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A Phase III Trial Of Hypofractionated External Beam Image-Guided Highly Targeted Radiotherapy for Prostate Cancer: The HEIGHT Trial

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SCHEMA

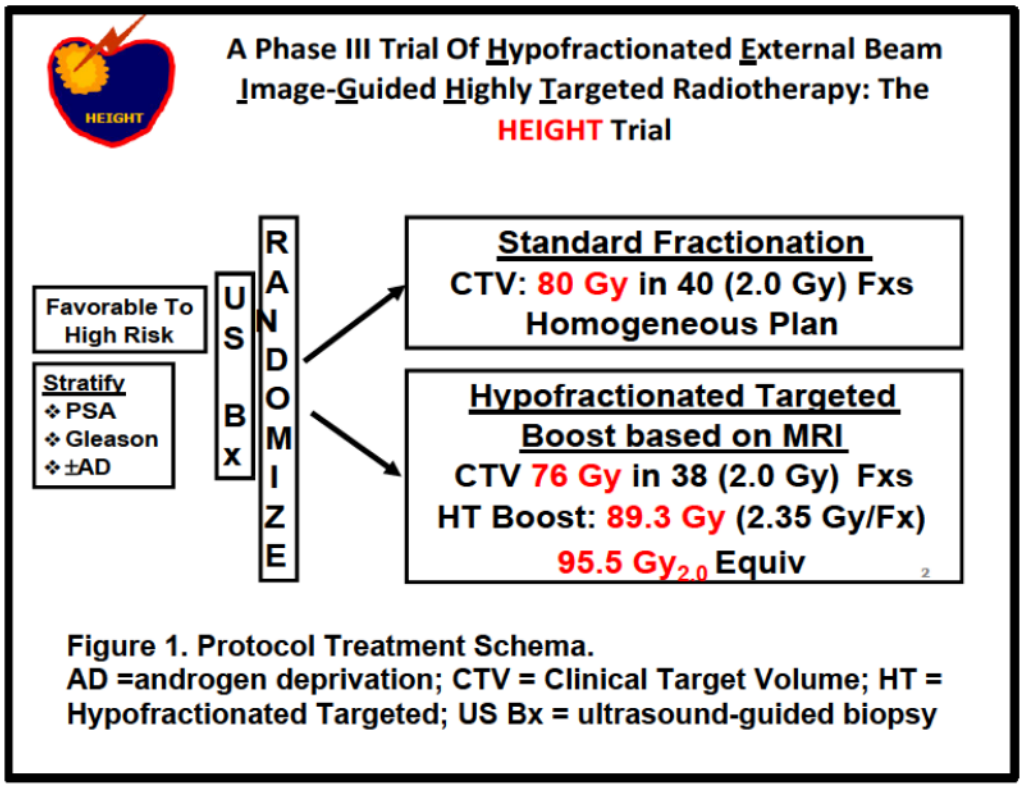

Figure 1. Protocol Treatment Schema.
AD =androgen deprivation; CTV = Clinical Target Volume; HT = Hypofractionated Targeted; US Bx = ultrasound-guided biopsy

1. **Randomization**
   A. *Arm I*: Standard Fractionated Intensity Modulated Radiotherapy (SIMRT)
   A total dose of 80 Gy will be delivered in 40 fractions to the Clinical Target Volume (CTV).
   B. *Arm II*: Hypofractionated Targeted Intensity Modulated Radiotherapy (HTIMRT)
   Dose escalation to the Multiparametric MRI (MP-MRI) by dose painting at 2.35-2.40 Gy per fraction, while the rest of the Clinical Target Volume (CTV) receives 2.0 Gy a fraction to 76 Gy. The hypofractionated targeted (HT) boost region will receive an absolute dose of 89.3-91.2 Gy. Assuming an α/β ratio of 3.0, this would be equivalent to 95.5 Gy in 2.0 Gy fractions.

2. **Stratification**
   A. PSA <10 vs. 10 to ≤100.
   B. Gleason Score 6-7 vs. 8-10. (Based on original diagnostic biopsy)
   C. Short Term Androgen Deprivation (STAD) – 4 to 6 months (Y vs. N).

3. **Eligibility Screening: Includes Multiparametric Functional MRI of Prostate and Pelvis**
   A. Biopsy confirmed adenocarcinoma of the prostate.
   B. T1-T3a disease based on digital rectal exam.
      a. T1a is permitted if peripheral zone biopsies are positive.

b. T3a disease based on MRI only is acceptable (no evidence of frank [clear cut] SV involvement or invasion of bladder or rectum.

C. No evidence of metastasis by any clinical criteria or available radiographic tests.

D. Gleason score 6-10.

E. Patients with Gleason score ≥8 must be offered long term androgen deprivation therapy (ADT) and refuse such treatment because only 4-6 months (short term ADT) is permitted on this protocol. Gleason score ≥8 patients should be recommended to receive 4-6 months (± 2 months) of ADT. When given, the ADT should begin after fiducial marker placement, if applicable; however, is permitted to have been started up two months prior to the signing of consent.
   a. Gleason 8-10 must have <40% of the tissue overall involved with Gleason 8-10 in the biopsy specimen.
   b. Patients with Gleason score ≤7 may be treated with 4-6 months of ADT if ≥20% of the biopsy tissue is, or ≥50% of the cores are, positive for tumor.

F. PSA ≤100 ng/mL within 3 months of enrollment. If PSA was above 100 and dropped to ≤100 with antibiotics, this is acceptable for enrollment

G. If PSA is >15 ng/ml or there is ≥ Gleason 8 disease, a bone scan should be obtained ≤4 months before enrollment and should be without evidence of metastasis. A questionable bone scan is acceptable if plain x-rays, CT and/or MRI are negative for metastasis.

H. No previous pelvic radiotherapy.

I. No previous history of radical/total prostatectomy (suprapubic prostatectomy is acceptable).

J. No concurrent, active malignancy, other than non-metastatic skin cancer or early stage chronic lymphocytic leukemia (well-differentiated small cell lymphocytic lymphoma). If a prior malignancy is in remission for ≥5 years then the patient is eligible.

K. Identifiable functional MRI (1.5T or 3.0T MRI) tumor lesion or lesions, that total in volume <33% of the prostate within 3 months prior to enrollment.

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

M. Zubrod performance status <2. (Karnofsky or ECOG performance status may be used to estimate Zubrod) See Appendix IV

N. Willingness to fill out quality of life/psychosocial forms.

O. .Age ≥35 and ≤85 years.

P. Serum testosterone is within 40% of normal assay limits (e.g., x=0.4*lower assay limit and x=0,4*upper assay limit + upper assay limit), taken within within 4 months of enrollment. Patients whom have been started on ADT prior to signing consent are not required to have a serum testosterone at this level prior to signing consent; but, a serum testosterone prior to fiducial marker placement is recommended.

Q. Serum LFTs, taken within within 3 months of enrollment.

R. Complete blood counts , taken within 3 months of enrollment.

4. <u>Prior to Treatment</u>

A. Transrectal research prostate biopsies and gold seed fiducial marker placement, if applicable:
   a. The pre-RT prostate biopsy is optional for the patient, while the fiducial marker placement is not. For the prostate biopsies, up to a maximum of 14 cores will be taken prior to fiducial marker placement. The number of biopsy cores taken would be up to the discretion of the urologist in conjunction with the team, and

does not have to be defined prior to biopsy if the patient agrees to undergo the procedure.

b. Ultrasound-guidance is standard for prostate biopsies. The Eigen Artemis® system may be used to fine tune the biopsy locations within the prostate using software to fuse the multiparameteric MRI to the ultrasound in real time as the ultrasound is acquiring the images. In addition, these biopsies may be obtained on an MRI directly using established techniques.

c. 3-4 gold seeds placed in prostate (4 preferred)

B. MRI-simulation: Limited study without contrast at least 1 week after gold fiducial placement.

C. CT-simulation and planning.

5. Treatment Technique

Treatment should start within 6 weeks of fiducial marker placement, if applicable.

A. Arm I: SIMRT

The Gross Tumor Volume (GTV) will be defined by the hypervascular region on DCE-MRI, except for anterior lesions, which must also have restricted water motion on DWI and/or increased choline + creatinine relative to citrate (≥0.9 ratio). For the SIMRT patients, the dose to the GTV will be the same as that to the CTV. The CTV, at the minimum, will include the prostate (including the GTV) and the proximal seminal vesicles (usually 7-10 mm and/or ≤50%, whichever is less). The clinical target volume (CTV) may include an extra 1-2 mm beyond the GTV in regions of known bulky disease and/or extracapsular extension as determined by the diagnostic biopsy information and/or MRI. The Planning Target Volume (PTV) will be 3-5 mm around the CTV in all dimensions. For tumors at the base, a margin of 5 mm on the proximal seminal vesicles is recommended. At least 95% of the PTV should receive 80 Gy in 40 fractions, at 2.0 Gy per fraction.

IMRT plans will be evaluated by dose-volume histogram analyses. Less than or equal to 17% and 35% of the rectum plus anus (rectanus) should receive ≥65 Gy and ≥40 Gy, respectively. Less than or equal to 25% and 50% of the bladder should receive ≥65 Gy and ≥40 Gy, respectively. At least 95% of the PTV should receive the prescription dose.

B. Arm II: HTIMRT

The dose to the functional MRI-defined dominant region(s) will be escalated by dose painting at 2.35 Gy per fraction. The HT boost region (GTV) will receive an absolute dose of 89.3 Gy. Assuming an α/β ratio of 3.0, this would be equivalent to 95.5 Gy in 2.0 Gy fractions. The GTV region will be shaped such that the posterior edge is ≥ 2 mm from the rectum to avoid excessive dose to the rectum. The maximum point dose to the rectum per day should not exceed 2.25 Gy. The normal tissue constraints are otherwise the same as for Arm I, considered in 2.0 Gy equivalent doses. The CTV volume is the same as for Arm I; at least 95% of the PTV should receive 76 Gy in 38 fractions, at 2.0 Gy per fraction.

HYPOTHESES

1. Delivery of directed hypofractionated targeted (HT) radiotherapy (RT) tumor boost to the dominant tumor lesion in the prostate as identified by multiparametric functional Magnetic Resonance Imaging (MRI).
2. Biomarker expression levels differ in the functional MRI defined suspicious and unsuspicious tumor regions.
3. 10-15% of men undergoing RT have Circulating DNA or tumor cells (CTC) that are related to an adverse treatment outcome.
4. Quality of life will not differ significantly between the treatment arms.
5. Prostate cancer-related anxiety will be reduced in the HTIMRT arm, because the patients will be aware that the dominant tumor will be targeted with higher radiation dose.

1.0 BACKGROUND

1.1 Study Disease

In 2009 more than 190,000 men were diagnosed with prostate cancer. Despite advances in diagnosis and treatment, failure rates continue to remain high (over 27,000 deaths). Local persistence of prostate cancer treated with RT is under-appreciated. Prostate cancer has a long natural history and the consequences of local persistence may not be realized for over ten years. There is significant evidence in support of doses of 78 Gy or higher for primary treatment of localized prostate.(1) There is some evidence to support,(2) and we hypothesize, that the regions in the prostate with the greatest tumor burden are the regions that are at highest risk of harboring persistent disease after RT. Multiparameter MRI and, in particular, DCE-MRI is very promising for the *in vivo* 3D localization of the dominant tumor area.(3) Delivery of a directed HT tumor boost to the functional MRI-identified dominant tumor lesion in the prostate is expected to increase the chance of complete tumor eradication from the prostate, which is a strong predictor of tumor control biochemically.

Our biomarker studies have revealed that molecular biomarkers found in pretreatment prostate biopsy material are associated with patient outcome. We have published a number of papers on biomarkers, including Ki-67,(4) p53,(5, 6) MDM2,(7, 8), bcl-2 and bax,(9) p16,(10, 11) cox-2,(12) and PKA(13) in which abnormal expression using immunohistochemistry (IHC) has been associated with worse patient outcome after radiotherapy. In addition, we have studied a number of tissue biomarkers in other prostate cancer patient populations that have proven to be associated with either biochemical failure, distant metastasis or mortality. These include HYAL1,(14, 15) osteopontin,(16) IL-8,(16) Vav3,(17) and GRP78.(18) However, no model incorporating such markers has gained acceptance in the clinic. The proposed studies in this protocol will provide the foundation for biomarker collection in different prostate tumor regions, comparing specifically the functional-MRI suspicious and unsuspicious regions.

Circulating tumor cells (CTC) have been correlated with prostate cancer disease progression.(19-21) CTCs, however, have not been adopted clinically because this is a relatively new concept and the technology for isolating CTCs reliably and preserving characteristics is still in evolution. There are data showing the promise of using the presence of CTCs in men with castrate resistant prostate cancer (CRPC) to follow treatment response,(21) but less on the characteristics of the tumor cells at the molecular level or the role of CTCs in men at earlier stages of the disease.

The presence of elevated levels of free circulating cell-free nucleic acids (fcDNA) in cancer patients has been well documented. Our preliminary results indicate that at a cut point of 180 ng/mL, fcDNA levels can differentiate prostate cancer from benign prostatic conditions such as prostatitis (PTIS) and benign prostatic hyperplasia (BPH) in patients with a PSA ≤ 8 ng/ml. DNA based biomarkers have promise as markers for targeted therapies since they are

chemically and biologically stable compared to RNA and protein markers. Studies have established that fcDNA in serum and plasma of cancer patients originates from tumor cells and that DNA methylation patterns in serum/plasma fcDNA closely match that of DNA isolated directly from tumor tissue. Hence fcDNA is a potential non-invasive biomarker for cancer with the advantages of high sensitivity and specificity.

Tissue biomarkers, fcDNA and CTCs have shown promise in predicting patient outcome in addition to standard clinical factors. Developing consequent biomarker and CTC models will contribute significantly to better defining the decision points in the patients with prostate cancer, as well as understanding the underlying mechanisms that predispose to progression, failure of primary therapy and/or the presence of occult metastatic disease.

1.2 Study Agent/Technique

We propose to deliver directed hypofractionated targeted (HT) radiation boost to the dominant tumor lesion(s) in the prostate as identified by MRI in the framework of a two-arm phase III randomized trial, deemed the Hypofractionated External Beam Image-Guided Highly Targeted Radiotherapy, or HEIGHT, Trial. We propose to escalate dose to the functional-MRI-defined dominant region(s) by dose painting at 2.35 Gy per fraction using IMRT (HTIMRT Arm), while the rest of the Clinical Target Volume (CTV) receives 2.0 Gy a fraction to 76 Gy. The HT boost region will receive an absolute dose of 89.3 Gy. Assuming an α/β ratio of 3.0, this would be equivalent to 95.5 Gy in 2.0 Gy fractions. The HTIMRT patients will be compared to patients treated with our standard IMRT (SIMRT) approach today, in which the CTV receives 80 Gy in 2.0 Gy fractions. The CTV doses are slightly different because the HTIMRT arm builds on a prior randomized trial of 76 Gy in 2.0 Gy fractions,(22, 23) while the SIMRT represents our current practice. The primary endpoint is prostate biopsy positivity at 2 years after completion of all therapy.

In this protocol we aim to examine biomarkers from the directed ultrasound-guided prostate biopsies. The patients will have the option of refusing the pre-RT prostate. Emphasis will be placed on biopsying regions in which the multiparametric functional MRI shows enhancement. The preferred method of protocol research biopsies will involve the Eigen Artemis® system, which allows for fusion of the MRI images to ultrasound in real time. The Artemis® system is an FDA approved transrectal ultrasound prostate biopsy device. . The Mri ultrasound (MRIus) fusion software will be used as a means of better targeting tumor regions, which are poorly seen on ultrasound alone. Recently Natarajan et al (24) described the UCLA experience, demonstrating that the proportion of positive biopsies was much higher using the MRIus fusion software, as compared to ultrasound alone. The patient may withdraw from the protocol upon learning the results of the biopsies.

If the Eigen Artemis system® is unavailable, ultrasound biopsies may be performed while viewing the functional MRI images on a separate monitor to enhance the probability of obtaining biomarkers more representative of patient outcome. A third option that will become available in March 2012 is to perform MRI-guided biopsies directly on the MRI scanner using a commercially available approach. Biomarkers from biopsies from the index lesion(s) will be compared to those from tumor in other areas of the prostate. Biopsy tissues will be collected pre- and post-treatment and analyzed by immunohistochemistry (IHC) for biomarker quantification.

We will also collect blood for quantification of novel blood product related information (CTCs and circulating free DNA).

Quality of Life (QOL) and psychosocial assessments will be conducted to evaluate treatment effects and anxiety.

1.3 Other Agent(s)

N/A

1.4 Rationale

1.4.1 Radiotherapy Dose Escalation for Prostate Cancer

The introduction of pretreatment PSA as a prognostic factor and the use of rising PSA as an endpoint have radically changed our understanding of the efficacy of radiotherapy in the treatment of prostate cancer. We now realize that radiation doses used in the 1980's were inadequate, leaving behind residual disease in the prostate. There are several non-randomized studies showing that radiotherapy dose is an important determinant of patient outcome.(1) A Phase III randomized dose escalation trial lead by the principal investigator at M.D. Anderson Cancer Center (MDACC) comparing 70 to 78 Gy (25-27) confirms the retrospective analyses. With a median follow-up of 8.7 years, the MDACC randomized trial showed a Phoenix definition(28) of freedom from biochemical failure (FFBF) at 10 years of 50% for the 70 Gy group versus 73% for the 78 Gy group. Similar results have been reported for three other contemporary PSA era randomized RT dose escalation trials.

A compelling reason for further escalating dose is that an analysis of the dose-response by the principal investigator(1) revealed a significant benefit of increasing RT dose beyond 80 Gy. After adjusting for pretreatment initial PSA (iPSA), Gleason score and T-category, there was a 2.2% improvement in FFBF for every 1 Gy added, even between 76 and 82 Gy. Thus, it is clear that significantly greater doses are needed to sterilize high tumor burden areas in the prostate.

1.4.2 Post-treatment Biopsy Tissue Assessments

Prostate biopsies after external beam radiotherapy have been studied fairly extensively; although, many prior series involved patients treated prior to the routine use of PSA and transrectal ultrasound-directed sextant (or higher) biopsies. The principal investigator has coordinated prostate biopsy assessments at two years after completion of treatment from two randomized trials, one from M.D. Anderson Cancer Center (29, 30) and one from Fox Chase Cancer Center.(2) Biopsy positivity in the M.D. Anderson Trial was associated with about a 50% risk of biochemical failure at 8-10 years after the biopsies were taken (2 yr after RT). From our analysis of the biopsies from Fox Chase Cancer Center (FCCC) protocol 02-602 (PI: Pollack), preliminary data indicate that nearly 50% of patients had residual tumor cells in the prostate at 2 years and that when the tumor burden was high on one side of the prostate, this appeared to predispose to a greater incidence of biopsy positivity on that same side.(2) Such an association has implications in how to approach the treatment of prostate cancer with radiotherapy; increasing RT dose to high tumor burden areas should lead to reduced local persistence and, consequently biochemical failure rates.

1.4.3 Molecular Biomarkers in Prostate Biopsies

Molecular markers have been associated with prostate cancer patient outcome after definitive therapy with radical prostatectomy or radiotherapy, but no model incorporating such markers has gained acceptance in the clinic. We hypothesize that a significant source of variation in biomarker expression is due to tumor heterogeneity and that it is molecular abnormalities in the dominant tumor areas that determine outcome.

DCE-MRI measures leaky vessels, which may be related to angiogenesis. Diffusion weighted MRI measure restricted water motion and MR-spectroscopy measures tumor metabolites. We anticipate that the tissue biomarkers under study, as well as other biomarkers that will be explored (e.g., AR, Hif-1α and VEGF), will be different in the dominant tumor areas defined by such functional MRI sequences and that by directing biopsies to these areas biomarker models will become more accurate.

1.4.4 Multiparametric Functional MRI for Identification of Tumor Location

Presently, the clinically acceptable method for the diagnosis of prostate cancer is Transrectal Ultrasound (TRUS)-guided biopsy. TRUS, however, cannot reliably visualize cancer

foci, with up to 40% of tumors being isoechoic.(31) Furthermore, the regional distribution of tumor in the prostate as revealed by this method relies on the expertise and somewhat subjective designations of biopsy location by the physician performing the procedure, and does not provide an accurate 3D representation of tumor location. Since the needle is not reliably directed to a cancer target, blind biopsies of 6-12 regions are routinely performed in addition to biopsies of suspicious hypoechoic areas. The technique misses up to 23% of cancers at the time of first biopsy.(32)

Multiparametric MRI is the most promising non-invasive technique for utilization in the clinic for detecting prostate cancer. MRI T2-weighted images (T2w-MRI) provide an excellent depiction of prostate anatomy with regions of healthy prostate tissue demonstrating higher signal intensity than prostate cancer.(33) The observed reduction in MRI image signal intensity is due to a loss of the normal glandular (ductal) morphology in regions of prostate cancer. However, other benign pathologies (e.g. inflammation, benign prostatic hyperplasia, blood) and radiation therapy also cause a loss of signal intensity on T2w-MRI.(33) Additionally, infiltrating prostate cancer may not cause a reduction in normal glandular morphology and therefore will not be hypointense on T2w-MRI. Due to these confounding factors, T2w-MRI alone identifies cancer larger than 0.5 cc in volume with only 65-74% sensitivity and low specificity.(34) Utilizing an endorectal coil in detecting cancer in the prostate improves MRI sensitivity (78%) but specificity still remains poor (55%).(35)

DCE-MRI of the prostate has demonstrated potential for discriminating between normal and cancerous tissues.(36, 37) In general, earlier and greater enhancement in cancer vs. normal tissue is due to tumor hypervascularity, which has been related to more aggressive tumor behavior. DCE-MRI combined with T2w-MRI increases the accuracy of detecting prostate cancer to over 80%.(38, 39) Further increases in sensitivity and specificity have been realized by adding diffusion weighted imaging (DWI) and MR spectroscopy (MRS), especially for anterior lesions (anterior to the peripheral zone).

1.4.5 Circulating Tumor Cells (CTCs) as Predictor of Prostate Cancer Response to Treatment.

Circulating tumor cells (CTCs) have been shown to have prognostic and predictive value in metastatic breast,(40-42) colon(43) and prostate cancer.(44) In prostate (as well as in breast and colon) cancer, quantification of CTCs before and after therapy has been shown to predict overall disease response, and the CellSearch assay has been approved by the FDA to assess such response. This assay, nevertheless, has limitations. Aside from associated costs, the assay depends on enrichment of CTCs based on their expression of EpCAM, a variably expressed cell surface marker. It is also likely that enumeration of CTCs alone may be inadequate as a prognostic or predictive marker for therapeutic response. Particular biomarkers expressed on CTCs may provide a wealth of additional information about clinical outcome and response to therapy. We have developed a microfabricated parylene membrane-based cassette capable of capturing CTCs based on their larger size relative to hematopoietic cells, and have shown its utility in capturing CTCs in cancer patient blood samples with high efficiency and with enhanced ease and speed.(45) There is exciting evidence that not only the capture, but also the characterization of CTCs provides additional information regarding optimal therapeutic efficacy, as demonstrated by the evaluation of EGFR mutations in lung cancer CTCs from patients who are candidates for anti-EGFR therapy.(46) Our microfilter cassette incorporates the capability for downstream molecular characterization, such as on-chip multi-marker immunohistochemistry and genetic tests, which adds a useful dimension besides CTC quantification. In particular, the captured CTCs can be characterized for expression of therapeutic targets and markers of response.

1.4.6 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.(47) 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.(48) 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.(49) 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).(50) Altimari et al.(51) showed that plasma fcDNA quantification distinguished between patients with prostate cancer and healthy controls, and correlated with pathologic tumor stage. Chun et al. (52) 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.(53) 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.

1.5 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.(54-59) Reports by Zelefsky et al(60, 61) 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 HEIGHT trial, all patients will receive IMRT. The Quality of Life (QOL) assessments will provide unique data on the effects of HTIMRT on QOL relative to SIMRT. 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) (Appendix VII). 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 around 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.(62).

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) (Appendix VIII) (63).

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 PCa 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-SF12 has demonstrated excellent reliability (i.e., Cronbach's α>.91) across sexual function and sexual bother composites. The EPIC-SF12 questionnaire will be used to measure changes in QOL over time.(64, 65)

Another measure of urinary function is the International Prostate Symptom Score (IPSS)(Appendix IX).(66) This scoring system has been established as a measure of radiation morbidity in patients treated for prostate cancer (67-70) and will be administered prior to treatment, at the end of radiotherapy and at each follow-up visit. The 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 ≥35 to ≤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

- To compare the rate of prostate biopsy positivity after HTIMRT to SIMRT at 2 years after all therapy.

2.2. Secondary Objectives

- To evaluate the impact of an HT boost on acute and late toxicity.
- To evaluate the influence of HTIMRT to health-related quality of life (HRQOL), prostate cancer-specific anxiety and prostate cancer-specific QOL.
- To quantify biomarker expression in different prostate tumor regions, comparing specifically the functional MRI suspicious regions to those that are not suspicious.
- To evaluate the incidence and relationship of circulating free DNA and tumor cells to tissue biomarkers and prostate biopsy positivity at 2 years after completion of therapy.
- To record other biochemical failure, clinical failure and mortality endpoints.

3.0 PATIENT SELECTION

3.1 Inclusion (Eligibility) Criteria

A. Biopsy confirmed adenocarcinoma of the prostate.
B. T1-T3a disease based on digital rectal exam.
    a. T1a is permitted if peripheral zone biopsies are positive.
    b. T3a disease based on MRI is acceptable.
C. No evidence of metastasis by any clinical criteria or available radiographic tests.
D. Gleason score 6-8.
E. Patients with Gleason score 8 must be offered long term androgen deprivation therapy (ADT) and refuse such treatment because only 4-6 (±2 months) months (short term ADT) is permitted on this protocol. Gleason score ≥ 8 patients should be

recommended to receive short term ADT in conjunction with RT. When given, the ADT recommended to begin after fiducial marker placement, if applicable; however, ADT is permitted to have been started up to two months prior to the signing of consent.

a. Patients with Gleason score 8 disease must have <40 of the diagnostic tumor tissue involved with tumor.
b. Patients with Gleason score ≤7 may be treated with 4-6 (±2 months) months of ADT.

F. PSA ≤100 ng/mL within 3 months of enrollment. If PSA was above 100 and dropped to ≤100 with antibiotics, this is acceptable for enrollment.
G. If PSA is >15 ng/ml or there is ≥ Gleason 8 disease, a bone scan should be obtained ≤4 months before enrollment and should be without evidence of metastasis. A questionable bone scan is acceptable if plain x-rays, CT and/or MRI are negative for metastasis.
H. No previous pelvic radiotherapy
I. No previous history of radical/total prostatectomy (suprapubic prostatectomy is acceptable)
J. No concurrent, active malignancy, other than non-metastatic skin cancer or early stage chronic lymphocytic leukemia (well-differentiated small cell lymphocytic lymphoma). If a prior malignancy is in remission for ≥ 5 years then the patient is eligible.
K. Identifiable multiparameter functional MRI defined tumor lesion or lesions using a 1.5T or 3.0T MRI (3.0T preferable), that total in volume <33% of the prostate within 3 months prior to enrollment.
    a. Multiparametric functional including DWI of prostate and pelvis is required prior to protocol consideration
L. Ability to understand and the willingness to sign a written informed consent document
M. Zubrod performance status <2 (Karnofsky or ECOG performance status may be used to estimate Zubrod)
N. Willingness to fill out quality of life/psychosocial forms.
O. Age ≥35 and ≤85 years.
P. Serum testosterone is within 40% of normal assay limits (e.g., x=0.4*lower assay limit and x=.04*upper assay limit + upper assay limit),, taken within 4 months of enrollment. Patients who have been started on ADT prior to signing consent are not required to have a serum testosterone at this level prior to signing consent; but, a serum testosterone prior to fiducial marker placement is recommended.
Q. Serum LFTs taken within 3 months of enrollment.
R. Complete blood counts taken within 3 months of enrollment.

3.2 Exclusion Criteria

A. Previous pelvic radiotherapy.
B. Previous history of radical prostatectomy.
C. Concurrent, active malignancy, which is *not* non-metastatic skin cancer or early stage chronic lymphocytic leukemia (well-differentiated small cell lymphocytic lymphoma). If a prior malignancy is in remission for < 5 years then the patient is not eligible
D. Not willing to fill out quality of life/psychosocial questionnaires.

3.3 Enrollment and Randomization Procedures

3.3.1. Enrollment

Patients can be registered only after a pretreatment evaluation is complete and eligibility criteria are met. The eligibility checklist must be completed prior to initiation of the registration process. All eligibility requirements must be reviewed prior to the patient being enrolled on this study. The following information must be provided at the time of enrollment:

1) Completed and signed eligibility checklist.
2) All pages of the original signed informed consent forms (ICFs), including HIPAA form B.
3) Relevant source documents such as: subject medical history and physical exam; admission or discharge notes; diagnostic reports; pathologic confirmation of diagnosis by University of Miami pathologists (UM review) and relevant subject-specific communication.

3.3.2 Cancellation Guidelines

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

3.3.3 Emergency Registration

If an emergency registration takes place after business hours, the items listed in 3.3.1 must be completed by the next business day.

3.3.4 Post-Enrollment Procedures Prior to Randomization

Patients who meet eligibility criteria and have been enrolled on study will undergo the placement of fiducial markers in the prostate and may, during that procedure, also undergo transrectal research prostate biopsies.

> Note: If a method of intrafraction prostate tracking is available which does not require fiducial markers, this will be adequate for this trial (i.e. 4D transperitoneal ultrasound, onboard MRI guidance [Viewray]).

The prostate biopsies are being done for several reasons, as described above and patients will be encouraged to participate, but have the option to refuse. Also, the number of biopsies obtained, up to 14, will be at the discretion of the urologist performing the biopsies. The platform for obtaining this transrectal prostate research biopsy and the 2.0-2.5 year endpoint biopsy includes using standard ultrasound-guidance, the Eigen Artemis® system (MRI-ultrasound fusion guided biopsies), or MRI-guided prostate biopsies. The Artemis® system software is FDA approved Of note, the Artemis system has been shown to result in a substantially higher proportion of positive biopsies, as compared to standard ultrasound guidance.(24).

As a consequence of the prostate biopsies, it is possible that in some cases the Gleason score will increase. If this turns out to be the case, the treating physician will discuss the treatment options available for the upgraded Gleason score. The protocol stipulates that treatment will be based entirely on the pre-protocol diagnostic prostate biopsies and not the research biopsies. The patient may at that point decide to withdraw from the study because a different treatment regimen, mainly involving the length of androgen deprivation therapy, might be appropriate. If the patients opts to be treated with the original treatment recommendation, based on the original biopsy information,, the patient will be randomized. The sequence of events, from protocol entry (consent) to enrollment to randomization is shown in **Figure 2**.

3.3.5 Randomization

Randomization of study patients will be done in equal proportion to Arm I (SIMRT) and Arm II (HTIMRT) using a permuted block design stratified by baseline PSA (<10 v 10 to ≤100), Gleason score (6-7 v 8-10), and short term androgen deprivation therapy (Y v N). The pre-study Gleason score, not that determined by post-MRI biopsy will be used in determining a patient's

stratum; however, patients will not be randomized until after the fiducial markers and prostate biopsies (if elected by the patient) have been performed. Patients whose Gleason score comes back higher and in whom the use or length of androgen deprivation becomes an issue, will then have the opportunity to withdraw from the study without creating potential imbalances. The ability for the patients to withdraw at any time will be described from outset. Based on prior experience, the proportion of patients that withdraw before treatment is about 1-2%. In this trial, the potential for withdrawal is estimated to be 2-3 times higher because of anticipated upgrading (higher Gleason scores in the post MRI biopsies).

Randomization lists for each stratum will be prepared by SCCC Biostatistics prior to the first patient enrollment and provided to the SCCC CRS office where they will be maintained independent of the study team. Members of the study team, including those responsible for patient enrollment, will not have access to the randomization lists.

After informed consent is signed; eligibility is confirmed, a determination has been made regarding optional STAD, the fiducial markers placed and, if elected, prostate biopsies performed, a member of the study team will randomize the subject as per CRS guidelines. The randomization should occur within two weeks after the fiducial marker placement, if applicable or after enrollment.

The nature of study treatment (40 SIMRT vs. 38 HTIMRT treatments) requires that the patients know their treatment. With respect to the collection, processing and analysis of study data, including that deriving from tissue and blood samples, only published data will be available to the patients.

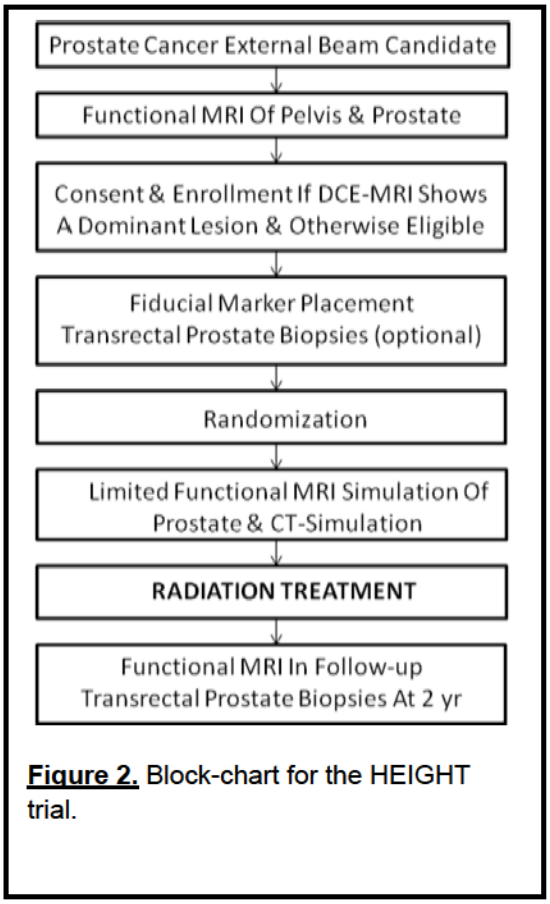

Figure 2. Block-chart for the HEIGHT trial.

4.0 TREATMENT PLAN

4.1 Pre-enrollment Multiparametric Functional-MRI

The block-chart shown in **Figure 2** illustrates the sequence that patients will go through to be evaluated for eligibility, enrolled and randomized. There are two MRI's that will be obtained. The first functional MRI exam of the pelvis and prostate is per standard routine at the University of Miami as part of external beam radiotherapy planning. T2, T1 non-contrast, T1 DCE and DWI MRI scans of the pelvis and prostate at 2.5 mm cuts are routinely performed; when possible (the standard exclusions for MRI with contrast apply). 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 attempted). Since the DCE-MRI scan involves the use of gadolinium, renal function is assessed to ensure it is adequate, as part of routine management. Again, this is routine clinical practice in our department and will be done prior to enrollment; the procedure is not part of this protocol, but the results are considered for eligibility.

An enema is administered within 2.0 hr. prior to all of the MRI and CT imaging studies to empty the bowel. A diet designed to reduce bowel gas is recommended to begin the day before

the diagnostic/planning DCE-MRI and before the post-fiducial MRI- and CT-simulation scans described below. The patient is instructed not to fully void before the scans, to mimic bladder position during treatment. The DCE-MRI scans include pre-contrast images and post-contrast images at approximately 30-40 sec intervals, for a minimum of 10 post-contrast scans. We also routinely acquire DWI imaging and plan to routinely acquire MRS when the new MRI install in the department of radiation oncology is complete.

4.2 Assessment of Protocol Eligibility and Enrollment

Patients who have an enhancing lesion (or lesions) with early contrast washin and eventual washout will be eligible if the volume sum of the lesion(s) is <33% of the prostate volume. This will be determined by contouring of the enhancing regions, with consideration of areas water restriction for anterior lesions. Semi-automated software has been developed to assist in this process, which may be used to assist in this evaluation. Eligible patients will be screened by the treating physicians and dedicated protocol nursing staff for fulfillment of eligibility criteria. If the patient is deemed a candidate, protocol consent will then be obtained. If all eligibility requirements are met, the patient will be enrolled. As outlined in **Figure 2**, enrollment occurs prior to fiducial marker placement and optional pretreatment prostate biopsies. ***Randomization occurs after fiducial marker placement, if applicable*** and the review any biopsies done at that time. The patient will be entered into the Radiation Oncology Prostate Cancer Database for data collection and interpretation.

4.3 Prostate Biopsy and Gold Seed Fiducial Marker Placement

Pre-treatment protocol prostate biopsies (optional), when done, and gold seed fiducial marker placement will be performed in a single setting/procedure, if applicable. As per the discretion of the urologist, antibiotic treatment before, during and after fiducial marker placement may be administered, Alsoprior to fiducial marker implantation/biopsy collection, antibiotic prophylaxis will be prescribed (e.g., Levaquin 500 mg daily, Ciprofloxacin 500 mg twice daily, or a similar antibiotic depending on allergy history and physician preference), may be prescribed/administered.

Pre-treatment transrectal prostate ultrasound-guided biopsies, when done, will be performed using the Eigen Artemis® system when available. The Eigen Artemis system fusion software (FDA approved) may be used to fine-tune the location of the tumor and biopsies by fusion of the previously obtained multiparametric MRI to the transrectal ultrasound in real time. The ultrasound is the true guidance imaging parameter that identifies the prostate boundaries and other nearby structures. The MRI is fused to the ultrasound such that the biopsies may be directed to a region in the ultrasound space. This system, is also described in sections 1.2 and 3.3.4.

No more than 14 needle core biopsies will be obtained. The number and location of the biopsies will be at the discretion of the Urologist performing the biopsies (with input from the PI and protocol team). Ideally, 2-4 of the biopsies will be from the tumor area(s), with a typical arrangement including the left lateral base (LLB), left lateral mid (LLM), left lateral apex (LLA), left medial base (LMB), left medial mid (LMM), left medial apex (LMA), right lateral base (RLB), right lateral mod (RLM), right lateral apex (RLA), right medial base (RMB), right medial mid (RMM) and right medial apex (RMA). 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 procedure will be performed by a urologist in the Department of Urology at University of Miami Miller School of Medicine. The biopsies will be paraffin embedded in pathology per routine procedures. A pathology reading of the material will be rendered and the remaining blocks will be stored for biomarker analyses. During the same procedure, four gold

fiducial markers will be implanted in the prostate gland, two in the superior region (bilateral bases), two in the inferior region (bilateral apices), laterally arranged. Optimally, the four fiducials should be placed 2 cm from each other and the triangulation should be at least 15 degrees.

4.4 Prostate Cancer Upgrading and Change of Treatment

In the event that the pre-treatment prostate biopsies result in cancer upgrading (higher Gleason score), the treating physician will discuss the appropriate treatment options with the patient. If the Gleason score, on the ultrasound-guided biopsies at the time of fiducial marker placement is higher, the patient must agree to be randomized and treated in accordance with the initial treatment plan, based on the pathologic parameters in the original diagnostic prostate biopsies and not the protocol prostate biopsies.

4.5 Prostate Biopsy Tissue Handling

Immediately following each biopsy core, the tissues will be fixed in 10% formalin per routine. The formalin fixed tissues will be delivered to the Department of Pathology for paraffin embedding and sectioning. The biopsies are to be placed in the tissue processor and processed routinely, and embedded in paraffin. Scheduling of the biopsies on Monday-Thursday is preferred so that the samples will be processed more quickly. Biopsies will be reviewed by a pathologist and the results (Gleason scoring and percent of tumor tissue) recorded in the patient's record per routine. The remainder of the block will be stored per institutional policy in the Department of Pathology and requests for the biomarker analyses made at a time batched staining is possible (after a number of cases have been accrued).

When the tissue is sectioned for biomarker analyses, the slides will be labeled with a research ID number and will not contain patient information. Biomarker data will be entered into the Radiation Oncology Prostate Database which links the patient Medical Record number to a participant's Research ID number and in which data on each patient related to biopsies and treatments will be recorded.

4.6 MRI and CT-Simulation

A second, limited prostate MRI study that includes T2w, T2*-weighted gradient echo sequence (T2-star for clear visualization of the gold markers (71)), and T1 sequences will be obtained at 2.0-2.5 mm cuts at least 1 week after fiducial marker placement, if applicable to facilitate fusion with CT-simulation images based on the markers. This limited MRI of the prostate will be fused to the original diagnostic MRI to ensure that the HTIMRT is accurately targeted to the center of the functional MRI-defined region.

CT-simulation will be obtained under the same conditions with typical pelvic immobilization. Images will be taken at 2.0 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.

4.7 Risk Assessment for RT and ADT Planning

- *Favorable Risk*: Clinical and MRI T1-T2, Gleason 6, and PSA ≤ 10. The biopsy information from the original diagnostic prostate biopsies will be used (not the information from the protocol prostate biopsies).
- *Intermediate Risk*: Clinical and MRI T1-T2, Gleason 7 or PSA >10 and ≤20 Patients are eligible for 4-6 (± 2 months) months of androgen deprivation therapy, starting up to 2 months prior to signing consent.
- *High Risk*: Palpitation T3a (with extraprostatic extension) or MRI<T3a or Gleason ≥8 or PSA >20: These patients must be offered and refuse long term ADT. If the patient accepts long term ADT, they may not be enrolled on the study. They will be strongly

encouraged to receive 4-6 months of ADT, with 6 months preferred. However, ADT may be refused. ADT may begin up to 2 months prior to signing the consent.

4.8 GTV and CTV Contouring, PTV Definition and Planning Parameters

The CT and MRI simulation scans will be loaded into a planning computer and fused based on the fiducial markers, if applicable. The DCE-MRI will be fused to the MRI-simulation images. At each slice level, the pelvic bones, bladder, rectum, prostate, and proximal seminal vesicles will be outlined based primarily on CT, but with MRI consideration.

The **Gross Tumor Volume** (GTV) region will consist of the early DCE-MRI enhancing regions, except for anterior regions. If an anterior region enhances early, is associated with water restriction on DWI and/or elevated choline + creatinine metabolites on MRS, these regions should be included in the GTV. The GTV will be shaped such that the posterior edge is ≥2 mm from the rectum to avoid excessive dose to the rectum. The Clinical Target Volume (CTV) will include the prostate (with GTV) and the proximal seminal vesicles (usually 7-10 mm and/or ≤50% of length, whichever is shorter). The CTV may include an extra 1-2 mm beyond the GTV in regions of known bulky disease and/or extracapsular extension as determined by the diagnostic biopsy information and/or MRI. The Planning Target Volume (PTV), will be 3-5 mm around the CTV in all dimensions. For tumors at the base, a margin of 5 mm on the proximal seminal vesicles is recommended.

- Arm I, SIMRT: At least 95% of the PTV should receive 80 Gy in 40 fractions, at 2.0 Gy per fraction. The maximum dose to the PTV should be <115% of the prescription dose.
- Arm II, HTIMRT: The dose to the GTV will be escalated by dose painting to 2.35 Gy per fraction. The HT boost region will receive an absolute dose of 89.3 Gy. Assuming an α/β ratio of 3.0, this would be equivalent to 95.5 Gy in 2.0 Gy fractions. The GTV region will be shaped such that the posterior edge is ≥ 2 mm from the rectum to avoid excessive dose to the rectum. The maximum dose to the rectum per day should not exceed 2.25 Gy. The normal tissue constraints are otherwise the same as for Arm I. The CTV volume is the same as for Arm I; at least 95% of the PTV should receive 76 Gy in 38 fractions, at 2.0 Gy per fraction. The maximum dose heterogeneity in PTV1 will be affected substantially by GTV (the area of the HT boost). High dose gradients are acceptable as long as the normal tissue constraints are met.

4.9 Normal Tissue Contouring and Constraints

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 3 cm above the ischial tuberosities inferiorly. The anus is defined as extending from the ischial tuberosities 3 cm superiorly. The constraints will be based on the composite structure, termed “Rectanus”, but dose volume histograms for the rectum and anus will be generated and recorded for the database and may be analyzed later. The entire bladder will be outlined. The femoral heads should be outlined down to the region between the greater and lesser trochanters. The pelvic lymph nodes will not be treated on this protocol as there is no Level I evidence that such treatment is beneficial. 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.

- Arm I, SIMRT: As described previously,(22) IMRT plans will be evaluated by dose-volume histogram analyses.

- *Rectanus*: Less than or equal to 17% and 35% of the rectum plus anus contoured volume should receive ≥65 Gy and ≥40 Gy, respectively, in calculated 2 Gy equivalent doses.(72)
- *Bladder*: 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.
- *Small/Large Bowel*: The potential bowel space limits are in terms of absolute volume.≤150 cc of potential bowel space should receive ≥45 Gy. A variation will be noted if > 150 cc to 250 cc of potential small bowel space receives ≥45 Gy. A violation is if >250 cc receives ≥45 Gy.

- Arm II, HTIMRT: IMRT plans will be evaluated by dose-volume histogram analyses, similar to that described for Arm I; however, the doses for the normal tissues will be calculated in 2 Gy equivalent doses. In terms of the doses delivered, the rectum maximum dose per fraction should not exceed 2.25 Gy per fraction.

4.10 Proteomic and Genomic Analyses of Blood and Urine

The objectives are to examine protein and single nucleotide polymorphisms in serum/plasma blood products, and hypermethylated DNA in urine for patterns that predict for patient outcome (e.g., prostate biopsy positivity, biochemical failure, and side effects). Serum, plasma and urine samples will be collected pre-RT, during the last week of RT, 3 months post RT and within a month prior to the prostate biopsies planned at 2-2.5 years after completion of all therapy. We plan to collect plasma and serum, as well as red cells and lymphocytes (buffy coat). While these are exploratory studies, of key importance is to have such samples collected prospectively on a well-defined group of patients. The project on genomics of urine samples builds on our results with the detection of hypermethylation of the glutathione S-transferase p1 (GSTP1) gene locus in urine.(73) 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 urine and blood

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4.11 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.

4.12 Duration of Therapy

- Within 4 weeks of enrollment, patients will be biopsied (optional) and fiducial markers placed, if applicable.
- Within 2 weeks of fiducial marker placement, if applicable, patients will be randomized.
- LHRH agonist or antagonist androgen deprivation therapy (ADT): LHRH agonist therapy may start up to two months prior to signing consent form or any time after signing consent form, up to two weeks after fiducial marker placement in men with intermediate or high risk prostate cancer (optional). Intermediate risk patients or high risk patients may receive 4-6 (+/- 2 months) months LHRH agonist therapy.
- Anti-androgen therapy: bicalutamide or flutamide will be administered in those planned to have LHRH agonist ADT 1-14 days prior to LHRH agonist therapy. Anti-androgen should be continued for 2-4 months (± 2 months), liver function tests or side effects permitting.
- Arm I: SIMRT will begin within 6 weeks of fiducial marker placement, if applicable. The therapy will consist of 40 fractions over 8 weeks.
- Arm II: HTIMRT will begin within 6 weeks of fiducial marker placement, if applicable. The therapy will consist of 38 fractions over 7.5 weeks.
- Treatment should 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 the intent-to-treat analysis. A work-up for metastasis during treatment will only be carried out if the treating physician deems necessary.
- Prostate biopsies will be taken at 2-2.5 years post completion of all therapy (referred to as 2 yr post-treatment protocol biopsies). These are research biopsies that are not typically done, but which have been shown to be of predictive value in our studies (29) and those of others.

5.0 CLINICAL AND LABORATORY EVALUATIONS

5.1 Baseline/pretreatment Evaluations

- History and physical exam, including evaluation of patient's ability to perform daily activities (Zubrod performance status Karnofsky or ECOG performance status may be used to estimate Zubrod), within 8 weeks prior to protocol entry.
- Blood tests: within 3 months prior to protocol enrollment unless otherwise indicated.
  - PSA Level.
  - Liver function tests.
  - Complete blood cell counts.
  - Lipid Profile

-Testosterone level - Serum testosterone will be drawn within 4 months of enrollment . This is only applicable to patients not started on ADT prior to signing consent. Patients who have been started on ADT prior to signing consent are not required to have a serum testosterone at this level prior to signing consent; but, a serum testosterone prior to fiducial marker placement is recommended.

- Bone scan (depending on PSA level and Gleason score) within 4 months of protocol enrollment.
- Multiparametric functional MRI of prostate/pelvis using a 1.5 or 3.0T MRI (preferably 3.0T) within 3 months prior to protocol enrollment.
- A pathology review at the University of Miami of the outside biopsy material prior to enrollment.
- Research fluids of plasma and serum (up to 4 tubes total) and approximately 50 ml urine will be obtained prior to fiducial marker placement, if possible after signing consent form.
- Psychosocial questionnaires after enrollment and prior to fiducial marker placement or randomization
  -The Expanded Prostate Cancer Index Composite Questionnaire-SF12 (EPIC-SF12).
  -Memorial Anxiety Scale for Prostate Cancer patients (MAX-PC).
  -International Prostate Symptom Score (IPSS).
- Gold marker placement, if applicable. and prostate biopsies (optional) within 4 weeks after enrollment CT and MRI simulation.

5.2 Evaluations During Treatment

- Weekly history and physical exam (mainly skin reaction assessment beginning after 5 days of therapy) (Zubrod performance status; Karnofsky or ECOG performance status may be used to estimate Zubrod).
- Blood will be drawn during the last week of RT from a vein for the following tests:
  - Serum Testosterone.
  - Liver function tests.
  - Complete cell counts.
  - Lipid profile.
- Research fluids consisting of plasma and serum (up to 4 tubes) and approximately 50 ml urine will be obtained during the last week of RT, if possible.
- Psychosocial questionnaires during the last week of RT
  - The Expanded Prostate Cancer Index Composite Questionnaire-SF12 (EPIC/SF12).
  - Memorial Anxiety Scale for Prostate Cancer patients (MAX-PC).
  - International Prostate Symptom Score (IPSS).

5.3 Post-treatment Evaluations

- History and focused physical exam at 6 weeks, 3 months and then every 6 months for 2.0-2.25 years after completion of RT and then at the discretion of the treating physician until 5-5.25 years after the completion of RT. (Zubrod performance status; *Karnofsky or ECOG performance status may be used to estimate Zubrod).*
- Blood work in relation to RT:
  -PSA at 6 weeks, 3 months and then every 6 months for 5.25 years.
  -Testosterone at 6 weeks, 3 months and 9 months. If testosterone remains abnormally low, tests will continue to be done at each follow-up visit.
  -Liver function tests at 6 weeks and 3 months.

-Lipid profile at 6 weeks, 3 months and 9 months and within 2 months of 2 yr. prostate post-treatment biopsy.

- Plasma and serum (up to 4 tubes), and urine (approximately 50 mL) for Research Fluid tests will be at 3 months and then within 2 months prior to 2 yr. prostate post-treatment biopsy, if possible.
- Multiparametric functional MRI's with timed contrast at 3 and 9 months, and within 2 months prior to the 2 yr. post-treatment prostate biopsy.
- Prostate biopsy at 2 – 2.5 years post completion of all therapy (2 yr. post-treatment biopsy). For this biopsy procedure, 12-14 biopsies are recommended with cores taken from sextant regions plus the bilateral lateral base, bilateral lateral mid-prostate, and bilateral lateral apex. At least 2-3 of these biopsies should be from suspicious/previously positive areas. The bilateral transition zone may be biopsies as well. Fewer biopsies may be obtained at the discretion of the urologist. The post-treatment biopsy will also be done, if possible, using the Eigen Artemis® system software for MRI-ultrasound fusion (see sections 1.2 and 3.3.4) that is in beta testing. The Eigen Artemis system fusion software (FDA approved) may be used to fine-tune the location of the tumor and biopsies by fusion of the previously obtained multiparametric MRI to the transrectal ultrasound in real time. The ultrasound is the true guidance imaging parameter that identifies the prostate boundaries and other nearby structures. The MRI is fused to the ultrasound such that the biopsies may be directed to a region in the ultrasound space. The patient will be informed of the results.
- Bone scan at the discretion of treating physician based on clinical suspicion of metastasis.
- Psychosocial questionnaires follow-up at 6 weeks, 3 months, 9 months, 15 months and yearly to 5.25 years.
  -The Expanded Prostate Cancer Index Composite Questionnaire-SF12 (EPIC-SF12).
  -Memorial Anxiety Scale for Prostate Cancer patients (MAX-PC).
- International Prostate Symptom Score (IPSS) will be done at each follow-up visit for 5.25 years. This includes 6 weeks, 3 months and every 6 months thereafter RT.

Note: Measurements and follow-up visits should occur ± 2 weeks up to the 3 month visit and ± 4 weeks for subsequent measurements/visits.

<u>If for whatever reason the patient is unable to return for follow up (e.g. insurance problems, moving out of town, etc.) we will continue to follow the patient via phone call and we will try to get their records from any outside facility.</u>

5.4 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 a HT boost of radiation delivered to the DCE-MRI-defined dominant region(s) by dose painting at 2.35 Gy per fraction. The HT boost region will receive an absolute dose of 89.3 Gy. Assuming an α/β ratio of 3.0, this would be equivalent to 95.5 Gy in 2.0 Gy fractions.

6.2 Other Agent(s)

Lupron (leuprolide acetate), Zoladex (goserelin), Casodex (bicalutamide) and Eulexin. (flutamide) or other equivalent generic agents are used in routine management of prostate cancer for androgen deprivation. These drugs are not study specific and are standard for prostate cancer; they will not be supplied by the pharmacy at SCCC.

Short term androgen deprivation (STAD) for 4-6 (+/- 2 months) months will be administered to some patients as described in section 4.6. This timing is based on LHRH agonist injections (not the bicalutamide)

STAD will consist of oral antiandrogen administration and LHRH agonist injections within 6 weeks of registration. The anti-androgen will be either flutamide at 250 mg p.o. TID or bicalutamide at 50 mg p.o. QD. Anti-androgen therapy should begin at approximately the same time as LHRH agonist injection but may be started up to two weeks earlier. Anti-androgen administration will be given for up to four months. The length of STAD therapy will be pegged to the anticipated duration of LHRH agonist therapy. LHRH agonist injections (Lupron or Zoladex) may be given in any possible combination, such that the total LHRH agonist treatment time is 4-6 (+/- 2 months) months. For example, LHRH agonist injection(s) may be given as a single 4-month injection, a 4-month injection and one to two 1-month injection(s), two 3-month injections, one to three 1-month and a 3-month injection (4-6 months total[+/- 2 months]), four to six 1-month injections, or a 6-month injection.

7.0 AGENT FORMULATION AND PROCUREMENT

7.1 Agents

Lupron, Zoladex, Degarelix, Casodex and Eulexin or other equivalent generic agents

7.1.1 Other names

- ***Lupron*** - leuprolide acetate
- ***Zoladex*** – goserelin
- ***Degarelis*** - **firmagon**
- ***Casodex*** - bicalutamide
- ***Eulexin*** - flutamide

7.1.2 Classification

- ***Lupron*** is a synthetic nanopeptide analog of naturally occurring gonadotropin-releasing hormone *(GnRH or LH-RH)*. The analog possesses greater potency than the natural hormone.
- ***Zoladex*** is a LHRH analog with substitutions for the L-amino acid Glycine in positions 6 and 10.
- ***Firmagon*** *is an LHRH antagonist that does not require anti-androgen.*
- ***Casodex*** is a nonsteroidal antiandrogen
- ***Eulexin*** is a nonsteroidal anti-androgen.

7.1.3 Storage and Stability

The agents are commercially available and received in the manufacturer's packaging. If administrated through syringe, the drugs are in sterile units and come in a sealed, light- and moisture-proof package. The packs should be stored at approximately 25° C (room temperature). Before being opened, each package must be inspected for damage in which case the syringe must not be used. The drugs that are administered orally also come in packs, which should be stored at room temperature and protected from excessive moisture. Since the drugs are part of the routine treatment of prostate cancer they will be handled by the treating physician according to the manufacturer specifications.

7.1.4. Dose Specifics

- ***Lupron*** is recommended as 7.5 mg (*one month*), 22.5 mg *(three month)* or 30 mg *(four month)* intramuscular depot injections in the combinations described above to achieve a total duration of 4-6 months.
- ***Zoladex*** is recommended as 3.8 mg (*one month*) or 10.8 mg (*three month*) depot subcutaneous injections in the combinations described above to achieve a total duration of 4-6 months.
- ***Firmagon*** *is recommended as 240mg given as two injections of 120mg each or 80mg administered as a single injection every 28 days.*
- ***Casodex*** is supplied as 50 mg tablets. Casodex has a long half-life compatible with once-daily dosing. Antiandrogen will be given for a maximum of four months.
- ***Eulexin*** is supplied as 125 mg capsules and is commercially available. Antiandrogen will be given for a maximum of four months.

7.1.6 Preparation

The agents are commercially available and no preparation is required.

7.1.7 Administration

The injectable agents will be administered by the study urologists in their offices, as part of routine clinical practice. The oral agents will be prescribed by the treating physician as part of routine clinical practice.

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7.1.8 Incompatibilities/Dose Modification

- ***Casodex*** should be discontinued in instances of chemical liver toxicity. AST or ALT will be measured pretreatment and then every other month during antiandrogen therapy. If the AST or ALT rises ≥ 2x the institutional upper limit of normal, ***Casodex*** must be discontinued. If liver enzymes are rising and of concern to the treating physician, Casodex may be discontinued earlier.
- ***Eulexin:*** If gastrointestinal disturbances (cramps, diarrhea) occur prior to initiation of radiotherapy, the drug will be withheld until the side effects subside; the drug will then be reintroduced at a dose of 250 mg/day and increased (at 3-day intervals) to 500 mg/day and then to 750 mg/day as tolerated. If gastrointestinal disturbances occur after administration of radiotherapy, it might be difficult to identify their cause. However, if severity of diarrhea exceeds the level commonly observed during pelvic irradiation, the toxicity will be ascribed to Eulexin and the drug will be permanently discontinued. AST or ALT will be measured pretreatment, then about every other month during oral antiandrogen therapy. If AST or ALT increases ≥ 2x the upper institutional limit of normal, flutamide must be discontinued.

7.1.9 Availability

The agents are commercially available and will <u>*not*</u> be dispensed by the Sylvester pharmacy. Casodex will be prescribed through routine mechanisms and obtained through community pharmacies per routine practice. The LHRH agonists may be administered by an urologist or other physician (sometimes this is done by a PCP when the drug is purchased directly from a pharmacy) at the University of Miami or in the community. Documentation of dose, delivery route and date must be obtained in writing from the administering physician and recorded in the University of Miami electronic record.

7.1.10 Side Effects

- ***Lupron*****:** In the majority of patients testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. The most common side effect of Leuprolide is vasomotor hot flashes; edema, gynecomastia, bone pain, thrombosis, and GI disturbances have occurred. Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in

patients with vertebral metastases and/or urinary obstruction or hematuria which, if aggravated, may lead to neurological problems such as temporary weakness and/or paresthesia of the lower limbs or worsening of urinary symptoms

- ***Zoladex:*** During routine screening of Zoladex, no significant pharmacological activity was apparent in the cardiovascular, respiratory, central nervous, renal, metabolic, coagulation or gastric acid secretory systems. Studies have shown that serum levels of testosterone can be reduced and maintained within the castrate range resulting in objective evidence of tumor regression. Other than the occasional transient worsening of cancer symptoms (tumor flare) due to an initial temporary rise in testosterone serum levels on initiating therapy, no significant toxicity apart from that attributed to castration (hot flashes, decreased erections, impotence) has been reported. In general, allergic reactions have been extremely uncommon with Zoladex therapy. There have been isolated reports of urethral obstruction, urticaria, or spinal cord compression.

Firmagon: The most frequently reported adverse reactions at the injection sites were pain (28%), erythema (17%), swelling (6%), induration (4%) and nodule (3%). These adverse reactions were mostly transient, of mild to moderate intensity, occurred primarily with the starting dose and led to few discontinuations (<1%). Grade 3 injection site reactions occurred in 2% or less of patients receiving degarelix.
Hepatic laboratory abnormalities were primarily Grade 1 or 2 and were generally reversible. Grade 3 hepatic laboratory abnormalities occurred in less than 1% of patients.
In 1-5% of patients the following adverse reactions, not already listed, were considered related to FIRMAGON by the investigator:
Body as a whole: Asthenia, fever, night sweats; Digestive system: Nausea; Nervous system: Dizziness, headache, insomnia.
The following adverse reactions, not already listed, were reported to be drug-related by the investigator in ≥1% of patients: erectile dysfunction, gynecomastia, hyperhidrosis, testicular atrophy, and diarrhea.

- ***Casodex:*** The drug is well tolerated and has good response rates in phase II trials. Non-pharmacological adverse events, reported in the trial using bicalutamide 50 mg as monotherapy include asthenia, pelvic pain, peripheral edema, pruritus, rash, constipation, impotence, dyspnea, nausea, and pain.(74) There has been no observed change in cardiac parameters during long-term administration of bicalutamide 50 mg daily. When bicalutamide 50 mg was given in combination with an LHRH analogue, the LHRH analogue adverse event profile predominated with a high incidence of hot flashes (49%) and relatively low incidences of gynecomastia (4.7%) and breast pain (3.2%), the associated pharmacological effects of bicalutamide monotherapy.(74) Bicalutamide or flutamide is recommended during the first month of LHRH agonist treatment.
- ***Eulexin:*** The reported side effects of treatment include diarrhea and anemia. A high percentage of patients treated with flutamide alone developed gynecomastia within 2-8 months. There have been post-marketing reports of hospitalization, and, rarely, death due to liver failure in patients taking flutamide. Evidence of hepatic injury included elevated serum transaminase levels, jaundice, hepatic encephalopathy, and death related to acute hepatic failure. The hepatic injury was reversible after prompt discontinuation of therapy in some patients. Approximately half of the reported cases occurred within the initial 3 months of treatment with flutamide.

7.1.11 Nursing Implications

N/A

7.1.12 Reported Adverse Events and Potential Risks

N/A

8.0 CORRELATIVE/SPECIAL STUDIES

Prior to treatment during fiducial marker placement, needle biopsy of the prostate will be performed if the patient agrees (optional). Tissue from paraffin blocks will be used for biomarker quantification and correlative studies with treatment outcome.

At 2-2.5 years after completion of treatment (radiotherapy or androgen deprivation – whichever is longer) all patients, with or without documented failure will undergo transrectal needle biopsy of the prostate, unless clinically contraindicated or the patient refuses. For this biopsy procedure, 12-14 biopsies are recommended with cores taken from sextant regions plus the bilateral lateral base, bilateral lateral mid-prostate, and bilateral lateral apex. At least 2-3 of these biopsies should be from suspicious/previously positive areas. The bilateral transition zone may be biopsied as well. Fewer biopsies may be obtained at the discretion of the urologist. The ultrasound is the true guidance imaging parameter that identifies the prostate boundaries and other nearby structures. The MRI is fused to the ultrasound such that the biopsies may be directed to a region in the ultrasound space. These data will enable us to evaluate the extent of disease eradication, as well as the prognostic significance of positive biopsies in men who are otherwise free of evidence of disease (low PSA and palpably normal prostate gland).

The 2 yr. post-treatment biopsy is for research purposes. If the biopsies contain prostate tumor cells, the results will be discussed with the patient and additional management considerations made apart from this clinical trial. Many times tumor cells are seen on prostate biopsies at 2-2.5 yr., but the cells show radiation treatment effect. In this situation, it is reasonable to continue to follow the PSA and re-biopsy a year later to look for clearance of the tumor cells. The strategy to re-biopsy will be up to the treating physician and will not be governed by the protocol.

9.0 MEASUREMENT OF EFFECT

Quantitative endpoints to assess study objectives are as follows:

9.1 Definitions

- *Biopsy failure rate:* The proportion of positive biopsy findings among patients without clinical or biochemical failure 2-2.5 years after completing study treatment (RT or ADT, whichever is longer).
- *Two-year failure rate:* The proportion of patients with either (i) biopsy failure 2-2.5 year after completing treatment (RT or ADT, whichever is longer) or (ii) evidence of biochemical and/or clinical failure (local, regional or distant failure) at any time prior to the planned 2 year post treatment biopsy.
- *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 local failure due to newly identified extension outside of the prostate after initial regression, or urinary obstructive symptoms with carcinoma found at TURP or regional/distant failure due to radiographic evidence metastasis (nodal or hematogenous spread. 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 the 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 extent will be recorded qualitatively using the definitions in Section 9.1.

9.2.2 PSA response: In 98% of patients treated with definitive radiotherapy there is a drop in PSA within 3 months. Those patients that have not responded should be investigated to define the site of progression (local-regional vs. distant metastases). In patients that have responded, a rising PSA later heralds relapse. Biochemical failure will be modeled after the Nadir+2 definition.(28) Evaluation of patients with a rising PSA profile will include a bone scan, MRI-pelvis/prostate, and prostate biopsy. ProstaScint scan has not been shown to be consistent for defining relapse pattern and is not recommended.

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

9.2.5 Quality of Life: As described in section 1.5, the EPIC-SF12 and MAX-PC questionnaires will be done at 6 weeks, 3 months, 9 months,15 months and yearly to 5.25 years after radiotherapy.

10.0 MEASUREMENT OF TOXICITY

Acute proctitis and cystitis lasting for up to 3 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*** (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.
Any laboratory abnormal value that leads to a change in subject management (eg, treatment discontinuation, requirement for additional medication or monitoring) or is considered to be of clinical significance by the investigator should be reported as an AE or SAE as appropriate, unless this value is consistent with the subject's present disease state or is consistent with values obtained prior to entry into the study.

11.1.2 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** are those that have been previously identified as resulting from administration of the agent.
11.1.4 An adverse event is considered ***unexpected*** when either the type of event or the severity of the event is *not* listed in: the current NCI Agent-Specific Adverse Event List; the investigator's brochure, drug package insert or the drug information section of this protocol.
11.1.5 The definition of ***related*** is that there is a reasonable possibility that the drug caused the adverse experience.
11.1.6 An ***investigational agent*** is a protocol drug administered under an Investigational New Drug Application (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.
11.1.7 ***Commercial agents*** are those agents not provided under an IND but obtained instead from a commercial source.
11.1.8 ***Concurrent administration:*** When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational, and reporting of adverse events would follow the guidelines for investigational agents.
11.1.9 ***Sequential administration****:* When a study includes an investigational agent(s) and a commercial agent(s) on the same study arm, but the commercial agent(s) is given for a period of time prior to starting the investigation agent(s), reporting of adverse events which occur prior to starting the investigational agent(s) would follow the guidelines for commercial agents. Once

therapy with the investigational agent(s) is initiated, all reporting of adverse events should follow the investigational guidelines.

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*.

11.3.1 All serious, unusual life-threatening or lethal adverse which may be study related will be reported within 24 hours by telephone to the Principal Investigator and must be followed by a written report which must be received by the Principal Investigator within 10 business days. The Principal Investigator shall also be responsible for promptly notifying the local Institutional Review Board of all such serious adverse events. For all fatal events (Grade 5) while on study or within 30 days of treatment, a written report will follow within 10 working days.
Hospitalizations scheduled only for study treatment will not be reported or collected as SAE's.

11.3.2 **FDA Reporting**

N/A

11.3.3 **IRB Reporting**

11.3.3.1 All adverse events that are serious adverse events **and** are unexpected **and** are related or possibly related must be reported to the IRB within ten (10) working days of being

made known to the Principal Investigator. Events that are more frequent than anticipated or more severe than expected must be reported to the IRB within ten (10) working days of being made known to the Principal Investigator.
All unanticipated deaths must be reported to the IRB within 24 hours of being made known to the Principal Investigator.

11.3.4 **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.

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.

A list of forms to be submitted, as well as expectation dates, may be found in Appendix IV.

14.0 STATISTICAL CONSIDERATIONS

14.1 Overview

This is a two-arm randomized Phase III trial with the primary objective of determining whether MRI-guided hypofractionated radiotherapy (HTIMRT), as compared with standard dose fractionation (SIMRT), reduces the two-year post treatment biopsy failure rate in men receiving primary radiotherapy for favorable to high risk prostate cancer. Secondary objectives include comparison of HTIMRT and SIMRT with respect to 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. It would not be practical or desirable to suspend accrual for an extended period of time to accommodate an interim assessment of the two year failure rate as would be needed to consider early stopping for efficacy or futility (lack of efficacy) based on the main study endpoint.

14.2 Sample size, accrual rate and study duration

Study size is based on our primary objective of demonstrating that, compared to SIMRT, HTIMRT reduces the two year post treatment failure rate, by which we mean the proportion of patients with either biopsy failure or earlier evidence (within two years of treatment completion) of biochemical and/or clinical failure. (See definition in Section 9.1.) We expect the two-year failure rate in the standard fractionation arm to be 52.5%, representing the combined effect of a small rate of biochemical or clinical failure within two years, approximately 5%, and a relatively high rate of positive biopsy among the remaining 95% of patients, namely 50% ($0.05 + 0.95 \times 0.50 = 0.525$). This estimate is based on prior findings on randomized trials previously

organized by the PI. (75) Assuming equal allocation of patients to SIMRT and HTIMRT and sufficient follow-up to determine failure status at two years, a study size of 36 patients in each treatment arm provides 80% power to detect an absolute reduction of 30% in the two-year failure rate (biochemical, clinical, or biopsy), from 52.5% to 22.5%, using a one-sided Fisher's exact test with 5% significance level. To ensure a minimum of 72 study patients evaluable for the two year failure rate as our main study endpoint, we plan to enroll a total of 76 patients.

Based on an accrual rate averaging 2 patients per month, we plan to complete enrollment in 3.2 years. Patients will be followed for five years giving total study duration of 8.2 years. Analyses of some secondary endpoints, including acute toxicity, psychosocial parameters, biomarker distribution on ultrasound-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. The main efficacy endpoint requires less than five years follow up and will be performed after all patients have been assessed for two year post treatment failure status (2 yr. biopsy). Final efficacy analysis will be at the conclusion of study when patients have been followed for 5.25 years.

14.3 Definitions and endpoints:

Evaluable: Patients who are study eligible and receive an initial dose of radiotherapy, either SIMRT or HTIMRT 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 complete radiation treatment and have follow up sufficient to include either the planned 2-year post treatment biopsy or earlier evidence of biochemical or clinical failure (within 2 years of treatment completion). These patients 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

Patients will be randomized in equal proportion to receive either HTIMRT or SIMRT using a permuted block design stratified by baseline PSA (<10 vs 10 to ≤100), Gleason score (6-7 vs 8-10) and short term (4 to 6 months) androgen deprivation (STAD) therapy (Y vs. N). Where appropriate, these factors will be used in the analysis of study data; for example, to stratify statistical tests comparing treatment arms or to adjust regression models. We note that STAD therapy will be recommended for all Gleason 8 patients; however, we allow for all eight possible combinations as strata in order to ensure equal treatment allocation in the event that enrollment includes a small number of patients with uncommon combinations of these factors.

14.5 Analysis plan

The main analysis of study findings will be done by treatment assignment (intention-to-treat) in all patients who meet evaluable criteria as stated in Section 14.3. We will report any instances of treatment crossover. As noted above, analyses of some secondary endpoints, including acute toxicity, psychosocial parameters, tissue and blood product-related biomarker distribution on ultrasound-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 two year post treatment failure status and a final analysis will be done at the completion of the planned 5 year follow up of all study patients. Statistical tests comparing treatment arms will be one-sided with 5% significance level and stratified where appropriate by the factors considered in randomization.

Statistical analysis will include descriptive statistics for patient demographics and baseline disease characteristics, both overall and by treatment arm. 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, sex, race/ethnicity, T-category, Gleason score, PSA, risk group and performance status. Biomarker measurements and proteomic/genomic profiles obtained from baseline biopsy will also be summarized with descriptive statistics. (76)

Treatment received will be summarized by the type of RT and STAD components of therapy, the number and duration of treatment delays, and the rates of discontinuation or completion. Summaries will be provided for each treatment arm. Safety analysis will include a detailed tabulation of acute and late occurring toxicity by type and grade, both overall and by treatment arm. 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 in each treatment arm. Death without the toxicity of interest will be treated as a competing risk, and toxicity rates will be compared by treatment arm using Gray's test. (77, 78)

The primary trial endpoint, two-year failure rate, will be estimated for each treatment arm as a proportion with corresponding 95% confidence interval by the exact binomial method. Comparison of the failure rate for SIMRT versus HTIMRT will be based on a one-sided Fisher's exact test at a 5% significance level. Similar estimation and comparison will be done for the biopsy failure rate among clinical/biochemical failure-free patients at the two year post RT follow up. Biopsy findings two years post RT will be further characterized as negative, atypical, carcinoma with treatment effect, or carcinoma without treatment effect and compared by treatment arm using Fisher's exact test. Biomarker and proteomic/genomic characteristics of prostate biopsy tissue obtained two-year post treatment, and changes relative to baseline, will be summarized by descriptive statistics. Change from baseline will be tested for significance using t-test (means) or McNemar's test (proportions) for paired data and comparison of changes by treatment arm will be based on two-sample tests (t-test or Fisher's exact test). (For biomarker studies, nonparametric tests or data transformations to attain approximate normal distributions will be applied as needed.) Logistic regression models adjusted for treatment will be used to investigate the association between baseline factors, including biomarkers and proteomic/genomic profiles, and biopsy failure two-years post treatment. Changes in biomarkers and proteomic/genomic characteristics will also be investigated for association with biopsy failure. (79)

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 treatment arm and failure type. Similarly, vital status will be tabulated by treatment arm and 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 the Table 14.5 (80, 77) Where the Kaplan Meier method is used, point estimates and 2-sided 95% confidence intervals 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. Treatment arms will be compared by the log rank test. Cox regression models including treatment as a covariate 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. Treatment comparison of event rates will be based on Gray's test and regression models investigating prognostic factors will be fit by the method of Fine and Gray. (78, 81) 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.

Finally, to assess the prognostic value of 2-year post treatment biopsy findings, we will further study patients who had this procedure without prior evidence of biochemical or clinical failure. Taking the date of biopsy as the start of follow up, we will analyze subsequent failure rates and failure-free survival and test for association with biopsy positivity and treatment arm.

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. Comparison by treatment arm at baseline and at treatment completion will be based on t-test (average score) and Fisher's exact test (percent improved). 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. The DSMC also reviews reports from internal audits of protocol compliance and data integrity conducted by the University of Miami, Office of Research Compliance Assessment. 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.(82, 83)

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 for each treatment arm. **Table 14.6.1** below shows specific instances where these stopping guidelines are met, thus suggesting early termination of one or more treatment arm 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 35	≥17%
7	28 to 33	≥21%	-	-	-
8	34 to 35	≥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 8 patients randomized to the same arm 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 corresponding treatment arm due to acute toxicity. Similarly for late G3+, suppose that a total of 8 patients randomized to the same arm 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 corresponding treatment arm 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, the extent of patient follow up needed to evaluate the primary efficacy endpoint is two years by which time accrual of 76 patients is expected to be complete or nearly complete. Thus data will not be available for an interim estimate of the primary efficacy endpoint during the period when a decision to stop enrollment would need to be made. Furthermore, no alternative efficacy endpoint suitable for assessment during the expected two year enrollment period is available in the context of this patient population and treatment.

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.

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, quality of life surveys, and 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 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.
- Functional MRI-defined tumor size and location (GTV).
- 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.

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 should be on file:

- 1572 (for studies involving IND drugs or devices).
- CV's and license of all investigators.
- IRB documentation/correspondance.
- Documentation of IRB certification.

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APPENDIX I
STUDY CALENDAR

Assessment	Prior to RT	Weekly during RT	Follow-up					Other
			During Last Week of RT	6 Weeks after RT	3 Mo after RT	Every 6 months thereafter up to 2-2.25 years post-end of all treatment	FU until 5-5.25 years (At the discretion of the physician)	
History & Physical Exam*	X	X	X	X	X	X	X	
Functional-MRI of prostate/pelvis[a]	X				X			At 9 mo., and within 2 mo. of 2 yr. prostate biopsy
Bone Scan[b]	X							As needed
Prostate protocol biopsy[c]	X							2 – 2.5 years post completion of all therapy (2 yr. biopsy)
Prostate fiducial markers[c]	X							
CT and MRI simulation	X							
PSA[a]	X			X	X	X	X	
Serum-Testosterone[d]	X		X	X	X			At 9 months after RT
Liver function tests[a]	X		X	X	X			
Complete blood cell counts[a]	X		X		X			
Lipid Profile[a]	X		X	X	X			At 9 months and within 2 mo. prior to 2 yr. prostate biopsy
EPIC-SF-12, MAX-PC[e]	X		X	X	X			At 9 months, 15 mo. and yearly to 5.25 years
IPSS[f]	X		X	X	X	X	X	At each follow-up visit
ADT[g]	X							
Plasma and serum, and urine collection for research[h]	X		X		X			Within 2 mo. prior to 2 yr. prostate biopsy

*Toxicity will be assessed at each scheduled history and physical exam visit. Interval history will be obtained during and following RT at these visits. History and physical within 8 weeks prior to protocol entry.

[(a)]Obtained ≤ 3 months of enrollment.

[(b)]Obtained ≤ 4 months of enrollment if PSA >15 ng/mL or Gleason score ≥8 disease. For all others, to be obtained at the discretion of the treating physician.

[c]The initial protocol prostate biopsy is optional per the patient's desire, as indicated on the consent, and will be carried out during fiducial marker placement, if applicable. In follow-up, prostate biopsy will be obtained at the first sign of local failure or a rising PSA, or at 2-2.5 years after treatment (after radiotherapy or androgen deprivation – whichever is longer) if there is no evidence of failure. The second biopsy is not optional (the patient must agree), but the biopsy may be refused later or may not be performed due to a medical contraindication.

[d]Serum testosterone will be drawn as part of routine workup within 4 months of enrollment or after enrollment but prior to the first radiation treatment. Serum testosterone will be drawn at 6 weeks, 3 and 9 months after radiotherapy. If testosterone remains abnormally low, tests will continue to be done at each follow-up visit. Patients who have been started on ADT prior to signing consent are not required to have a serum testosterone at this level; but, a serum testosterone prior to fiducial marker placement is recommended.

[e]After enrollment and prior to fiducial marker placement, if applicable. At 6 weeks, 3 mo., 9 mo. and then yearly to 2.0-2.255.25 years after the completion of radiotherapy and then at the discretion of the treating physician until 5.-5.25 years after completing radiotherapy

[f]International Prostate Symptom Score will be administered pretreatment, at the end of treatment and at each follow-up visit.

[g]Androgen deprivation therapy: Anti-androgen treatment should begin 1-14 days prior to LHRH agonist injections, which may occur up to 2 months prior the signing of consent. Anti-androgen is not needed when an LHRH antagonist is used.

[h]After signing consent form, up to four tubes of blood and approximately 50 mL of urine will be collected, as described in Sections 4.11, 4.12 and 5.0 for research studies, if possible.

Note: Measurements and visits during treatment should occur ± 3 days; measurements and visits during follow-up should occur ± 2 weeks up to the 3 month visit and ± 4 weeks for subsequent measurements/visits.

If for whatever reason the patient is unable to return for follow up (e.g. insurance problems, moving out of town, etc.) we will continue to follow the patient via phone call and we will try to get their records from any outside facility.

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

The NCI CTCAE criteria may 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 toxicity and feasibility. The guidelines appearing in Section 11.0 are offered for DSMC consideration in assessing adverse events. In addition, the DSMC will review reports from all audits, site visits, or study reviews pertaining to this clinical trial and take appropriate action.

The SCCC DSM Plan to which this study is subject can be found at [redacted]

APPENDIX IV
DATA SUBMISSION SCHEDULE

FORM	TO BE COMPLETED
BASELINE	
Eligibility Checklist	Prior to registration
SCCC Protocol Enrollment Form	
Consent Forms Signed/dated	
On-study Form	Within 30 days of registration
DURING PROTOCOL THERAPY	
	Due every week for phase I studies, every cycle for phase II-IV studies
AFTER PROTOCOL THERAPY	
Off Treatment Form	Within 14 days of discontinuation/completion of protocol therapy
FOLLOW-UP SCHEDULE (for studies with long term follow-up)	
Follow-up Form	At RT completion, and after RT at 6 weeks, 3 months, and every 6 months to 5.25 yr after RT.
Progression/Relapse	Within 4 weeks of knowledge of progression/relapse
Notice of Death Form	Within 4 weeks of knowledge of death
Subsequent Malignancy	Within 4 weeks of knowledge of another malignancy

APPENDIX V
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 VI

PERFORMANCE SCALES

ZUBROD PERFORMANCE 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 PERFORMANCE 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

ZUBROD/KARNOFSKY COMPARISON

- Zubrod 0 equals Karnofsky 100; 90–100
- Zubrod 1 equals Karnofsky 80–90; 70–80
- Zubrod 2 equals Karnofsky 60–70; 50–60
- Zubrod 3 equals Karnofsky 40–50; 30–40
- Zubrod 4 equals Karnofsky 20–30;10–20

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