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A Phase II Randomized Trial of MRI-Mapped Dose-Escalated Salvage Radiotherapy Post-Prostatectomy: The MAPS Trial

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SCHEMA:

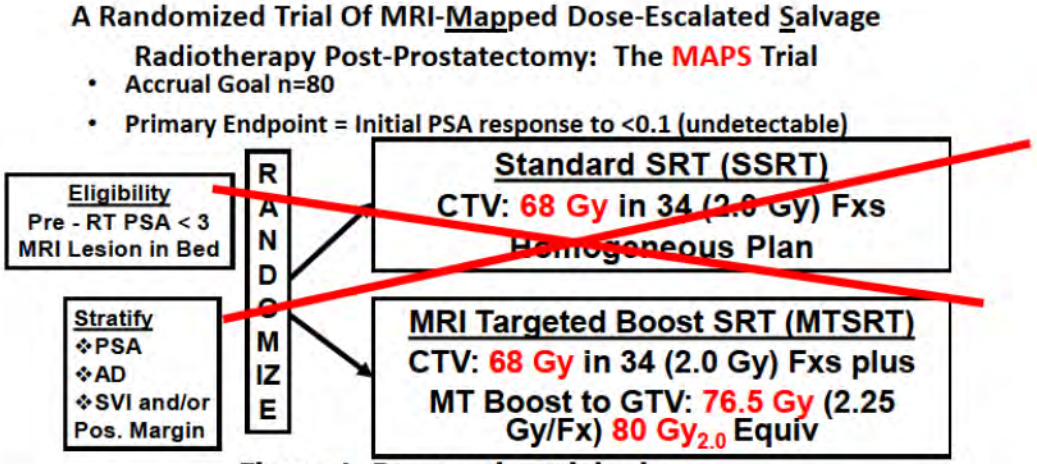

Figure 1: Prospective trial schema

PSA = Prostate-Specific Antigen; RT = Radiation Therapy; MRI= Magnetic resonance Imaging; SVI = Seminal Vesicles Invasion; SRT = Salvage Radiation Therapy; CTV = Clinical Target Volume; GTV = Gross Tumor Volume as defined by MRI; MT = Mapped Tumor, AD = Androgen Deprivation.

Randomization is not applicable as of version 8.0 of the protocol.

1. **Randomization**

   A. *Arm I*: *Standard Salvage Radiation Treatment (**SSRT**)*

   A total dose of 68 Gy will be delivered in 34 fractions to the Clinical Target Volume (CTV), 51 Gy in 34 fractions can be given to the pelvic nodes. (Closed as of protocol version 8.0)

   B. *Arm II*: *MRI Targeted Boost SRT (**MTSRT**)*

   Dose escalation to the Dynamic Contrast Enhanced MRI (DCE-MRI)-defined dominant region(s) by dose painting at 2.25 Gy per fraction, while the rest of the Clinical Target Volume (CTV) receives 2.0 Gy a fraction to 68 Gy. The mapped tumor (MT) boost region will receive an absolute dose of 76.5 Gy. Assuming an α/β ratio of 3.0, this would be equivalent to 80 Gy in 2.0 Gy fractions.

2. **Stratification (no longer required as of protocol version 8.0)**

   A. PSA (≤1 vs. >1 ng/mL)

   B. SVI or Positive Margins (Y = one or both vs. N =neither)

   C. Androgen Deprivation (Y vs. N)

3. **Eligibility Screening: Includes Dynamic Contrast Enhanced (DCE)-MRI/PET of prostate bed and pelvis**

   A. PSA of at least 0.1 and up to 4.0 ng/mL within 3 months prior to enrollment.

   B. Patients with or without palpable abnormalities on digital rectal exam (DRE) are eligible.

   C. Minimum of 3 months since prostatectomy to allow for return of urinary continence and healing.

D. Identifiable tumor lesion or lesions. The enhancing lesion in the prostate bed or regional LN should be at least 0.4 cc and a maximum of 6 cc and was obtained ≤ 3 months prior to protocol entry or enrollment.

E. No evidence of metastatic (distant) disease (pelvic nodes are allowed up to common iliac).

F. Negative bone scan if deemed necessary by treating physician obtained ≤ 4 months prior to protocol entry or enrollment.

G. No previous pelvic radiotherapy.

H. Serum total testosterone taken within 3 months prior to enrollment.

I. No concurrent, active malignancy, other than nonmetastatic skin cancer or early stage chronic lymphocytic leukemia (well-differentiated small cell lymphocytic lymphoma). If a prior malignancy is in remission for ≥ 3 years then the patient is eligible.

J. Ability to understand and the willingness to sign a written informed consent document.

K. Zubrod performance status < 2.

L. Patients must agree to fill out quality of life/psychosocial questionnaires.

M. Age ≥35 and ≤85 years.

4. Enrollment

A. Optional US-guided biopsies. A minimum of 2 cores and a maximum of 5 will be obtained from the MRI–detected lesion.

B. CT-simulation and planning.

5. Treatment Technique

A. **(Closed as of protocol v. 8.0) Arm I, Standard Salvage RT (SSRT):**

Patients will receive 68 Gy in 2 Gy fractions to the prostate bed clinical target volume (CTV). The CTV will include the Prostate/Seminal Vesicles (SV) bed (with GTV). The Planning Target Volume (PTV) will be 7-8 mm around the CTV in all dimensions. All plans will be generated using IMRT. Image-guided technique using cone beam CT daily will be used to minimize uncertainty. The pelvic lymph nodes may be treated to a dose of 51 Gy at treating physician discretion.

IMRT plans will be evaluated by dose-volume histogram analysis. Less than or equal to 35% and 55% of the rectum should receive ≥65 Gy and ≥40 Gy, respectively, in calculated 2 Gy equivalent doses. Less than or equal to 50% and 70% of the bladder should receive ≥65 Gy and ≥40 Gy, respectively, in calculated 2.0 Gy equivalent doses. At least 95% of the PTV should receive the prescription dose (a minor variation will be <95% to ≥90% of the prescription dose).

B. **Arm II, Mapped Tumor Salvage RT (MTSRT)**:

Patients will receive the same treatment to the CTV of 68 Gy in 34 fractions and the GTV defined by functional imaging will receive 2.25 Gy per day for a total of 76.5 Gy (biological equivalent to 80 Gy in 2.0 Gy fractions assuming an α/β ratio of 3).

HYPOTHESIS

1. We hypothesize that increasing radiation dose to the functional imaging defined lesion in the prostate bed/pelvis will result in an improved initial complete response (reduction in PSA to < 0.1 ng/mL), which is related to long-term outcome biochemically.
2. Biomarker expression levels differ in the DCE-MRI enhancing and non-enhancing tumor regions (when applicable).
3. 10-15% of men undergoing RT have free circulating DNA (fcDNA) or tumor cells (CTC) that are related to an adverse treatment outcome.
4. Prostate cancer-related anxiety will be reduced in the MRI targeted SRT arm, because the patients will be aware that the dominant tumor will be targeted with higher radiation dose. (compared to those pts who were treated on standard arm prior to its closure).

1.0 BACKGROUND

1.1 Study Disease

Despite considerable advances in radiation delivery methods and assessing patient risk by integrating PSA parameters into decision-making for men with a rising PSA post-prostatectomy, failure rates from Salvage Radiotherapy (SRT) are relatively high overall[1, 2] and there is poor understanding of which patients are curable with standard SRT doses. Since on average about half of these men will experience a biochemical failure within 5 years after SRT, and over 30% of men undergoing radical prostatectomy will be referred for salvage radiotherapy, this is a management problem of enormous magnitude. The analysis of biomarkers is expected to improve upon the risk assessments now in practice and provide much needed molecular information that could lead to targeted therapeutic breakthroughs later.

The measurement of biomarkers from tissue in men being considered for SRT is confounded by reliance on the tissue from the prostatectomy specimen. Some studies indicate that the prostatectomy tumor tissue is representative when biomarkers are performed.[3] We plan to request archival prostatectomy tissue (if available in the Department of Pathology) for biomarker assessment and also to obtain biopsies of the surgical bed under US guidance. The biopsy of functional MRI-defined regions for biomarker analysis has never before been described to our knowledge.

Recent MRI imaging data from our group[4] and others[5-7] indicate that part of the problem with the efficacy of SRT may stem from the fact that about 70% have identifiable functional imaging abnormalities in the prostate bed, suggesting bulkier disease than previously appreciated using CT or by digital rectal exam. Radiation doses used for SRT have traditionally been low based on the belief that the disease is subclinical and microscopic. The realization of larger lesions in a potentially hypoxic environment might best be treated with a more aggressive SRT dosing strategy.

More recently additional functional imaging including fluciclovine F18/choline/PSMA or similar PET imaging to evaluate for nodal or metastatic prostate cancer has become available and FDA approved as of 2017 with others available internationally. Clinical trials have shown that this imaging technology has changed treatment planning for patients with biochemical recurrence after prostatectomy and could likewise be utilized for targeted radiation therapy boosts to areas in the prostate bed/regional lymph nodes identified.[8-12]

There is now evidence in small series that SRT dose may be an important determinant of outcome and is safe.[13, 14] There are no published Phase III trials of how best to apply SRT, although several are in progress that focus on combining androgen deprivation with SRT. There are no prospective randomized trials examining the effect of increasing SRT dose, let alone specifying this increased dose to an MRI-

defined dominant area. Also, there are no reports of a systematic effort to characterize such MRI-defined areas by biopsies and biomarker studies.

1.2 Study Agent Technique

Patients will be treated to 68Gy in 2 Gy fractions to the bed with a simultaneous incorporated boost to the DCE-MRI/PET identified lesion. Image-guided technique will be used to deliver the fractionation treatments to minimize the dosimetric error. The Clinical Target Volume (CTV) will include the Prostate/SV bed (with GTV). The Planning Target Volume (PTV) will be 3-5 mm around the CTV in all dimensions.

IMRT plans will be evaluated by dose-volume histogram analysis. Less than or equal to 17% and 35% of the rectum should receive ≥65 Gy and ≥40 Gy, respectively, in calculated 2 Gy equivalent doses.[15] Less than or equal to 25% and 50% of the bladder should receive ≥65 Gy and ≥40 Gy, respectively, in calculated 2.0 Gy equivalent doses. At least 95% of the PTV should receive the prescription dose (a minor variation will be <95% to ≥90% of the prescription dose).

1.3 Other Agent(s)

N/A

1.4 Rationale

1.4.1 Post-prostatectomy Radiotherapy

The only curative option for men with a detectable and rising PSA after prostatectomy is SRT. As prostatectomy has gained acceptance as the most common treatment for localized prostate cancer over the last 10 years, so has there been an increase in men experiencing biochemical failure and consequently the use of post-prostatectomy radiotherapy. Radiotherapy has become the mainstay of treatment for these patients. Unfortunately, there are no randomized trials that have been published for men treated with SRT. One trial, RTOG 96-01, has completed accrual but has not yet been published. The major question in this trial was whether the addition of long-term androgen deprivation therapy to SRT would result in improved survival as compared to men treated with SRT alone. Clearly, more research needs to be done in terms of how best to treat men with a rising PSA post-prostatectomy. The randomized trials in progress by cooperative groups in the United States and Europe are focusing on the use of androgen deprivation therapy combined with radiation and the extent of the radiation field (treating the pelvic lymph nodes). There are no studies related to dose escalation; yet, there is compelling evidence that the tumor burden in the prostate bed, even with men with a relatively low PSA, may be substantial and require higher radiation doses. Moreover, preliminary SRT dose escalation results from small single institution studies are promising.[13, 14]

Given that there are no randomized trials in men who have a rising PSA post-prostatectomy, conclusions about the efficacy of radiation are drawn from smaller single institution studies of SRT and the results obtained with adjuvant radiotherapy for men with high risk pathologic features in the prostatectomy specimen and an undetectable PSA (defined here as <0.1 ng/mL). The findings of a European Organization for Research and Treatment of Cancer trial (EORTC 22911)[16] showed that adjuvant RT resulted in a significant delay in biochemical and clinical failure. A report of a German Cancer Society trial, ARO 96-02/AUO AP 09/95,[17] reported a significant reduction in biochemical progression that was similar in extent to the EORTC findings. A recent report from a Southwest Oncology Group trial, SWOG 8794,[18] demonstrated a reduction in metastasis and mortality. Adjuvant RT is effective at reducing progression.

Whereas, there is no level I evidence concerning the efficacy of SRT and prolonging metastasis free or overall survival, there is an important retrospective series from Johns Hopkins reported by Trock et al[19] indicating that SRT results in a significant increase in prostate cancer-specific survival, over patients not treated with radiotherapy. However, failure rates in their experience were high and improved methods for treating men with a rising PSA post-prostatectomy are needed.

We hypothesize that increasing radiation dose to the functional imaging defined lesion in the prostate bed/pelvic nodes will result in an improved initial complete response (reduction in PSA to < 0.1 ng/mL), which is related to long-term outcome biochemically. Bernard and colleagues[14] described a biochemical dose response for men treated with SRT going from <64.8 Gy, 64.8-66.6 Gy and >66.6 Gy. King and Kapp[13] estimated a proportional gain in freedom from biochemical failure (FFBF) of about 3% per incremental 1 Gy. Another report described a series of 104 patients with a median follow-up of 36 months after treatment with adjuvant radiation using IMRT after radical prostatectomy (with or without androgen deprivation) to a median dose of 74 Gy prescribed to the planning target volume. In the salvage setting, dose escalation using IMRT has been well tolerated using doses of ≥75 Gy. Preliminary results indicate that IMRT allows for dose escalation, and grade 3 toxicity has been extremely low. Since our plan is to focus the increased dose to the functional imaging defined abnormality, toxicity will likely remain low.

1.4.2 Post-prostatectomy Functional imaging in Men with a Rising PSA

MRI performed for a rising PSA post-prostatectomy identifies residual disease in the prostate bed in the majority of cases when scrutinized by radiologists who are experts in the field.[20] The use of DCE-MRI compliments T2x-MRI and the localization of residual disease is simplified. Recurrences present as lobulated masses with intermediate signal intensity on T2w images, slightly higher than that of muscle or fibrosis and they enhance early after intravenous injection of contrast medium.[5] Two recent studies on 51 and 72 patients, with a mean PSA level of 1.9 ng/mL (range 0.1–6) and 1.23 ng/mL (range 0.2–8.8), respectively, found sensitivities and specificities of 48–61.4% and 52–82.1% for T2 imaging alone. In the same patients, DCE imaging either alone or in combination with T2 imaging, significantly improved sensitivity and specificity to 84.1–88% and 89.3–100%, respectively.[6, 7]

Similarly, PET imaging similarly has shown promise in identifying foci of residual or recurrent disease with minimize trials showing that these imaging techniques can affect treatment decisions with PSA levels as low as 0.4 or even lower in some cases.[9, 10, 21]

1.4.3 Biomarkers Related to Outcome after Salvage Radiotherapy

There are very few studies relating tissue biomarkers from prostatectomy specimens to outcome after salvage radiotherapy. One of the few papers on this topic is from our experience with Ki-67, which is a good example of the potential of biomarkers in this setting.[3] We hypothesize that tissue from US-directed biopsies of the prostate bed will yield more relevant tissue biomarker information because the recurrent tumor is likely to have different features, as compared to the tumor at prostatectomy. In the proposed work, we will be able to compare the biomarker distribution of archival prostatectomy tissue that is retrieved with that of tissue obtained via US targeted biopsies, obtained in this trial.

1.4.4 Circulating Tumor Cells in Men who are Candidates for Salvage Radiotherapy

There is only one publication to our knowledge on the topic of circulating tumor cells in men treated with salvage radiotherapy. Tombal and colleagues[22] assessed the value of RT-PCR detection of circulating prostate cells in the blood of men with a rising PSA. There were only 15 men who received SRT; but, the results were encouraging. Progression was seen in 3/5 who were positive, whereas complete responses

were seen in 7/10 who were negative. The investigation of CTCs is very promising in this patient population.

1.4.5 Free Circulating DNA

The presence of circulating cell-free nucleic acids in cancer patients has been well documented, and the correlation between elevated levels of free circulating DNA (fcDNA) and cancer has been established. In 1977, Leon et al.[23] reported increased levels of serum DNA in cancer patients compared with healthy controls. This was followed by other studies showing elevated levels of circulating serum or plasma DNA in patients with malignant tumors compared with benign controls. Sozzi et al.[24] examined plasma fcDNA levels as a marker for lung cancer and found that the median fcDNA levels in plasma were 8 times greater in cancer than that in control samples. The use of fcDNA as a biomarker for prostate cancer has been evaluated in several studies. Jung et al.[25] described no difference in fcDNA levels between patients with localized prostate cancer and BPH, although fcDNA levels were found to be significantly elevated in metastatic prostate cancer patients. Another study examined levels of a noncancer gene prostaglandin-endoperoxidase synthase 2 in 168 prostate cancer, 42 BPH, and 11 healthy individuals and found significantly elevated fcDNA levels in prostate cancer (median, 70.2 ng/mL) compared with that of BPH and healthy controls (10.5 and 7.1 ng/mL, respectively).[26] Altimari et al.[27] showed that plasma fcDNA quantification distinguished between patients with prostate cancer and healthy controls, and correlated with pathologic tumor stage. Chun et al. [28] prospectively assessed plasma fcDNA in 142 men with localized prostate cancer and 19 BPH controls and found that fcDNA is an accurate and informative predictor of prostate cancer independent of the established clinical variables such as age and PSA. Bastian et al.[29] showed a significant association of increased preoperative serum fcDNA levels in men with localized prostate cancer with PSA recurrence after radical prostatectomy, indicating that serum fcDNA levels may be a useful prognostic biomarker in patients undergoing radical prostatectomy. However, there have been no studies evaluating the role of fcDNA as a biomarker of radiation treatment response. In the present study, we will collect blood samples prospectively and assess fcDNA levels before and after RT.

1.4.6. Preliminary Data

1.4.6.1Functional MRI Analysis of Men with a Rising PSA Post-Prostatectomy

A series of post-prostatectomy patients were studied using DCE-MRI at the University of Miami. The DCE-MRI data were obtained on a 3.0T MR scanner (Siemens Trio Tim, Erlangen, Germany): resolution 0.7 mm × 0.7 mm × 2.5 mm; field of view: 360 × 264 mm; 72 slices (no gap); 5.1 ms repetition time/2.3 ms echo time; flip angle 10º. Prior to contrast injection, one set of MR images was acquired, followed by 11-12 post-contrast image datasets (37 s each). The DCE-MRI images were analyzed with software utilizing pattern recognition techniques for deconvolution of the contrast-to-time patterns. Briefly, Principal Component Analysis (PCA) is applied to detect the number of significant Principal Components. PCA also identifies sources of variations resulting from movement and other such artifacts. The image series from time points with unwanted variations are removed from further analysis. The data are then analyzed with the constrained non-negative matrix factorization (cNMF)[30] method which assumes each image represents a mixture of *k* tissue components. *k* is estimated from the number of significant principal components. A characteristic contrast-to-time curve is associated with each tissue component. cNMF determines the shape of the *k* basic curves and their weights, displayed as a heat map representing the location of the particular tissue subcomponent, related to its corresponding curve. A major advantage of the technique is that the identified curves have direct physical interpretation. We can visually inspect the temporal pattern of the contrast enhancement (fast, slow, constant) and relate the amplitude (weight) of the pattern to a particular tissue. Specifically, tumors are detected by their characteristic temporal profile, defined by relatively fast contrast uptake and washout.

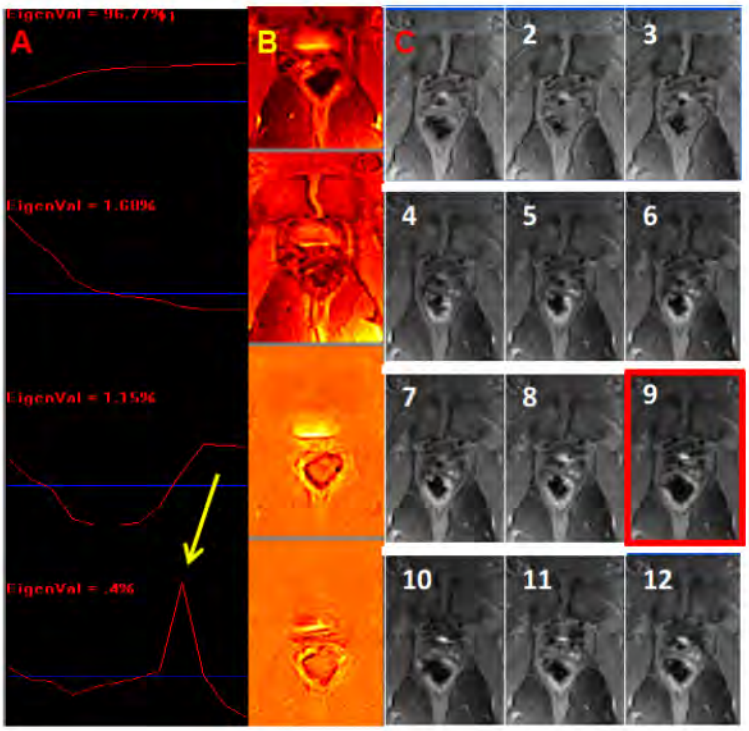

Figure 2. PCA analysis of DCE-MRI data of post-prostatectomy patient. (A) First four PCs, together with the fraction of total variance they explain. Arrow indicates an abrupt change in the 9th time-point of DCE acquisition; (B) Spatial distribution of the magnitude of the corresponding PCs scores; (C) Raw image data from the same axial slice over the course of the DCE-MRI data collection (12 time points). There is a change in the rectum shape (yellow arrow) in the 9th series (red box).

Ten of the fifteen (67%) studied patients had positive margins, two (13%) had seminal vesicle (SV) involvement, and seven (47%) had extracapsular extension. The median time to RT after prostatectomy was 18 months (3–120). Principal component analysis was applied to the DCE-MRI dataset from each patient. Visual inspection of the principal components can be extremely informative about the number and types of variations present in the data. In Figure 2, for example, the first four principal components from a DCE-MRI dataset are shown. It is clear that while the first three have a smooth character, the fourth has a spike at the 9th time-point of acquisition (marked with an arrow). Based on the corresponding score-image, it can be inferred that there was a sudden deformation of the rectum.

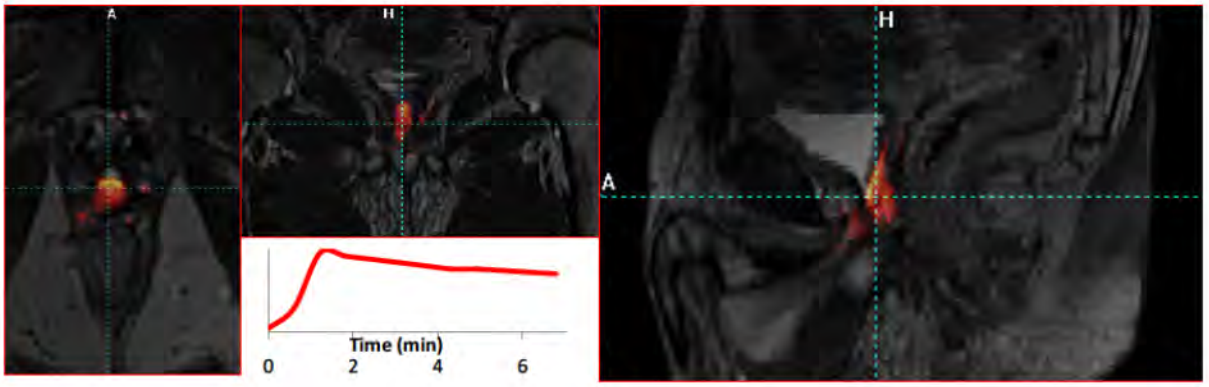

Figure 3. Analysis of DCE-MRI dataset from patient post-prostatectomy. Axial, coronal and sagittal views overlaid with a color map depicting the area of the tumor. Insert: Temporal contrast uptake and washout pattern of the tumor.

Indeed, a close inspection of the image data from this slice at this time point indicates changes in the rectum shape. These "flawed" series were removed from further analysis. Further, the Region of Interest (ROI) was outlined and cNMF applied, seeking as many patterns as the number of significant principal components. In Figure 3 cNMF results from another patient are presented. The area of the tumor, corresponding to the characteristic tumor temporal pattern is depicted with a heat map on the T2w sequences. It is clear that in this case a significant volume around the base of the bladder is suspicious for malignancy. Overall (73.3%) patients had findings suggestive of tumor as visualized by DCE-MRI; four of these (36%) had a palpable abnormality on digital rectal examination prior to RT. A total of 17 areas suspicious for malignancy were identified: 10 in the prostate bed; 4 in lymph nodes; and 3 in the SV remnants. Thus, our data indicate that T2w MRI, combined with DCE, detects abnormalities suggestive of residual tumor in the prostate bed in over 70% of patients evaluated for RT. Because patients treated with salvage RT often develop a rising PSA later and there is some evidence for an RT dose response, targeting of the contrast-enhancing areas specifically may improve tumor control and limit toxicity.

1.5 Quality of Life

IMRT is an advanced technology that delivers the total radiation dose in a pattern that closely matches the shape of the target volume in three dimensions and avoids normal tissues. This sparing of normal tissue, which is best accomplished using IMRT, decreases bladder and rectal toxicities and improves quality of life after prostate cancer therapy.[31-36] Reports by Zelefsky et al[37, 38] indicate that treatment with IMRT reduces the incidence of late grade 2 rectal toxicity compared to 3DCRT. The 8-year risk of ≥grade 2 rectal bleeding was 1.6%. The 8-year rate of ≥grade 2 urinary toxicity was 12%.

In the MAPS trial, all patients will receive IMRT. The Quality of Life (QOL) assessments will provide unique data on the effects of standard SRT on QOL relative to MRI boost SRT. We have selected a group of measures that have been used extensively in prostate cancer populations.

As an index of Prostate Cancer-Specific Anxiety we will administer the Memorial Anxiety Scale for Prostate Cancer patients (MAX-PC). The MAX-PC is an 18-item instrument designed to detect symptoms of anxiety in prostate cancer patients. It is designed to evaluate three separate aspects of prostate cancer specific anxiety on 3 subscales: anxiety related to prostate cancer in general (prostate cancer anxiety subscale), anxiety specifically centered on PSA testing (PSA anxiety subscale) and fears of cancer recurrence (fear of recurrence subscale). The MAX-PC demonstrated high internal reliability with a Cronbach's alpha of 0.89, with subscale reliabilities between 0.59-0.90 and has been validated in prostate cancer patient samples.[39]

Prostate Cancer-specific Quality of Life and Health-Related Quality of Life will be measured with the Expanded PCa Index Composite-SF-12 (EPIC-SF12).[40] Development of the EPIC-SF12 was based on the widely used University of California Los Angeles Prostate Cancer Index and has been used extensively to assess post-treatment related dysfunction among prostate cancer patients. A sub-section of this survey yields a score for the following Health Related Quality of Life subscales: physical functioning, role limitations due to physical functioning, body pain and general health. The mental summary score is comprised of vitality, social functioning, role limitations due to emotional functioning and mental health subscales. The EPIC-SF-12 has demonstrated excellent reliability (i.e., Cronbach's α>.91) across sexual function and sexual bother composites. The EPIC-SF-12 questionnaire will be used to measure changes in QOL over time.[41, 42]

Another measure of urinary function is the International Prostate Symptom Score (IPSS).[43] This scoring system has been established as a measure of radiation morbidity in patients treated for prostate cancer.[44-47] Questionnaires are available in English and Spanish.

1.6 Age, Gender and Ethnicity

Prostate cancer is a disease of adult men, with exceptionally few diagnosed at 35 years of age. We have chosen an age range of $\geq$35 to $\leq$85 years, which represents nearly all patients treated locally with radiotherapy for adenocarcinoma of the prostate. Therefore, women and children are not candidates for this protocol. Based on standard NIH definitions, we estimate that approximately 40% of patients will be White, 24% African American, 35% Hispanic and 1% other at the University of Miami.

2.0 OBJECTIVES

2.1 Primary Objectives

- The primary objective is to determine the effect of radiation boost to the imaging detected lesions on initial complete biochemical response.

2.2. Secondary Objectives

- To determine the impact of SRT boost to the MRI-identified lesion on toxicity, health-related quality of life (HRQOL), prostate cancer-specific anxiety, and prostate cancer-specific QOL.
- To evaluate biochemical and clinical failure, failure-free survival, and overall survival.
- To determine the distribution and degree of expression of tissue biomarkers by US-directed biopsies for patients who choose to undergo the optional biopsies.
- Compare PET and MRI detected lesions
- To determine the incidence and relationship of circulating DNA and tumor cells to tissue biomarkers and initial complete biochemical response.

3.0 PATIENT SELECTION

Up to 80 participants will be accrued for the entire study (Phase II and Phase III). The study is currently in Phase II which will accrue up to 40 participants. For a description of the Phase III component of the trial, please refer to protocol version 7.0, dated 10/14/2015.

3.1 Inclusion Criteria

Unless otherwise specified, the following are required at enrollment:

A. Prostate cancer patients with a PSA after prostatectomy of at least 0.1 ng/mL and up to 4.0 ng/mL within 3 months prior to enrollment.

B. Patients with or without palpable abnormalities on digital rectal exam (DRE) are eligible.

C. Minimum of 3 months since prostatectomy to allow for return of urinary continence and healing.

D. Imaging detectable lesion or lesions in prostate bed or regional LN. Each lesion should be at least 0.4 cc and a maximum of 6 cc and was obtained ≤ 3 months prior to protocol entry or enrollment.

E. No evidence of metastatic (distant) disease (pelvic nodes are allowed up to common iliac).

F. Negative bone scan if deemed necessary by treating physician obtained ≤ 4 months prior to protocol entry or enrollment..

G. No previous pelvic radiotherapy.

H. Serum total testosterone taken within 3 months prior to enrollment.

I. No concurrent, active malignancy, other than nonmetastatic skin cancer or early stage chronic lymphocytic leukemia (well-differentiated small cell lymphocytic lymphoma). If a prior malignancy is in remission for ≥ 3 years then the patient is eligible.

J. Ability to understand and the willingness to sign a written informed consent document.

K. Zubrod performance status <2.

L. Patients must agree to fill out quality of life/psychosocial questionnaires.

M. Age ≥35 and ≤85 years.

3.2 Exclusion Criteria

Unless otherwise specified, the following are required at enrollment:

A. Prior androgen deprivation therapy is not permitted if it was within 6 months previous to signing consent form. (NOTE: Therapy given as part of the planned course of radiation is allowed)

3.3 Enrollment Procedures

3.3.1 Enrollment

Patients can be enrolled only after eligibility criteria are met. The eligibility checklist must be completed prior to initiation of the registration process.

All eligibility requirements should be reviewed by the study coordinator and the eligibility checklist should be completed and signed by the local Principal Investigator or designated Sub-PI prior to the patient being enrolled into the study.

3.3.2 Cancellation Guidelines

If a patient does not receive protocol therapy, the patient may be withdrawn from the study. Patients who are enrolled on study but not treated will be excluded from all analyses.

3.3.3 Emergency Registration

N/A.

4.0 TREATMENT PLAN

4.1 Pre-Enrollment Imaging

T2, T1 non-contrast, T1 DCE and DWI MRI scans will be done routinely, when possible, in all patients being planned for external beam radiotherapy for prostate cancer. These sequences will be routinely obtained at 2.5 mm intervals to include the pelvis and prostatic bed. It is suggested that a diet designed to reduce bowel gas may be recommended the day before the MRI. The patient will be instructed not to void before the scan, to mimic bladder position during treatment. MRI exclusions include ferromagnetic metal in body/eye, pacemaker, defibrillator, other mechanical device, or extreme claustrophobia (medication with anti-anxiety agents, such as Ativan, may be used). Since the DCE-MRI scan involves the use of gadolinium, renal function will be assessed to ensure it is adequate.

PET imaging when obtained (flucicloving F 18, Choline, PSMA or other): Will be performed per imaging center.

4.2 Screening

Eligible patients will be screened by dedicated protocol study team staff for fulfillment of eligibility criteria as described in Sections 3.1 (Inclusion Criteria) and 3.2 (Exclusion Criteria).If the patient is deemed eligible, protocol consent will then be obtained. Enrollment will proceed as described in Section 3.3. Data collection and storage procedures are described in 15.5

4.3 Prostate Bed Biopsy

In cases when the post-treatment MRI identifies a suspicious lesion, the treating physician will recommend a US-guided biopsy (typically 2-2.5 years post-treatment). The specifications for this biopsy are described below.

As per the discretion of the urologist, prior to biopsy collection, antibiotic prophylaxis may be prescribed (e.g. Levaquin 500 mg daily, Ciprofloxacin 500 mg twice daily, or a similar antibiotic depending on allergy history and physician preference), will be delivered for five days beginning the day before the procedure. Other antibiotic treatment may be administered as part of the biopsy procedure. Aspirin, anticoagulants and vitamin supplements will be temporarily discontinued at least one week prior to the procedure. Therapy may be restarted per standard practice for prostate bed biopsies (typically a day later if there is no bleeding). All patients will be placed in the left lateral decubitus position. Immediately prior to the procedure, 10 cc of 1% Lidocaine will be injected into the bed under ultrasound guidance, typically using a 22 gauge 7-inch needle. The syringe will be aspirated before the lidocaine injection to prevent unintentional injection into the vascular compartment. An ultrasonographic wheal will be viewed in the sagittal plane between the rectal wall and base of the seminal vesicles.

For patients who undergo prostate bed targeted biopsies, (the actual number of cores collected will depend on the size of the lesion. Transrectal ultrasound biopsies will be performed using spring-loaded biopsy gun with an 18 gauge Tru-cut biopsy needle or a similar device. The procedure will be performed by a urologist in the Department of Urology at University of Miami Medical School of Medicine using the ArtemisTM system (Eigen Inc., Grass Valley, California) for US biopsies or other dedicated MRI guided biopsy device. The image fusion system which may be utilized with the Artemis system is FDA approved and is being utilized to localize biopsies for research purposes only. Every attempt will be made to collect at least one biopsy within the area of the tumor, as indicated by MRI, using standard methods for a prostate bed biopsy. During the course of the procedure, hemorrhage may be visualized within the bladder following needle biopsy. If this is the case, or if gross blood is noted at the urethral meatus, bladder catheterization and clot irrigation may be indicated, as determined by the urologist. The biopsies will be paraffin embedded in pathology per routine procedure.

4.4 CT-Simulation

The MRI (Section 4.1) will be fused to the CT-simulation scan. CT-simulation will then be obtained under the same conditions with typical pelvic immobilization. Images will be taken at 1.5 mm intervals from the top of the sacrum to 1 cm below the ischial tuberosities (to include the entire bladder and rectum). All patients will have tattoos placed at the anterior, right lateral, and left lateral isocenter skin points. Patients are instructed to use a rectal enema prior to coming into the department for simulation, which is part of the routine procedures.

4.5 Normal Tissue Contouring Guidelines

Normal tissues will be outlined as solid structures, including the rectum, bladder and femoral heads. The penile bulb will be outlined as a reference structure. No constraints will be placed on the penile bulb, but doses will be recorded. The rectum will be outlined from the anterior flexion of the rectosigmoid superiorly to the ischial tuberosities inferiorly. The bladder and contents will be contoured. The femoral heads should be outlined down to the region between the greater and lesser trochanters.

The potential bowel space within 5 cuts of the CTV should be outlined to minimize dose to the bowel. The potential bowel space includes the areas on either side of the bladder medially.

4.6 Prostate Bed Conformal PTV Planning and Constraints

Patients will be randomized to one of two study arms as described in Section 3.3. Image-guided technique will be used to deliver the fractionation treatments to minimize the dosemetric error. The Clinical Target Volume (CTV), will include the Prostate/SV bed (with MRI GTV). The Planning Target Volume (PTV) will

be 7 mm around the CTV in all dimensions. All patients will be treated with IMRT. The isodose level of the prescription dose shall be kept to 85% or higher, covering the clinical target volume (CTV: prostate bed) plus a planning target volume (PTV) for uncertainty of 7 mm everywhere, except posteriorly, where the margin would be an average 7 mm (6 – 8 mm is acceptable). The pelvic lymph may be treated to a dose of 51-54 Gy at the treating physicians discretion as long as dose constraints for normal tissues are met. The prescription dose to at least 95% of the PTV is 68 Gy using IMRT in 34 fractions, the mapped tumor (MT) boost region will receive an absolute dose of 76.5 Gy in 34 fractions. Assuming an α/β ratio of 3.0, this would be equivalent to 80 Gy in 2.0 Gy fractions.

Treatments usually are given 5 times per week. The bladder, rectum, penile bulb and urethra will be defined on the CT and MRI scans. Dose volume histogram (DVH) analysis will be used to assess plan acceptance per the RTOG guidelines. These include:

Rectum: Less than or equal to 35% and 55% of the rectum should receive ≥ 65 Gy and ≥ 40 Gy, respectively. A variation will be noted if up to an additional 10% of the rectal volume receives above the target doses specified. The inclusion of rectal volumes beyond these constraints will be considered a protocol violation. In many patients, these constraints may be easily met and every attempt should be made to achieve the best dose distribution possible.

Bladder: Less than or equal to 50% and 70% of the bladder (minus prostate bed CTV) should receive ≥ 65 Gy and ≥ 40 Gy, respectively. The criteria for the bladder have been relaxed because the dosemetric relationship of volume exposed to the specified marker doses is much less clear and the bladder neck is included in the CTV. A primary variation will be noted if up to an additional 7.5% of the bladder volume receives above the target doses specified. The inclusion of bladder volumes beyond these constraints will be considered a secondary protocol variation; it will not be considered a protocol violation. In some patients, the bladder will be relatively empty and the majority will be in the PTV.

4.7 Proteomic and Genomic Analyses of Blood

The objectives are to examine protein and single nucleotide polymorphisms in blood products for patterns that predict patient outcomes (e.g., prostate bed biopsy positivity, biochemical failure, and side effects). Blood samples will be collected according to the time points described in the Study Schedule (Appendix I). While these are exploratory studies, of key importance is to have such samples collected prospectively on a well-defined group of patients. Promoter hypermethylation is a common mechanism for tumor suppressor inactivation in human cancers and is a promising target for molecular detection of prostate cancer in blood (see section 4.10 on free circulating DNA in blood below).

4.8 Circulating Tumor Cells (CTCs) in Blood.

The objective is to capture CTCs in patients' peripheral blood samples and to study the CTCs for expression of biologically relevant protein markers by an immunocytochemical staining procedure. Peripheral blood will be collected in .5 ml SST plus blood collection tubes (BD Vacutainer). After 10 minutes, serum will be separated by centrifugation at 3500 rpm for 15 minutes at room temperature after which DNA will be extracted immediately. DNA will be extracted from 1 ml serum out using QIAamp UltraSens virus kit (Qiagen) following the manufacturer's protocol and stored and -20°C until further analysis. 5 ml from the anonymized blood samples will be used for CTC analysis, which includes enumeration and biomarker quantification.

We will test whether absolute pretreatment CTC counts and treatment-induced changes in CTC counts correlate with response to therapy as defined in sections 9.0 and 14.0. As a further validation of microfilter CTC capture, parallel samples will be analyzed using the currently-available FDA approved CTC collection platform, Veridex CellSearch. Blood samples will be collected at the time points

described in Study Calendar (Appendix I) or upon evidence of disease progression, whichever comes first.

Upon receipt, whole blood samples will be immediately diluted 1:1 in 1x PBS and 1% formalin for a final volume of 15ml, for 10 minutes at room temperature. Following partial fixation, blood is passed through the microfilter device using a syringe with steady low pressure. Following microfiltration, the filter will be disengaged from the device, and placed on a clean glass slide. 1uL drops of CureMount (Instrumedics) will be placed under each of the four corners of the microfilter. The microfilter and glass slide will be incubated under a UV lamp for 1-2 minutes. Our exclusive filter design enables higher CTC recovery as compared to the currently approved CellSearch technologies.[48] A clear advantage of our system is the ability to do cell analysis, including IF, directly on membrane. CTC will be defined as intact epithelial cells staining positive for cytokeratin and negative for CD45. Following UV crosslinking, the microfilters are subjected to IF. Total numbers of CTC will be counted and recorded by examining the entire area of the microfilter. At the same time, parallel samples will be collected and transported for overnight delivery to Quest Diagnostics, CA where CTC enumeration will be performed using the commercially available FDA approved CellSearch platform.

4.9 Free Circulating DNA (fcDNA) in Blood

Blood will be collected in 10 mL serum plus blood collection tubes (BD Vacutainer) at the time points described in the Study Calendar (Appendix I) or upon evidence of disease progression, whichever comes first. Serum will be separated by centrifugation at 3,500 rpm for 15 minutes at room temperature, after which DNA will be extracted immediately. DNA will be extracted from 1 mL serum using QIAamp UltraSens virus kit (Qiagen) following the manufacturer's protocol and stored at −20°C until further analysis.

Serum DNA will be quantified by real-time PCR for glutathione S-transferase, pi (GSTP1), based on the previous study by Bastian et al [29]. Amplification primers (forward, 5′ AGG CCT TCG CTG GAG TTT C 3’; reverse, 5′ CCA TGC TGG GAG CTC TGAG 3’) and an amplicon-specific fluorogenic hybridization probe (6FAMCGC CGC AGT CTT CGC CACCTAMRA) will be used. The PCR will be carried out in an iCycler (Biorad). The PCR mixture will consist of 12.5 µL of Taqman Universal master mix (Applied Biosystems), 5 pmoles of probe, and 5 pmoles each of the forward and reverse primer in a 25 µL reaction volume. Each sample will be analyzed in triplicate. All PCR runs will include a negative control using water blanks. A standard curve will be generated for each PCR run using serial dilutions of human placental DNA (Sigma) at concentrations ranging between 160 ng/µL to 160 pg/µL. For calculation of DNA concentrations, the standard curve will be interpolated with the threshold cycle of unknown target samples.

4.10 Supportive Care Guidelines

All supportive therapy for optimal medical care will be given during the study period at the discretion of the managing physician(s) within the parameters of the protocol and documented. Most patients have grade 2 or lower urinary or bowel symptoms during and after treatment. Symptoms will be documented at least once a week as part of routine treatment clinic. In very rare cases, patients may experience extreme symptoms, such as urinary obstruction, diarrhea or significant bleeding requiring transfusion. Supportive measures, catheter placement and medication will be instituted as needed. Common supportive medications include:

- Antidiarrheals: Antidiarrheals, such as loperamide hydrochloride or diphenoxylate-atropine, may be used as needed. The amounts of the drug(s) and dates used should be documented as much as possible.

- Antispasmatics: Antispasmatics, such as oxybutynin or tolterodine tartrate, may be used as needed. The amounts of the drug(s) and dates used should be documented as much as possible.
- Alpha Blockers: Alpha blockers, such as doxazosin mesylate, terazosin hydrochloride or tamsulosin hydrochloride may be used as needed. The amounts of the drug(s) and dates used should be documented as much as possible.
- Analgesics: Analgesics is a broad category, including non-narcotic and narcotic agents. The use of non-narcotic agents, such as acetaminophen, non-steroidal anti-inflammatory agents or phenazopyridine hydrochloride for radiotherapy treatment-related pain should be documented as much as possible. Narcotic use as a consequence of treatment should also be recorded.
- Erectile Dysfunction: Erectile dysfunction may be treated with medical management (e.g., phosphodiesterase inhibitors), vacuum pumps or other devices as appropriate. The amounts of the drug(s) used and the dates that medical management or the use of mechanical devices was started should be documented.

4.11 Duration of Therapy

- The therapy will be delivered over approximately 7– 8 weeks.
- Treatment will be stopped for grade 4 acute toxicity (according to the current version of Common Terminology Criteria for Adverse Events (CTCAE version 4), but may be resumed per protocol if the treatment break is less than 10 working days. Since we have never observed grade 4 toxicity acutely using IMRT such an event is unlikely. If grade 4 toxicity resolves beyond the 10 days the treating physician will decide whether to give additional RT.
- Treatment will be stopped if metastasis is detected by radiographic or pathologic evidence and the patient will be removed from the study, but not from intent-to-treat analysis. A work-up for metastasis during treatment will only be carried out if the treating physician deems necessary.
- In case that the 2-year MRI exam identifies a suspicious for cancer lesion, US-guided biopsies will be taken.

5.0 CLINICAL AND LABORATORY EVALUATIONS

5.1 Baseline/Pretreatment Evaluations

Prior to Enrollment

- History and physical exam, including evaluation of patient's ability to perform daily activities (Zubrod performance status) within 8 weeks prior to protocol entry.
- Blood tests within 3 months prior to protocol entry or enrollment unless otherwise indicated. Up to five tubes of blood will be collected:
    - PSA level
    - Serum testosterone .
- Blood will be collected for research fluid testsBone scan if deemed necessary by treating physician obtained ≤ 4 months prior to protocol entry or enrollment.
- DCE-MRI and or PET of prostate bed/pelvis at 1.5T or 3.0T MRI (preferably 3.0T) within 3 months prior to enrollment. Identifiable DCE-MRI tumor lesion or lesions. The enhancing lesion(s) in the prostate bed should be at least 0.4 cc and a maximum of 6 cc in total. (While PET may be used to identify GTV, MRI is still required for RT tx planning)
- A pathology review at the University of Miami of the outside biopsy material prior to enrollment.
- Psycho-Social Questionnaires:

- The Expanded Prostate Cancer Index Composite Questionnaire-SF12 (EPIC-SF12)
- Memorial Anxiety Scale for Prostate Cancer patients (MAX-PC)

- International Prostate Symptom Score (IPSS).

After enrollment and Prior to RT

- CT simulation.

5.2 Evaluations during Radiation Therapy

- Weekly history and physical including performance status (Zubrod), and toxicity.

5.3 Evaluations During the Last Week of Radiation Therapy

- History and physical including performance status (Zubrod), and toxicity.
- Blood (up to 5 tubes) will be collected:
    - PSAlevel I
    - Blood for research fluid tests
-
- Psychosocial questionnaires:
    - The Expanded Prostate Cancer Index Composite Questionnaire-SF12 (EPIC-SF-12)
    - Memorial Anxiety Scale for Prostate Cancer patients (MAX-PC)
- International Prostate Symptom Score (IPSS)

5.4 Post-treatment Evaluations

- History and physical, performance status (Zubrod), and toxicity at 6 weeks, 3 months, and then every 6 months for 5.25 years after completion of RT.
- Blood (up to 5 tubes) work in relation to RT:
    - PSA at 6 weeks, 3 months, and then every 6 months for 5.25 years.
    - Serum total testosterone 9 months after completion of RT.
    - Blood for research fluid tests will be collected at 3 months, 9 months and 2-2.5 years after completion of RT.
- DCE-MRI and or PET with timed contrast at 3 months, 9 months, and 2-2.5 years after completion of RT.
    - Should a lesion be identified, the treating physician will discuss management decisions with the participant
- Bone scan for a PSA of ≥2 or physician concern for metastasis.
- Psychosocial questionnaires will be administered at follow-up at 6 weeks, 3 months, 9 months, 15 months and yearly to 5.25 years:
    - Memorial Anxiety Scale for Prostate Cancer patients (MAX-PC).
    - The Expanded Prostate Cancer Index Composite Questionnaire-SF-12 (EPIC-SF12).

- International Prostate Symptom Scale (IPSS) at will be done at each follow-up visit for 5.25 years. This includes 6 weeks, 3 months and every 6 months after RT for 5.25 years.

Note: Measurements and follow-up visits should occur within ± 2 weeks up to the 3 months visit and within ±8 weeks for subsequent measurements/visits

5.5 Early Discontinuation of Therapy

See Criteria for Discontinuation of therapy in section 12.0.

6.0 DOSING DELAYS/DOSE MODIFICATIONS

6.1 Study Agent

The study agent in this protocol is radiation. The experimental component of the treatment is an MT boost of radiation delivered to the DCE-MRI-defined dominant region(s) by dose painting at 2.25 Gy per fraction. The MT boost region will receive an absolute dose of 76.5 Gy.

6.2 Other Agents

N/A

7.0 AGENT FORMULATION AND PROCUREMENT

N/A

8.0 CORRELATIVE/SPECIAL STUDIES

Isolation, quantification and staining of CTC's will be done. It is expected that over 30% of patients in the MAPS trial will have detectable CTC's. CTC levels will be obtained pretreatment and at the time of the 9-month blood draw at which time the endpoint PSA will be determined. The incidence and characteristics of the CTC's will be studied. Along these lines, fcDNA in serum will be quantified at both time points. We will test the relationship of baseline and endpoint obtained CTCs and fcDNA levels to biochemical complete response and nine months. The changes in CTC and fcDNA levels from baseline to the 9-month endpoint will be tested using paired t-test or signed rank test. Changes in the proportion of patients with levels above180 ng/mL will be examined with McNemar's test.

9.0 MEASUREMENT OF EFFECT

The primary endpoint of the MAPS trial, referred to below as *PSA response rate*, is the proportion of study patients with PSA <0.1 ng/mL at 21 months after completion of study treatment. All patients will be evaluated for clinical or biochemical evidence of relapse as defined below. Section 14 provides further details with respect to quantitative endpoints.

9.1 Definitions

- *PSA response rate*: The proportion of study patients with PSA <0.1 ng/mL at 21 months after completion of study treatment.
- *Acute toxicity:* Toxicity occurring during treatment and within three months of completing treatment.
- *Late toxicity:* Toxicity occurring more than three months after treatment completion. *Failure rate:* The cumulative incidence of biochemical or clinical failure allowing for competing risk as needed. Clinical failure is defined as at least a 25% increase in the size of the tumor relative to the smallest volume recorded, or new extension of tumor beyond the capsule, or re-extension of tumor beyond the capsule after initial regression, or urinary obstructive symptoms with carcinoma found at TURP. Biochemical failure is defined as PSA ≥ nadir + 2 ng/mL.

- *Failure-free Survival (FFS):* The elapsed time from start of radiotherapy to first documented evidence of biochemical or clinical failure or death from any cause, whichever occurs first. In the absence of any event defining failure, follow-up time will be censored at the date of last documented failure-free status.
- *Overall Survival (OS):* The elapsed time from start of radiotherapy to death from any cause. For surviving patients, follow-up will be censored at the date of last contact.
- *Biomarker expression:* Quantification of the amount of the biomarker specific immunohistochemical staining in the area of tumor.
- *QOL:* **Two** contemporary instruments will be utilized to assess patient function and bother (Expanded Prostate Cancer Index Composite-SF12 (EPIC-SF12) and prostate cancer-specific anxiety Memorial Anxiety Scale for Prostate Cancer patients (MAX-PC).

9.2 Guidelines for Evaluation of Measurable Disease

9.2.1 Clinical primary tumor response will be measured by palpation and recorded in the following ways:

- Pretreatment: A representative drawing of the pretreatment tumor status on DRE, if palpable, will be recorded in the radiotherapy chart.
- Post-treatment: The change in palpable tumor volume will be recorded qualitatively.

9.2.2 PSA levels:

In 98% of patients treated with salvage radiotherapy there is a drop in PSA within 3 months. Those patients that PSA levels have not dropped should be investigated to define the site of progression (local-regional vs. distant metastases). In the rest of the patients, a rising PSA later heralds relapse. Biochemical failure will be modeled after the Nadir+2 definition.[49] Evaluation of patients with a rising PSA profile will include a bone scan, MRI-pelvis/prostate bed, and prostate bed biopsy.

9.2.3 Nodal Relapse

Nodal relapse will be scored as having occurred when appropriate clinical-radiographic evidence(CT or MRI evidence) of this becomes evident (biopsy proof not required in the presence of a rising PSA).

9.2.4 Hematogenous Relapse

Hematogenous relapse will be scored as having occurred when appropriate clinical-radiographic evidence, shows this to be so (biopsy proof not required).

10.0 MEASUREMENT OF TOXICIY

Acute proctitis and cystitis lasting for up to 4 months after completion of radiotherapy are accompaniments of radiotherapy for carcinoma of the prostate. The severity of these reactions is routinely evaluated during treatment and will be scored according to the criteria outlined in Appendix II. In our extensive experience, grade 3 or 4 acute toxicities are rare.

Delayed toxicities are usually related to urinary, rectal, and sexual function. The anticipated urinary and rectal toxicities and severity criteria are those shown in Appendix II. Other untoward clinical events will, however, also be documented.

11.0 ADVERSE EVENT REPORTING

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/reporting/ctc.html).

11.1 Definitions

11.1.1 Adverse events

Adverse events (AE's) will use the descriptions and grading scales found in the NCI Common Toxicity Criteria in Appendix II.

Adverse events: Any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). Each AE is a unique representation of a specific event used for medical documentation and scientific analysis.

11.1.2 Serious Adverse Events

A ***serious adverse event*** (SAE) is defined in the FDA CFR 312 as any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization, or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

SAE's are defined by FDA and therefore seriousness (not severity) serves as a guide for defining regulatory reporting obligations for patient/subject safety. **Serious** is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning.

The definition of serious adverse event (experience) also includes ***important medical events***. Medical and scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or **may require intervention** to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

11.1.3 Expected Events

Expected events are those that have been previously identified as resulting from administration of the agent.

11.2 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (please follow directions for routine reporting provided in the Data Reporting Section). Additionally, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care. The following sections provide information about expedited reporting.

Events resulting from concurrent illnesses and reactions to concurrent medications must be reported as adverse events.

Any worsening of the patient's clinical condition while the patient is on study will be considered to be an adverse event unless it is within the normal range of disease fluctuation for that patient.

11.2.1 Determination of Reporting Requirements

Reporting requirements may include the following considerations:

1. Whether the patient has received an investigational or commercial agent;
2. The characteristics of the adverse event including the grade (severity), the relationship to the study therapy (attribution), and the prior experience (expectedness) of the adverse event;
3. The Phase (1, 2, or 3) of the trial; and
4. Whether or not hospitalization or prolongation of hospitalization was associated with the event.

11.2.2 Steps to determine if an adverse event is to be reported in an expedited manner:

- Step 1: *Identify the type of event using the NCI Common Toxicity Criteria (CTC).*

  The CTC provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTC can be downloaded from the CTEP home page (http://ctep.cancer.gov). Additionally, if assistance is needed, the NCI has an Index to the CTC that provides help for classifying and locating terms. All appropriate treatment locations should have access to a copy of the CTC.

- Step 2: *Grade the event using the NCI CTC.*
- Step 3: *Determine whether the adverse event is related to the protocol therapy (investigational or commercial).*Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.
- Step 4: *Determine the prior experience of the adverse event.*

11.3 Reporting Methods

11.3.1 FDA Reporting

N/A

11.3.2 IRB Reporting

Report of AEs and SAEs must be reported according to UM IRB policy and procedures.

11.3.3 Follow-up Reporting

For all SAE's, the investigator is obligated to pursue and provide follow-up reporting information until the event has resolved or until an acceptable medical endpoint has been reached or the patient is lost to follow-up.

12.0 CRITERIA FOR DISCONTINUATION OF THERAPY

Treatment will be stopped for grade 4 acute toxicity (according to the current version of Common Terminology Criteria for Adverse Events (CTCAE version 4), but may be resumed per protocol if the treatment break is less than 10 working days. If grade 4 toxicity resolves beyond the 10 days the treating physician will decide whether to give additional RT.

Treatment will be stopped if metastasis is detected by radiographic or pathologic evidence and the patient will be removed from the study. A work-up for metastasis during treatment will only be carried out if the treating physician deems necessary.

Patients may discontinue therapy at the treating physican's discretion, i.e. due to non-compliance. Patients may withdraw their consent at any time.

13.0 DATA REPORTING

Data must be submitted according to the protocol requirements for ALL patients registered. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.0 STATISTICAL CONSIDERATIONS

Up to 80 participants will be accrued for the entire study (Phase II and Phase III).The study is currently in Phase II which will accrue up to 40 participants. For a description of the statistical considerations of the Phase III component of the trial, please refer to protocol version 7.0, dated 10/14/2015.

14.1 Overview

This is a single-arm Phase II trial with the primary objective of determining whether MRI-targeted boost SRT (MTSRT) improves the rate of PSA response (i.e., PSA < 0.1 21 months post treatment completion) in men receiving radiation therapy due to rising PSA post-prostatectomy. Secondary objectives include evaluation acute and late occurring toxicity, quality of life, biochemical and clinical failure, and survival. Additionally, blood and biopsy tissue samples from study patients will provide data for various biomarker studies described in the Bankhead Coley Team Science project "Integrated biomarkers for individualized prostate cancer therapy".

A single stage design without interim analysis of the primary endpoint is proposed for this trial because it would not be practical or desirable to suspend accrual to accommodate an interim assessment of PSA response, which requires nine months follow-up. Moreover, PSA response is not a perfect near term surrogate for long term benefit and thus not a definitive basis for an early conclusion regarding efficacy. The trial involves standard therapy with dose escalation, and an evaluation of PSA response based on accrual of 40 evaluable patients will provide information needed to design a subsequent trial evaluating long term outcome. Early stopping rules based on monitoring the toxicity of study treatment are provided in Section 14.6.

14.2 Sample size, accrual rate and study duration

Sample size is based on the primary objective of demonstrating that MTSRT increases the rate of PSA response to treatment, by which we mean undetectable PSA level (<0.1) when assessed 21 months after completing treatment. We expect the PSA response rate in the standard SRT to be 60%.[50] Assuming sufficient follow-up to determine PSA nine months post treatment, a total of 40 patients in the single-arm study provides 83.9% power to detect an absolute increase of 20% in the PSA response rate, from 60% to 80%, using a one-sided Fisher's exact test with 5% significance level. To ensure a minimum of 40 study patients evaluable for PSA response as our main study endpoint, we plan to enroll a total of 44 patients assuming 10% drop-out.

We plan to accrue 1 patient per month during the first year of this protocol. After the ramp-up phase is completed, we anticipate 1.5 patients per month. This rate was also calculated considering increasing prostate cancer volumes due to expansion of the department (anticipated growth at Sylvester main and Deerfield branch). Thus accrual will be complete in about 3 years; 12 in year 1 and 18 per year in year 2 and 3. Patients will be followed for a minimum of five years, giving total study duration of 8 years. The main efficacy endpoint will be analyzed after enrollment is complete and all patients have been

assessed for PSA response nine months post treatment, and a final efficacy analysis of all endpoints will be carried out at the conclusion of study when patients have been followed for 5 years. Analyses of some secondary endpoints, including acute toxicity, psychosocial parameters, and biomarker distribution on US guided biopsies, and initial MRI findings may be reported before the efficacy analyses. These secondary endpoints will be analyzed after all planned patients have been accrued, completed treatment and have a minimal potential follow-up of 3 months from the end of RT.

14.3 Definitions and endpoints:

Evaluable: Patients who are study eligible and receive an initial dose of *MTSRT* will be considered *evaluable for safety*, regardless of whether or not the full course of radiation treatment is completed according to protocol. To be *evaluable for efficacy,* study eligible patients must either (1) complete radiation treatment and the nine month post treatment PSA assessment or (2) initiate therapy but develop evidence of biochemical or clinical failure, or die from causes related to prostate cancer, within nine months of stopping or completing treatment. In the latter case (2), which is expected to be rare, patients will be included as non-responders in the evaluation of PSA response rate. The set of patients who are evaluable for efficacy comprise the main analysis set.

Exclusions: Any patient who is enrolled on study but does not receive an initial dose of radiation treatment will be excluded from all efficacy analyses. Any patient who initiates treatment and is later found to be ineligible for study (e.g., protocol violation) will be withdrawn from study but will be followed for toxicity and clinical outcome; the experience of such patients will be characterized separately from that of patients who are evaluable for efficacy. Reasons for exclusion of enrolled patients from analysis of safety or efficacy will be characterized.

Study endpoints are defined in **Section 9.1.**

14.4 Stratification Factors

Not applicable

14.5 Analysis plan

The main analysis of study findings will be done for all patients who meet evaluable criteria as stated in Section 14.3. As noted above, analyses of some secondary endpoints, including acute toxicity, psychosocial parameters, tissue and blood product-related biomarker distribution on US-guided biopsies, and initial MRI findings may be reported before the efficacy endpoints, including the primary endpoint. These secondary endpoints will be analyzed after all planned patients have been accrued, completed treatment and have a minimal potential follow-up of 3 months from the end of RT. An initial analysis of clinical outcome (efficacy) is planned after all patients have been assessed for PSA levels at 9 months and a final analysis will be done at the completion of the planned 5 year follow-up of all study patients. Statistical tests will be two-sided with 5% significance level.

Statistical analysis will include descriptive statistics for patient demographics and baseline disease characteristics. Counts and percentages will be used to summarize the distribution of categorical variables while median, range, mean and standard deviation will be used for continuous variables. Baseline characteristics will include age, race/ethnicity, PSA, PSA doubling time, pT-category, pathologic Gleason score, and performance status. Biomarker measurements and proteomic/genomic profiles obtained from baseline biopsy will also be summarized with descriptive statistics.[51]

Treatment received will be summarized by the number and duration of treatment delays, and the rates of discontinuation or completion. Safety analysis will include a detailed tabulation of acute and late occurring toxicity by type and grade. Additionally, we will estimate the cumulative incidence (from start of treatment) of grade 2+ and 3+ genitourinary (GU) toxicity and of grade 2+ and 3+ gastrointestinal

(GI) toxicity. Death without the toxicity of interest will be treated as a competing risk, and toxicity rates will be reported.

The primary trial endpoint, *PSA response rate*, will be estimated as a proportion with corresponding 95% confidence interval by the exact binomial method. Biomarker and proteomic/genomic characteristics of baseline prostate bed biopsy tissue will be summarized by descriptive statistics. Additionally, biomarker and proteomic/genomic characteristics measured in blood samples obtained at baseline, RT completion, and 3 months post RT will also be studied and changes from baseline will be tested for significance using t-test (means) or McNemar's test (proportions) for paired data. (For biomarker studies, nonparametric tests or data transformations to attain approximate normal distributions will be applied as needed.) Logistic regression models will be used to investigate the association between baseline factors, including biomarkers and proteomic/genomic profiles, and PSA response. Changes in biomarkers and proteomic/genomic characteristics measured in blood will also be investigated for association with PSA response.[52]

Patients will be followed for disease progression and vital status for a period of five years after completing study treatment. Progression of disease will be categorized as biochemical failure (BF), clinical failure (CF), or combined (BF + CF), where combined failure refers to documented evidence of BF and CF occurring within 6 months of each other with the earlier date used. CFs will be further categorized as local, nodal, or distant. Start of subsequent therapy will be considered a failure event for selected analyses as indicated in the table below. Deaths will be categorized as related/unrelated to prostate cancer. The number of observed failures will be tabulated by failure type. Similarly, vital status will be tabulated by presence or absence of disease at last follow-up.

Time to event endpoints will be analyzed by Kaplan-Meier (KM) or competing risk (CR) methods as indicated in Table 14.5.[53, 54] Where the Kaplan Meier method is used, point estimates and 2-sided 95% confidence intervals for event-free rates will be reported for selected times such as 1, 2 and 5 years from treatment start using Greenwood's variance and the log-log transform method. Median event-free or overall survival time, if attained, will also be reported. Cox regression models will be used to explore the prognostic effect of baseline characteristics as well as biomarkers and proteomic and genomic profiles. Regression findings will be expressed as hazard ratios and corresponding 95% confidence intervals. For analyses involving competing risks, cumulative incidence rates will be reported for selected times with corresponding 2-sided 95% confidence intervals based on the variance estimator of Aalen and the log-log transform method. Regression models investigating prognostic factors will be fit by the method of Fine and Gray. [55, 56] Where study data indicate that at most a small number of competing risk events have occurred, analysis will be simplified by treating such events as censored observations in a Kaplan-Meier analysis, since the resulting overestimation of the event rate will be negligible.

Table 14.5. Time-to-event endpoints.

Endpoint	Analysis	Events (earliest)	Competing risks	Censoring
Failure rate	CR	CF, BF, BF+ CF (within 6 months of each other). Start subsequent therapy. Death related to prca without prior evidence of failure.	Death unrelated to prca	Last clinical +PSA assessment
Toxicity rate (to be done separately for GI and GU)	CR	Onset of grade 2+ and 3+ toxicity	Start subsequent therapy Death, any cause	Last contact
Failure free survival (FFS)	KM	CF, BF, BF+ CF. Start subsequent therapy. Death, any cause.	n/a	Last clinical or PSA assessment
Prostate cancer mortality	CR	Death related to prca	Death unrelated to prca	Last contact
Overall survival (OS)	KM	Death, any cause	n/a	Last contact

KM: Kaplan-Meier. **CR**: competing risk. **BF**: Biochemical failure. **CF**: clinical failure. **prca**: prostate cancer. **GI**: gastrointestinal. **GU**: genitourinary.

QOL scores will be calculated in accordance with established scoring methods for each instrument. Descriptive summaries of scores at baseline and each subsequent follow-up will include median and range, means and standard deviations. Where criteria for clinically meaningful differences have been established, we will also categorize changes in these scores (computed by subtracting baseline from subsequent score) as indicating improvement, worsening, or no change and summarize these by counts and percentages. Further analysis allowing for repeated measurement will be conducted using mixed models.

14.6 Interim monitoring

The Research Team will continuously monitor study accruals, toxicities and clinical outcome. The Sylvester Comprehensive Cancer Center's Data and Safety Monitoring Committee (DSMC) will monitor this protocol according to the Cancer Center's DSM Plan. DSMC oversight of the conduct of this trial includes ongoing review of adverse event data and periodic review of trial outcomes. Additionally, the Sylvester Protocol Review Committee will monitor study progress with respect to patient accrual.

Early stopping for excess toxicity. We propose the following guidelines for the Sylvester DSMC (see also Appendix III) in its review of accumulating data on toxicity of study treatment. The proposed guidelines were developed using Bayesian methods, which can be applied at any stage of enrollment without advance specification of the number of interim analyses to be performed, or the number of patients evaluable for toxicity at the time such assessments are made.[57, 58]

Under the Bayesian method, we assign a prior probability (level of belief at the start of the trial) to a range of possible values for the true toxicity rate. As data on treated patients become available, the prior probability distribution is revised and the resulting posterior probability becomes the basis for recommending either early termination or continuation of the study. Specific stopping guidelines based on posterior probabilities for both acute and late occurring toxicity are given below along with underlying assumptions for the prior distributions.

Acute safety monitoring will be based on the occurrence of treatment related grade 3 or higher GI or GU toxicity occurring during study treatment or within 3 months of treatment completion. Early stopping (suspension and possibly termination) will be considered if there is evidence that the proportion of patients experiencing such toxicity exceeds 15%. Specifically, we suggest as a guideline for early termination a posterior probability of 80% or higher that the rate of grade 3 or higher GI/GU toxicity exceeds 15%. Similarly, we will monitor the rate of grade 3 or higher late occurring toxicity (onset of toxicity 3 months or more after completing RT) and apply a guideline for early termination based on 80% or higher posterior probability that this rate exceeds 10%. The rate of acute and late toxicity will be monitored. **Table 14.6.1** below shows specific instances where these stopping guidelines are met, thus suggesting early termination of the study due to evidence of excessive toxicity.

Table 14.6.1. Stopping rules for toxicity

Number of patients with acute **G3+ toxicity***	Total pts evaluated	Observed rate	Number of patients with late **G3+toxicity#**	Total pts evaluated	Observed rate
2	3 to 6	≥33%	2	3 to 8	≥25%
3	7 to 11	≥27%	3	9 to 16	≥19%
4	12 to 16	≥25%	4	17 to 24	≥17%
5	17 to 21	≥24%	5	25 to 32	≥16%
6	22 to 27	≥22%	6	33 to 40	≥15%
7	28 to 33	≥21%	-	-	-
8	34 to 38	≥21%	-	-	-
9	39 to 40	≥23%	-	-	-

* **Acute G3+**: treatment-related (possible, probable, or definite) grade 3 or higher GI/GU toxicity occurring within 3 months (acute) of RT completion.

Late **G3+**: treatment-related (possible, probable, or definite) grade 3 or higher GI/GU toxicity occurring more than 3 months (late) after RT completion.

To illustrate the stopping guidelines, suppose that 4 patients have been assessed for toxicity and 3 of them have experienced grade 3 treatment-related toxicity during or within 3 months of completing radiotherapy (second row, left panel). Under this circumstance, the observed rate of acute G3+ toxicity is 37.5%, resulting in a posterior probability of 90.4% that the true underlying rate exceeds 15% thus suggesting early termination of the study due to acute toxicity. Similarly for late G3+, suppose that a total of 8 patients have been followed sufficiently for assessment of late toxicity and 2 have experienced grade 3 treatment-related toxicity starting more than 3 months after treatment completion (first row, right panel). These data give a 25% observed rate of late G3+ toxicity and a posterior probability of 82.6% that the true underlying rate exceeds 10% thus suggesting early termination of the study due to late toxicity.

Posterior probabilities used to derive guidelines for acute toxicity are calculated under a prior beta distribution with parameters $\beta_1 = 0.3$ and $\beta_2 = 1.7$, which corresponds to an expected rate of 15% based

on prior information roughly equivalent to having studied 2 patients. Furthermore, this prior distribution assigns a small a priori chance (32%) to the possibility that the true rate of unacceptable toxicity is 15% or greater. For late toxicity, the parameters of the prior distribution are $\beta_1 = 0.2$ and $\beta_2 = 1.8$, giving an a priori chance of 27% that the true rate of late toxicity is 10% or greater.

No early stopping for efficacy. We do not propose early stopping of this trial based on interim assessment of efficacy for the following reasons. First, it would not be practical or desirable to suspend accrual to accommodate an interim assessment of the primary efficacy endpoint, PSA response, which requires nine months follow-up. Moreover, PSA response is not a perfect near term surrogate for long term benefit and thus not a definitive basis for an early conclusion regarding efficacy. The trial involves standard therapy with dose escalation, and an evaluation of PSA response based on accrual of 24 evaluable patients will provide information needed to design a subsequent trial evaluating long term outcome.

14.7 Reporting and Exclusions

N/A

15.0 INVESTIGATOR'S RESPONSIBILITIES

15.1 Investigator Responsibility/Performance

The investigator will ensure that this study is conducted in accordance with all regulations governing the protection of human subjects and Good Clinical Practices (GCP) guidelines.

The investigator will ensure that all work and services described in or associated with this protocol will be conducted in accordance with the investigational plan, applicable regulations, and the highest standards of medical and clinical research practice.

15.2 Confidentiality

The investigator must ensure that each subject's anonymity will be maintained and each subject's identity will be protected from unauthorized parties. A number will be assigned to each subject upon study entry and the number and the subject's initials will be used to identify the subject for the duration of the study. The investigator will maintain all documents related to this study in strict confidence.

15.3 Informed Consent and Permission to Use Protected Health Information

It is the responsibility of the investigator to obtain written informed consent from each subject participating in this study after adequate explanation, in lay language, of the methods, objectives, anticipated benefits, and potential hazards of the study. The investigator must also explain that the subject is completely free to refuse to enter the study or to discontinue participation at any time (for any reason) and receive alternative conventional therapy as indicated. Prior to study participation, each subject will sign an IRB approved informed consent form and receive a copy of same (and information leaflet, if appropriate). For subjects not qualified or able to give legal consent, consent must be obtained from a parent, legal guardian, or custodian.

The investigator or designee **must** explain to the subject before enrollment into the study that for evaluation of study results, the subject's protected health information obtained during the study may be shared with the study sponsor, regulatory agencies, and the IRB. It is the investigator's (or designee's) responsibility to obtain permission to use protected health information per HIPAA from each subject, or if appropriate, the subjects' parent or legal guardian.

15.4 Source Documentation and Investigator Files

The investigator will maintain adequate and accurate records to fully document the conduct of the study and to ensure that study data can be subsequently verified. These documents will be classified into two separate categories: 1) investigator study file and (2) subject clinical source documents that corroborate data collected on the CRF's. Subject clinical source documents will include hospital/clinic patient records; physician's and nurse's notes; original laboratory, radiology, pathology, and quality of life surveys, signed informed consent forms. When the CRF or any form is used as the source document, this will be clearly stated in the investigator study file.

At a minimum, the following documents will be collected:

- Medical history/physical condition and diagnosis of the subject before involvement in the study sufficient to verify protocol entry criteria
- Study number, assigned subject number, and verification that written informed consent was obtained (each recorded in dated and signed notes on the day of entry into the study)
- Progress notes for each subject visit, including treatment toxicity
- Documentation of treatment
- Laboratory test results
- Adverse events (action taken and resolution)
- Condition and response of subject upon completion of or early termination from the study
- Quality of life surveys
- DCE-MRI tumor size and location generated by the in-house developed software
- Radiation treatment Dose Volume Histograms.

15.5 Recording and Processing of Data

If using hard copies of CRF's, study center personnel will complete individual CRF's in black ink. All corrections to entered data will be made by drawing a single line through the information to be corrected without obscuring it. All corrections will be initialed, dated and explained, if necessary. **Do not use "white-out" or obscuring correction tape.** A CRF is required for every patient who received any amount of study treatment. The investigator will ensure that the CRF's are accurate, complete, legible and timely. Separate source records are required to support all CRF entries.

Patients will be entered into the Radiation Oncology Prostate Cancer Database for data collection and interpretation. The database links the patient Medical Record number to a participant's Research ID number and collects data on each patient related to biopsies and treatments.

15.6 Non-Protocol Research

No investigative procedures other than those described in this protocol will be undertaken on the enrolled subjects without the agreement of the IRB.

15.7 Ethics

The investigator agrees to conduct the study in compliance with the protocol, current good clinical practices, and all applicable (local, FDA) regulatory guidelines and standard of ethics.

15.8 Essential Documents for the Conduct of a Clinical Trial

Essential documents are those documents with individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced.

The following documents (at minimum) will be on file:

- CV's and license of all investigators
- IRB documentation/correspondance
- Documentation of IRB certification
- Study Protocol
- Informed Consent Forms
- Delegation of Authority Log
- Screening and Randomization Log
- Training Documents
- Laboratory Documents

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APPENDIX I. STUDY CALENDAR – MAPS

Assessment	Prior to Enrollment	After Enrollment and Prior to RT	Weekly during RT	Follow-up				
				During Last Week of RT	6 Weeks after RT	3 Months after RT	Every 6 months thereafter up to 5.25 years post-RT	Other
History & Physical Exam; Performance Status (Zubrod) Within 8 weeks prior to protocol entry and Zubrod < 2. **Toxicity** During RT and at all follow-up visits; use CTCAE 4.0.	X		X	X	X	X	X	
PSA PSA of at least 0.1 and up to 4.0 ng/mL and obtained ≤ 3 months prior to enrollment	X[a]			X	X	X	X	
Serum total testosterone Obtained ≤ 3 months prior to enrollment	X[a]							At 9 months
Blood collection for research	x[a]			X		X		At 9 months, 2-2.5 years
Bone Scan	X[b]							[c]If deemed necessary by treating physician
DCE-MRI and or PET of prostate bed/pelvis Obtained ≤ 3 months prior to enrollment and the enhancing lesion in the prostate bed should be at least 0.4 cc and a maximum of 6 cc	X					X		[d]At 9 months and 2-2.5 years
Pathology Review of outside biopsy material prior to enrollment	X							
MRI/US prostate bed biopsy If the MRI shows a new lesion, an optional MRI/US-guided biopsy may be obtained						X[e]		[e]At 9 months and 2 – 2.5 years post completion in case of identified by MRI lesion

EPIC- SF-12, MAX-PC After enrollment and prior to US biopsy.	X			X	X	X		At 9 months, 15 months and yearly to 5.25 years
IPSS	X			X	X	X	X	
CT simulation		X						

Note: Measurements and follow-up visits should occur within ± 2 weeks up to the 3 month visit and within ± 8 weeks for subsequent measurements/visits.

See Eligibility Criteria for detailed description for evaluations.

[a] If possible, blood collected prior to enrollment should be obtained prior to androgen deprivation therapy.

[b] If deemed necessary, obtained ≤ 4 months prior to enrollment

[c] To be conducted for a PSA of ≥2 or physician concern for metastasis.

[d] MRI at 9 months and 2-2.5 years will be obtained per the PI's discretion.

[e] Biopsy collection is optional

APPENDIX II. NATIONAL CANCER INSTITUTE (NCI) COMMON TOXICITY CRITERIA (CTC)

The NCI CTC can be viewed on-line at the following NCI web site:

http://ctep.cancer.gov/reporting/ctc.html

APPENDIX III. DATA AND SAFETY MONITORING PLAN

The Sylvester Comprehensive Cancer Center (SCCC) Data and Safety Monitoring Committee (DSMC) will monitor this clinical trial according to the Cancer Center's DSM Plan. In its oversight capacity, the DSMC bears responsibility for suspending or terminating this study.

DSMC oversight of the conduct of this trial includes ongoing review of accrual and adverse event data, and periodic review of response to treatment. The guidelines appearing in Sections 9.0 and 14.0 are offered for DSMC consideration in assessing adverse events and treatment response. In addition, the DSMC will review reports from all audits, site visits, or study reviews pertaining to this clinical trial and take appropriate action.

APPENDIX IV. ADDITIONAL ITEMS

For the safety of our patients, please refrain from using the following prohibited and/or misleading abbreviations in the treatment and dose modification sections of the protocol.

Abbreviation	Definition	Term to Use
U	**For unit**	**Unit**
IU	**For international unit**	**International unit**
Pharmacy abbreviations	**Example, qd for daily**	**Daily**
1.0 mg	**Trailing zero**	**1 mg**
.1 mg	**Lack of leading zero**	**0.1 mg**
Drug name abbreviations	**Example, MS for morphine sulfate**	**Write out drug name**
µg	**microgram**	**mcg**
d/c	**Discharge**	**Discharge**
Cc	**cubic centimeter**	**ml (milliliter)**
>	**Greater than**	**Write out meaning**
<	**Less than**	**Write out meaning**

APPENDIX V PERFORMANCE SCALES

ZUBROD SCALE

0	Fully active, able to carry on all pre-disease 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

KARNOFSKY SCALE

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 sign 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; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

Comparison between Zubrod and Karnofsky Scale

ECOG / WHO / Zubrod	Karnofsky
Zubrod 0	Karnofsky 90-100
Zubrod 1	Karnofsky 70-80
Zubrod 2	Karnofsky 50-60
Zubrod 3	Karnofsky 30-40
Zubrod 4	Karnofsky 10-20
Death	

These scales may be used interchangeably as documentation of performance status in the research record.