, unless clinically contraindicated. The simulation should be performed in the supine treatment position, in the custom made immobilization device, with the fiducial markers and rectal balloon in place (where utilized). Axial cuts of 2.0 mm or less will be acquired throughout the pelvis and prostate from the top of the iliac crests superiorly to the perineum inferiorly.

Contrast

CT scans with and without IV contrast are required, unless contraindicated. Dose calculations will be based on the non-contrast study, and the contrast study if obtained will be used to delineate prostate and surrounding organs at risk including bladder.

6.2 Radiation Therapy Adverse Events

All patients will be seen in the radiation oncology department during radiation therapy. Any observations regarding radiation reactions will be recorded and should include attention to the following potential side effects:

- Small bowel or rectal irritation manifesting as abdominal cramping, diarrhea, rectal urgency, proctitis, or hematochezia
- Bladder complications including urinary frequency/urgency, dysuria, hematuria, urinary tract infection, and incontinence
- Radiation dermatitis

Clinical discretion may be exercised to treat side effects from radiation therapy. Examples of typical medications used in the management of side effects, such as diarrhea, include diphenoxylate or loperamide. Bladder or rectal spasms are usually treated with anticholinergic agents or tolterodine. Bladder irritation may be managed with phenazopyridine. Erectile dysfunction is often treated with medical management or mechanical devices. A record of the incidence and management of side effects will be recorded in the electronic medical record as a usual course of care and the data will be reported in a Case Report Form.

Definition of an Adverse Event (AE): Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines Adverse Event Reporting Requirements. January 2005; http://ctep.cancer.gov/reporting/adeers.html]

Definition of an SAE: Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:

- Death
- A life-threatening adverse experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

Important medical events that do not result in death, are not life threatening, or do not require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 for reporting of adverse events (AEs). The CTCAE version 4 is identified and located on the CTEP web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.

The SAEs will be reported per Case Comprehensive Cancer Center policy.

Significance of Adverse Event	Study Related (Possible/Probable/Definite)		Not Study Related (Unrelated/Unlikely)	
Attribution of Adverse Event	**Expected**	**Unexpected**	**Expected**	**Unexpected**
Fatal Events (Grade 5)	5 working days	5 working days*	Summarize in Continuing Review	10 working days
Life-Threatening or disabling (Grade 4)	Summarize in Continuing Review	10 working days	Summarize in Continuing Review	Summarize in continuing review report
Severe and undesirable (Grade 3)	Summarize in Continuing Review	10 working days	Not reportable to IRB	Summarize in continuing review report
Moderate and Mild Grades 1 & 2	Not reportable to IRB			
Unanticipated Problem that is a reportable Event	**5 working days and reportable to HHS agency head and OHRP**			

*All study related, unexpected deaths should be carefully assessed against the definition of unanticipated problem.

The SAE is to be entered into Oncore and the regulatory coordinator and DSTC coordinators will then work with the PI to submit it to the IRB and DSTC. The SAE is to be placed into Oncore within 2 working days of notification to the study coordinator.

7.0 Study Procedures

Screening procedures will be performed up to 28 days before registration unless otherwise stated. Study visits will have a 2-3 study window unless otherwise stated.

7.1 Screening Visits

Screening Visit – visit #1

- Informed Consent (for patients who meet screening criteria)
- Demographics
- Medical History
- Height
- Weight
- Vitals including blood pressure, pulse, respiratory rate, temperature
- Physical examination
- Concomitant medication assessment
- ECOG performance status
- Assessment of baseline symptoms
- Quality of Life scores (standard of care) IPSS and SHIM
- Research Quality of Life scores (EPIC, EPIC Supplement Sexual Medicines/Devices, EQ-5D)
- Laboratory Studies:
    - Complete Blood Count (CBC) with differential**,** platelets

- Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
- Calculated creatinine clearance will be done if creatinine and/or BUN are abnormal
- Testosterone

- Pelvic mpMRI with contrast and multiparametric sequences (SOC for staging) (must be within 180 days of screening visit)
- Bone Scan when clinically indicated per standard-of-care (must be within 90 days of screening visit)
- PSA (must be within 90 days of screening visit)
- DRE (must be within 90 days of screening visit)

7.2 Study Visits

Biopsy and Fiducial Placement – visit #2

- Weight
- Vitals including blood pressure, pulse, respiratory rate, temperature
- Physical examination
- Guided biopsy
- Fiducial placement

MRI and CT scans for RT SIM – visit #3

- RT CT (with contrast unless contraindicated) for simulation
- Pelvic MRI with Contrast
- Pelvic CT for SIM

SBRT #1 – visit #4

- RT treatment

SBRT #2 – visit #5

- RT treatment

MRI – visit #6

- Pelvic mpMRI with Contrast

SBRT #3 – visit #7

- Adverse events assessment (may be completed by telephone call within 7 days post visit 7)
- RT treatment

Follow up, every 3 months for up to 24 months – visits #8 - #16

- Weight
- Vitals including blood pressure, pulse, respiratory rate, temperature
- Physical examination
- ECOG performance status
- Quality of life Score standard of care IPSS and SHIM Scores
- Adverse events assessment

Post SBRT Follow up Measurements

- PSA to be completed at **ALL** follow up visits

- DRE to be completed at **ALL** follow up visits
- Serum Creatinine and BUN Blood Draw at **6, 12, and 24** months follow up prior to MRI
- Pelvic MRI to be completed at **6, 12, and 24** month follow up visits with contrast
- EPIC EQ D5, Sexual Medication/Device screening to be completed at **6, 12 and 24** months

Any positive results for staging Post RT (positive digital rectal exam or evidence of biochemical failure using the clinical nadir +2 definition (serum PSA rise above 2ng/mL from the post therapy nadir (Phoenix, Abramowitz 2007) may trigger clinical indication for SOC staging MRI to rule out disease progression. If acquired, this data will be collected for comparison to other serial MRI data. Should a patient be deemed to have failed therapy using the Phoenix criteria (nadir +2ng/mL PSA) the subject/s will be referred for consultation for review of options for salvage therapy, and if the patient elects a second treatment the subject will be taken off study.

7.3 Study Calendar

Study Days	**Screen Visit 1**	**Biopsy and Fiducial Placement Visit 2**	**MRI* & CT Scans for RT SIM Visit 3**	**SBRT #1 Visit 4**	**SBRT #2 Visit 5**	**MRI Visit 6**	**SBRT #3 Visit 7**	**30 days post RT Visit 8**	**3 mo post RT Visit 9**	**6 mo post RT Visit 10**	**9 mo post RT Visit 11**	**12 mo post RT Visit 12**	**15, 18 & 21 months post RT Visits 13-15**	**24 mo Post RT Visit 16**
REQUIRED ASSESSMENTS			2-3 wks Post Fiducials	2-3 wks Post SIM										
Informed Consent	X													
Demographics	X													
Medical History	X													
Height	X													
Weight	X	X						X	X	X	X	X	X	X
Vitals (BP Respiration Pulse Temp)	X	X						X	X	X	X	X	X	X
Physical Examination	X	X						X	X	X	X	X	X	X
Concomitant medication assessment including hormone therapy	X							X	X	X	X	X	X	X
ECOG PS	X							X	X	X	X	X	X	X
Baseline Symptoms	X													
IPSS/SHIM QoL Scores	X							Xa	Xa	Xa	Xa	Xa	Xa	Xa
Adverse Event Assessment							X[2]	X	X	X	X	X	X	X
CBC w diff /platelets /testosterone	X													
Serum Chemistry [1]	X													
Guided biopsy		X												
Fiducial placement		X												
RT simulation			X											
RT TREATMENT				X	X		X							

Study Days	Screen Visit 1	Biopsy and Fiducial Placement Visit 2	MRI* & CT Scans for RT SIM Visit 3	SBRT #1 Visit 4	SBRT #2 Visit 5	MRI Visit 6	SBRT #3 Visit 7	30 days post RT Visit 8	3 mo post RT Visit 9	6 mo post RT Visit 10	9 mo post RT Visit 11	12 mo post RT Visit 12	15, 18 & 21 months post RT Visits 13-15	24 mo Post RT Visit 16
DISEASE ASSESSMENT														
Pelvic MRI *	X[3,4]		X*			X*				X*		X*		X*
Pelvic CT for SIM			X*											
Bone Scan	X[4]													
PSA	X[4]								X	X	X	X	X	X
DRE	X[4]								X	X	X	X	X	X
EPIC EQ D5, Sexual Medication, Device Screening	X									X		X		X

1: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium. Calculated creatinine clearance will be done if creatinine and/or BUN are abnormal

2: Post treatment A/E assessment may be a telephone call within 7 days post end of therapy.

3: SOC Staging MRI

4: Must have been completed within 90 days of screening visit

a: Physician or Nurse Practitioner consult at post RT visits

* Serum Creatinine And BUN Blood Draw performed prior to pelvic MRI with contrast (mandatory for eligibility)per institutional guidelines.

8.0 Correlative / Special Studies

not applicable

9.0 Safety and Effectiveness Assessments

The primary goal of this pilot study is to determine if MRI with multiparametric sequences mpMRI can be used as a mapping tool for correlation with histopathology results, providing a more informed method for the delivery of focal hypofractionation treatments. Hypofractionated radiation using SBRT is a promising tool for delivery with intent to cure. The use of focal partial prostate SBRT should show lower toxicity, and will be evaluated for equivalent efficacy. A co-primary end point of the pilot study will be to show that patients maintain acceptable HRQOL status as compared to baseline. There will be two co- primary endpoints based on summary scores from the bowel and urinary domains of the EPIC questionnaire. Although HRQOL is collected at multiple time points, it has been decided that EPIC, EQ D5 and Sexual Medication/Device Screening data collected at 6, 12 and 24 months post therapy will be compared to baseline to test the primary hypothesis. The percentage of patients with change in EPIC bowel domain score (baseline to 1-year) that was worse than 5 points and a change in EPIC urinary domain score that was worse than 2 points are felt to be clinically meaningful endpoints to assess for tolerability and safety. A rate for the worse-than-5 point change in bowel score of up to 35% of patients will be considered acceptable, with a rate ≥55% specified as unacceptable. Similarly, a rate for the worse-than-2 point change in urinary score of up to 40% will be considered acceptable, with a rate ≥60% unacceptable. The PSA results along with serial MRI assessments will be used to test the hypothesis of equivalent disease control compared to historical data for whole gland therapy using SBRT. Standard of care quality of life assessments International Prostate Symptom Score (IPSS) and sexual health inventory for men (SHIM) scores will be acquired as part of the standard care prior to and following SBRT. When collected, this data will be collected and reported.

Analysis of the Primary Endpoints

Treatment efficacy will be analyzed through PSA response, clinical exam, with the addition of serial MRI evaluations. Confirmation of multiparametric MR targets for focal SBRT with image guided biopsy, histopathology and fiducial marker position tracking will be evaluated for reporting accuracy of multiparametric and standard MRI sequences to detect disease. Prostate MRI including T2-weighted, contrast-enhanced, and diffusion weighted imaging along with computer aided detection (CAD) may be used to identify suspicious lesions for targeted biopsy and fiducial placement. Chi-square and cluster analysis will be used to correlate degree of suspicion on MR pulse sequences with incidence of cancer detected on biopsy and subsequently targeted for focal therapy. Post therapy MRI will be used to report response to therapy as either complete, partial, stable or progressive by RECIST criteria.

9.1 Safety and Efficacy Endpoints

Assessment of early clinical outcomes in focal SBRT for low risk prostate cancer patients. Twenty-four hormone naïve low to intermediate risk prostate cancer patients will be screened for PSA level, acute toxicities and quality of life (QOL) measures at baseline and twelve will be followed at longitudinal follow-up appointments.

Acute and Late GI and GU Adverse Events (AEs)

Adverse events are evaluated by the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE). We will record in Oncore the highest grade reported during a reporting period. The treatment-related attribution includes definitely, probably or possibly related to treatment. An acute adverse event is defined as the first occurrence of worst severity of the adverse event ≤30 days after the completion of RT. We will evaluate the acute radiation therapy-related adverse events. Specifically, we are interested in the percentage of acute GI and GU Grade 3+ adverse events that may occur, which is considered to be similar to the high RT dose arm of RTOG 0126 in terms of RT dose. If our partial prostate hypofractionated regimen has an acceptable percentage, then it will be deemed to have an acceptable adverse event profile. We will report the percentage for the regimen as well as the one-sided 97.5% confidence interval. For example, the number of patients in the high dose arm of RTOG 0126 Phase II reported that 1% of patients experienced Grade 3+ GI/GU acute toxicity, with no patient experiencing Grade 4 or 5 toxicities (citation) should be greater than this pilot study. A late adverse event is defined as the first occurrence of worst severity of adverse event >180 days after RT completion. Late Grade 3+ GU/GI toxicity information will be collected and reported also.

PSA Failure

Failure occurs when the PSA is first noted to be 2 ng/mL or more than the patient's nadir value post RT completion (Phoenix, Abramowitz 2009). PSA failure at 6, 12 and 24 months following RT will be estimated for the series by the cumulative incidence method (Gray 1988). Also, confidence intervals will be reported.

Disease-Free Survival (DFS)

The disease-free survival duration will be measured from the date of treatment to the date of documentation of disease progression or until the date of death from any cause. DFS at 6, 12 and 24 months for each patient and the series by the Kaplan-Meier method (Kaplan 1958). Also, 95% confidence intervals will be reported.

Analysis for Endpoints Related to HRQOL

We will use three instruments to measure HRQOL: the Expanded Prostate Cancer Index Composite (EPIC), the Utilization of Sexual Medications/Devices, and EQ-5D. Protocol eligible patients will be included in the HRQOL analysis only if they have provided baseline and at least one subsequent measurement. All HRQOL instruments (EPIC, the Utilization of Sexual Medications/Devices and EQ-5D) will be collected on all cases participating in the trial. The standard departments QOL instruments may also be used to report outcomes with both the International Prostate Symptom Score (IPSS) and Sexual Health Information Measurement (SHIM) obtained from chart review.

The EPIC Supplement Utilization of Sexual Medications/Devices, and EQ-5D will be collected at pretreatment (baseline) and at 6, 12 and 24 months after radiation therapy ends. Patient self-assessment of symptoms will be performed using four primary EPIC scales: urinary, bowel, hormonal and sexual symptoms. The Utilization of Sexual Medications/Devices and EQ-5D Questionnaires are found in Appendix 3.

For all primary HRQOL analyses we will estimate the degree of change from baseline to 6, 12 and 24 months as continuous variables. For this endpoint, in each domain, the actual change score will be used as the statistic and a t-test will be used to evaluate if the change is different from 0. Confidence intervals also will be computed

The primary objective in HRQOL analysis is to estimate the change from baseline to 24 months. The response will be the change of measurement from baseline to 24 months (or the last available HRQOL data point where data are missing). The one-sample t- test will be used to test the null hypothesis that response change is 0. For the regimen to maintain the overall significance level for testing three HRQOL instruments. In addition, we will describe the distributions of HRQOL data collection patterns over all collection points in each treatment arm.

Demonstrate dosimetric and biological advantage of focal SBRT versus whole-gland therapy
Treatment plans from focal versus simulated whole-gland SBRT for each patient will be compared for target volume size, dose distribution, and dose reduction to organs at risk (OAR). Additional assessments for planning volumes based solely on imaging versus with correlated histopathology to define PTVs will be collected, evaluated and reported. Biological modeling will be used to evaluate tumor control probability and normal tissue complication probability (NTCP) between the two treatment paradigms (focal versus virtual simulation of whole gland treatment using conventional treatment per institutional standards). Standard independent methods of dosimetry calculations will be evaluated by Medical Physics staff and reported by Medical Physics co-investigators, utilizing such programs as Pinnacle and MUcheck, and Monte Carlo simulations. Subject data sets appropriately de-identified by a study co-author may be additionally evaluated utilizing advanced software MRI analysis for predictive modeling and comparison to tumor volume selection as identified with histopathology validation.

We estimate that 12 patients will be treated on study, and that 24 patients may be screened. MRI and histopathology data will be collected for all patients consented to the study and screened.

Interim Reports to Monitor Study Progress
Patients will have imaging sessions (MRI and CT Simulation) for treatment planning and delivery of radiation therapy. Interim imaging reports will be provided to the funding partners following the first 3-6 subjects screened, along with case study descriptions, and limited de-identified treatment plan screen shots along with composite image sets. Other interim reports will evaluate workflow and carepath processes.

9.2 Effectiveness Assessments

Clinical information from subjects will be recorded onto Case Report Forms and subsequently transferred into OnCore. Patients who additionally consent to a separate Urology Registry will have their data added to the Urologic Oncology & Minimally Invasive Therapies Database for UHHS Faculty.

Should any unanticipated adverse events occur during the course of the study, the clinical research coordinator will ensure that they are documented by the investigator and reported to the appropriate Institutional Review Board per its then-current guidelines. If the determination is made that an unanticipated adverse event presents an unreasonable risk to subjects, the clinical evaluation will be paused, or if deemed appropriate (to enable further investigation), the subject will be withdrawn as soon as safely possible.

Adverse events, grade 3 and above, will be captured in OnCore and will be reported in accordance with the Data and Safety Monitoring Plan (DSMP) that is approved by the Cancer Center Protocol Review and Monitoring Committee (and aligned with the NCI-approved plan).

Antitumor Effect – Solid Tumors

For the purposes of this study, subject PSA, DRE and PSA data will be recorded in Oncore as evaluations for response to radiation therapy, per standard of care procedure during post radiation therapy follow-up visits. In addition to PSA and DRE evaluations, RECIST (v.1.1) measurements will be acquired using mpMRI surveillance. Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria. We will also analyze volumetric response to therapy based on serial MRI data that will be evaluated using radiation oncology treatment planning computers.

Definitions

Evaluable for toxicity All patients will be evaluable for acute toxicity within 90 days from the time of the end of the course of radiation therapy.

Evaluable for objective response

Evaluable Non-Target Disease Response Patients who have lesions present at baseline that are evaluable, but do not meet the definitions of measurable disease, have completed a course of SBRT, and have had their disease re-evaluated by imaging will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

Disease Parameters

Radiologic Surveillance

Standard of care follow-up post RT will include contrast enhanced MRI and parametric imaging unless clinically contraindicated should include contrast.

Measurement of Response

Measurement of Response Prior to Study Entry

The revised RECIST guideline, v. 1.1. [European J of Cancer. 45: 228-247, 2009] will be used as applicable to the protocol. See http://ctep.info.nih.gov/protocolDevelopment/docs/recist_guideline.pdf for further details. Additional definitions beyond the RECIST guidelines specific to this protocol are incorporated to define local control as described below (Eisenhauer 2009). We will evaluate and report RECIST measures minimally at 12 and 24 months post radiation therapy.

Response Criteria: Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions taking as reference the baseline sum diameters
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (includes the baseline sum if that is the smallest on study). The sum must also demonstrate an absolute increase of at least 5 mm. The appearance of new lesion(s).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking the smallest sum diameters as reference while on study.

3D Lesion Volumes
In addition to RECIST criteria evaluation on follow-up scans, we will report 3 D volumetric data of individual lesions based on pre and post treatment images over time, for comparison to 2 D RECIST measurements (Guiou 2012 and Eisenhauer 2009).

Measurable Disease Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter for non-nodal lesions and short axis for nodal lesions to be recorded) as $\geq$ 20 mm by chest x-ray, as $\geq$ 10 mm with CT scan, or $\geq$ 10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measurable disease All other lesions (or sites of disease), including small lesions (< 5 mm longest diameter) will be considered non-measurable disease. The presence of lymph nodes suspicious for metastatic disease during screening will be defined as an ineligibility criterion.

Target lesions Only a single target lesion which is biopsy positive will be selected for focal therapy and identified as the dominant target lesion and recorded and measured at baseline. Target lesion should be selected on the basis of size (lesions with the longest diameter). We will use T2 weighted MRI image sets with contrast for the baseline measurement.

Non-target lesions All other suspicious lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Methods for Evaluation of Measurable Disease
All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment. The same method of assessment and technique should be used to characterize the dominant lesion at baseline and during follow-up. Use of 3T MRI T2 scans with contrast is required for the baseline measurement and is the preferred method and technique for all imaging-based evaluations. The mpMRI image data will additionally be recorded, evaluated and reported separately.

Response Criteria
Evaluation of Target lesions

Response	**Evaluation of Target Lesions**
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the

	relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. **Note**: the appearance of one or more new lesions is also considered progression.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target lesions less than 5mm and /or detected on screening biopsy to involve less than 5% of the submitted tissue for carcinoma.

Response	**Evaluation of Non-Target Lesions**
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis). **Note:** If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
Non-CR/ Non-PD [Incomplete response/ Stable Disease (SD)]	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD)	Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Although a clear progression of 'non-target' lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥ 4 wks. Confirmation **
CR	Non-CR/Non-PD	No	PR	≥ 4 wks. Confirmation **

CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥ 4 wks from baseline **
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD ***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as *"symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesion	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD *
Not all evaluated	No	Not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

RECIST (Eisenhauer 2009) Tumor Response
Tumor measurements will be defined by the PI or treating physician, and confirmed by an objective radiation oncologist or radiologist not associated with this study.

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for stable disease (SD), partial response (PR) or complete response (CR) - whichever is first recorded, until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started)

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented. CR will be reported as unconfirmed CR until a repeat image shows duration of response.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

Biochemical Disease-Free Survival: The absence of PSA Clinical Nadir plus 2 ng/mL (Phoenix, Abramowitz (2007).

10.0 Statistical Plan

10.1 Data Collection

All study-related data will be entered into OnCore. Access will be limited via a password known only to the investigator and designated research personnel (study nurse(s), data manager(s)).

10.2 Statistics

Statistical Considerations

Chi-square and cluster re-sampling analyses will be used to correlate suspicion on multiparametric magnetic resonance imaging and the incidence of cancer detected on biopsy.

The primary goal of this study is to evaluate acute and late toxicities. In addition clinical data will be collected to monitor for tumor control. Digital rectal examination (DRE) and serum prostate antigen (PSA) will be evaluated every 3 months for two years. Toxicity will be evaluated EPIC EQ D5, Sexual Medication, Device Screening Questionnaires completed by the patients or in conversation with the patient by the clinical staff, at baseline, 6, 12 and 24 months following the end of radiation therapy (+/- 14 days). Rates of acute and late side effects and adverse events will be summarized as proportions, with 95% confidence intervals.

Biochemical failure will be based on PSA values using the Phoenix definition (clinical nadir +2ng/mL). Data from all patients will be pooled. Survival rates estimated from the Kaplan-Meier curves will be estimated with 95% confidence intervals. We will also track virtual treatment plans based on standard models for treatment to the whole gland versus partial gland MRI-TPUS validated planning to report change in dosimetric parameters of the focal SBRT versus traditional whole-gland treatment plans for statistical comparison.

Either a positive DRE or rising PSA may be used as clinical indication for additional MRI surveillance. When additional MRI are available, tumor volume will be summarized by mean ±STD and the difference between two time points (pre and post treatment) will be examined using paired T-test. Radiographic efficacy will be summarized by calculating Kaplan-Meier curves for the following: disease-free survival, time to local progression, time to distant failure. Descriptive reports of RECIST (1.1) and volumetric findings will be provided.

Acute/Late Toxicity and Quality of Life Measurements

Using multivariate analysis, we will report acute and late (>180 days post SBRT) rates of GI toxicity with dose-volume histogram. We will also report time to event analyses collected for all available HRQOL data collected.

Temporal pattern of quality of life scores will be summarized graphically; and repeated measures analysis of variance (ANOVA) will be conducted to test for changes in scores over time. The predictive value of demographic, pathological and clinical factors on the scores will be examined by mixed models assuming missing values are missing at random.

Sample Size

Twelve patients will be evaluated in this pilot study. As a proof-of-principle study, it's not design to have the appropriate power (80%) for detecting significant difference in clinic outcomes (i.e.

toxicities, survival or QOL), but to provide some preliminary data for future studies. A sample of 12 patients, however, achieves 78% power to detect 8% difference of urinary toxicity against historical controls under whole gland therapy using a two-sided binomial test with the target significance level of 0.2. We anticipate that a minimum of twenty four patients will be screened leading to twelve patients who will be treated and evaluated on-study in this pilot study.

11.0 COSTS AND COMPENSATION

The costs of procedures, tests, visits and hospitalizations in connection with the radiation therapy are standard of care and will be billed to the subject's insurer and/or to the subject. This includes costs for pre-treatment diagnostic scans, fiducial markers and fiducial marker placement, treatment planning, radiation therapy treatments, and post-operative follow-up for radiation therapy, are standard of care and will be charged accordingly. Therefore, subjects and their insurers will be fully responsible for the costs related to this research evaluating and comparing standard of care procedures.

Subjects will not be paid for their participation in this study.

12.0 Risks

12.1 Anticipated Risks

Risks include those that result from the special nature of radiosurgery standard of care, including errors in giving the radiation. This may include giving radiation to normal tissue around the tumor and not to the cancer, or giving the wrong dose of radiation, either too much or too little. Any of these problems could potentially be severe, possibly even fatal.

Subjects may have a number of CT scans, nuclear scans and MRI scans that are part of the regular care for this condition, whether or not they participate in this research. These studies will not add to the risk of the research. However, subjects with concerns about the overall radiation exposure or MRI safety issues should be discussed with a study physician.

The risks associated with the MRI scans are the same risks as those posed by clinically indicated tests (non-research). A known risk related to MRI examinations is that the MRI magnet could attract certain kinds of metal that may cause injury to the patient. In order to avoid that, patients will be screened for any hazardous metal object that they may have or is implanted inside their body which includes pacemakers, intracranial aneurysm clips, heart valve prostheses and other implanted devices that are not compatible with MRI. Although there is no risk from ionizing radiation with MRI, subjects will be exposed to strong magnetic fields and radio waves, neither of which are associated with any known detrimental health effects.

We will use an MRI contrast agent that is approved by the FDA and commercially available. There is a risk of an allergic or fibrotic reaction, which occurs more often with iodine based contrast (for CT) than with MRI contrast agents. Every effort will be made to minimize the risk of such reactions in this study by excluding subjects who have a history of kidney disease, which is the cohort who most frequently exhibits an allergic reaction. Generally, an injection of 10-20 ml IV contrast agent will be used, provided that the subject has no known reaction to contrast agents used in previous MRI scans. As with all such injections, bleeding, bruising, dizziness, fainting or infection may occur. Also,

the injection may be painful but the discomfort should be brief and efforts will be made to minimize the pain.

All data will be entered and managed in computer systems having limited access and password protected. There is some risk that subjects' personal protected health information could be breached and health information made available to unauthorized individuals.

Adverse events are not anticipated as related to the delivery of focal therapy, beyond the normal risks of radiation therapy with curative intent for localized prostate cancer.

Intravenous MRI contrast agents will be applied to stage each patient's stage of disease, looking for local disease extension. Subjects who have a history of adverse reactions to contrast media will be excluded from that portion of the study as will subjects with a history of kidney disease or unacceptable values of creatinine and/or Glomerular Filtration Rate [GFR] (see exclusion criteria). Subjects who have a history of adverse reactions to contrast media will be excluded from the study as will subjects with a history of kidney disease or unacceptable values of creatinine and/or Glomerular Filtration Rate [GFR] (see exclusion criteria).

In addition, we will use the MRI images obtained for staging to also map locations of intraprostatic tumor foci, to map the location/s of disease. Just prior to fiducial marker placement, patients will be consented for a biopsy procedure during fiducial marker placement for radiation therapy set up, for the purpose of establishing a map of known disease within the gland. Biopsy cavities will be marked with in-vivo fiducials and/or using temporary *in-situ* marker tracking, such as the use of the echogenic needle tip coordinates on ultrasound. Such recorded TRUS ultrasound coordinates will be tracked and evaluated for subsequent correlation of histopathology data and the mpMRI images – using all available image data (for example the treatment simulation MRI and CT) to inform our treatment planning to improve se localization of known true positive tumor foci.

Additional biopsy samples will be acquired just prior to fiducial marking (permanent or temporary as defined above) in a sextant fashion to map disease across the prostate gland for use in treatment planning and staging. The risks associated with prostate biopsy sampling are similar in nature to those associated with the patient's diagnostic biopsy that confirmed the presence of adenocarcinoma. These risks include the risk associated with bleeding, and the possibility of infection that could be serious. There is additional discomfort that may be associated with the insertion of use of a rectal ultrasound probe that may be managed by light sedation. The fiducial marker placement procedure will be lengthened by several minutes during which time biopsy mapping will occur. This procedure will include the use of general sedation, which is customary with transperineal fiducial marker placement and or biopsy procedures. However, additional risk may be associated with the use of such sedation measures over an increased timeframe during the additional biopsy sampling procedure.

12.2 Benefits

There are potential benefits for individuals who may elect to participate in this particular study. The staging biopsy and image guided fiducial marker placement with correlation to serial MRI scans may allow improved staging information for these screened patients. Our efforts to apply advanced imaging with histopathology correlation may allow us to refine treatment planning contours, aimed a reduction in toxicity while completing therapy with curative intent. It is, however, unknown if this treatment schema will be proven safe and effective. The diagnosis and treatment decisions will be based on the standard of care imaging. There may be a benefit for future patient populations using MRI with multiparametric sequences and histopathology correlation for the management of prostate cancer using focal SBRT.

12.3 Alternatives to participation

This study does not involve a change to the clinical care of the participant. There will be no consequences to individuals who withdraw or step down from the study. The subject will not undergo the additional MRI scans, nor focal SBRT if a patient refuses to take part in the study. Only the clinically indicated diagnostic standard of care imaging will be performed. If a subject withdraws during the procedure of the study, the investigators will use the data as acquired up to the point of withdrawal.

13.0 Data Reporting

The OnCore Database will be utilized, as required by the Case Comprehensive Cancer Center, to provide data collection for both accrual entry and trial data management. OnCore is a Clinical Trials Management System housed on secure servers maintained at Case Western Reserve University. OnCore properly used is compliant with Title 21 CFR Part 11. Access to data through OnCore is restricted by user accounts and assigned roles. Once logged into the OnCore system with a user ID and password, OnCore defines roles for each user which limits access to appropriate data. User information and password can be obtained by contacting the OnCore Administrator at oncore-registration@case.edu. This study will utilize electronic Case Report Form completion in the OnCore database. A calendar of events and required forms are available in OnCore.

14.0 Regulatory Considerations

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

14.1 Written Informed consent

Provision of written informed consent must be obtained prior to any study-related procedures.

The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The original, signed written Informed Consent Form must be kept with the Research Shadow Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the subject.

Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

Accessing Electronic Medical Records for University Hospitals Health System

This study will access electronic medical records systems to obtain medical information for the subjects enrolled to this study.

In order to insure patient safety, investigators and study personnel must have up-to-the-minute health information for subjects enrolled to this study. Therefore, electronic medical records must be utilized to obtain medical information in a timely manner.

Institutional electronic systems will be used to manage subject data, such as the Mosaiq radiation oncology EMR; Athena; UH Physician Portal to access lab results and physician notes; PCOSS LITE as necessary to locate archived medical records; COPATH to locate archived pathology records; PACS to access radiological imaging results; MySecureCare (Sunrise Clinical Manager) to access some or all of the above information when this application is fully functional; OnCore clinical trials management system.

Access to these systems is required for the life of this research study, per institutional policy.

Information obtained from electronic systems will be copied into the Seidman Cancer Center Clinical Trials Unit research chart and/or printed (lab results, physician notes, etc.) and stored in the research chart. Research charts are kept secure and destroyed according to UH policy.

Study data will be obtained by the PI, co-investigators, study coordinator, and/or data manager for this study via password-protected login. All study personnel involved in this research will adhere to the UH policies regarding confidentiality and Protected Health Information.

15.0 Study Closure

The PI will notify the IRB in writing when the study closes.

16.0 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the Research Quality Assurance Office, IRB, the sponsor, and government regulatory bodies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. diagnostic laboratory, etc.).

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the center to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the

protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements.

17.0 Ethics

Incorporate the following, as written

This study will be conducted in compliance with the protocol approved by the Institutional Review Board, the relevant federal regulations, and IRB policies and procedures and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB according to its policies and procedures.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of all subjects will be sought using the IRB-approved consent form. Before a subject undergoes any study procedure, an informed consent discussion will be conducted and written informed consent obtained with a consent form signed by the subject or legally acceptable surrogate if applicable. An investigator-designated research professional will obtain written informed consent from subjects.

18.0 Study Finances

18.1 Funding Sources

Funding for this study will be provided through the Elekta SBRT Research Grant Program, Stockholm, Sweden. In addition, support will be provided by Invivo, a wholly owned subsidiary of Philips Medical Systems (PMS), Cleveland, Ohio. PMS will provide an FDA approved UroNav (Invivo) a Percunav system (a software system that supports ultrasound and mpMRI fusion and guided prostate interventions) for use in this research to guide biopsy and fiducial tracking as part of this research.

18.2 Conflict of Interest

Any investigator who has a conflict of interest with this study as defined by the Case Comprehensive Cancer Center policies. All investigators will follow the conflict of interest policy.

Subject Stipends or Travel Reimbursements

There will be no subject stipend or travel reimbursements.

19.0 Publication Plan

Any investigator involved with this study will be obligated to provide the sponsor and funding partner with complete test results and all data derived from the study. The PI has the responsibility to report the study findings.

- Abstracts and manuscripts in peer-reviewed conferences and journals
- Correlation of multiparametic MRI with histopathology for focal therapy
- Dosimetric and radiobiological models of focal SBRT vs. whole-gland therapy
- Clinical feasibility of focal SBRT on Agility MLC on Synergy S Platform
- Acute toxicity associated with focal SBRT

- Late toxicity and early response to therapy
- Development of clinical workflow and quality check lists for prostate SBRT programs
- De-identified data sets (MRI, CT, dosimetric plans) for advanced concept development for prostate SBRT on Agility Synergy S Platform and the UroNav System

References

Alaei P, Ding G, and Guan H. Inclusion of the dose from kilovoltage cone beam CT in the radiation therapy treatment plans. Medical Physics 2010; 37(1): 244-8.

American Cancer Society: Cancer facts and figures 2013. http://www.cancer.org/Research/CancerFacts Figures/CancerFactsFigures/cancer-facts-figures-2013

Abramowitz MC, Li T, Buyyounouski MK, et al. The Phoenix definition of biochemical failure predicts for overall survival in patients with prostate cancer. American Cancer Society J Cancer 2007; 112 (1): 55–60.

Barkati M, Williams SG, Foroudi F et al. High-dose-rate brachytherapy as a monotherapy for favorable-risk prostate cancer: a Phase II trial. Int J Radiat Oncol Biol Phys 2012;82:1889–96.

Bolzicco G, Favretto MS, Scremin E, et al. Image-guided stereotactic body radiation therapy for clinically localized prostate cancer: preliminary clinical results. Technology in Cancer Research & Treatment 2010; 9(5):473-7.

Bomers JG, et al. MR imaging-guided focal cryoablation in patients with recurrent prostate cancer. Radiology 2013 Mar 22 [Epub ahead of print].

Brenner DJ, Hall EJ. Fractionation and protaraction for radiotherapy of prostate carcinoma. Int J Radiat Oncol Biol Phys 1999;43:1095-101.

Chen LN, Suy S, Uhm S, et al. Stereotactic body radiation therapy (SBRT) for clinically localized prostate cancer: the Georgetown University experience. Radiation Oncology 2013; 8(58): 1-10.

Cosset JM, Cathelineau X, Wakil G, et al. Focal brachytherapy for selected low-risk prostate cancers: A pilot study. Brachytherapy 2013;12:331-337.

Egevad L, et al. Implications of the International Society of Urological Pathology Modified Gleason

Eggener SE, Scardino PT, Carroll PR, Zelefsky MJ et al. for the International Task Force on Prostate Cancer and the Focal Lesion Paradigm. Focal therapy for localized prostate cancer: a critical appraisal of rationale and modalities. J Urol 2007;178(6):2260-7.

Eisenhauer EA, Pherasse P, Bogaerts J. et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1) European J Cancer 2009;45:228-247.

Ellis RJ, Kaminsky DA, Zhou EH, Fu P, Chen WD, Brelin A, Faulhaber PF, Bodner D. 10-year outcomes: the clinical utility of SPECT/CT Capromab Pendetide (PROSTASCINT) in a cohort diagnosed with localized prostate cancer. Int J Radiat Oncol Biol Phys 2010; 81(1):29-34.

Ellis RJ and Kaminsky DA, Method of defining a biological target for treatment. United States Patent Office No. US 7,831,293 B2 Nov. 9, 2010.

Fang, LC, Merrick GS, Butler WM, Galbreath RW, et al. High-risk prostate cancer with Gleason Score 8–10 and PSA level ≤15ng/mL treated with permanent interstitial brachytherapy. Intl J Radiat Oncol Biol Phys 2011; 81(4): 992–996.

Focal cryotherapy: an update from the COLD registry (November 18, 2011). http://prostatecancerinfolink.net/2011/11/18/focal-cryotherapy-and-update-from-the-cold-registry/ (accessed 5/31/13)

Friedland JL, Freeman DE, Masterson-McGary ME, Spellberg DM. Stereotactic body radiotherapy: an emerging treatment approach for localized prostate cancer. Technology in Cancer Research & Treatment.2009; 8(5):387-92.

Grading System. Arch Pathol Lab Med 2012; 136:426-34.
Gulati R, et al. What if I don't treat my PSA-detected prostate cancer? Answers from three natural history modes. Cancer Epidemiol Biomarkrs Pref; 20(5) May 2011.

Hodges JC. Lotan Y. Boike TP. Benton R. Barrier A. Timmerman RD.
Cost-effectiveness analysis of SBRT versus IMRT: an emerging initial radiation treatment option for organ-confined prostate cancer. American Journal of Managed Care 2012;18(5):e186-93.

Hou AH, Sullivan KF, Crawford ED. Targeted focal therapy for prostate cancer: a review. Curr Opin Urol 2009; 19(3):289-9.

Jabbari S. Weinberg VK. Kaprealian T. Hsu IC. Ma L. Chuang C. Descovich M. Shiao S. Shinohara K. Roach M 3rd. Gottschalk AR. Stereotactic body radiotherapy as monotherapy or post-external beam radiotherapy boost for prostate cancer: technique, early toxicity, and PSA response. International Journal of Radiation Oncology, Biology, Physics 2012; 82(1):228-34.

Kaplan EL and Meier P. Nonparametric Estimation from Incomplete Observations. J American Statistical Assoc 1958; 53(282): 457-481.

Katz AJ, Santoro M, Ashley R, Diblasio F, Witten M. Stereotactic Body Radiotherapy as Boost for Organ-confined Prostate Cancer. 2010;9(6):575-582.

Kelloff GJ, Choyke P, Coffey DS. Prostate Cancer Imaging Working Group. Challenges in clinical prostate cancer: role of imaging. AJR Am J Roentgenol. 2009 Jun;192(6):1455-70.

Low RN. Fuller DB. Muradyan N. Dynamic gadolinium-enhanced perfusion MRI of prostate cancer: assessment of response to hypofractionated robotic stereotactic body radiation therapy.
AJR. American Journal of Roentgenology. 197(4):907-15, 2011 Oct**.**

Martino P, Scattoni V, Galosi AB, et al. Role of imaging and biopsy to assess local recurrence after definitive treatment for prostate carcinoma (surgery, radiotherapy, cryotherapy, HIFU). World Journal of Urology 2011; 29(5):595-605.

Martinez AA, Gonzalez J, Ye H, et al. Dose escalation improves cancer-related events at 10 years for intermediate- and high-risk prostate cancer patients treated with hypofractionated high-dose-rate boost and external beam radiotherapy. Int. J. Radiation Oncology Biol. Phys. 2011; 79(2): 363–370.

Michalski JM, Yan Y, Watkins-Bruner D, et al. Preliminary toxicity analysis of 3-dimensional conformal radiation therapy versus intensity modulated radiation therapy on the high-dose arm of the radiation therapy oncology group 0126 prostate cancer trial. Intl J Radiat Oncol Biol Phys. 2013;87(5):932-8.

Pinto AP, Chung PH, Rastinehad AR, et al. Magnetic resonance imaging/ultrasound fusion guided prostate biopsy improves cancer detection following transrectal ultrasound biopsy and correlates with multiiparametric magnetic resonance imaging. J Urol 2011;186(4):1281-1285.

Pisters LL. Cryotherapy for prostate cancer: ready for prime time? Curr Opin Urol 2010; 20(3):218-22.

Polascik TJ, Mouraviev V. Focal therapy for prostate cancer. Curr Opin Urol 2008; 18(3):269-74.

Rapiti E, et al. Importance and determinants of Gleason score undergrading on biopsy sample of prostate cancer in a population-based study. BMC Urol 2013; 13(19): 1-6.

Scardio PT. Focal therapy for prostate cancer. Nat Rev Urol 2009;6:175.

Valerio M, Ahmed HU, Emberton M, et al. The Role of Focal Therapy in the Management of Localised Prostate Cancer: A Systematic Review. European Urology 2013; E-pub ahead of print. Doi: 10.1016/j.eururo.2013.05.048

Ward JF, Jones JS. Focal cryotherapy for localized prostate cancer: a report from the national Cryo On-Line Database (COLD) Registry. BJU Int. 2012;109(11):1648-54.

Wright JL, et al. Differences in prostate cancer outcomes between cases with Gleason 4+3 and Gleason 3+4 tumors in a population-based cohort. J Urol 2009; 182(6):2702-7.

Yoshioka Y, Yoshida K, Yamazaki H, et al. The emerging role of high-dose-rate (HDR) brachytherapy as monotherapy for prostate cancer. Journal or Radiation Research, 2013, 54,781-788).

Zhou EH, Ellis RJ, et al. Radiotherapy and survival in prostate cancer patients: a population-based study. Int. J. Radiation Oncology Biol. Phys 2009; 73(1):15–23.

APPENDIX 1

AJCC STAGING SYSTEM

PROSTATE, 7th Edition DEFINITIONS OF TNM

Source: Edge, SB, ed. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.

Primary Tumor, Clinical (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

T1 Clinically unapparent tumor neither palpable nor visible by imaging
T1a Tumor incidental histologic finding in 5% or less of tissue resected
T1b Tumor incidental histologic finding in more than 5% of tissue resected
T1c Tumor identified by needle biopsy (e.g., because of elevated PSA)

T2 Tumor confined with prostate*
T2a Tumor involves one-half of one lobe or less
T2b Tumor involves more than one-half of one lobe but not both lobes
T2c Tumor involves both lobes

T3 Tumor extends through the prostate capsule**
T3a Extracapsular extension (unilateral or bilateral)
T3b Tumor involves the seminal vesicle(s)

T4 Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles and/or pelvic wall

*Note: Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c

**Note: Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3 but as T2.

Primary Tumor, Pathologic

(pT) * pT2 Organ confined
pT2a Unilateral, one-half of one side or less
pT2b Unilateral, involving more than one-half of side but not both sides
pT2c Bilateral disease
pT3 Extraprostatic extension
pT3a Extraprostatic extension or microscopic invasion of bladder neck**
pT3b Seminal vesicle invasion
pT4 Invasion of rectum, levator muscles, and/or pelvic wall

*Note: There is no pathologic T1 classification
**Note: Positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease).

Regional Lymph Nodes (N)

Clinical

NX Regional lymph nodes were not assessed
N0 No regional lymph node metastasis
N1 Metastasis in regional lymph node(s)

Pathologic

pNX Regional nodes not sampled
pN0 No positive regional nodes
pN1 Metastases in regional node(s)

Distant Metastasis (M)*

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

*Note: When more than one site of metastasis is present, the most advanced category is used; pM1c is most advanced.

Histologic Grade (G)

Gleason X Gleason score cannot be processed
Gleason ≤6 Well-differentiated (slight anaplasia)
Gleason 7 Moderately differentiated (moderate anaplasia)
Gleason 8-10 Poorly differentiated/undifferentiated (marked anaplasia)

Anatomic Stage/Prognostic Groups*

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

APPENDIX 2 ECOG PERFORMANCE SCALE

ECOG Performance Scale	
Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light howework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours..
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX 3 TOXICITY ASSESSMENT INSTRUMENTS

International Prostate Symptom Score (I-PSS)

Patient Name:_____ Date of birth:_____ Date completed _____

In the past month:	Not at all	Less than 1 in 5 Times	Less than Half the Time	About Half the Time	More than Half the Time	Almost Always	Your score
1. Incomplete Emptying How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5	
2. Frequency How often have you had to urinate less than every two hours?	0	1	2	3	4	5	
3. Intermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency How often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak Stream How often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining How often have you had to strain to start urination?	0	1	2	3	4	5	
	None	**1 Time**	**2 Times**	**3 Times**	**4 Times**	**5 Times**	
7. Nocturia How many times did you typically get up at night to urinate?	0	1	2	3	4	5	
Total I-PSS Score							

Score: 1-7: *Mild* 8-19: *Moderate* 20-35: *Severe*

Quality of Life Due to Urinary Symptoms	Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
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?	0	1	2	3	4	5	6

About the I-PSS

The International Prostate Symptom Score (I-PSS) is based on the answers to seven questions concerning urinary symptoms and one question concerning quality of life. Each question concerning urinary symptoms allows the patient to choose one out of six answers indicating increasing severity of the particular symptom. The answers are assigned points from 0 to 5. The total score can therefore range from 0 to 35 (asymptomatic to very symptomatic).

The questions refer to the following urinary symptoms:

Question	Symptom
1	Incomplete emptying
2	Frequency
3	Intermittency
4	Urgency
5	Weak Stream
6	Straining
7	Nocturia

Question eight refers to the patient's perceived quality of life.

The first seven questions of the I-PSS are identical to the questions appearing on the American Urological Association (AUA) Symptom Index which currently categorizes symptoms as follows:

> Mild (symptom score less than of equal to 7) Moderate (symptom score range 8-19) Severe (symptom score range 20-35)

The International Scientific Committee (SCI), under the patronage of the World Health Organization (WHO) and the International Union Against Cancer (UICC), recommends the use of only a single question to assess the quality of life. The answers to this question range from "delighted" to "terrible" or 0 to 6. Although this single question may or may not capture the global impact of benign prostatic hyperplasia (BPH) Symptoms or quality of life, it may serve as a valuable starting point for a doctor-patient conversation.

The SCI has agreed to use the symptom index for BPH, which has been developed by the AUA Measurement Committee, as the official worldwide symptoms assessment tool for patients suffering from prostatitis.

The SCI recommends that physicians consider the following components for a basic diagnostic workup: history; physical exam; appropriate labs, such as U/A, creatinine, etc.; and DRE or other evaluation to rule out prostate cancer.

Expanded Prostate Index Composite (EPIC)

Prostate cancer-specific HRQOL as measured by the Expanded Prostate Index Composite (EPIC) Instrument development was based on advice from an expert panel and prostate cancer patients, which led to expanding the 20-item University of California-Los Angeles Prostate Cancer Index (UCLA-PCI) to the 50-item EPIC. Summary and subscale scores were derived by content and factor analyses. Test-retest reliability and internal consistency were high for EPIC urinary, bowel, sexual, and hormonal domain summary scores (each $r \geq 0.80$ and Cronbach's alpha≥ 0.82) and for most domain-specific subscales. Correlations between function and bother subscales within domains were high ($r > 0.60$). Correlations between different primary domains were consistently lower, indicating that these domains assess distinct HRQOL components. EPIC domains had weak to modest correlations with the Medical Outcomes Study 12-item Short-Form Health Survey (SF-12). Moderate agreement was observed between EPIC domains relevant to the Functional Assessment of Cancer Therapy Prostate module (FACT-P) and the American Urological Association Symptom Index (AUA-SI), providing criterion validity without excessive overlap (Wei 2000). EPIC is a robust prostate cancer HRQOL instrument that measures a broad spectrum of symptoms; however, to decrease patient burden we will only use the domains most pertinent to this study: urinary, bowel, sexual, and hormonal. The domains were validated separately, and since each domain will be used intact, there is no threat to validity. This reduces patient burden

EPIC

Favorable Risk Prostate Cancer

Utilization of Sexual Medications/Devices

Patient Initials **Patient ID**

AMENDED DATA ☐ YES

INSTRUCTIONS: This page must be completed by the medical staff (nurse, data manager, physician, etc.) Questionnaires for all time points are required even if submission time points deviate from the specified intervals. Only patient death or documented patient refusal will be an acceptable reason for omission of the QOL questionnaires. **However, this page must be completed and submitted for every time point on the calendar regardless of whether the QOL questionnaire was completed. Every effort possible should be made to collect the data on time.**

1 ___ **TIME POINT**(1)

1 Pretreatment
2 One year follow-up
3 Two year follow-up
4 Five year follow-up

2 ___ **WAS PATIENT QUESTIONNAIRE COMPLETED?**(2)

1 No (Skip to question 3)
2 Yes

2A DATE PATIENT QUESTIONNAIRE COMPLETED

_____-_____-_____(3)

3 ___ **REASON PATIENT QUESTIONNAIRE WAS NOT COMPLETED**(4)

0 Not applicable, questionnaire was completed
1 Patient refused due to illness
2 Patient refused for other reason, specify_____(5)
3 Unable to contact patient
4 Institutional error
5 Tool not available in patient's language
6 Other reason, specify _____(6)
9 Unknown

4 ___ **SPECIFY METHOD OF COMPLETION**(7)

1 At appointment
2 By mail
3 By telephone
9 Unknown

5 ___ **DID THE PATIENT REQUIRE ANY ASSISTANCE IN COMPLETING THE QUESTIONNAIRE?**(8)

1 No
2 Yes
9 Unknown if assistance was given

6 ___ **SPECIFY THE PERSON WHO ASSISTED THE PATIENT**(9)

1 Staff member
2 Family
3 Other, specify_____(10)
9 Unknown

7 ___ **EXTENT OF THE ASSISTANCE**(11)

1 Read items to patient
2 Interpreted items for patient
3 Marked items per patient's response
4 Combination of above, specify _____(12)
5 Other, specify_____(13)
9 Unknown

_____
Signature of person completing this form(14)

_____-_____-_____
Date form completed(15)

The Expanded Prostate Cancer Index Composite (EPIC)

This questionnaire is designed to measure Quality of Life issues in patients with Prostate Cancer. To help us get the most accurate measurement, it is important that you answer all questions honestly and completely.

Remember, as with all medical records, information contained within this survey will remain strictly confidential.

Today's Date: _____/_____/_____

Name: *(Last, First, M.I.)*_____

Date of Birth: _____/_____/_____

URINARY FUNCTION
This section is about your urinary habits. Please consider **ONLY THE LAST 4 WEEKS**.

1. Over the **past 4 weeks**, how often have you leaked urine?
   - More than once a day.....1
   - About once a day.....2
   - More than once a week .....3 (Circle one number)
   - About once a week 4
   - Rarely or never 5

2. Over the **past 4 weeks**, how often have you urinated blood?
   - More than once a day.....1
   - About once a day.....2
   - More than once a week .....3 (Circle one number)
   - About once a week 4
   - Rarely or never 5

3. Over the **past 4 weeks**, how often have you had pain or burning with urination?
   - More than once a day.....1
   - About once a day.....2
   - More than once a week .....3 (Circle one number)
   - About once a week 4
   - Rarely or never 5

4. Which of the following best describes your urinary control **during the last 4 weeks**?
   - No urinary control whatsoever.....1
   - Frequent dribbling.....2 (Circle one number)
   - Occasional dribbling 3
   - Total control 4

5. How many pads or adult diapers per day did you usually use to control leakage **during the last 4 weeks**?
   - None.....0
   - 1 pad per day.....1
   - 2 pads per day .....2 (Circle one number)
   - 3 or more pads per day.....3

6. How big a problem, if any, has each of the following been for you **during the last 4 weeks**?

(Circle one number on each line)	No problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a. Dripping or leaking urine	0	1	2	3	4
b. Pain or burning on urination	0	1	2	3	4
c. Bleeding with urination	0	1	2	3	4
d. Weak urine stream or incomplete emptying	0	1	2	3	4
e. Waking up to urinate	0	1	2	3	4
f. Need to urinate frequently during the day	0	1	2	3	4

7. Overall, how big a problem has your urinary function been for you **during the last 4 weeks**?

No problem 1
Very small problem 2
Small problem.....3 (Circle one number)
Moderate problem.....4
Big problem.....5

BOWEL HABITS
The next section is about your bowel habits and abdominal pain.
Please consider **ONLY THE LAST 4 WEEKS**.

8. How often have you had rectal urgency (felt like I had to pass stool, but did not) **during the last 4 weeks**?

More than once a day.....1
About once a day.....2
More than once a week .....3 (Circle one number)
About once a week 4
Rarely or never 5

9. How often have you had uncontrolled leakage of stool or feces?

More than once a day.....1
About once a day.....2
More than once a week .....3 (Circle one number)
About once a week 4
Rarely or never 5

10. How often have you had stools (bowel movements) that were loose or liquid (no form, watery, mushy) **during the last 4 weeks**?

Never.....1
Rarely.....2
About half the time.....3 (Circle one number)
Usually.....4
Always.....5

11. How often have you had bloody stools **during the last 4 weeks**?

Never.....1
Rarely.....2
About half the time.....3 (Circle one number)
Usually.....4
Always.....5

12. How often have your bowel movements been painful **during the last 4 weeks**?

Never.....1
Rarely.....2
About half the time.....3 (Circle one number)
Usually.....4
Always.....5

13. How many bowel movements have you had on a typical day **during the last 4 weeks**?

Two or less 1
Three to four .....2 (Circle one number)
Five or more.....3

14. How often have you had crampy pain in your abdomen, pelvis or rectum **during the last 4 weeks**?

More than once a day.....1
About once a day.....2
More than once a week .....3 (Circle one number)
About once a week 4
Rarely or never 5

15. How big a problem, if any, has each of the following been for you?

(Circle one number on each line)	No problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a. Urgency to have a bowel movement	0	1	2	3	4
b. Increased frequency of bowel movements	0	1	2	3	4
c. Watery bowel movements	0	1	2	3	4
d. Losing control of your stools	0	1	2	3	4
e. Bloody stools	0	1	2	3	4
f. Abdominal/Pelvic/Rectal pain	0	1	2	3	4

16. Overall, how big a problem have your bowel habits been for you **during the last 4 weeks**?

No problem 1
Very small problem 2
Small problem.....3 (Circle one number)
Moderate problem.....4
Big problem.....5

SEXUAL FUNCTION
The next section is about your **current** sexual function and sexual satisfaction. Many of the questions are very personal, but they will help us understand the important issues that you face every day. Remember, THIS SURVEY INFORMATION IS COMPLETELY **CONFIDENTIAL**. Please answer honestly about **THE LAST 4 WEEKS ONLY**.

17. How would you rate each of the following during the last 4 weeks?

(Circle one number on each line)	Very Poor to None	Poor	Fair	Good	Very Good
a. Your level of sexual desire?	0	1	2	3	4
b. Your level of sexual desire?	0	1	2	3	4
c. Your ability to have an erection?	0	1	2	3	4
d. Your ability to reach orgasm (climax)	0	1	2	3	4

18. How would you describe the usual QUALITY of your erections **during the last 4 weeks**?
None at all.....1
Not firm enough for any sexual activity.....2
Firm enough for masturbation and foreplay only.....3 (Circle one number)
Firm enough for intercourse 4

19. How would you describe the FREQUENCY of your erections **during the last 4 weeks**?
I NEVER had an erection when I wanted one 1
I had an erection LESS THAN HALF the time I wanted one.....2
I had an erection ABOUT HALF the time I wanted one.....3 (Circle one number)
I had an erection MORE THAN HALF the time I wanted one 4
I had an erection WHENEVER I wanted one 5

20. How often have you awakened in the morning or night with an erection **during the last 4 weeks**?
Never.....1
Less than once a week.....2
About once a week .....3 (Circle one number)
Several times a week.....4
Daily.....5

21. **During the last 4 weeks**, how often did you have any sexual activity?
Not at all.....1
Less than once a week.....2
About once a week .....3 (Circle one number)
Several times a week.....4
Daily.....5

22. **During the last 4 weeks**, how often did you have sexual intercourse?
Not at all.....1
Less than once a week.....2
About once a week .....3 (Circle one number)
Several times a week.....4
Daily.....5

23. Overall, how would you rate your ability to function sexually **during the last 4 weeks**?

Very poor 1
Poor.....2
Fair.....3 (Circle one number)
Good.....4
Very good 5

24. How big a problem **during the last 4 weeks**, if any, has each of the following been for you?

(Circle one number on each line)	No problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a. Your level of sexual desire	0	1	2	3	4
b. Your ability to have an erection	0	1	2	3	4
c. Your ability to reach an orgasm	0	1	2	3	4

25. Overall, how big a problem has your sexual function or lack of sexual function been for you **during the last 4 weeks**?

No problem 1
Very small problem 2
Small problem.....3 (Circle one number)
Moderate problem.....4
Big problem.....5

HORMONAL FUNCTION
The next section is about your hormonal function. Please consider **ONLY THE LAST 4 WEEKS**.

26. **Over the last 4 weeks,** how often have you experienced hot flashes?

More than once a day.....1
About once a day.....2
More than once a week .....3 (Circle one number)
About once a week 4
Rarely or never 5

27. How often have you had breast tenderness **during the last 4 weeks**?

More than once a day.....1
About once a day.....2
More than once a week .....3 (Circle one number)
About once a week 4
Rarely or never 5

28. **During the last 4 weeks,** how often have you felt depressed?

More than once a day.....1
About once a day.....2
More than once a week .....3 (Circle one number)
About once a week 4
Rarely or never 5

29. **During the last 4 weeks,** how often have you felt a lack of energy?

More than once a day.....1
About once a day.....2
More than once a week .....3 (Circle one number)
About once a week 4
Rarely or never 5

30. How much change in your weight have you experienced **during the last 4 weeks**, if any?

Gained 10 pounds or more.....1
Gained less than 10 pounds.....2
No change in weight .....3 (Circle one number)
Lost less than 10 pounds.....4
Lost 10 pounds or more.....5

31. How big a problem **during the last 4 weeks**, if any, has each of the following been for you?

(Circle one number on each line)	No problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a. Hot flashes	0	1	2	3	4
b. Breast tenderness/enlargement	0	1	2	3	4
c. Loss of Body Hair	0	1	2	3	4
d. Feeling depressed	0	1	2	3	4
e. Lack of energy	0	1	2	3	4
f. Change in body weight	0	1	2	3	4

OVERALL SATISFACTION

32. Overall, how satisfied are you with the treatment you received for your prostate cancer?

Extremely dissatisfied 1
Dissatisfied 2
Uncertain .....3 (Circle one number)
Satisfied 4
Extremely satisfied.....5

THANK YOU VERY MUCH!

EQ-5D

Patient Initials **Patient ID**

AMENDED DATA YES	**INSTRUCTIONS:** This page must be completed by the medical staff (nurse, data manager, physician, etc.) Questionnaires for all time points are required even if submission time points deviate from the specified intervals. Only patient death or documented patient refusal will be an acceptable reason for omission of the QOL questionnaires. **However, this page must be completed and submitted for every time point on the calendar regardless of whether the QOL questionnaire was completed. Every effort possible should be made to collect the data on time.**

1 ___ **TIME POINT**(1)

- Pretreatment
- One year follow-up
- Two year follow-up
- Five year follow-up

2 ___ **WAS PATIENT QUESTIONNAIRE COMPLETED?**(2)

1 No (Skip to question 3)
2 Yes

2A DATE PATIENT QUESTIONNAIRE COMPLETED

_____-_____-_____(3)

3 ___**REASON PATIENT QUESTIONNAIRE WAS NOT COMPLETED**(4)

0 Not applicable, questionnaire was completed
1 Patient refused due to illness
2 Patient refused for other reason, specify_____(5)
3 Unable to contact patient
4 Institutional error
5 Tool not available in patient's language
6 Other reason, specify _____(6)
9 Unknown

4 ___**SPECIFY METHOD OF COMPLETION**(7)

1 At appointment
2 By mail
3 By telephone
9 Unknown

5 ___**DID THE PATIENT REQUIRE ANY ASSISTANCE IN COMPLETING THE QUESTIONNAIRE?**(8)

1 No
2 Yes
9 Unknown if assistance was given

6 ___**SPECIFY THE PERSON WHO ASSISTED THE PATIENT**(9)

1 Staff member
2 Family
3 Other, specify_____(10)
9 Unknown

7 ___**EXTENT OF THE ASSISTANCE**(11)

1 Read items to patient
2 Interpreted items for patient
3 Marked items per patient's response
4 Combination of above, specify _____(12)
5 Other, specify_____(13)
9 Unknown

8 **PATIENT'S HEALTH SCORE**(14)
(completed by investigator or staff based on patient's answer to the "Best Imaginable Health Scale" on page 3)

_____ _____
Signature of person completing this form(15) Date form completed(16)

Date form completed_____-_____-_____

Patient Instructions: Please answer one statement in each group below.

Mobility

Please circle one statement in each group below which best describes your health today.

1 I have no problems in walking about

2 I have some problems in walking about

3 I am confined to bed

Self-Care

Please circle one statement in each group below which best describes your health today.

1 I have no problems with self-care

2 I have some problems washing or dressing myself

3 I am unable to wash or dress myself

Usual Activities

Please circle one statement in each group below which best describes your health today.

1 I have no problems with performing my usual activities

2 I have some problems with performing my usual activities

3 I am unable to perform my usual activities

Pain/Discomfort

Please circle one statement in each group below which best describes your health today.

1 I have no pain or discomfort

2 I have moderate pain or discomfort

3 I have extreme pain or discomfort

Anxiety/Depression

Please circle one statement in each group below which best describes your health today.

1 I am not anxious or depressed

2 I am moderately anxious or depressed

3 I am extremely anxious or depressed

The EQ5D Group. EQ5D- a new facility for the measurement of health-related quality of life. Health Policy 1990;(16)3:199-208

QF

Patient Initials

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked by 100 and the worst state you can imagine is marked by 0.

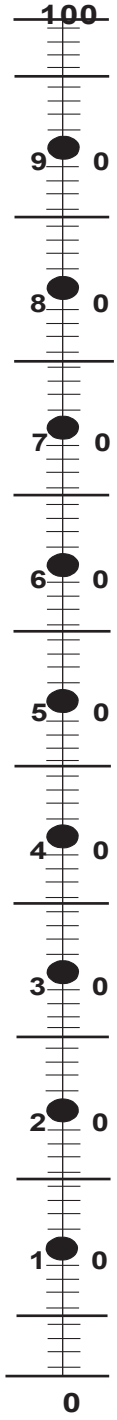
We would like you to indicate in this scale how good or bad is your own health today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your current health is.

Your own health state today

Patient's signature

Date

Best Imaginable Health Scale



Worst Imaginable Health Scale

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