RAD 1203 – Pilot Trial Evaluating Stereotactic Body Radiotherapy with Integrated Boost for Clinically Localized Prostate Cancer

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APPENDICES

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Document History Table

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1.0 OBJECTIVES

1.1 Primary: Clinically assess the early toxicity of SBRT with integrated boost for clinically localized prostate cancer

1.2 Secondary: Determine the technical feasibility (see section 9.2) of stereotactic body radiotherapy (SBRT) with integrated boost for clinically localized prostate cancer

1.2.1 Determine the treatment planning and dosimetric feasibility

1.2.2 Evaluate the treatment delivery quality assurance

1.3 Secondary: Clinically assess early efficacy, late toxicity, and quality of life for patients receiving SBRT with integrated boost for clinically localized prostate cancer

2.0 BACKGROUND AND RATIONALE

2.1 Prostate Cancer Overview

Prostate cancer is the most common non-cutaneous cancer in men in the United States, with 186,000 new cases in 2008. It is the second most common cause of cancer mortality, with 28,600 deaths per year[1]. The median age at diagnosis is 70 years, and the vast majority of prostate cancers are pathologically classified as adenocarcinomas. About two thirds of all prostate cancers arise in the peripheral zone of the prostate. Patients are often grouped into low, intermediate, or high risk cohorts according to risk stratification schemes based upon well established risk factors including PSA level, Gleason score, and clinical stage (see Appendix 1).

Definitive treatment options for patients with clinically localized prostate cancer include radical prostatectomy, external beam radiotherapy, and brachytherapy or a combination of external beam radiotherapy and brachytherapy, with or without androgen deprivation[2]. To date, no randomized trials have directly compared treatment modalities. The selection of the appropriate treatment option involves a complex decision making process, with patients and their treating physicians weighing the risks and benefits of each option to select the appropriate treatment modality.

Of those eligible for definitive treatment, a large cohort of patients will elect to undergo external beam radiotherapy. This is generally delivered as a daily Monday through Friday, outpatient-based procedure, with each

treatment time lasting about 5-15 minutes per treatment and total treatment duration lasting between 5-8 weeks.

2.2 Prostate cancer has a low alpha/beta ratio

Cell survival after doses of radiation is modeled by an exponential function with both a linear (alpha) and quadratic (beta) component. The ratio of alpha/beta for normal tissues and tumors predicts the differential repair of normal tissues and tumor tissues with fractionated radiation therapy. Normal tissues generally have an alpha/beta ratio of approximately 3, while the value for tumors is usually around 10, though this value can vary significantly between different types of tumors[3]. Initially these fundamental models, as well as clinical experience, lead to a standard treatment for prostate cancer that consists of approximately 8 weeks of daily radiation treatments. However, more recent biological and clinical data would suggest that the alpha/beta ratio for prostate cancer cells is lower than previously believed, with analytical estimations and clinical models revealing values for prostate cancer in the range of 1-4 (Table 2.2). Clinical investigators have accepted an alpha beta ratio of ~1.5 as a foundation for formulating dose fractionations schemes when devising recent prostate SBRT clinical trials[5,6]. This lower alpha beta ratio for prostate cancer would suggest a benefit in tumor control with shorter courses of radiation and larger doses per fraction. A shorter treatment schedule would also be more convenient to patients and more cost effective as well.

Table 2.2: Summary of alpha/beta estimates

Author	Type of Estimate	Estimated alpha/beta ratio
King [4]	Analytical estimation	1.8
Brenner [5]	Clinical Model	1.2
Williams [6]	Clinical Model	3.7

2.3 Short course (hypofractionated) radiation dose schedules are feasible

Numerous institutions have implemented hypofractionated (short course) regimens for prostate cancer. These regimens initially reduced treatment times from 8 weeks, to 5 weeks, with more recent reports of 1-2 week courses of radiation[7-11]. The feasibility of delivering these hypofractionated dose levels has been greatly facilitated by the better daily targeting providing by advanced radiation techniques such as intensity modulated radiation therapy and daily CT-based image guidance. The limit to abbreviating the treatment time is acute and late normal tissue toxicity; specifically, rectal, urethral, and bladder toxicity. Recent reports from one to two week SBRT regimens have shown grade 3 (G3) or higher acute and late GU and GI toxicities of less than 5% [9-11]. The Stereotactic Hypofractionated Accurate Radiation to the Prostate (SHARP) trial used a fraction regimen of 6.7 Gy in 5 fractions for a total of 33.5 Gy total for the treatment of low risk patients[9]. Most of the patients on this trial were treated on consecutive days. The toxicity of the SHARP regimen has been reported as less than 3% for acute G3 GU side effects and no acute G3 GI or late G3 GU or GI side effects were reported. Based upon the favorable acute and late toxicity profiles, the SHARP investigators suggested that further dose escalation should be possible, thus future trials have attempted to increase the dose while closely monitoring for adverse side effects.

In the prostate SBRT phase II clinical trial at Stanford University, patients were treated with 7.25 Gy per fraction to a total dose of 36.25 Gy with treatment initially being delivered once daily, then subsequent protocol modifications dictated that patients be treated in an every other day fashion. This trial included mostly low-risk patients, but some selected intermediate risk patients were allowed as well if a limited number of biopsy cores involved adenocarcinoma. A total of 67 patients were accrued to this trial, with two patients (3.5%) having G3 late urinary toxicity and none having G3 rectal toxicity, and no patient having any Grade 4 acute or late toxicities. There were no instances of urinary incontinence, persistent hematuria, or complete urinary obstruction. The 4-year actuarial biochemical freedom from recurrence was 94% and the investigators concluded that their data supports consideration of SBRT as a therapeutic option for localized prostate cancer.

In an effort to match dosages achieved in prostate HDR brachytherapy, the University of Texas Southwestern has reported a Phase I dose-escalation SBRT study (45 → 47.5 → 50 Gy in 5 fractions) for low- and intermediate-risk prostate cancer, once again demonstrating favorable acute and late toxicities, even at doses as high as 50 Gy in 5 fractions. These results are summarized in the table below.

Table 2.3: Summary of GU and GI toxicity from prostate SBRT trials

Author	Institution	# Patients	G3 Acute GU	G3 Acute GI	G3 Late GU	G3 Late GI
Madsen [9] "SHARP"	Virginia Mason	40	1 (2.5%)	0	0	0
King [10]	Stanford University	67	0	0	2 (3.5%)	0
Boike [11]	Texas Southwestern	45	0	0	2 (4.4%)	0

2.4 Radiation dose escalation

Radiation dose escalation has demonstrated a benefit in the treatment of prostate cancer. Dose escalation has been shown to be safe and beneficial when using conventional fractionation schedules (8 weeks, 1.8 – 2.0 Gy/day) comparing 78 Gy to 70 Gy[12]. The efficacy of dose escalation has been tested through additional studies and has consistently shown a biochemical relapse free survival advantage for higher doses with only slightly higher incidences of acute GI toxicity[13-14].

In the SHARP trial, eligible patients received prostate SBRT with 6.7 Gy for 5 fractions for a total dose of 33.5 Gy. The PSA control rate was 70% at 40 months median follow-up. This biochemical control rate is lower than what investigators initially projected and was somewhat lower than those reported in previous standard fractionation (1.8-2.0 Gy/fraction to 78 Gy) and hypofractionated (2.5 Gy/fraction to 70 Gy) regimens [7,12-14]. Subsequent prostate SBRT researchers have suggested that dose-escalation above that utilized in the SHARP trial is necessary to improve efficacy. Results from the updated Stanford experience have shown improved PSA control rates at 4-years (94%) over that of SHARP trial, with Stanford utilizing a slightly higher dose regimen of 7.5 Gy in 5 fractions versus the SHARP regimen of 6.7 Gy in 5 fractions.
The level of radiation dose escalation that is possible is limited by the toxicities of the adjacent normal tissues, but as technological advances in

treatment planning and delivery (IMRT, volumetric modulated arc therapy, IGRT) continue to improve, higher doses with favorable side effect profiles have become possible.

The most mature clinical data for dose escalation involve homogenous dose escalation to the entire prostate[12-14]. With improved imaging modalities there has also been recent interest in selectively boosting dominant prostate nodules or areas at high risk for local recurrence to even higher doses while treating the surrounding prostate to a more conventional dose level, rather than homogenously continuing to boost the entire prostate (see Section 2.5.1).

2.5 Magnetic resonance imaging (MRI) for prostate cancer

MRI and MR spectroscopy (MRS) can provide valuable information regarding prostate tumor extent, localization, and aggressiveness[15]. Traditionally, prostate MRI was utilized for localizing prostate cancer when suspicion for malignancy was high (elevated PSA) and a previous trans-rectal ultrasound guided biopsy had failed to detect prostate cancer. Optimal MR imaging included use of 1.5 Tesla (T) strength magnetic field and an endorectal coil. 1.5T endorectal coil T2-weighted MRI and MRS images when combined yield a localization accuracy of ~80%[16].

With improvements in the precision of definitive treatment modalities, an accurate assessment of tumor extension has become increasingly important. New high-field-strength MR scanners (ie, 3T) are becoming more widely available in the clinical setting. The increased signal-to-noise ratio inherent at 3T as compared with 1.5T offers advantages for clinical MRI/MRS such as shortening of acquisition time and increased spatial resolution, or a combination of these two. This may improve local staging and localization accuracy in prostate cancer patients[17]. Studies have shown that 3T MR localization of prostate cancer without an endorectal coil is comparable to that of 1.5T with an endorectal coil[18].

2.5.1 The value of MRI/MRS in radiotherapy treatment planning

Although the classic approach to external beam radiation therapy applies homogeneous dose distributions within the targeted tumor to avoid under-dosing tumor deposits, recent advances in imaging provide an approach to define anatomic subregions of the tumor according to their level of radiosensitivity or radioresistance. IMRT provides an approach for differential dose painting to selectively increase the dose to specific tumor-bearing regions. With IMRT techniques, radiation dose distributions can be produced that permit simultaneous delivery of different dose

prescriptions to multiple target sites. To be able to "dose paint" with IMRT, one needs to know the tumor location, volume, and extent. MRI /MRS provide the best imaging modality for determining prostate cancer localization, volume, and extent[15].

Traditionally, the planning target volume for prostate external beam radiotherapy has included the whole prostate, with a goal of a homogenous dose distribution throughout the entirety of the prostate. However, more recent tumor control probability models have suggested that a "selective boosting" technique that delivers higher radiotherapy dosages to high risk tumor subvolumes (versus homogenous dose escalation) may be optimal for prostate cancer local tumor control while minimizing side effects from radiotherapy damage to adjacent normal tissues[19]. Similarly, dose distributions for prostate brachytherapy also utilize an approach that delivers higher doses to areas more likely harboring disease (peripheral zone), while relatively under-dosing areas less likely to have malignant cells yet are close to dose-limiting structures such as the transitional zone or peri-urtheral areas.

2.5.2 Clinical usage of MRI/MRS for determination of high-risk prostate cancer volumes

Treatment planning studies have shown that IMRT can be used to increase the dose to selected tumor-bearing regions within the prostate as identified with MRI/MRS[20]. A Phase I study at the NCI proved feasibility for utilization of MRI for localization of dominant intra-prostatic lesions to deliver a simultaneous integrated boost (SIB) of 94.5 Gy at 2.25 Gy per fraction to the dominant lesion while the surrounding prostate received a dose of 75.6 Gy at 1.8 Gy per fraction[21].

2.6 Rationale for dose selection in the current trial

Reports from the three aforementioned prospective prostate SBRT trials have demonstrated excellent toxicity profiles and good early efficacy for the treatment of low and intermediate risk prostate cancer. The excellent side effect profile but less favorable biochemical control reported in the SHARP trial has led investigators to favor higher SBRT dosages.
The optimal dose that achieves appropriate tumor control with a favorable side effect profile is yet to be determined. In addition to the prospective trials outlined above, a retrospective report of a large cohort of patients (n = 234) having been treated by a 7.25 Gy per fraction for five fractions SBRT regimen has also reported excellent safety, quality of life, and early efficacy[22].

At dosages as high as those administered for prostate SBRT, even slight increases in dose per fraction can have a significant impact on overall cell kill and calculated biological equivalent dose (BED).

$$BED = D \cdot \left(1 + \frac{d}{\alpha/\beta}\right)$$

Where BED = biologically equivalent dose, D= total dose, d= dose per fraction, and α/β= the dose at which cell killing by nonrepairable damage is equal to that of repairable damage. Table 3 demonstrates equivalent standard fractionation (2.0 Gy/fraction) BED's for selected relevant prostate SBRT fractionation schemes when considering an alpha beta ratio of 1.5.

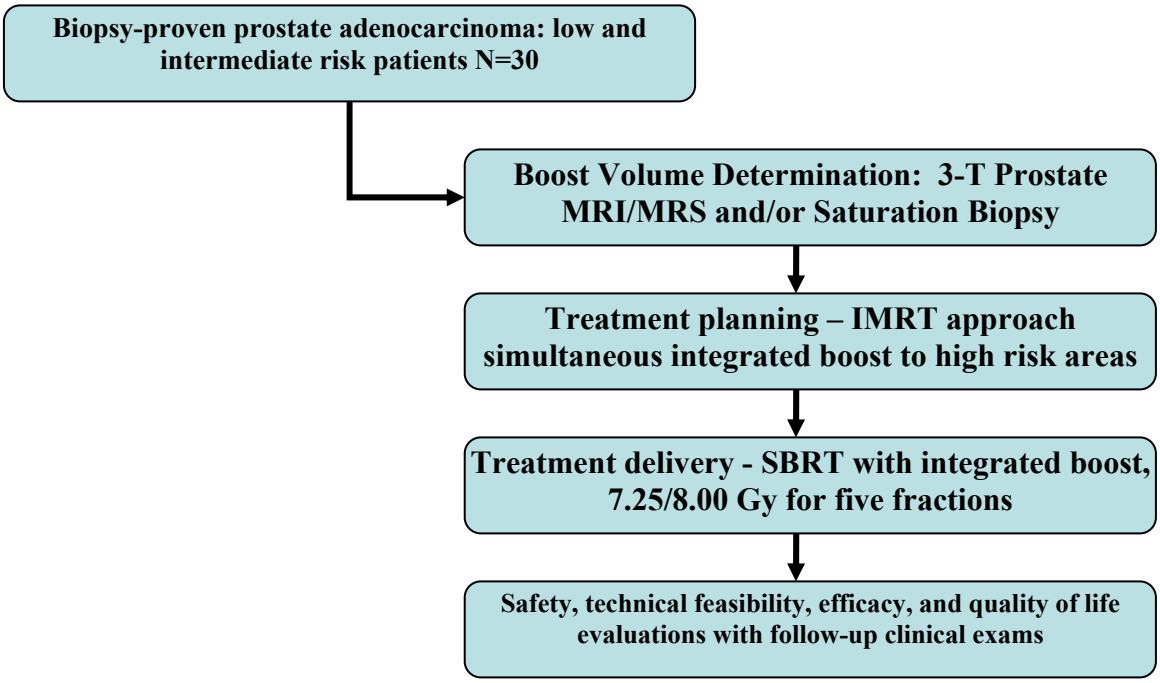
Table 3: Biological equivalent doses for prostate SBRT dose schedules

Prostate SBRT Dose schema	2.0 Gy per fraction equivalent
6.70 Gy x 5	78.5 Gy
7.25 Gy x 5	90.6 Gy
8.00 Gy x 5	108.5 Gy
10.0 Gy x 5	130.0 Gy

Based on earlier prostate SBRT trials and clinical models suggesting a benefit for a selective boosting technique, this protocol is designed for administration of 7.25 Gy X 5 fractions to whole prostate with an additional 0.75 Gy integrated boost (for a total of 8.0 Gy per fraction) to a high-risk area administered in an every-other-day fashion. Thus, the whole prostate would receive 36.25 Gy while a smaller sub-volume of the prostate would receive 40 Gy over a total of five treatments. The high-risk boost volume will be determined from prostate MRI/MRS, biopsy results, and clinical exam findings (see section 6.2.1).

The current trial will attempt to determine the early clinical toxicity of SBRT with integrated boost for clinically localized prostate cancer. Technical feasibility, early efficacy, late toxicity, and quality-of-life will also be investigated.

3.0 SCHEMA



3.1 Patients will be accrued after a pathological diagnosis of prostate adenocarcinoma is made and patient meets enrollment criteria. We anticipate a total of 30 patients to be accrued.

3.2 Enrolled patients will undergo a 3-T MRI/MRS evaluation of the prostate without the use of an endorectal coil. If a pre-biopsy MRI/MRS has been obtained within s ix months of patient enrollment and is deemed clinically acceptable for treatment planning purposes by the treating physician, then reacquisition of post-biopsy MRI/MRS is not necessary.

3.3 Patients may have gold-fiducial markers placed in the prostate under trans-rectal ultrasound guidance, but decision and timing of fiducial placement is optional and at the discretion of the treating physician.

3.4 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 section 6.1.2). Prescribed dose will be 8.0 Gy per fraction to the high risk area and 7.25 Gy to the surrounding prostate for a total of five fractions, delivered via a simultaneous integrated boost technique.

3.5 SBRT will be delivered in 7 to 17 calendar days, with every other day fashion in an outpatient clinic setting with an every-other day fashion treatment schedule recommended though not required (see section 6.7.1)

3.6 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).

4.0 PATIENT SELCTION CRITERIA

4.1 Inclusion criteria

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

4.1.2 NCCN risk category very low, low, or intermediate risk (Appendix D)

- Combined Gleason score ≤ 7
- PSA within three months of enrollment <20 ng/ml
- Clinical stage $T1_{a\text{-}c}N0M0$ or clinical stage T2aN0M0
  - Patients that have prostate MRI "upstaging" showing cT2bN0M0 or cT2cN0M0 disease will still be considered intermediate risk and eligible for study
  - Patients that have prostate MRI "upstaging" to cT3N0M0 disease are not eligible

4.1.3 Life expectancy >5 years

4.1.4 Risk of malignant lymph node involvement < 15% as calculated on Partin tables (Appendix E).

4.1.5 Karnofsky performance status (KPS) ≥ 60 (Appendix B)

4.1.6 Age ≥ 19 years

4.1.7 Subjects given written informed consent

4.2 Exclusion criteria

4.2.1 History of inflammatory bowel disease

4.2.2 Prior radical prostate surgery, transurethral resection of the prostate (TURP), or prostate cryotherapy

4.2.3 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 are not considered an exclusion criteria.

4.2.4 Platelet count < 70

4.2.5 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.

4.2.6 Pre-SBRT prostate volume >120 cc as estimated by trans-rectal ultrasound at time of prostate biopsy (TRUS biopsy).

4.2.7 Risk of malignant lymph node involvement > 15% as calculated on Partin tables

5.0 DRUG INFORMATION

5.1 No experimental drugs are utilized in this study.

6.0 TREATMENT PLAN

6.1 Treatment planning CT-simulation and contour/volume delineation

6.1.1 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.

6.1.2 CT-simulation images will be electronically fused with MRI/MRS images where applicable within the treatment planning software and are to be used for contours and treatment planning.

6.1.2.1 The treating physician will define the prostate volume, high risk boost volume, and adjacent organs at risk. Boost volume is to be defined as the area most likely to harbor malignant cells, as determined by available clinical data including prostate MRI, clinical exam, and biopsy localization. In some cases MR spectroscopy and this information will be included if available to determine the target volume.

6.1.2.2 Boost volume must not be >50% of the prostate volume.

6.1.2.3 Clinical target volume 1 (CTV1) will encompass the entire prostate volume minus the high risk boost volume .

6.1.2.4 CTV2 be the high risk boost volume. The volume of the CTV2 must not be >50% of the volume of the prostate.

6.1.2.5 Planning target volume 1 (PTV1) consists of a volumetric expansion of the CTV1 by 5mm in all directions except for posteriorly, as a 3mm expansion is utilized.

6.1.2.6 PTV2 consists of a volumetric expansion of CTV2 by 5mm in all directions except for posteriorly, as a 3mm expansion is utilized.

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

6.2 SBRT dose specifications

6.2.1 The prescribed dose will be 36.25 Gy to the PTV1 and 40.0 Gy to the PTV2, delivered as 7.25 Gy and 8.0 Gy per fraction, respectively, for a total of five fractions.

6.2.2 For the PTV2, 95% of the PTV2 prescription must cover ≥ 95% of the PTV2.

6.2.3 In addition, 95% of the PTV1 must be encompassed by at least that 34.4 Gy isodose line (95% of PTV1 prescription dose). Attempts should be made to normalize plans to deliver 100% of the PTV1 prescription dose (36.25 Gy) to 95% of the PTV1 volume. The

minimum PTV1 dose must be > 34.4 Gy (95% of PTV1 prescription).

6.2.4 Rapid dose falloff outside the PTV is to be prioritized over PTV dose uniformity and may result in considerable dose heterogeneity within the PTV.

6.2.5 Prescribed dose to pelvic lymph nodes will not be allowed

6.3 Critical structures

6.3.1 Rectal dose-volume histogram (DVH) goals are <50% of the volume of the rectum receiving 50% of PTV1 prescription dose, <20% receiving 80% of PTV1 dose, <10% receiving 90% of PTV1 dose), < 5% receiving 100% of PTV1 dose, and maximum dose (defined as 1 cc volume) <105% of PTV1 prescription. Only less than 3cc's of rectum may receive more than 34.4 Gy.

6.3.2 Bladder dose-volume histogram (DVH) goals are <50% of the volume of the bladder receiving 50% of PTV1 prescription dose, <10% receiving 90% of PTV1 prescription dose, and maximum dose (defined as 1cc volume) <105% of PTV1 prescription.

6.3.3 Maximum urethra dose <107% of PTV1 prescription.

6.3.4 Femoral head maximum point dose <30 Gy and the volume receiving >20 Gy must not exceed 10 cc (cumulative, both sides).

6.3.5 The dose to a small volume of the PTV1 or PTV2 may be reduced below the prescription to meet the above constraints at the discretion of the treating radiation oncologist. Thus, coverage of PTV1 or PTV2 may be relaxed if the treating physician cannot meet critical structure dose constraints.

6.4 Treatment plan physics quality assurance

6.4.1 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.

6.4.2 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.

6.5 Technical factors

6.5.1 All treatment plans will be devised utilizing an intensity modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), or helical tomotherapy platform utilizing a simultaneous integrated boost approach.

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

6.6 Treatment delivery

6.6.1 Patients will be instructed to have a full bladder and empty rectum for treatments. Utilization of bowel preparation with oral or suppository medications is left up to the treating physician. Endorectal balloons may be utilized at the discretion of the treating physician.

6.6.2 Image-guidance with kilovolatage orthogonal x-rays and cone-beam CT scans (or equivalent tomotherapy imaging) 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 fiducial marker seeds (preferably) or the prostate-rectum interface if there are no fiducial markers.

6.7 Treatment delivery schedule

6.7.1 Radiation treatments will be delivered per the standard outpatient setting radiation oncology clinic. Treatment must be completed in within the time frame of 7 to 17 calendar days, with day of first treatment being considered day 1. Treatment must not be given on five consecutive days, and an every-other day fashion treatment schedule is recommended though not required. Exact treatment schedule is left to the discretion of the treating physician.

7.0 THERAPY MODIFICATIONS

7.1 No dose escalation or de-escalation modifications are to be made outside of the selected prescription dose for this study

7.2 Non-Study Treatment

7.2.1 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

7.2.2 Hormonal blockade agents such as leuprolide or bicalutamide administered for purposes of treatment or prostate downsizing are permitted if administered within 9 months of study enrollment. Concurrent or adjuvant usage of hormonal blockade agents is permitted as well, and usage thereof at the discretion of the treating physician

7.2.3 The use of standard prescription or non-prescription medication to manage symptoms of disease or treatment is left up to 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

7.3 Concomitant Medication

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

7.3.2 No cytotoxic chemotherapies are to be administered during the study evaluation period

7.3.3 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.

7.3.4 Prophylactic (or continued) usage of tamsulosin or alfuzosin (or other alpha-blocker medication) is mandated. This medication must be started on the day of (or before) the first radiotherapy treatment and will continue to at least 30 days after the last radiotherapy treatment.

7.3.5 Androgen deprivation therapy (ADT) will be utilized at the discretion of the treating physician. Investigators suggest no androgen deprivation for NCCN low risk patients, and short term (3-6 months) neoadjuvant/concurrent ADT where appropriate for

intermediate risk patients. Long term androgen deprivation therapy is not recommended.

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

7.4.1 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.

7.4.2 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 (section 9.0)
- Urinary retention/obstruction requiring catheterization, though officially scored as a grade 2 toxicity by CTCAE v4.0, will be considered a SAE on this protocol.

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.

7.5 Guidelines for adverse event recording

7.5.1 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

7.5.2 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

7.6 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).

7.7 Adverse event reporting

7.7.1 Notification of all SAE's must be reported to the Principal Investigator (Dr. John Fiveash) 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.

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

7.8 Data and safety monitoring plan

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

7.8.2 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.

7.9 Early Termination

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

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

7.9.2 The patient requests to be withdrawn from the study

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

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

7.9.5 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.

8.5 An optional median long-term quality of life evaluation will take place after the required evaluations and therapies. AUA Symptom Score, SHIM, and EPIC questionnaire (Appendix C) will be mailed to study participants who are > 3 years from completion of radiotherapy.

Table 8.1 Required evaluations and therapies

	Baseline	**Week 1-2**	**Week 5/Mo 1**	**Mo 3, 6, 9, 12, 18, 24**	**>3 year from completion of RT**
PSA	**x**+		**x**	**x**	
H and P	**x**^		**x**^	**x**^	
Karnofsky PS	**x**		**x**	**x**	
Quality of Life Indices/Questionnaires*	**x**	**x**#, ^	**x**	**x**	
Optional QOL*					**X**
CTCAE v4.0 Toxicity Grading	**x**	**x**	**x**	**x**	
SBRT		**xxxxx**			

* AUA Symptom Score, SHIM, and EPIC questionnaire – Appendix C

\# To be completed on the final day of treatment

^ Medications will be recorded

\+ PSA value within 3 months of enrollment is acceptable as "baseline"

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.

9.2 Technical feasibility

For the purposes of this study, technical feasibility encompasses two major components: treatment planning and treatment delivery. Treatment planning includes integration of clinical data (exam, biopsy, and medical imaging) to create targets (PTV1 and PTV2) 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 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 6.2 and 6.3. Feasibility will be defined as the ability of the treatment planner to create a plan that meets the following criteria:

- 100% of PTV1 prescription (36.25 Gy) covers ≥ 95% of the PTV1

- At least 95% of the PTV2 prescription (38.0 Gy) covers 95% of PTV2 volume

- All normal tissue dose constraints are met (see section 6.2 and 6.3)

9.2.2 **Treatment delivery**

9.2.3 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. Treatment delivery will be considered feasible if each pre-treatment set up images are approved by the treating physician(s) prior to administration of radiotherapy.

9.3 Treatment phase

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

9.3.2 On the final day of treatment (fraction five), 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.

9.4 Follow-up

9.4.1 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.

9.4.2 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.

9.4.3 After the required follow-up visits and evaluations, an optional quality of life evaluation using AUA Symptom score, SHIM, and EPIC questionnaire (Appendix C) will be mailed to study participants who are > 3 years from completion of radiotherapy. Study participants will be contacted by phone call no more than three times in order to notify them that they received quality of life questionnaires and to remind them to complete and return these forms. Study participants will return the completed quality of life questionnaires by mail or in person to:

University of Alabama at Birmingham (UAB)
Department of Radiation Oncology
Research and Clinical Trials Office
Care of: Jared Maas, MD
1700 6th Avenue South (HSROC),
Suite 1242
Birmingham, Alabama 35233

9.4.4 Research participants will be contacted by phone call using the following script: "Hello, I am calling to reach [Study participant]. [Study participant will confirm identity with name and date of birth]. This is [Researcher's name] at UAB Radiation Oncology calling from [Attending physician's name]'s office. I am calling you because you are a participant in the RAD 1203 Prostate Radiosurgery trial. We are hoping to collect some final long-term quality of life data from you, so I wanted to notify you that we have mailed you quality of life questionnaires to your address. [Confirm address and receipt of forms]. These forms are the same forms you have previously completed during your follow up clinic visits to assess short term quality of life. Please complete these forms at your earliest convenience and return the completed forms to our office either by mail or in person. [Provide mailing address]. If you have any additional questions, please call our office at [Provide phone number]. Thank you! Goodbye.

10.0 PATIENT REGISTRATION

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

11.0 STATISTICAL CONSIDERATIONS

11.1 The primary endpoint of this study is to clinically assess early toxicity – specifically, to determine whether the rate of urinary retention or obstruction requiring catheterization is >15%.

11.2 Secondary endpoints include technical feasibility and clinical toxicity and efficacy assessments.

11.2.1 Determine the technical feasibility of stereotactic body radiotherapy (SBRT) with integrated boost for clinically localized prostate cancer

11.2.2 Clinically assess early toxicity, early efficacy, late toxicity, and quality of life for patients receiving SBRT with integrated boost for clinically localized prostate cancer

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 Toxicity rates

Urinary retention or obstruction requiring catheterization occurring in >15% of patients is considered significantly higher than the catheterization rate occurring for the standard UAB prostate hypofractionation scheme (70 Gy at 2.5 Gy/fraction) and prostate low-dose rate brachytherapy.

11.5 Sample Size

Sample size (N=25-30) is determined based upon the statistical power needed to confidently identify urinary retention toxicity (requiring catheterization) rates in enrolled patients significantly exceeding the rates noted for UAB hypofractionated prostate radiotherapy and LDR

brachytherapy experiences. Urinary retention or obstruction requiring catheterization occurring in >15% of patients will be considered significantly higher than the catheterization rate occurring for the standard UAB prostate hypofractionation scheme (70 Gy at 2.5 Gy/fraction) and that of prostate brachytherapy (two radiotherapy treatment options given most often for this subset of patients). A one sided exact binomial test of the null hypothesis that the catheterization rate is 15% vs the alternative that it exceeds 15% will be performed at the 0.20 significance level. If the actual rate is 30% that test will have 80% power.

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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 . All investigators should have access to a copy of the CTCAE version 4.0.

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.

Appendix E: Partin Tables

This study will utilize the Partin Tables to generate a table value that reflects the pathologic stage of prostate cancer. The Partin Tables can be accessed at: http://urology.jhu.edu/prostate/partintables.php