RAD 1801/UAB 1803 –Pilot Study of Intra-Urethral Radiotransponder Beacon Guided Focal Prostate Stereotactic Body Radiotherapy

TABLE OF CONTENTS

TABLE OF CONTENTS

Approval Dates: _____ CTRC _____ IRB

Principle Investigator

Andrew M. McDonald, MD, MS
University of Alabama at Birmingham
Hazelrig-Salter Radiation Oncology Center
1700 6th Avenue South, 176F, Suite 2230
Birmingham, AL 35233
Phone: 205-996-5669

Urology Co-Principle Investigator

Soroush Rais-Bahrami, MD
University of Alabama at Birmingham
Department of Urology
1530 3rd Avenue South, FOT 1105
Birmingham, AL 35294
Phone: 205-975-0088

Co-Investigators

John Fiveash, MD; Michael Dobelbower, MD, PhD; Rojymon Jacob, MD; Robert Kim, MD; Eddy Yang, MD, PhD; Richard Popple, PhD; Rex Cardan, PhD; Ivan Brezovich, PhD; Jeffrey Nix, MD

Biostatistician

Robert A. Oster, PhD

Research Nurse & Data Coordinator

TBD

Regulatory

Kristin Webb, CCRP

Document History Table

	Version/Update Date
Amendment # 1	**May 12, 2020**
Original & Activation	**January 24, 2018**

Summary of Changes

Protocol Amendment # 1
Protocol Version Date: May 12, 2020

#	Section	Comments
1	Footer	The protocol version and amendment number has been updated.
2	8.1	Due to COVID-19, Amendment # 1 is to allow study procedures that may need to be conducted remotely, if necessary.
3	9.1	The following sentence has been added as the last sentence of the paragraph, "*Due to COVID-19, these study procedures may be conducted remotely, if necessary*."
4	9.5.2	The following sentence has been added as the last sentence of the paragraph, "*Some of these study procedures may be conducted remotely, if necessary*."
5		

1.0 OBJECTIVES

1.1 Primary: Confirm the technical feasibility of focal prostate stereotactic body radiotherapy (SBRT) with real time guidance by intra-urethral radiotransponder beacons.

1.2 Secondary: Clinically assess early efficacy, late toxicity, and quality of life for men receiving focal prostate SBRT for low and low-intermediate risk prostate cancer.

2.0 BACKGROUND AND RATIONALE

2.1 Prostate cancer overview

Prostate cancer is the most common non-cutaneous malignancy among men, with over 180,000 annual incident cases leading to an estimated 28,600 deaths in 2016[1]. Men with prostate cancer are grouped into low, intermediate, or high risk cohorts according to risk stratification schemes based upon well-established risk factors including PSA level, Gleason score (histologic grade), and clinical stage[2]. Definitive treatment options for patients with clinically localized prostate cancer include radical prostatectomy, external beam radiotherapy (RT), and brachytherapy or a combination of external beam RT and brachytherapy, with or without androgen deprivation (ADT)[2].

For men without high risk features, active surveillance is an alternative strategy to definitive treatment[2]. The decision to initiate therapy is based on the patient's life expectancy, individual risk factors, and goals. Currently, the National Comprehensive Cancer Network (NCCN) recommends active surveillance for men with newly diagnosed low risk prostate cancer; however, more than half of men will develop indications for definitive treatment within 10 years[3].

2.2 Rationale for focal therapy for prostate cancer

Traditional prostate cancer therapies such as surgical resection (prostatectomy) and traditional radiation therapy involve treatment of the entire prostate gland. Currently, men who are diagnosed with low or low-intermediate risk prostate cancer must therefore choose between active surveillance or whole prostate treatments, which can result in significant morbidity[4]. Since many these men would likely have indolent prostate cancer that would not become life threatening, the morbidity of traditional whole prostate treatment options may not justify their use.

Focal therapy for prostate cancer may offer an ability to improve the risk-benefit ratio of therapy for early prostate cancer by reducing the morbidity of treatment while maintaining oncologic efficacy. Since about half of men who initially elect for active surveillance will undergo definitive treatment within 10 years, earlier intervention with focal therapy may

actually have the potential to lower the overall symptom burden from prostate cancer by reducing the need for more toxic treatments.

2.3 Current state of focal therapy for prostate cancer

Focal therapy options have yet to be fully endorsed by national professional groups such as the NCCN or American Urological Association; however, national patterns of care studies indicate that focal therapy is becoming increasingly utilized[5-7]. The three most common forms of focal therapy utilized currently are high-intensity focal ultrasound (HIFU), photodynamic therapy, and cryoablation, with each modality having relative strengths and weaknesses. While significant heterogeneity among previous studies, biochemical control among well-selected patients who have also undergone multiparametric MRI appear to fall within the range of 60-85% at 5-years[8]. By comparison, the 5-year biochemical control of men with low-risk prostate cancer who undergo definitive radiation therapy or radical prostatectomy exceeds 90% among nearly all modern series.

2.4 SBRT for prostate cancer

The rationale for prostate SBRT stems from a combination of the theorized sensitivity of prostate cancer to larger fractions of radiation (i.e. low α/β) in combination with the ability of modern radiation planning, targeting, and delivery techniques to accurately administer higher doses of radiation with small uncertainty margins. A growing body of literature supports that prostate SBRT, typically with a dose of 36.25 Gy to the entire prostate over 5 fractions, is associated with toxicity rates similar to fractionated regimens[9]. Early efficacy results also support that whole prostate SBRT is associated with high rates of biochemical control for men with NCCN defined low or low-intermediate risk prostate cancer[9]. Recently, prostate SBRT was endorsed by the American Society for Therapeutic Radiation Oncology as an option for first-line therapy for men with low-risk prostate cancer.

At the University of Alabama at Birmingham prostate SBRT, has generally been performed as part of a recently completed prospective clinical trial (NCT01856855). In this study, the entire prostate gland was treated to a dose of 36.25 Gy in 5 fractions and MRI-defined focal nodules received a simultaneous integrated boost to 40 Gy in 5 fractions. This study met its primary safety endpoint of fewer than 15% of patients experiencing acute urinary retention requiring temporary placement of a Foley catheter (7.7% observed rate). Biochemical follow-up data are maturing.

2.5 Rationale of SBRT for focal treatment

Despite the fact that whole gland prostate SBRT is associated low rates of severe grade 3 genitourinary (GU) and gastrointestinal (GI), with adverse effects rates on the order of 1%, lower grade late toxicities are

significantly more common. The most common grade 2 late complications include hematochezia (5-15%), diarrhea (5-10%), hematuria (10-15%), and urethral structuring causing urinary retention (5-10%)[9]. Erectile dysfunctional will also manifest in more than half of men who are sexually active prior to radiation therapy[10]. By reducing the irradiated volume with focal SBRT, radiation dose to the tissues responsible for the toxicities associated with whole-prostate radiation may be reduced.

One key advantage of SBRT over current focal therapy modalities is the ability to account for microscopic disease extension beyond the imaging abnormality. Whole mount pathology correlate studies have consistently shown that microscopic prostate cancer may extend up to 1 cm beyond the lesion seen on MRI[11]. This discrepancy between imaging and pathologic tumor extension poses a challenge for conventional focal therapies such as HIFU and cryotherapy due to the relatively small area of tumoricidal effect around the interstitial probe[8]. In order to account for this limitation, the probe is generally placed in multiple positions in and around the lesion; however, this technique is operator dependent and time consuming[8]. In contrast, SBRT planning techniques allow for the target volume to be enlarged to account for microscopic disease extension (i.e. a clinical target volume expansion) beyond the MRI-defined nodule. Since expansions will generally consist of a geometric margin around the nodule they are less susceptible to inter-operator differences.

Another potential advantage of the SBRT technique proposed in this trial over previously described focal therapy techniques is the ability to administer treatment without violating the perineum. Cryotherapy, HIFU, and photodynamic therapy all require placement of a transperineal interstitial probe. Though the rate of severe complication from probe placement is extremely low[8], this invasive procedure is uncomfortable and necessitates the use of sedation or anesthesia.

2.6 Role of radiotransponder beacons in prostate cancer

The primary technical challenge anticipated for the use of SBRT as a focal therapy modality is managing inter- and intra-treatment target position verification and monitoring without interfering with our ability to accurately delineate the focal nodule. Accurate target verification and monitoring is a vital component of SBRT since it allows for reduction in the size of the planning target volume (PTV) expansion.

The most common technique to confirm the positioning of the prostate before and during treatment is transperineal implantation of radiopaque fiducial markers or Calypso radiotransponder beacons within the prostate gland. The position of radiopaque beacons can be confirmed prior to treatment with orthogonal kV radiographs and cone beam CT. Orthogonal radiographs can also be performed during radiation delivery

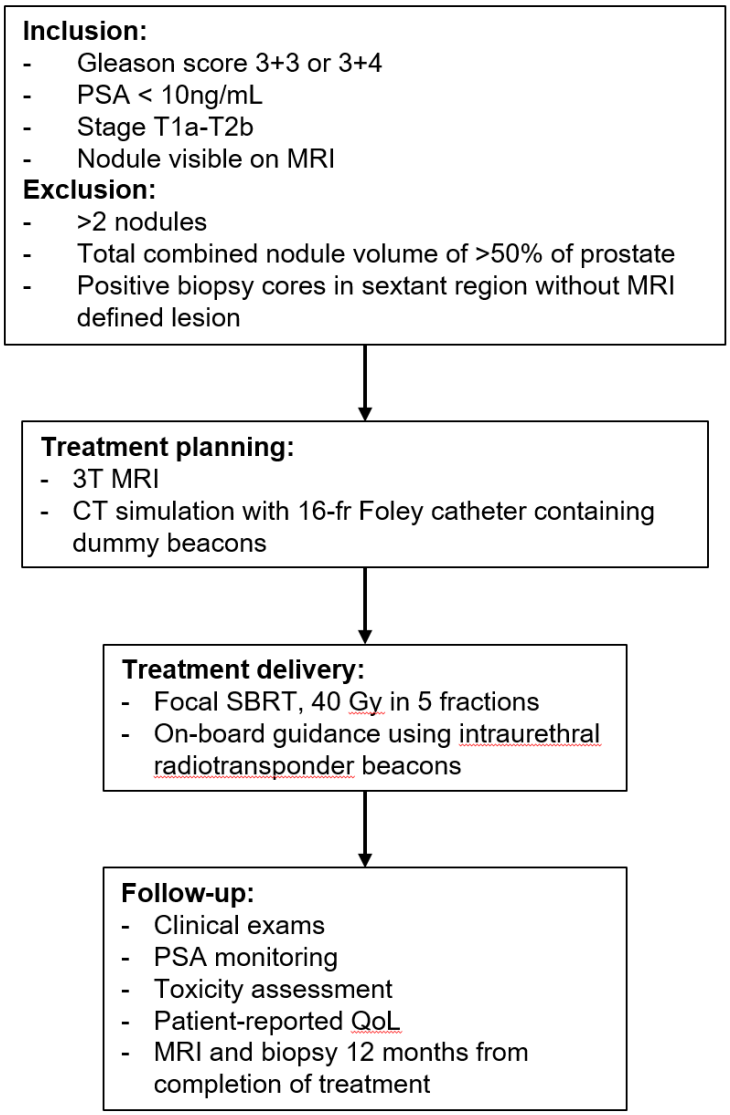
to provide intra-treatment of target positioning. The position of radiotransponder beacons are continuously assessed via an electromagnetic tracing station which is placed slightly above the patient. The advantage of radiotransponder beacons over radiopaque fiducial markers is that the Calypso system allows for constant verification of the 3-dimensional position of the beacons whereas each kV radiograph provides only a 2-dimensional projection.

2.7 Rationale for intra-urethral radiotransponder beacons

Unfortunately, both radiopaque fiducial markers and radiotransponder beacons have the potential to significantly interfere with accurate targeting of MRI-defined focal nodules. For instance, markers placed into the prostate prior to MRI acquisition will result in significant artifact that may obscure visualization of the nodule. On the other hand, if the markers are placed into the prostate after the MRI is acquired, this could result in subtle changes in prostate anatomy that have the potential to result in a marginal miss. Historically this issue was considered of little clinical significance since the target volume has consisted of the entire prostate gland which, unlike focal nodules, is visible on the CT scan obtained for SBRT planning. However, we believe that the ability to accurately delineate the focal nodules is paramount for focal therapy thus another method is needed to maintain MRI image quality.

Temporary placement of radiotransponder beacons within the urethra (via a Foley catheter, with technique to be described subsequently) will allow for removal of the beacons during imaging to prevent artifact. Since the radiotransponder beacons will be removed following delivery of SBRT, future MRIs obtained for follow-up will not be subject to severe artifact. An additional advantage of intraurethral placement of the radiotransponder beacons is that this technique will obviate the need for needle placement through the perineum

3.0 SCHEMA



3.1 Patients who meet the enrollment criteria will be enrolled following the decision to proceed with RT for pathologically proven prostate adenocarcinoma. N=10 patients will be enrolled in the study.

3.2 Baseline urinary symptoms, rectal symptoms, sexual function, and global quality of life will be assessed using validated patient-reported questionnaires.

3.3 A 3-Tesla pelvic MRI containing an axial T2 sequence will be performed without a rectal coil. The use of IV contrast is at the discretion of the treating physician. If an MRI obtained within 3 months prior to enrollment

is deemed clinically acceptable for treatment purposes by the treating physician then reacquisition is not necessary.

3.4 CT simulation will be performed with a Foley catheter in place. Radiopaque dummy seeds will be used to mark the anticipated location of the radiotransponder beacons within the catheter.

3.5 Utilizing available clinical data (biopsy, physical exam, MRI/MRS, and CT-simulation) physicians, medical dosimetrists, and physicists will create and approve a treatment plan if all dosimetric and quality assurance measurements are met (see sections 6.3 – 6.5). Prescribed dose will be 8.0 Gy per fraction for a total of 5 fractions.

3.6 SBRT will be delivered in 9 to 17 calendar days, with every other day fashion in an outpatient clinic setting with an every-other day fashion treatment schedule (see section 6.8). Intraurethral radiotransponder guidance will be performed for all treatments (see section 6.6.4).

3.7 Following completion of treatment, patients will be evaluated with clinical exams, laboratory PSA testing, and quality-of-life questionnaires at regular intervals (1, 3, 6, 9, 12, 18, and 24 months post-radiation)

3.8 Post-treatment multiparametric MRI and biopsy 1 year from completion of SBRT.

4.0 PATIENT SELECTION CRITERIA

4.1 Inclusion criteria

4.1.1 All patients must have histologically confirmed adenocarcinoma of the prostate, with biopsies obtained within 12 months of registration

4.1.1.1 Gleason score 3+3 or 3+4

4.1.1.2 PSA <10 ng/mL within 3 months of enrollment

4.1.1.3 Clinical stage T1a-T2a by digital rectal exam

4.1.1.4 Up to 2 intraprostatic nodules visible on MRI, with combined volume <50% of the total prostate volume

4.1.2 Karnofsky Performance Status (KPS) >70%.

4.1.3 Life expectancy >10 years

4.1.4 Age ≥ 19 years

4.1.5 Subjects given written informed consent

4.2 Exclusion criteria

4.2.1 >2 MRI defined nodules representing prostate cancer

4.2.2 Total volume of MRI nodules exceeding 50% of total prostate volume

4.2.3 Positive biopsy core in sextant region without MRI defined nodule (i.e. biopsy proven MRI occult prostate cancer)

4.2.4 American Urological Association (AUA) urinary score ≥ 18.

4.2.5 History of inflammatory bowel disease.

4.2.6 Prior pelvic surgery

4.2.7 Prior treatment for prostate cancer

4.2.8 Patients using immunosuppressive medications or other medications that may increase radiation toxicity such as methotrexate, sirolimus, tacrolimus, or colchicine that are unable to discontinue these medications during SBRT course. Use of corticosteroids is not considered an exclusion criteria.

4.2.9 Platelet count < 70,000/μL

4.2.10 Patients unable to discontinue anti-platelet or anti-coagulant medicine such as clopidogrel, dabigatran, warfarin, or low molecular weight heparin. Use of aspirin is not an exclusion criteria.

4.2.11 Contraindication to MRI such as implanted devices.

4.2.12 Metallic pelvic implants resulting in imaging artifact within the prostate on MRI or CT.

5.0 DRUG INFORMATION

No experimental drugs are utilized in this study.

6.0 TREATMENT PLAN

6.1 MRI acquisition

Patients enrolled on this study will undergo acquisition of a 3-T MRI containing an axially acquired T2 sequence without a rectal coil. If a pre-biopsy 3T MRI has been obtained within three months of patient enrollment and is deemed clinically acceptable for treatment planning purposes by the treating physician, then reacquisition of post-biopsy MRI is not necessary.

6.2 Treatment planning CT-simulation and contour/volume delineation

6.2.1 Patients will undergo a pre-treatment CT-simulation scan in the supine position. Patients will be instructed to have a full bladder and an empty rectum during CT-simulation. A 16-french Foley catheter will be placed with dummy seeds instead of radiotransponder beacons (see Section 6.7).

6.2.2 CT-simulation images will be electronically fused with MRI images within the treatment planning software and are to be used for contours and treatment planning

6.2.3 The treating physician will define the prostate, gross tumor volume (GTV), and adjacent organs at risk. The GTV will be defined as the T2 hypodense nodule along with any other area suspicious for tumor based on other available clinical data such as other sequences from the multiparametric MRI.

6.2.4 The clinical target volume (CTV) will consist of a 0.5 cm expansion around the GTV but shall not extend beyond the capsule of the prostate or into the urethra.

6.2.4.1 A CTV expansion of 0.5 cm was chosen after considering reports of studies correlating MRI imaging findings with whole-mount pathology specimens[11].

6.2.5 The planning target volume (PTV) consists of a volumetric expansion of the CTV by 3mm in all directions.

6.2.6 Adjacent organs at risk to be contoured include the bladder, rectum, bilateral femoral heads, bowel, urethra, and penile bulb.

6.2.7 Naming conventions for target volumes and organs at risk will follow the AAPM TG-263 recommendations.

6.2.8 The dummy seeds placed in the urethral catheter will be contoured and reviewed by a physicist.

6.2.8.1 The dummy seed contours will be projected onto the reference DRRs of an orthogonal pair of setup fields.

6.2.8.2 The DICOM coordinates of the centroid of each dummy seed and the isocenter will be transferred to the Calypso workstation.

6.2.8.3 The Calypso system will be configured for Gating, Usage Mode: Set zero and track.

6.3 SBRT dose specifications

6.3.1 The prescribed dose will be 40 Gy to the PTV, delivered at 8.0 Gy per fraction for a total of 5 fractions.

6.3.2 At least 95% of the PTV should receive 100% of the prescribed dose.

6.3.2.1 Coverage of 90-95% of the PTV by 100% of the prescribed dose will be considered a minor but acceptable deviation whereas coverage of <90% by 100% of the prescription dose will be considered a major unacceptable deviation.

6.3.3 Rapid dose falloff outside the PTV is to be prioritized over PTV dose uniformity and may result in considerable dose heterogeneity within the PTV, but the maximum dose within the PTV should be limited to 130% of the prescription.

6.4 Critical Structures

The organ at risk planning guidelines for the study are given below. All reasonable attempts should be maintained to minimize radiation to organs at risk if PTV coverage is not compromised.

Pilot cohort (40 Gy in 5 fractions)*		
Organ	**Volume**	**Dose (Gy)**
Rectum	Maximum point dose (1cc)	≤ 38.06 Gy
	Less than 3cc	< 34.4 Gy
	90% of the rectum	≤ 32.625 Gy
	80% of the rectum	≤ 29 Gy
	50% of the rectum	≤ 18.125 Gy
Bladder	Maximum point dose (1cc)	≤ 38.06 Gy
	90% of the bladder	≤ 32.625 Gy
	50% of the bladder	≤ 18.125 Gy
Urethra	Maximum point dose	≤ 38.78 Gy
Femoral heads	Less than 10cc cumulative (both sides)	20 Gy

	Maximum point dose	30 Gy

*****Constraints used in prior UAB protocol of prostate SBRT that included 40 Gy in 5 fraction focal boost (NCT01856855).

6.5 Treatment plan physics quality assurance

6.5.1 All treatment plan dose distributions will be verified by UAB staff physicists and must meet the quality assurance standards set forth by the Department of Radiation Oncology prior to patient SBRT administration.

6.5.2 Dose will be validated by either an ion chamber/film combination in a solid water phantom or a dose calibrated diode array. In either case, the phantom will be irradiated with the same plan as the patient including all couch angles and beam projections. A dose plane will be calculated and exported from the treatment planning system and will be compared with the measured dose plane from the one of the above techniques. Dose comparisons will be analyzed using the gamma criteria of 3%/3mm and will be considered valid if 95% of points have gamma values of less than 1.

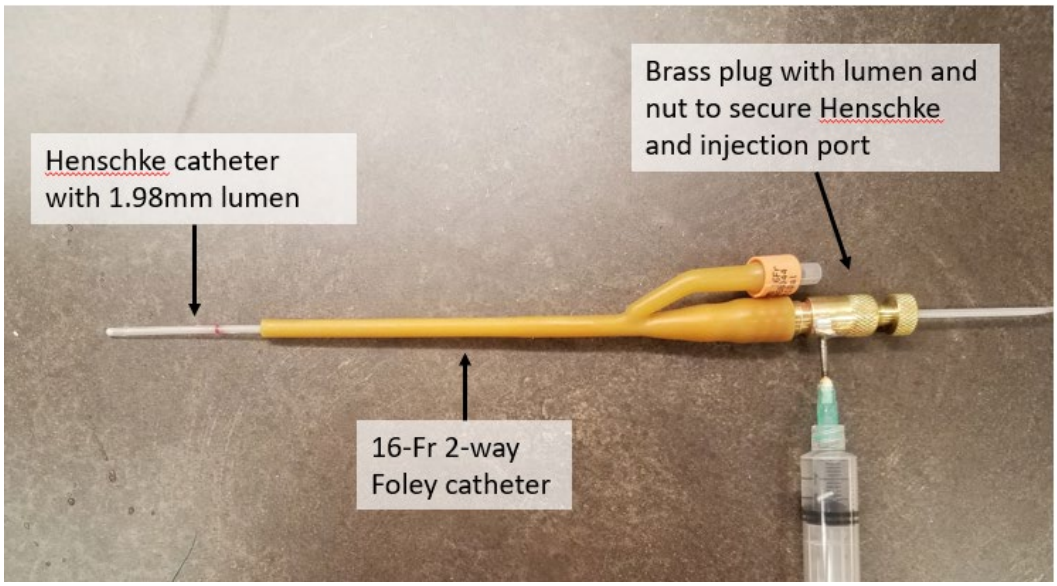
6.6 Technical factors

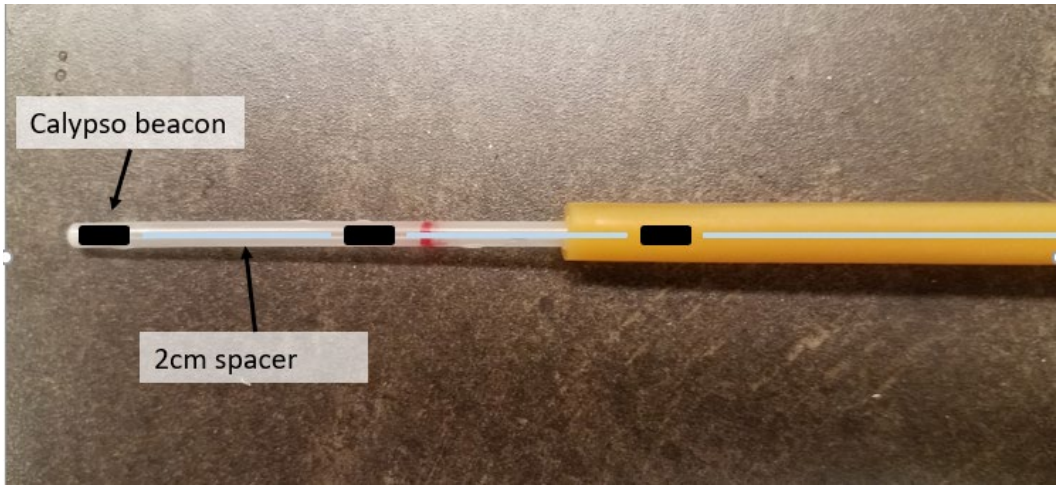
6.6.1 All treatment plans will be devised utilizing a volumetric modulated arc therapy (VMAT) approach. No restrictions are placed on the number and position of treatment arcs.

6.6.2 Treatments will be delivered on appropriately selected linear accelerators at the discretion of the treating physician

6.7 Treatment delivery

6.6.1 Patients will be instructed to arrive in the clinic at least 1 hour prior to planned treatment delivery and a 16-french Foley catheter will be placed and urine allowed to drain. A Henschke style catheter containing 3 Calypso radiotransponder beacons will be placed into the urinary lumen of the Foley catheter as shown below:





6.6.2 Patients will be instructed to have an empty rectum for treatments. Utilization of bowel preparation with oral or suppository medications is left up to the treating physician. Endorectal balloons are not allowed on this study.

6.6.3 Image-guidance with kilovoltage orthogonal x-rays and cone beam CT scans are to be utilized prior to administration of each radiotherapy fraction. A physician is to approve appropriate patient positioning based upon set-up imaging, with the patient being aligned to the urinary catheter and prostate-rectum interface.

6.6.4 The positions of the transponders of the kV orthogonal x-rays and the CBCT will be compared with the dummy seed reference contours. The catheter position will be adjusted as needed. After

the patient is correctly positioned, the Calypso reference position (zero) will be set.

6.8 Treatment delivery schedule

Radiation treatments will be delivered per the standard outpatient setting radiation oncology clinic. Treatment must be completed in within 17 calendar days, with day of first treatment being considered day 1. Exact treatment schedule is left to the discretion of the treating physician.

7.0 THERAPY MODIFICATIONS

7.1 Non-Study Treatment

7.1.1 All medications and other treatment taken by the subject during the study, including those treatments initiated prior to study enrollment, must be recorded within the medical record

7.1.2 Hormonal blockade agents such as leuprolide or bicalutamide will not be allowed in this study.

7.1.3 The use of standard prescription or non-prescription medication to manage symptoms of disease or treatment is left to the discretion of the treating physician. Examples of common medications prescribed for treatment of disease or radiation-related side effects will likely include tamsulosin, phenazopyridine, and/or loperamide

7.2 Concomitant Medication

7.2.1 All medications administered since protocol enrollment will be recorded in the medical record

7.2.2 No cytotoxic chemotherapies or hormonal therapies are to be administered during the study evaluation period

7.2.3 Immediate pre or post-treatment usage of steroids (for example, dexamethasone 4 mg po one hour prior to radiation) is at the discretion of the treating physician.

7.2.4 Prophylactic (or continued) usage of tamsulosin or alfuzosin (or other alpha-blocker medication) allowed at the discretion of the treating physician.

7.3 Adverse Events (AE's) and Serious Adverse Events (SAE's)

7.3.1 Definition of AE: Any untoward medical occurrence, which does not necessarily have a causal relationship with the study

treatment. This includes any physical or clinical change experienced by the subject, whether or not considered related to the study treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal lab finding, for example), symptom, or disease (including the onset of new illness and the exacerbation of pre-existing conditions) temporally associated with the study treatment. Progressive prostate cancer disease is not considered to be an AE. Typical symptoms of radiotherapy treatment including grade ≤ 3 urinary or gastrointestinal toxicity will not be considered an AE, though they will be documented in the medical record (section 9.0). AE's will be recorded in the medical record.

7.3.2 Definition of SAE: Any event occurring during the study evaluation period that results in any of the following outcomes

- Death
- Inpatient hospitalization
- Bleeding requiring administration of blood products
- Any grade ≥ 3 urinary or gastrointestinal toxicity

Note that urinary retention requiring temporary urinary catheter placement is considered a grade 2 toxicity by the CTCAE 4.03

All SAE's must be recorded in the medical record. The onset and end dates, severity, duration, effect on study administration (discontinuation/cancellation, for example), relationship to study treatment, and administration of any drugs or therapies to treat the SAE's will be recorded in the medical record.

7.4 Guidelines for adverse event recording

7.4.1 The Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0, http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf) will be used for grading adverse events

7.4.2 The investigator must assess the relationship of any AE or SAE to the use of study treatment using the following guidelines outlined in the table below:

Table 7.5.3	**ATTRIBUTION OF ADVERSE EVENTS**	
Code	**Descriptor**	**Definition**
5	Definite	The adverse event is clearly related to the investigational treatment
4	Probable	The adverse event is likely related to the investigational treatment
3	Possible	The adverse event may be related to the investigational treatment

2	Unlikely	The adverse event is doubtfully related to the investigational treatment
1	Unrelated	The adverse event clearly not related to the investigational treatment

7.5 Monitoring of adverse events

Subjects having AE's or SAE's will be monitored with relevant clinical assessments and laboratory tests as determined by the subject's treating physician. All adverse events must be followed to satisfactory resolution or stabilization of the event(s). Any actions taken and follow-up results must be recorded in the subject's medical record. For all AE's or SAE's which require the subject to be discontinued from the study, relevant clinical assessments and laboratory tests will be repeated as clinically indicated, until final resolution or stabilization of the event(s).

7.6 Adverse event reporting

7.6.1 Notification of all SAE's must be reported to the Principal Investigator (Dr. Andrew McDonald) or his designee by calling (205) 975-2880. A written report should be submitted to the appropriate Institutional Review Board (IRB) and UAB Clinical Trials Monitoring Committee per institutional policy.

7.6.2 Adverse events will be reported to the Clinical Trials Monitoring Committee.

7.7 Data and safety monitoring plan

7.7.1 This protocol will follow the UAB Data and Safety Monitoring Plan maintained by the UAB Comprehensive Cancer Center.

7.7.2 Serious adverse events will be reviewed in the UAB radiation oncology treatment planning or new patient conference and the Department of Radiation Oncology Quality Assurance committees.

7.8 Early Termination

Patients may be discontinued from study prior to completion of study requirements for any of the following reasons:

7.8.1 The patient has a clinically significant adverse event as determined by the principal investigator

7.8.2 The patient requests to be withdrawn from the study

7.8.3 The patient fails to comply with the requirement for study evaluation/visits

7.8.4 Other conditions for which, in the investigator's opinion, it is in the patient's best interest to be withdrawn from the study

7.8.5 Patient did not meet eligibility requirements

8.0 STUDY PARAMETERS

8.1 For the purposes of this study, acute toxicity will be defined as event(s) that occur within 90 days of the completion of radiotherapy. Acute toxicity will be determined by both intra-treatment examinations and by scheduled follow-up evaluations after the treatment has completed. Late toxicity will be defined as any toxicity occurring > 90 days after the completion of treatment.

8.2 Baseline evaluations of enrolled patients must occur within six weeks of study enrollment

8.3 "Day 1" will be defined as the date of the first radiotherapy treatment. "Day 42/Week 5/Month 1" will represent the one month follow-up visit after the completion of the last radiotherapy treatment. Day 1 and Day 43/Week 5/Month 1 evaluations may be done within +/- 7 days of the specified day.

8.4 "Month 1, 3, 6, 9, 12, 18, and 24" will be defined as the respective follow up visits after the completion of radiotherapy. Month 3-24 evaluations may be done within +/- 30 days of the specified day.

Table 8.1 Required evaluations and therapies

	Baseline	Week 1-2	Week 5/Mo 1	Mo 3, 6, 9, 12, 18, 24
PSA	**x+**		**x**	**x**
H and P**	**x^**		**x^**	**x^**
Karnofsky PS	**x**		**x**	**x**
Platelet count or CBC	**x**			
Quality of Life Indices/Questionnaires*/ **	**x**	**x#, ^**	**x**	**x**
CTCAE v4.0 Toxicity Grading	**x**	**x**	**x**	**x**
SBRT		**xxxxx**		
Prostate Biopsy	**x**			**Month 12**

* AUA Symptom Score, SHIM, and EPIC questionnaire - Appendix

\# To be completed on the final day of treatment

^ Medications will be recorded

+ PSA value within 3 months of enrollment is acceptable as “baseline”

** Due to COVID-19, these study procedures may be conducted remotely, if necessary.

9.0 EVALUATION CRITERIA

9.1 Pretreatment evaluations (baseline)

- Complete medical history
- Physical examination including digital rectal/prostate examination
- Vital signs including weight
- Karnofsky performance status (Appendix B)
- Prostate MRI (a subset of patients may also have MR spectroscopy).
- Completion of quality of life patient questionnaires and surveys, including an American Urological Association (AUA) symptom score survey, Sexual Health Inventory for Men survey, and an Expanded Prostate Cancer Index Composite (EPIC) questionnaire for bowel, sexual, and urinary quality of life. (Appendix C)
- PSA blood work

To be eligible for enrollment, the patient must meet all inclusion criteria. Results of all baseline or screening evaluations, which assure that all inclusion and exclusion criteria have been satisfied, must be reviewed by the investigator prior to enrollment of each patient. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule, required evaluations, and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. Due to COVID-19, these study procedures may be conducted remotely, if necessary.

9.2 Technical feasibility

For the purposes of this study, technical feasibility encompasses two major components: implementation of the intraurethral radiotransponder motion management technique and treatment planning and treatment delivery of single fraction focal SBRT. Treatment planning includes integration of clinical data (exam, biopsy, and medical imaging) to create targets for radiotherapy treatment. Treatment delivery includes the ability to administer planned radiotherapy dose accurately, including pre-treatment physics quality assurance and accurate patient positioning and image guidance.

9.2.1 Intraurethral radiotransponder feasibility

Feasibility of implementing the intraurethral transponder technique will be determined by

- Successful use of the treatment planning system to anticipate the location of the radiotransponder beacons based on the CT simulation scan anatomy
- Successful placement of the beacon-loaded Foley catheter by the treatment planning team
- Appropriate detection of the beacons by the Calypso detection unit
- Transponder beacons continually monitored without interruption during treatment delivery

9.2.2 Treatment planning feasibility

The treatment planning feasibility will be determined by the ability of the treating physician and involved dosimetrists and physicists to produce a radiotherapy treatment plan that meets the specifications in section 6.3 and 6.4.

9.3 Treatment delivery

9.3.1 All treatment plan dose distributions will be verified by UAB staff physicists and must meet the quality assurance standards set forth by the Department of Radiation Oncology prior to patient SBRT administration. Pre-treatment tissue phantom quality assurance checks will be completed. The phantom will be irradiated with the same plan as the patient including all couch angles and beam projections. A dose plane will be calculated and exported from the treatment planning system and will be compared with the measured dose plane from the one of the above techniques. Dose comparisons will be analyzed using the gamma criteria of 3%/3mm and will be considered valid if 95% of points have gamma values of less than 1.

Once plans have met physics quality assurance parameters, treatment delivery will commence. Clinical treatment delivery feasibility will be determined by the ability of the patient to be set up accurately with confirmation of appropriate geometry on kilovoltage imaging.

9.4 Treatment phase

9.4.1 The patient will be evaluated at least once by the treating physician during the time that he is undergoing radiotherapy treatment.

9.4.2 On the final day of treatment the patient will complete an AUA symptom score, SHIM, and EPIC questionnaires and the treating physician will give toxicity grades for any toxicity present at the time.

9.5 Follow-up

9.5.1 As outlined in section 8.0, follow-up examinations will occur at regularly scheduled intervals, occurring every three months for one year and then every six months at the year one to two interval in order to appropriately monitor acute and late toxicity, quality of life, and PSA response.

9.5.2 For each follow up visit, the treating physician will complete an updated medical history and perform a physical examination, evaluate KPS, and grade any toxicity noted. Symptom score surveys and questionnaires will be completed by the patient and PSA lab draws will be performed. Some of these study procedures may be conducted remotely, if necessary.

10.0 PATIENT REGISTRATION

Patients can be registered by calling 205-975-2879.

11.0 STATISTICAL CONSIDERATIONS

11.1 Endpoints and measure of success

11.1.1 The primary endpoint of the pilot portion of this study is feasibility of focal treatment using the intra-urethral radiotransponder beacon technique as defined in section 9.2.

11.1.2 This pilot study will be considered successful if at least 9 of 10 patients who begin treatment are able to complete treatment using the described technique.

11.2 Secondary endpoints include clinical toxicity and efficacy assessments.

11.2.1 Clinically assess early toxicity, early efficacy, late toxicity, and quality of life for patients receiving focal prostate SBRT.

11.3 Toxicity evaluation

11.3.1 Acute and late toxicity will be graded per the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0,

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf).

11.3.2 Definition of acute toxicity: any possible, probable, or definite treatment-related AE or SAE occurring within three months of the completion of radiotherapy.

11.3.3 Definition of late toxicity: any possible, probable, or definite treatment-related AE or SAE occurring after three months of the completion of radiotherapy.

11.4 Efficacy assessments of secondary endpoints

11.4.1 Efficacy will be assessed using PSA measurements and biopsy results. Efficacy assessments will be made at the time points indicated in Table 8.1 (“Required evaluations and therapies”).

11.4.2 Quality of life will be assessed using the American Urological Association Benign Prostatic Hyperplasia Symptom Score (AUA Symptom Score), the Sexual Health Inventory for Men (SHIM) and The Expanded Prostate Cancer Index Composite (EPIC). EPIC includes bowel, urinary, and sexual assessments. Quality of life assessments will be made at the time points indicated in Table 8.1 (“Required evaluations and therapies”).

11.5 Statistical Analyses

11.5.1 All statistical analyses will be descriptive. No formal statistical comparisons are planned. Descriptive statistics will be calculated at baseline and at various follow-up time points as indicated in Table 8.1 (“Required evaluations and therapies”). These include means, standard deviations, medians, and ranges for continuous variables and frequencies and percentages for categorical variables. In addition, 95% confidence intervals will be calculated for means and exact binomial 95% confidence intervals will be calculated for proportions (such as toxicity rates).

11.5.2 Continuous variables include PSA measurements and the composite scores from all three quality of life questionnaires, i.e. the composite AUA Symptom Score, the composite SHIM score, and the composite EPIC score. Categorical variables include toxicity results and biopsy results.

11.5.3 Statistical analyses will be performed using SAS, version 9.4 or later (SAS Institute, Inc.; Cary, NC).

11.6 Sample Size

11.6.1 A total of 10 patients will be enrolled into this feasibility study. The study will be considered successful if at least 9 of 10 patients who begin treatment are able to complete treatment using the described technique. A success rate of 90% in 10 patients will lead to an exact binomial 95% confidence interval of (0.5550, 0.9975). This wide confidence interval (width=0.4425) is expected given our small sample size. If all 10 patients are able to complete treatment, the lower confidence limit of the corresponding exact binomial 95% confidence interval will be 0.6915.

12.0 REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA: a cancer journal for clinicians 2017;67:7-30.
2. Mohler JL, Armstrong AJ, Bahnson RR, et al. Prostate Cancer, Version 1.2016. Journal of the National Comprehensive Cancer Network : JNCCN 2016;14:19-30.
3. Hamdy FC, Donovan JL, Lane JA, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. The New England journal of medicine 2016;375:1415-24.
4. Lardas M, Liew M, van den Bergh RC, et al. Quality of Life Outcomes after Primary Treatment for Clinically Localised Prostate Cancer: A Systematic Review. European urology 2017.
5. Crouzet S, Murat FJ, Pasticier G, Cassier P, Chapelon JY, Gelet A. High intensity focused ultrasound (HIFU) for prostate cancer: current clinical status, outcomes and future perspectives. International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group 2010;26:796-803.
6. Shafirstein G, Bellnier D, Oakley E, et al. Interstitial Photodynamic Therapy-A Focused Review. Cancers 2017;9.
7. Loppenberg B, Sood A, Dalela D, et al. Variation in Locoregional Prostate Cancer Care and Treatment Trends at Commission on Cancer Designated Facilities: A National Cancer Data Base Analysis 2004 to 2013. Clinical genitourinary cancer 2017.
8. Ouzzane A, Betrouni N, Valerio M, Rastinehad A, Colin P, Ploussard G. Focal therapy as primary treatment for localized prostate cancer: definition, needs and future. Future oncology (London, England) 2017;13:727-41.
9. Kishan AU, King CR. Stereotactic Body Radiotherapy for Low- and Intermediate-Risk Prostate Cancer. Seminars in radiation oncology 2017;27:268-78.
10. Potosky AL, Davis WW, Hoffman RM, et al. Five-year outcomes after prostatectomy or radiotherapy for prostate cancer: the prostate cancer outcomes study. Journal of the National Cancer Institute 2004;96:1358-67.
11. Priester A, Natarajan S, Khoshnoodi P, et al. Magnetic Resonance Imaging Underestimation of Prostate Cancer Geometry: Use of Patient Specific Molds to Correlate Images with Whole Mount Pathology. The Journal of urology 2017;197:320-6.

APPENDICES

Appendix A: Toxicity Criteria

This study will utilize NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for toxicity and Adverse Event Reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Appendix B: Karnofsky Performance Status (KPS)

100	Normal. No complaints; No evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospital admission is indicated although death is not imminent
20	Very sick; hospital admission necessary, active supportive treatment necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

Appendix C: Quality of Life Questionnaires and Surveys (Please see attached)

-American Urological Association Symptom Index (AUA SI)
-Sexual Health Inventory for Men (SHIM)
-The Expanded Prostate Index Composite (EPIC)
*Bowel Assessment
*Urinary Assessment
*Sexual Assessment

Appendix D: NCCN Clinical Practice Guidelines in Oncology

This study will utilize the NCCN Guidelines for Prostate Cancer. The NCCN Guidelines outlined at http://www.nccn.org/professionals/physicians_gls/f_guidelines.asp#site will be used to divide patients into the following risk categories: very low, low, or intermediate.