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Version 3

Rush University Medical Center

RUMC XXXX

A PROSPECTIVE EVALUATION OF MULTI-PARAMETRIC MAGNETIC RESONANCE IMAGING (mpMRI) GUIDED STEREOTACTIC BODY RADIATION TREATMENT FOR LOCALIZED PROSTATE CANCER

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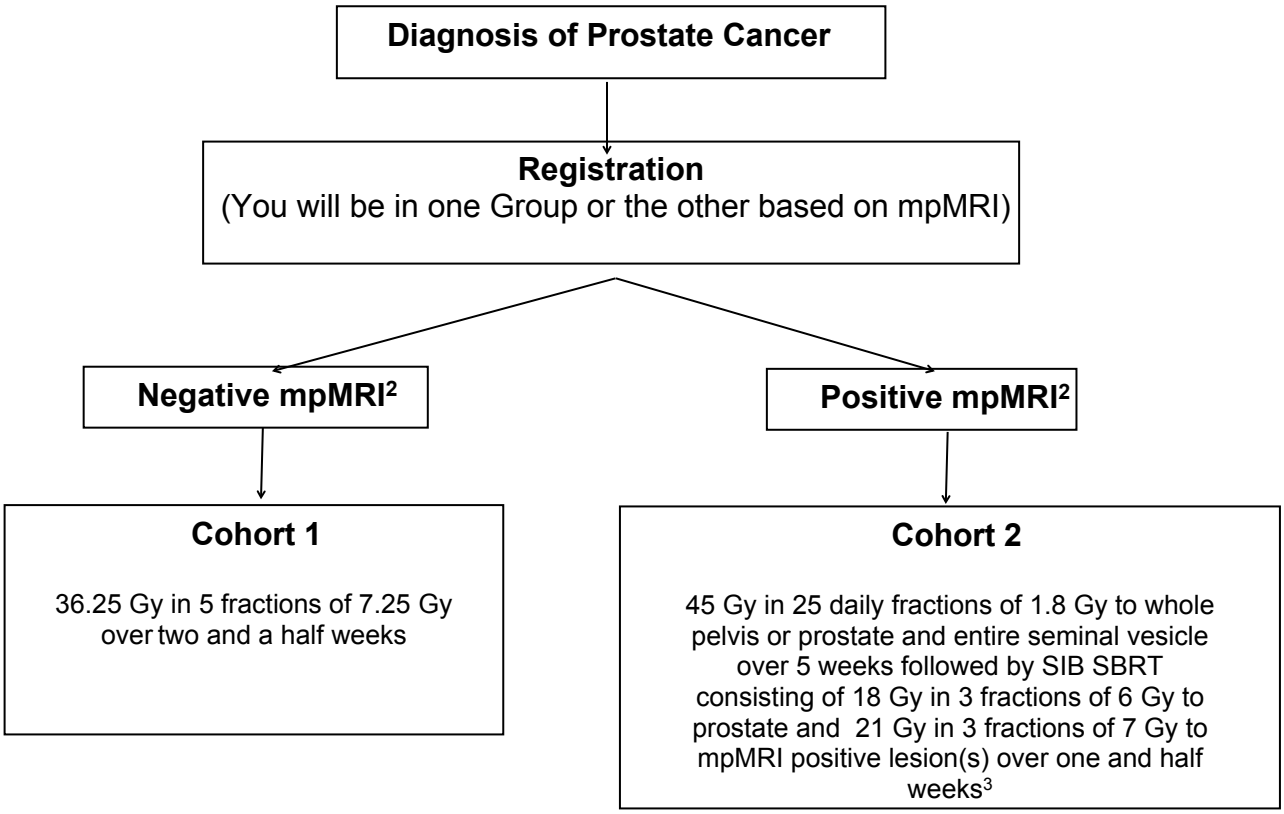
SCHEMA



1. 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) is allowed for both cohorts.
2. According to American College of Radiology, Prostate Imaging and Reporting and Data System (PI-RADS) version 2, Accessed March 20, 2015, from http://www.acr.org/Quality-Safety/Resources/PIRADS/. (http://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/Resources/PIRADS/PIRADS%20V2.pdf) will be used to define multi-parametric MRI, mpMRI, positive and negative lesions using DCE, DWI, and T2 sequences. Lesions will be scored on a scale of 3-15. mpMRI negative will be defined as class I or II lesions (total score <= 6). mpMRI positive will be defined as class III, IV, or V lesions (total score 7-15).
3. Whole pelvic IMRT vs. prostate and seminal vesicle IMRT is allowed at the discretion of treating physician.

Patient Population: (See Section 3.0 for Eligibility)
Histologically confirmed diagnosis of adenocarcinoma of the prostate within 365 days (1 year) of registration; PSA should not be obtained within 10 days after prostate biopsy.

Required Sample Size: **67 for each cohort**

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ELIGIBILITY CHECKLIST
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_____(Y) 1. Does the patient have a histologically confirmed diagnosis of adenocarcinoma of the prostate within 2 years of registration?

_____(Y) 2. Is the history/physical examination with digital rectal examination of the prostate within 60 days prior to registration?

____ (Y) 3. Was the mpMRI completed within 90 days of registration?

_____(Y) 4. Is there a histological evaluation of the prostate biopsy with assignment of a Gleason score to the biopsy material; Gleason scores 2-10 within 2 year of registration?

_____(Y) 5. Is the clinical stage a T1-4 (AJCC 7th edition) within 90 days of registration?

_____(Y) 6. Is the PSA within 60 days prior to registration? PSA should not be obtained within 10 days after prostate biopsy.

_____(Y) 7. Is the Zubrod Performance Status 0-1 within 60 days prior to registration?

_____(Y) 8. Has the patient provided study-specific informed consent prior to study entry?

_____(Y) 9. Has the patient completed the international prostate symptom score (IPSS) and the Sexual Health Inventory for men (SHIM) questionnaire?

_____(N) 10. Does the patient have a prior or concurrent invasive malignancy (except non-melanomatous skin cancer) or lymphomatous/hematogenous malignancy unless continually disease free for a minimum of 5 years? All patients with in situ carcinoma are eligible for this study (for example, carcinoma in situ of the oral cavity is eligible) except patients with carcinoma of the bladder (including in situ bladder cancer or superficial bladder cancer)

_____(N) 11. Is there evidence of distant metastases?

_____(N) 12. Is there evidence of regional lymph node involvement?

_____(N) 13. Has the patient had previous radical surgery (prostatectomy), cryosurgery, or HIFU for prostate cancer?

_____(N) 14 Has the patient had previous pelvic irradiation, or prostate brachytherapy?

_____(N/Y) 15.Has the patient had 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)?

_____(N) 16. Does the patient have a history of previous or concurrent cytotoxic chemotherapy for prostate cancer?

_____(N) 17. Does the patient have severe, active co-morbidity, defined as unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months?

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ELIGIBILITY CHECKLIST
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_____(N) 18. Has the patient had transmural myocardial infarction within the last 6 months?

_____(N) 19. Does the patient have acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration?

_____(N) 20. Does the patient have chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration?

_____(N) 21. Does the patient have hepatic insufficiency resulting in clinical jaundice and/or coagulation defects? (Note 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.)

_____(N) 22. Does the patient have Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition? (Note 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.)

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ELIGIBILITY CHECKLIST
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The following questions will be asked at Study Registration:

_____ 1. Institutional person registering case.

_____(Y) 2. Has the Eligibility Checklist been completed?

_____(Y) 3. In the opinion of the investigator, is the patient eligible?

_____ 4. Date informed consent signed

_____ 5. Patient's Initials (First Middle Last)

_____ 6. Verifying Physician

_____ 7. Patient ID

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Ethnicity

_____ 11. Gender

_____ 12. Country of Residence

_____ 13. Zip Code (U.S. Residents)

_____ 14. Method of Payment

_____ 15. Calendar Base Date

_____ 16. Registration date

The Eligibility Checklist must be completed in its entirety prior to registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during the IRB audit.

Completed by _____ Date _____

1. BACKGROUND AND RATIONALE

Prostate cancer is the most common non-skin cancer diagnosed in American men with an estimated 230,000 new cases in 2014, accounting for 27% of new cancer cases in 2014 (1). Radiotherapy is one of the primary modalities for treating adenocarcinoma of the prostate. Currently, the standard radiotherapy technique for treating prostate cancer is 3D conformal radiotherapy (3DCRT). Recently, newer techniques, such as image-guided intensity-modulated radiotherapy (IG-IMRT), have been developed to accurately deliver even more conformal radiation dose distribution than 3DCRT (2, 3). IG-IMRT utilizes pretreatment 3D volumetric images such as CT images for target localization prior to IMRT (4-6). The IG-IMRT may offer potential benefits in tumor coverage and decreases in normal tissue complications (7-9).

Prostate cancer is a prime example of a situation where IMRT can provide additional benefit as compared to 3DCRT (2,3). Dose escalation using 3DCRT for localized prostate cancer has shown superior outcomes for patients with intermediate-risk and high-risk factors (8-13). Unfortunately, dose escalation also increases the risk of radiation damage to surrounding normal tissues such as the bladder and rectum (14, 15). For this reason, late toxicity in these organs, especially the rectum, is considered to be a limiting factor for high-dose 3DCRT. Additionally, prospective randomized data from the RTOG (16) and several retrospective reviews (17-20) have indicated that prostate cancer patients who are at risk of disease spread to pelvic lymph nodes benefit from radiation to the pelvis. Pelvic radiation in addition to dose escalation of the prostate increases the risk for acute and late radiation induced complications. This is a situation where IMRT's superior dose conformality is desirable to minimize the risk of complications to normal tissue while also assuring coverage of microscopic disease. In support of this idea Teh et al (21) and Zelefsky et al (22) have demonstrated not only that high-dose IMRT is feasible and safe for patients with localized prostate cancer, but also improves dose conformity relative to tumor coverage, reduces exposure to normal tissue, and decreases GI toxicity in comparison with 3DCRT.

With greater tumor conformality available from IMRT, it is possible to deliver an increased radiation dose to the prostate and still spare surrounding tissues. Prostate radiation currently utilizes conventional fractionation schemes of 1.8 to 2.0 Gy per fraction. These doses are based on empiricism, years of clinical experience, and classic radiobiology principles. Recent studies have shown that prostate cancer cells, which are slowly dividing cells, actually have a very low α/β ratio, estimated at 1.5-3 (23-26) which is actually *less* than most late responding tissues (usually given a value of 3). This suggests that prostate cancer cells might be more effectively treated with higher doses per fraction. The Biologically Equivalent Dose (BED) is a calculation using the α/β ratio that can determine equivalent doses for different fractionation schemes (see Appendix V for BED Dosing comparison). For example, a "conventional" prostate treatment of 72 Gy (36 X 2 Gy per fraction) would be equivalent, in terms of BED, to 63.8 Gy (25 x 2.55 Gy/fx) if α/β ratio of 3.0 is used, or to 62.4 Gy (25 x 2.50 Gy/fx) if α/β ratio of 1.5 is used. The concept of delivering a higher dose of radiation per fraction, but with fewer fractions and to a lower total dose, is known as hypofractionation. Hypofractionated EBRT has the potential to reduce acute toxicity, because of the lower total dose, while providing biologically equivalent doses and, therefore, potentially equal tumor control. Prostate cancer might especially benefit from hypofractionation because of its low α/β ratio. In fact, multiple clinical studies support this hypothesis. Collins et al (27, 28) reported their 22-year experience on 232 patients treated with 36 Gy (6 X 6 Gy per fraction) from 1962 to 1984. They have shown that this 6 X 6 Gy per fraction regimen produced comparable local response and minimal late morbidity in comparison with local contemporary "conventional" fractionation regimen. Livesy et al (29) reported their experience in over 700 pts treated to 50.08 Gy (16 x 3.13 Gy/fxn) and showed similar tumor control and normal-tissue toxicity compared to standard treatments. Additionally, the Cleveland Clinic has published their prospective, non-randomized short-course IMRT (SCIMRT) experience of 70 Gy (2.5 Gy X 28) and reported equivalent biochemical control, acute and late toxicities, and quality of life when compared to the historical 3DCRT experience of 78 Gy (2 Gy X 39) (30-32). Their data show a trend toward less Grade 2 and 3 rectal toxicity (5% for SCIMRT and 12% for 3D CRT p=0.24), and improved sexual functioning (p=0.017) compared to conventional fractionation regimens. Recently the long-term results after the above SCIMRT were updated (33). With a median follow-up of 66 months, 5-year biochemical relapse-free survival rates using the ASTRO definition were 97%, 88% and 70%, for low, intermediate and high-risk disease, respectively. The acute rectal toxicity scores were 0/20, 1/61, and 2 in 19 patients. The acute urinary toxicity scores were 0 in 9, 1 in 76, and 2 in 15 patients. The late rectal

toxicity scores were 0 in 71, 1 in 19, 2 in 7, and 3 in 3 patients. The actuarial late grade 3 rectal toxicity rate at 5 years was 3%. At their last follow-up, the rate of combined grade 2 and 3 late rectal toxicity at 5 years was only 5%.

Recent progress of Hypofractionated EBRT:
There are additional benefits to hypofractionation besides radiobiology. Using hypofractionation in conjunction with IMRT could result in more cost effective and safer care. Fewer treatments make the process more convenient for patients and more cost effective for the institution. There would be decreased facility burden, less personnel requirements (from radiation therapist to nurse, dosimetrists, physicists, and physicians). In recent years researchers have looked at even shorter radiotherapy schedules.

M. A. Ritter (2009) (34) reported results of a phase I/II NIH-sponsored clinical trial carried out by 5 institutions that explored the tolerance and efficacy of increasingly hypofractionated radiation therapy for localized prostate cancer. Three increasing dose-per-fraction schedules were evaluated. These regimens were designed to maintain equivalent predicted late toxicity. Predicted tumor EQD2 doses were in excess of 82 Gy if the tumor α/β of 1.5 Gy is assumed. Fraction size escalations were contingent upon acceptable acute and late toxicity. The three hypofractionated levels, 1, 2, and 3 were: 64.7 Gy/22 fx of 2.94 Gy, 58.08 Gy/16 fx of 3.63 Gy and 51.6 Gy/12 fx of 4.3 Gy. All patients were treated with tomotherapy or linac based IMRT with daily image guidance.

A total of 307 patients were accrued. Clinical parameters for these favorable-to-intermediate risk patients were: clinical stage T1/T2: 75%/25%; Gleason <7/7: 58%/42%; PSA <10/≥10: 82%/18%; median PSA: 6.2 ng/ml. Levels 1, 2, and 3 are 42, 19, and 16 months, respectively. Toxicities were acceptable: Depending on the hypofractionation level, 20-30% of patients had acute Grade 2 GU symptoms during or shortly after treatment, primarily related to alpha blocker initiation. Average international prostate symptom scores (IPSS) returned to baseline by 3 months post treatment. Four to nine percent of patients had Grade 2+ GI symptoms during treatment, declining to 2% by 2 years. Actuarial rectal bleeding at two years was 8 +/- 1.7%, with all cases resolving either spontaneously or after minor intervention and with similar rates among hypofractionation levels ($p = 0.2$). The 5-year, nadir+2 actuarial biochemical progression-free survival (bPFS) for Level 1 was 94.7 +/-2.7%, with no difference between HPFX level 1, and levels 2 and 3 at 3 years ($p = 0.95$). Initial PSA, Gleason score, and T stage did not correlate with outcome ($p = 0.63, 0.71, 0.96$, resp.). To date, 8 patients had failed biochemically, but 3 were within the first 4 months of follow-up. The authors conclude that toxicities were acceptable and similar across all hypofractionation levels, consistent with the α/β of 3 assumed for late effects. Furthermore, actuarial bPFS rates at 3-5 years were high, comparable to expectations with dose escalated standard fractionation.

Meanwhile, Stanford University reported on 41 low risk patients treated with 36.25 Gy in 5 fractions using stereotactic body radiotherapy (35, 36). The first 21 patients were treated on consecutive days but, due to higher than expected rectal toxicity treatments were modified to be given every other day (three fractions a week). With these changes no patients experienced Grade 3 or higher toxicity. Median follow up was 33 months in this study.

Considering the above investigations, Radiation Therapeutic Oncology Group (RTOG) has initiated a phase II trial (RTOG 0938) to randomize low-risk prostate cancer patients to receive either 36.25 Gy in 5 fractions of 7.25 Gy over two and a half weeks (in 15-17 days) vs. 51.6 Gy in 12 fractions of 4.3 Gy over two and a half weeks (in 16-18 days). Patient accruals were just completed.

Meanwhile, in 2014, American Society of Therapeutic Radiation Oncology (ASTRO) has reviewed the data of short radiation regimens including stereotactic body radiation treatment (SBRT, 5 daily fractions over 2 and half weeks) and has concluded that SBRT can be considered a primary form of treatment for prostate cancer. The results of long-term clinical trials supporting the safety and efficacy of stereotactic body radiation in treating prostate cancer led ASTRO to announce the decision. The results of clinical studies show patient outcomes with SBRT are at least as good as other forms of radiotherapy treatments.

Multi-parametric magnetic resonance imaging (mpMRI) and mpMRI-CT fusion guided Radiotherapy: Recent work suggested that multi-parametric magnetic resonance imaging (mpMRI), which combines a number of different MR imaging sequences such as dynamic contrast enhancement (DCE), diffusion-weighted imaging (DWI) and so on beyond the standard T1- and T2-weighted images, show a promise in detecting aggressive, high-grade, bulking invasive prostate cancer (37,38), according to American College of Radiology, Prostate Imaging and Reporting and Data System (PI-RADS) version 2, Accessed March 20, 2015, from http://www.acr.org/Quality-Safety/Resources/PIRADS/(http://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/Resources/PIRADS/PIRADS%20V2.pdf). mpMRI allows for reliable detection of adverse pathological features such as extra capsular extension, high-grade tumor and seminal vesicle invasion (39). Moreover, it has been shown to lead to substantial tumor upstaging and can thus affect treatment decisions. All these unfavorable tumor features are associated with heavy tumor burden and high risks for extra capsular extension and/or pelvic nodal involvement that require protracted high-dose radiation treatment. Furthermore, the co-registration of the mpMRI and ultrasound has recently been reported to significantly enhance the detection of high-grade invasive prostate cancer (40). At our institution, recently we have successfully piloted the co-registration of the advanced mpMRI and planning CT images using fiducial markers, to enhance the tumor target delineation and to deliver high dose radiotherapy planning for a prostatic lesion(s) only.

In summary, IG-IMRT can accurately deliver highly conformal dose to the target while minimize radiation dose to the adjacent normal structures such as rectum and bladder. Prostate hypofractionation such as SBRT may have many potential benefits: biological, logistical, and financial, in radiotherapy management of prostate cancer. Nonetheless, the current approach is to deliver high-dose radiotherapy to entire prostate gland and a portion of anterior wall of rectum and posterior wall of bladder are in the high-dose field, which leads to a risk for the late toxicity such as rectal bleeding. Treatment-related toxicity reductions are critically important for this cohort of patients since a long life expectancy (>10 years) is expected after a curative treatment. Therefore, it is highly desirable to identify the intra-prostatic lesions that are detected by mpMRI, and could be targeted by high- dose radiotherapy. Using this approach adjacent normal tissue such as rectum and bladder will be further spared from high dose, which theoretically translates to the reduction of late tissue toxicity.

In this protocol, we will utilize a pretreatment mpMRI to select and stratify patients (integral biomarker) for two separate SBRT regimens depending on whether prostate lesions are present. For all patients with a diagnosis of localized prostate cancer, we plan to obtain a prostatic mpMRI. For the patients without any positive mpMRI lesions, a SBRT monotherapy (36.25 Gy in 5 fractions) will be delivered to the prostate only as done in the previous RTOG 0938 study. For the patients with a positive mpMRI lesion(s), the prostatic lesion(s) will be identified and contoured by one of the radiology co-chairs. The mpMRI and planning CT images will then be co-registered by the medical physics team. IG-IMRT (45 Gy in 25 fractions of 1.8 Gy) will be given to whole pelvis or prostate and entire seminal vesicles over 5 weeks. This is followed by simultaneously integrated boost, SIB, SBRT 18 Gy in 3 fractions to the entire prostate and 21 Gy in 3 fractions of 7 Gy to the prostatic lesion(s) only. Biologic equivalent doses of this protracted course are higher than standard fractionation regimen, but lower than the combination regimen (external beam radiation treatment and high-dose-rate brachytherapy) used in the RTOG 0815 and RTOG 0924 (see the comparison table in the Appendix IV)

2.0 OBJECTIVES

2.1 Primary Objective

To estimate the rate of late grade 3-5 genitourinary and gastrointestinal toxicity following mpMRI-guided radiation treatment. Late toxicity will be defined as toxicity occurring more than nine months from the start of radiotherapy. It is graded based on CTCAE v4.0.

2.2 **Secondary Objectives**

2.2.1 To estimate acute toxicity
2.2.2 To estimate PSA failure in each cohort at 1, 2, and 5 years
2.2.3 To estimate disease free survival (DFS) in each cohort at 1, 2, and 5 years

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility

3.1.1 Histologically confirmed diagnosis of adenocarcinoma of the prostate within 365 days (1 year) of randomization
3.1.1.1 Patients previously diagnosed with prostate cancer within 365 days (1 year) of the biopsy procedure.
3.1.2 History/physical examination with digital rectal examination of the prostate within 60 days prior to registration
3.1.3 Histological evaluation of prostate biopsy with assignment of a Gleason score to the biopsy material
3.1.4 Clinical T stage (AJCC 7th edition) within 90 days of registration
3.1.5 PSA should be obtained within 60 days prior to registration. PSA should not be obtained within 10 days after prostate biopsy. (Every effort should be made to obtain all serum PSA values obtained in the 1 year prior to treatment to allow for calculation of PSA kinetics.)
3.1.6 Zubrod Performance Status 0-1 within 60 days prior to registration
3.1.7 Age ≥ 18
3.1.8 Patient must be able to provide study-specific informed consent prior to study entry.
3.1.9 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) is allowed at the discretion of treating physician.

3.2 Conditions for Patient Ineligibility

3.2.1 Prior or concurrent invasive malignancy (except non-melanomatous skin cancer) or lymphomatous/hematogenous malignancy unless continually disease free for a minimum of 5 years. All patients with in situ carcinoma are eligible for this study (for example, carcinoma in situ of the oral cavity is eligible) except for patients with carcinoma of the bladder (including in situ bladder cancer or superficial bladder cancer).
3.2.2 Evidence of distant metastases
3.2.3 Regional lymph node involvement
3.2.4 Previous radical surgery (prostatectomy), cryosurgery, or HIFU for prostate cancer
3.2.5 Previous pelvic irradiation, or prostate brachytherapy
3.2.6 Use of finasteride within 30 days prior to registration. PSA should not be obtained prior to 30 days after stopping finasteride.
3.2.7 Use of dutasteride within 90 days prior to registration. PSA should not be obtained prior to 90 days after stopping dutasteride.
3.2.8 Previous or concurrent cytotoxic chemotherapy for prostate cancer
3.2.9 Severe, active co-morbidity, defined as follows:
3.2.9.1 Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months
3.2.9.2 Transmural myocardial infarction within the last 6 months
3.2.9.3 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
3.2.9.4 Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration
3.2.9.5 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.)
3.2.9.6 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.

4.0 PRETREATMENT EALUATIONS/MANAGEMENT

4.1 Highly Recommended Evaluations/Management

4.1.1 Visualization of the urethra at the time of CT simulation or CT scan for treatment planning or through fusion of images (e.g., MRI) with CT simulation images at that time is recommended. For patients where the maximum dose to a point that has a volume of 0.03 cc exceeds 38.78 Gy in cohort 1 (5 fraction) or exceeds 22.47 Gy in cohort 2 SBRT boost component (3 fractions), visualization of the urethra would be required.

4.1.2 Baseline testosterone (optional)

5.0 REGISTRATION PROCEDURES

Eligible patients must sign the informed consent prior to radiotherapy. Inclusion and exclusion criteria will be verified by the principal investigator by completing and signing the eligibility checklist and the registration case report form will be completed.

6.0 RADIATION THERAPY

Protocol treatment must begin within 6 weeks after registration. This protocol requires the use of IG-IMRT.

6.1 Dose Specifications

6.1.1 Total Prescribed Dose

In Cohort 1 of the study patients will receive 5 fractions of radiation to prostate only; each fraction size will be 7.25 Gy. The total dose will be 36.25 Gy. The 5 treatments will be scheduled to be delivered twice a week over approximately 15-17 days. A minimum of 2 days and a maximum of 5 days should separate each treatment. No more than 2 fractions will be delivered per week. The total duration of treatment will be no shorter than 15 days and no longer than 20 days.

PTV: 36.25 Gy in 5 fractions of 7.25 Gy

In Cohort 2 of the study patients will receive IG-IMRT 45 Gy in 25 daily fractions (1.8 Gy per fraction, 5 days a week) to whole pelvis or prostate gland and seminal vesicle followed by SIB SBRT, 18 Gy in 3 fractions to the entire prostate and 21 Gy in 3 fractions of 7 Gy to the prostatic lesion(s) only The 3 treatments will be scheduled to be delivered twice a week over approximately 10-12 days. A minimum of 2 days and a maximum of 5 days should separate each SBRT treatment. No more than 2 SBRT fractions will be delivered per week. SBRT must be initiated within 2 weeks after the completion of IG-IMRT.

PTV1: 45 Gy in 25 fractions to either whole pelvis vs. prostate gland and entire seminal vesicle (can be treated at Rush Oak Park Hospital).

PTV2: 18 Gy in 3 fractions of 6 Gy

PTV3: 21 Gy in 3 fractions of 7 Gy

6.1.2 Dose Coverage

For both cohorts, the isodose line used for the prescription dose should cover a minimum of 95% of the PTV.

6.1.3 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.

6.2 Supportive Measures

6.2.1 Urinary

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

6.2.2 Bladder

Patients will be asked to have a full urinary bladder both during simulation and treatment for all techniques. 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.

6.3 Technical Factors

6.3.1 Radiotherapy

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 volumetric data.

6.3.2 Radiotherapy Delivery

6.3.2.1 *Photons*

This protocol requires the use of IMRT (VMAT, DMLC or SMLC). The recommended photon energies for this protocol are 6-10 MV. The use of beams with higher energy is discouraged. These energies will result in an increased neutron dose reaching the patient's total body. However, it is recognized that increasing the energy has advantages in improving dose distributions for larger patients. For this reason, beams as high as 15 MV will be allowed only when clinically significant improvement of the dose distribution is evident to the treatment planner.

6.3.2.2 *IGRT and Fiducial markers Used for Target Localization and Field Adjustment*

6.3.2.2.1 Allowed x-ray IGRT techniques with or without real-time tracking:

The x-ray IGRT system that can be used for this study are:

- 2D and 3D IGRT systems are allowed for this protocol
  - These systems can use either kV or MV x-rays
  - A computerized method for image registration is required for determination of the patient shift information
  - The image registration can be either manual (drag and drop images) or automatic

The use of target tracking during treatment is encouraged when this technology is available and strongly encouraged when the treatment time from initial beam-on to the end of dose delivery is longer than 7 minutes. Repeat IGRT procedures can be used to detect and correct field positions when real-time tracking is not available. Treatments that take less than 5 minutes do not require an end-of-treatment IGRT procedure. An end-of-treatment IGRT procedure should be obtained when real-time tracking is not used, and the time period from the last IGRT procedure exceeds 5 minutes.

Use of fiducial markers: Fiducial markers (polyMark 1 mm diameter, 3 mm long) must be placed within the prostate, by an experienced urologist before the mpMRI exam. It is recommended that at least three (3) markers be placed: one in the apex, one in the base and one in the lobe for which the biopsy results were negative. Proper placement will facilitate easy alignment of the prostate prior to RT.

6.4 Set-up, Localization and Tracking

6.4.1 Patient Set-up for SBRT delivery

Patients will be positioned supine in a comfortable posture. The immobilization device consists of a SBRT body frame (CIVCO Medical) with knee cushion and lower leg immobilization. The knees will be held in place by the mini vaclok connected to a U frame. The head should rest on a comfortable pillow and the arms should be cross over the chest holding an "O" ring. Prone position is discouraged but allowed if tracking is used. The degree of bladder fullness should be made to duplicate what is anticipated for daily treatment, i.e., if the patient is instructed to maintain a full bladder for treatment, he should be simulated as such. Consistent bladder filling procedure should be used for an individual patient for simulation and for each treatment. The degree of bladder filling for each patient entered into this study will be documented for future analysis. The use of rectal balloons will be allowed but are not required in this protocol. The use of a rectal balloon will be documented for each patient for future analysis. In order to facilitate urethra visualization an 8Fr straight catheter will be inserted into the bladder using standard sterile procedures.

6.4.2 Localization
Daily IGRT is required to locate prostate using fiducial markers.

6.5 **Treatment Planning**

6.5.1 Simulation

6.5.1.1 *Computed Tomography (CT)*
CT will be the primary image platform for treatment planning. The simulation should be performed in the supine treatment position, with the fiducial markers/rectal balloon in place (where utilized). Axial cuts of 3 mm or less will be acquired throughout the pelvis and prostate from the top of the iliac crests superiorly to the perineum inferiorly. Patients enrolled in Arm2 of the protocol will require two CT simulations, one for each phase.
For patients having one metallic hip replacement the CT reconstruction must include the Orthopedic Metal Artifact Reduction, OMAR, sequence. Patients with bilateral hip replacements will be excluded from the protocol due to very pronounced artifacts on CT images as well as distortions in the MR images.

6.5.1.2 *Multi-parametric Magnetic Resonance Imaging* (mp*MRI)*
mpMRI images with 3-4 mm slice thickness are required for this study. The following sequences are recommended: T1 FS Post, T2, Vibe Dixon, DWI and DCE. The MRI study must be performed following the implantation of fiducial markers in order to facilitate the image co-registration of the planning CT with Vibe Dixon MR sequence

6.5.1.3 *Contrast*
Oral contrast for small bowels is required. Intra-venous,IV, urethral, and bladder contrast are allowed but not required.

6.5.2 Treatment Planning/Target Volumes

6.5.2.1 The definition of volumes will be in accordance with the ICRU Report #50 and ICRU Report #62: Prescribing, Recording, and Reporting Photon Beam Therapy.

6.5.2.2 The Gross Tumor Volume (GTV) for the purpose of this protocol is defined by mpMRI.
- For the cohort 1, no GTV is contoured since mpMRI is negative.
- For the cohort 2, GTV is a lesion(s) defined by mpMRI and should be contoured with assistance from one of radiology co-chairs.

6.5.2.3 The clinical target volume 1 (CTV1) will be prostate only for the cohort 1, and entire seminal vesicle and prostate or the whole pelvis (see next paragraph) for the cohort 2 in non-contrast axial CT scan images.
- For cohort 1, CTV is the prostate only.
- For cohort 2, CTV1 is either whole pelvis or entire seminal vesicle and prostate at the discretion of treating physician; CTV 2 is prostate only for SBRT boost; CTV3 is GTV for the SBRT boost.

Details for whole pelvis CTV1: The CTV1 will include the prostate and entire seminal vesicles (SV), the obturator, external iliac, proximal internal iliac and common iliac nodes, using the vascular structures, up to a level corresponding to the top of L4-L5. The presacral nodes from L5-S1 to S3 may be included if desired depending on whether the dose constraints to the rectum are achievable. The CTV1 will extend superiorly from L4-5 to 0.5 cm below the tip of the urethral contrast dye (if used) and no less than the entire prostate gland. Lateral borders will be at least 1 cm from the pelvic brim. In the lateral fields, the external and internal iliac nodes below the SI joints, and the posterior extension of the seminal vesicles should be covered. The usual posterior border is approximately S2-3, but CT anatomy should take precedence. The inferior extent of the external iliac lymph nodes is at the top of the femoral heads. The inferior extent of the external iliac nodes is at the top of the symphysis pubis. The CTV1 will include 7 mm margin in 3-dimensions to the contoured iliac vessels, but not extend outside of the true pelvis, into the pelvic musculature nor into adjacent identifiable organs, such as the bladder, rectum or other bowel. Extension of the CTV into adjacent bone may be carved out.

Details for prostate only CTV1: prostate and entire seminal vesicles are included.

6.5.2.4 The planning target volume (PTV) will be defined as the CTV plus margins.
- For the cohort 1, PTV is CTV plus a 3 mm margin posteriorly and 5

mm in all other dimensions. To meet the dose constraints, if necessary, the anterior margin can be reduced to 3 mm.

- For the cohort 2, PTV1 is CTV1 plus a 5 mm margin in all directions; PTV2 is CTV2 plus a 3 mm margin posteriorly and 5 mm in all other dimensions. To meet the dose constraints, if necessary, the anterior margin can be reduced to 3 mm. PTV3 is CTV3 plus 1-2 mm margin.

6.5.3 Dosimetry

6.5.3.1 The use of coplanar or non-coplanar static beam IMRT is permitted. A minimum of 5 gantry angles is required. The use of coplanar or non-coplanar VMAT is permitted. For planning purposes PTV3 will, always, overlap PTV2 and the dose volume constraints will reflect this reality

6.5.3.2 For all cases, the prescription isodose line must encompass a minimum of 95% of the PTV. For cohort 1, the maximum dose within the PTV is 7% above the prescribed dose for a point that is 0.03 cc in size.
For cohort 2, the maximum total dose with the PTV is 10% above the prescribed dose for a point that is 0.03 cc in size.

6.5.3.3 The prescription doses must not occur outside of the PTV. Any hotspots should be manipulated to avoid the prostate-rectal and prostate-bladder interfaces as defined by the CTV.

6.6 **Critical Structures**

6.6.1 Critical Organ Dose-Volume Limits

6.6.1.1 The normal tissue volume to be contoured will include bladder, rectum, bilateral femoral heads (to the level of ischial tuberosity), seminal vesicles, penile bulb, skin, small bowel and urethra. For patients where the maximum point dose to a point that is 0.03 cc exceeds 7% prescription dose in the SBRT component, visualization of the urethra is required.

6.6.1.2 The normal tissues will be contoured and considered as solid organs rather than contouring the bladder and rectal walls.

6.6.1.3 The bladder should be contoured from its base to the dome.

6.6.1.4 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.

6.6.1.5 The tissue within the skin and outside all other critical normal structures and PTVs are designated as unspecified tissue.

6.6.1.6 The following tables list maximum dose limits to a point or volume within several critical organs. These are absolute limits, and treatment delivery that does not abide by these limits will constitute either an acceptable deviation or an unacceptable protocol violation deviation.

Cohort 1 (5 Fraction SBRT)

		Dosimetry Parameters for 5 fraction arm
Organ	**Volume**	**Dose (Gy)**
Prostate (PTV)	Maximum point dose (0.03cc)	≤ 38.78 Gy 107% of prescription dose *
	Minimum dose received by 95% of PTV	≥ 36.25 Gy 100% of prescription dose
	Minimum dose received by PTV	≥ 34.4 Gy 95% of prescription dose
Rectum	Maximum point dose (0.03cc)	≤ 38.06 Gy 105% of the prescription dose
	Less than 3 cc	≤34.4 Gy 95% of prescription dose
	90% rectum	≤ 32.625 Gy 90% of prescription dose
	80% rectum	≤29 Gy 80% of prescription dose
	50% rectum	≤18.125 Gy 50% of prescription dose
Bladder	Maximum point dose (0.03cc)	≤38.06 Gy 105% of prescription dose
	90% Bladder	≤ 32.625 Gy 90% of prescription dose
	50% Bladder	≤18.125 Gy 50% of prescription dose
Penile bulb (recommended)	Maximum point dose	No more than 100% of prescription dose
	Less than 3 cc	≤20 Gy 54% of prescription dose
Femoral heads	Less than 10 cc cumulative (both sides)	20 Gy 54% of prescription dose
Skin (recommended)	Maximum point dose	30 Gy 81% of prescription dose
Urethra dose		≤ 38.78Gy * 107% of prescription dose
Small bowel	Maximum point dose	≤ 15Gy 41% of prescription dose

*Visualization of the urethra would be required to confirm urethral dose is ≤38.78Gy – 107% of prescription dose where the max point dose (0.03cc) within the PTV exceeds 38.78Gy – 107% of prescription dose

Cohort 2 (IG-IMRT 45 Gy in 25 daily fractions to prostate and entire seminal vesicle followed by SBRT 21 Gy in 3 fractions to prostate tumor only)

Initial IMRT phase PTV1 will receive treatment prescription

		Dosimetry Parameters for 45 Gy in 25 treatment schedule cohort (Initial IMRT phase)
Organ	**Volume**	**Dose (Gy)**
PTV1	Prescription dose to 98% of the PTV1	≥ 45 Gy, 100% of prescription dose
	Minimum dose to 0.03 cc of the PTV1	≥ 42.75 Gy, 95% of prescription dose
	Maximum dose to 0.03 cc of the PTV1 (Per protocol)	≤ 48.2 Gy
	Maximum dose to 0.03 cc of the PTV1 (Variation acceptable)	≤ 48.2 Gy -49.5 Gy
	Maximal dose to 0.03 cc of the PTV1 (Deviation unacceptable)	≤ 49.5 Gy
Rectum	Maximum point dose(0.03cc)	≤ 49.5 Gy, 110% of the prescription dose
	90% rectum (Per protocol)	≤ 40.5 Gy, 90% of prescription dose
	85% rectum (Variation acceptable)	≤ 40.5 Gy, 90% of prescription dose
	50% rectum	≤ 34 Gy; 75% of prescription dose
Bladder	Maximum point dose(0.03cc)	≤ 49.5 110% of prescription dose
	80% Bladder	≤ 40.5 Gy, 90% of prescription dose
	50% Bladder	≤ 36 Gy, 75% of prescription dose
Penile bulb*	Mean dose	≤ 30 Gy, 67% of prescription dose
Femoral heads*	Maximal point dose	≤ 27 Gy, 60% of prescription dose
Small bowel	Maximal dose to 0.03 cc	≤ 50 Gy
	90% Small bowel	≤ 45 Gy

*recommended only

		Dosimetry Parameters for 3 treatment schedule cohort (SIB SBRT boost) * **
Organ	**Volume**	**Dose (Gy)**
PTV2	Maximum point dose (0.03 cc)	≤ 22.47 Gy, 107% of prescription dose *
	Minimum dose received by 95% of PTV	≥ 18 Gy, 100% of prescription dose
	Minimum dose received by PTV	≥ 17.1 Gy, 95% of prescription dose
PTV3**	Maximum point dose (0.03 cc)	≤ 22.47 Gy, 107% of prescription dose*
	Minimum dose received by 95% of PTV	≥ 21 Gy, 100% of prescription dose
	Minimum dose received by PTV	≥ 19.95 Gy, 95% of prescription dose
Rectum	Maximum point dose(0.03cc)	≤ 22.02 Gy, 105% of the prescription dose for PTV3
	Less than 2 cc	≤ 19.5 Gy, 93% of prescription dose for PTV3
	90% rectum	≤ 18.0Gy, 86% of prescription dose for PTV3
	80% rectum	≤ 16.0 Gy, 76% of prescription dose for PTV3
	50% rectum	≤ 13.6 Gy; 65% of prescription dose for PTV3
Bladder	Maximal point dose (0.03 cc)	≤ 22.02 Gy, 105% of the prescription dose for PTV3
	80% Bladder	≤ 17 Gy, 80% of prescription dose for PTV3
	50% bladder	≤ 14.7 Gy, 70% of prescription dose for PTV3
Penile bulb*	Mean dose	≤ 12.6 Gy, 60% of prescription dose for PTV3
Femoral heads *	Maximum point dose	≤ 12.6 Gy, 60% of prescription dose for PTV3
Small bowel	Maximal point dose	≤ 3 Gy
Urethra	Maximal point dose	22.47 Gy – 107% of prescription dose (0.03 cc)

*recommended only

** PTV3 overlaps with PTV2 for SIB planning and delivery

*** The OAR's dose constraints for cohort 2 phase 1 and 2 were set based on cumulative EQD2 calculations using α/β=3.

6.6.1.7 For future analysis, DVH will be generated for inner rectal wall and inner bladder wall. The inner rectal wall and the inner bladder wall for this DVH will be contoured for a distance of 18mm beyond the most inferior and superior contoured prostate slice. If a rectal balloon is used, the inner anterior rectal wall should be extracted from the rectum wall contour with a 3mm margin concentric ring inside the rectum contour. The inner rectal wall needs to be the same length as the rectum.

6.7 **Image/Signal-Guidance for Target Localization**

6.7.1 After patient is set up on the treatment table, The Exactrac systems that locate the fiducial

markers, placed inside the prostate, will be used to align the patient with the treatment machine geometry based on the treatment plan. The alignment result will be evaluated by the attending physician and/or attending physicist and be approved for treatment by attending physician. The alignment data will be recorded. A rectal balloon may be used to immobilize the prostate.

6.7.2 If a tracking system is available for prostate localization, it will be used during the treatment to track the target motion. A correction action will be performed if the target migrated more than 2 mm for more than 20 seconds in any of three orthogonal coordinates.

6.7.3 Cone-beam CT (CBCT) will be taken prior to radiation delivery but after image-guidance and also taken immediately after the SBRT. CBCT images will be used to assess the level of bladder and rectal filling and the presence of gas in the rectum. The rotation of the prostate will also be assessed prior to treatment. If significant deviations are found the patient will repeat the treatment preparation procedures. For some special cases, CBCT images may be taken more frequently during the treatment per physician's clinical judgment.

6.7.4 The initial localizations and alignment is based on the center of mass of the fiducial markers. Small rotations may be corrected at initial localization stage, and intra-fractional rotations will be ignored. Further adjustment during the treatment will be translational shift of the center of mass determined via IGRT technique, using remote couch motion.

6.7.5 In view of intrafraction motion and to ensure the target coverage during treatment, periodic target localization will be employed during fix gantry angle IMRT, every 7 minutes from initial beam-on. The physicist will be on-site for image guidance and treatment. For Rapid Arc delivery the position of the target will be rechecked after every 180 degrees arc.

6.7.6 For any image-guidance procedure, comparison with reference images or baseline data should be performed and reviewed and approved by both physician and physicist on site.

6.7.6.1 The comparison can be done both manually and automatically. For any image-guidance method, if any deviation is larger than 2 mm, correction should be performed.

6.7.6.2 All image/signal-guidance data should be recorded and saved for post treatment review and analysis. In some cases, re-planning (either offline or online) based on anatomy of the day may be performed. Such request will be made by the attending physician.

6.8 R.T. Quality Assurance Reviews

All treatment prescription and verification images of each case will be reviewed by study chair/ physics co-chairs before treatment, and will also be archived for later review when a later toxicity occurs.

6.9 Radiation Therapy Adverse Events

6.9.1 All patients will be seen weekly by their radiation oncologist during radiation therapy. Any observations regarding radiation reactions will be recorded and should include attention to the following potential side effects:

6.9.1.1 Small bowel or rectal irritation manifesting as abdominal cramping, diarrhea, rectal urgency, proctitis, or hematochezia;

6.9.1.2 Bladder complications including urinary frequency/urgency, dysuria, hematuria, urinary tract infection, and incontinence;

6.9.1.3 Radiation dermatitis.

6.9.2 Clinical discretion may be exercised to treat side effects from radiation therapy at the discretion of treating physician. Examples of typical medications used in the management of rectal 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.

6.9.3 Adverse Events (AEs) and Serious Adverse Events (SAEs) and Unanticipated Problems (UP) Reporting Requirements

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4. 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.

6.9.3.1 Definition of an AE: Any untoward or unfavorable medical occurrence in a human subject including any unintended abnormal sign, symptom, or disease whether or not it is considered related to the human subject's participation in research.

6.9.3.2 Definition of a Serious Adverse Event (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.

6.9.3.3 Definition of an Unanticipated Problems (UP): Includes any incident, experience, or outcome that meet all of the following criteria:

- Unexpected
- Related, probably related, or possibly related to participation in the research
- Suggests that the research places participants or others at a greater risk of harm

6.9.3.4 Reporting Requirements

All SAEs must be submitted to the Rush University Medical Center IRB and the Rush Protocol Review and Monitoring Committee within 48 hours of learning of the event. UPs must be submitted to the Rush University Medical Center IRB and Rush Protocol Review and Monitoring committee within 10 days of learning of the event.

7.0 DRUG THERAPY

Hormone therapy is allowed for this study at the discretion of treating physician. The 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) is acceptable for this study. In principle, hormone therapy is not recommended to the patients with low-risk factors (PSA<10, GS 6 or less, and T1-T2a), a short-term hormone therapy (4 to 6 months) is acceptable to the patients with intermediate-risk factors (T2b-2c or PSA >10 or GS 7). A long-term hormone (28-32 months) therapy is highly recommended to the patients with high-risk factors (GS 8 or more, PSA >20 or T3-4).

8.0 OTHER THERAPY

8.1 Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

8.1.1 Diarrhea/rectal frequency/urgency may be managed with diphenoxylate or loperamide.Bladder irritation may be mitigated with phenazopyridine. Urinary frequency/urgency can be managed with anticholinergic agents or alpha-blockers such as tamsulosin. Erectile dysfunction can be managed with phosphodiesterase (PDE) inhibitors such as sildenafil.

9.0 PATIENT ASSESSMENTS

9.1 Study Parameters

See Appendix I for a summary of study assessments and time frames.

9.2 Pre-Treatment Evaluation

9.2.1 PSA should not be obtained for at least 10 days after prostate biopsy.

9.2.2 Patients must have the following evaluations prior to starting study treatment:

- History/Physical exam including a digital rectal exam
- Performance status
- Prostate biopsy with Gleason Score
- PSA
- Adverse Event Evaluation
- mpMRI
- Bone Scan and CT of Pelvis
    - Required for Cohort 2, but optional for Cohort 1

9.2.3 Recommended pre-treatment evaluation (not required)

- Imaging of urethra (see section 4.1)
- Testosterone

9.3 Evaluation During Treatment

9.3.1 Required evaluations during study treatment (to be completed weekly while on treatment):

- Physical exam
- Performance status
- Adverse event evaluation

9.3.2 Delay in treatment is discouraged unless the patient's medical condition or side-effects of treatment merit a delay. Delay of treatment will be at the discretion of the treating radiation oncologist.

9.4 Evaluation Following Treatment

9.4.1 Required Evaluations Following Study Treatment (every 3 months until month 24):

- Physical exam including a digital rectal exam
- Performance status
- PSA
- Adverse event evaluation

9.4.2 After the second year (24 months) following radiation, follow-up will continue every 6 months for years 3, 4, and 5; then annually thereafter.

9.4.3 A needle biopsy is encouraged: from the site of original tumor within the prostate and/or other site of original tumor identified by the transrectal ultrasound, as indicated for rising PSA or clinical failure.

9.4.4 A bone scan will be performed as clinically indicated, e.g., if the patient develops a PSA recurrence with a rapid doubling time (< 6 months) or if the patient develops symptoms suggesting the presence of metastatic disease.

9.4.5 When documentation of disease progression is noted within 5 years, follow up will be as per protocol. When the disease progression occurs after 5 years, follow up will be at the discretion of the treating physician.

9.5 Criteria for Biochemical Recurrence

9.5.1 Biochemical (PSA) recurrence is defined according to the proposed new Radiation Therapy Oncology Group/American Society for Therapeutic Radiology and Oncology (RTOG-ASTRO) criteria also known as the RTOG Phoenix definition: an increase of the PSA level at least 2 ng/mL greater than the minimum level reached after therapy (lowest PSA+ 2 criterion) (H. Sandler, personal communication, December 2005). All PSA levels done during a follow-up interval will be recorded on the data forms.

9.6 Criteria for Local Recurrence

9.6.1 Clinical criteria for local recurrence are progression (increase in palpable abnormality) at any time, failure of regression of the palpable tumor by 2 years, and redevelopment of a palpable abnormality after complete disappearance of previous abnormalities. Needle biopsy is recommended. The presence of palpable disease must be recorded on the data collection forms for initial and follow-up evaluations of the patient.

9.6.2 Histologic criteria for local recurrence are presence of prostatic carcinoma upon biopsy and positive biopsy of the palpably normal prostate more than 2 years after the start of treatment.

9.7 Criteria for Nonlocal Recurrence

9.7.1 Distant metastasis will be documented if clinical or bone scan evidence is demonstrated. Ultrasound evaluation of the prostate with needle biopsy as indicated by the findings is recommended at the time distant metastasis is reported.

Regional metastasis will be documented if there is radiographic evidence (CT or MRI) of lymphadenopathy and histologic confirmation.

9.8 Other Response Parameters

9.8.1 Disease-Free Survival

Disease-free survival will be measured from the date of registration to the date of documentation of recurrence or until the date of death. This endpoint includes all measures of disease including physical exam, PSA, bone scans, CT/MRI, and biopsies.

9.8.2 Time to Local Progression

The time to progression will be measured from the date of registration to the date of documented local progression. Patients who have a normal exam and no evidence of having a PSA recurrence will be considered controlled locally. Patients with a residual abnormality or a PSA failure shall undergo biopsy to distinguish between local and distant failures. If their exam is normal or if they are post orchiectomy, they will be censored at the last point in time they were considered locally controlled and considered "not evaluable" for further assessment of local control.

9.8.3 Time to Distant and/or Regional Failure

The time to distant or regional failure will be measured from the date of registration to the date of documented regional nodal recurrence or distant disease relapse. Patients with evidence of biochemical failure, but a negative prostate biopsy, will be considered as distant or regional failure only.

9.8.4 Disease-Specific Survival

Disease-specific survival duration will be measured from the date of registration to the date of death due to prostate cancer. Causes of death may require review by the study chair or their designee. Death due to prostate cancer will be defined as:

9.8.4.1 Primary cause of death certified as due to prostate cancer

9.8.4.2 Death in association with any of the following conditions:

9.8.4.2.1 Further clinical tumor progression occurring after initiation of "salvage" anti-tumor (e.g., (androgen suppression) therapy

9.8.4.2.2 A rise (that exceeds 1.0 ng/mL) in the serum PSA level on at least two consecutive occasions that occurs during or after "salvage" androgen suppression therapy

9.8.4.2.3 Disease progression in the absence of any anti-tumor therapy

9.8.4.2.4 Death from a complication of therapy, irrespective of disease status.

9.8.5 Freedom from Biochemical (PSA) Recurrence (FFBR)

The time to PSA failure will be measured from the date of registration to the date of a rise by 2 ng/mL or more above the nadir PSA. Nadir PSA is defined as the lowest PSA value after randomization and before the call date PSA. That is, the time of failure will be the date of the first PSA that is 2 ng/mL or more above the lowest prior post-randomization PSA value.

9.8.6 Overall Survival

Survival duration will be measured from the date of registration to the date of death from any cause. A post-mortem examination will be performed whenever possible.

9.8.7 Primary Outcome Measure

Acute and late toxicity (primary endpoint) will be measured according to the NCI Common Toxicity Criteria *(CTCAE v4.0)* at designated follow-up visits.

9.9 **Criteria for Discontinuation of Protocol Treatment**

9.9.7 Patients who are experiencing excessive adverse events as deemed by their treating physician may be discontinued from the initiated protocol treatment. All attempts should be made to manage adverse events adequately so as to avoid this circumstance.

9.9.8 Study analyses will be based on “intent to treat”. If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol.

10.0 DATA COLLECTION

Data will be collected on study specific case report forms. The timing of the form collection is detailed in the table below. Toxicities, PSA, biochemical and local recurrence, distant progression, second primary malignancy, and death will be documented on the case report forms and stored at Rush University Medical Center.

FORM	DUE
Registration	Prior to beginning protocol therapy
Baseline	After registration Prior to beginning protocol therapy
On Treatment	Weekly while receiving protocol therapy

Follow-Up	Every 3 months post RT for 24 months Every 6 months after 24 months for years 3 and 4, and then annually

11.0 STATISTICAL CONSIDERATIONS

11.1 Primary Endpoint

18-month late GU/GI toxicity

11.2 Secondary Endpoints

11.2.1 Acute GU toxicity

11.2.1.1 PSA failure

11.2.1.2 Disease free survival

Patient Groups

There are two separate and independent patient cohorts as defined by the Hypofractionation schedule: Cohort 1 patients treated with 36.25 Gy (5 fractions of 7.25 Gy over two weeks), and Cohort 2 patients treated with IG-IMRT 45 Gy in 25 daily fractions (over 5 weeks) to entire seminal vesicle followed by a SBRT of 21 Gy in 3 fractions to the prostatic tumor only (over one and a half weeks).

11.3 Sample Size Derivation and Accrual

11.3.1 Sample Size

Overview: The primary goal of this phase II study is to estimate the rate of late grade 3-5 genitourinary and gastrointestinal toxicity following treatment with either SBRT alone vs. IMRT followed by SBRT as a boost. Late toxicity will be defined as toxicity occurring more than nine months from the start of radiotherapy. It is graded based on CTCAE v4.0

Sample size derivation: The study is designed to test whether the 18-month late GU/GI toxicity following the protocol treatment is above 10%. The sample size is determined so that the probability of rejecting the treatment because of excessive late toxicity is 90% if the true late toxicity rate is 20%. Using confidence level of 95% and statistical power of 80%, we require a sample size of 61 patients to have a statistical power of 80% with one-tailed z-test of proportions. Considering 10% ineligible cases due to loss of follow-up or death, **the total sample size of the study is 67 patients for each cohort**.

References for the above statistical considerations:

Chow, S.C.; Shao, J.; Wang, H. 2003. Sample Size Calculations in Clinical Research. Marcel Dekker. New York.

Fleiss, J. L., Levin, B., Paik, M.C. 2003. Statistical Methods for Rates and Proportions. Third Edition. John Wiley & Sons. New York.

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Machin, D., Campbell, M., Fayers, P., and Pinol, A. 1997. Sample Size Tables for Clinical Studies, 2nd Edition. Blackwell Science. Malden, Mass.

Zar, Jerrold H. 1984. Biostatistical Analysis (Second Edition). Prentice-Hall. Englewood Cliffs, New Jersey.

11.3.2 Accrual and Duration

It is expected that it will take approximately 5 years to complete accrual. The analysis for late toxicity will be carried out after each patient has had at least 18 months of follow-up. For another secondary endpoint of biochemical failure, an additional two years of follow-up are needed to estimate the 3-year failure rate.

Data Safety Monitoring (DMC) Plan-As part of the data safety monitoring plan, all patients will be seen at least once a week by a physician while the patient is under treatment and an assessment of symptoms made. If a SAE is noted a report will be generated immediately and the IRB notified. In addition, all the patient data and toxicity information will be reviewed once at least once a month by the PI. The DMC meeting will be held every January and

July, to review and report safety issues. The DMC meeting results will be included in the interim reports, submitted to the Rush IRB every January and July.

11.3.3 Analysis of the Acute GI and GU adverse events (Secondary Endpoint)

Adverse acute events are evaluated by the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE). 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. For each cohort, 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 occur in each arm, which is considered to be similar to the high RT dose arm of RTOG 0126 in terms of RT dose. For this arm, a reported 1% of patients experienced Grade 3+ GI/GU acute toxicity, with no patient experiencing Grade 4 or 5 toxicities. If either hypofractionated arm has an acceptable percentage, then that arm will be deemed to have an acceptable adverse event profile. We will report the percentage for each arm as well as the one-sided 97.5% confidence interval. Note that the number of patients in the high dose arm of RTOG 0126 (a Phase III) trial is much greater than each arm of this Phase II study. For each arm, if the lower limit of the interval is >1% then that arm will be further investigated for acceptability in terms of CTC toxicity

11.3.4 PSA Failure

Failure occurs when the PSA is first noted to be 2 ng/mL or more than the current nadir value (PSA > current nadir + 2) post RT completion. PSA failure at 1, 2, and 5 years will be estimated for each cohort by the cumulative incidence method (41). Also, confidence intervals will be reported.

11.3.5 Disease-Free Survival (DFS)

The disease-free survival duration will be measured from the date of registration to the date of documentation of disease progression or until the date of death from any cause. DFS at 1, 2, and 5 years will be estimated for each cohort by the Kaplan-Meier method (42). Also, 95% confidence intervals will be reported.

11.4 Interim Reports to Monitor Study Progress

The study chairs will meet every 6 months to monitor the trial for safety. Interim reports with descriptive statistics will be prepared twice a year until the initial paper reporting the treatment results has been accepted for publication. In general, the interim reports will contain information about the patient accrual rate with a projected completion date for the accrual phase; data quality; compliance rate of treatment delivery with the distributions of important prognostic baseline variables; and the frequencies and severity of adverse events. The interim reports will not contain results from the treatment comparisons with respect to the primary or secondary endpoints.

11.5 Gender and Minorities

In conformance with the National Institute of Health Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, we will make every effort to accrue minority patients. However, there is no specific projection for this institutional trial, mainly due to limitation of patient source.

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APPENDIX I

STUDY PARAMETER TABLE

See Sections 3.0 and 4.0 (pre-study entry) and 11.2 through 11.4 (during treatment/follow up) for details and/or exceptions.

	Pre-study Entry (may be required for eligibility)				**During Treatment**	**Follow-up (months), Every 6 months for years 3, 4 and 5, then annually**							
	≤60 days	≤90 day	≤180 days	≤365 days	Weekly during RT	3	6	9	12	15	18	21	24[b]
History/physical exam including a digital rectal exam	X												
Physical exam including a digital rectal exam					X	X	X	X	X	X	X	X	X[b]
Performance status	X				X	X	X	X	X	X	X	X	X[b]
Prostate biopsy w/ Gleason score				X									
PSA	X[a]					X	X	X	X	X	X	X	X[b]
Testosterone			X[c]										
mpMRI		X											
Imaging of urethra	See Sect. 4. 1[c]												
Bone scan and CT pelvis	X (required for Cohort 2, but required only when both PSA>10 and GS >6) exist for cohort 1)												X[b]
T Stage Evaluation		X											
Adverse event evaluation	X				X	X	X	X	X	X	X	X	X[b]

[a] PSA should not be obtained for at least 10 days after prostate biopsy

[b] After the second year (24 months) following radiation, follow-up will continue every 6 months for years 3, 4, and 5; then annually thereafter.

[c] Optional (Recommended)

APPENDIX II

ZUBROD PERFORMANCE SCALE

0	**Fully active, able to carry on all predisease activities without restriction**
1	**Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work**
2	**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	**Capable of only limited self-care, confined to bed or chair 50% or more of waking hours**
4	**Completely disabled. Cannot carry on self-care. Totally confined to bed**
5	**Death**

APPENDIX III

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 inapparent 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 Non-regional 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
	T1a-c	N0	M0	PSA ≥10<20	Gleason ≤6
	T2a	N0	M0	PSA <20	Gleason ≤7
	T2b	N0	M0	PSA <20	Gleason ≤7
	T2b	N0	M0	PSA X	Gleason 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

*Note: When either PSA or Gleason is not available, grouping should be determined by T stage and/or either PSA or Gleason as available.

Date: 03/10/2016
Version 3

APPENDIX IV

BED Dose Calculation Comparison

Studies	Treatment schema	HDR or SBRT DOSE	EQD_2* PTV α/β=3	EQD_2 PTV α/β=1.5
Cohort 1[1]	SBRT monotherapy (previously used in RTOG 0938)	SBRT 7.25 Gy x 5 fractions	74.3 Gy	90.6 Gy
Cohort 2[2]	IMRT 45 Gy followed by SBRT boost	SBRT 6 Gy X 3 to entire prostate	75.6 Gy	81.0 Gy
		SBRT 7 Gy x 3 to mpMRI+ lesion	85.2 Gy	93.4 Gy
RTOG 0321 Phase II[3]	EBRT 45 Gy followed by HDR boost	HDR 9.5 Gy X 2 fractions	90.7 Gy	102.1Gy
RTOG 0815 Phase III[3]	IMRT 45 Gy followed by HDR boost	HDR 10.5 Gy x 2 fractions	99.9 Gy	114.4 Gy
RTOG 0924 Phase III[3]	IMRT 45 Gy followed by HDR boost	HDR 15 Gy x 1 fraction	97.2 Gy	113.1 Gy
Standard Fractionation[4]	IMRT 79.20 Gy in 44 fractions (1.8 Gy/fraction)	N/A	76.0 Gy	74.7 Gy

1. Prescribed to 98% PTV, PTV=prostate plus 3-5 mm; In this protocol, all patients will have 3 fiducial markers placed into the prostate prior to radiation simulation and daily CBCT is used to localize fiducial markers prior to each radiation treatment and motion of fiducial markers will be tracked during course of SBRT.
2. Simultaneously integrated boost (SIB) of 18 Gy in 3 fractions to 95% PTV including entire prostate plus 3-5 mm, and 21 Gy in 3 fractions to 95% of PTV including intra-prostatic lesion (GTV) by mpMRI, plus 2-3 mm. In this protocol, all patients will have 3 fiducial markers placed into the prostate prior to radiation simulation and daily CBCT is used to localize fiducial markers prior to each radiation treatment and motion of fiducial markers will be tracked during course of SBRT.
3. For EBRT, prescribed to 95-98% PTV including prostate pelvis plus/minus pelvic nodes plus 5-10 mm margin. For HDR brachytherapy boost, Prescribed to >90% PTV, PTV=prostate only, the prescription to >80% PTV is considered acceptable (minor variation).
4. For IMRT, prescribed to 98% PTV, PTV = prostate plus 5 mm margin for prostate-RT only. This is a commonly used regimen in RTOG 0126, RTOG 0815 and RTOG 0924.

* EQD_2 = Equivalent 2Gy dose = $n * d * (d + \alpha/\beta) / (2 + \alpha/\beta)$