



SCCC # (PROVIDED BY CRS)

EProst # (20100389)

NCT01411319

A Phase I Trial Of MRI-Guided Lattice Extreme Ablative Dose Radiotherapy For Prostate Cancer

PRINCIPAL INVESTIGATOR:

Alan Pollack, M.D., Ph.D.
Chair and Professor of Radiation Oncology
Department of Radiation Oncology
Phone: 305-243-4916
E-mail: APollack@med.miami.edu

CO-INVESTIGATOR(S):

Matthew Abramowitz, M.D.

SUB-INVESTIGATORS

Laura Freedman, M.D.
Roberto Manzano, MD
Merce Jorda, M.D.
Arnold Markoe, M.D., Sc.D.
Lorraine Portelance, M.D.
Aaron Wolfson, M.D.
Sturt Samuels, MD
Alan L. Dal Pra, MD
Radka Stoyanova, Ph.D.
Eric Mellon, MD
Anesa Ahamad, MD

STATISTICIAN:

Isildinha Reis

VERSION #:

8

VERSION DATE:

03/11/2018

CONTACT INFORMATION

PRINCIPAL INVESTIGATOR:

Alan Pollack, M.D., Ph.D.
Chair and Professor of Radiation Oncology
Department of Radiation Oncology

[Redacted]

[Redacted]

Lorraine Portelance, M.D.
Attending Physician
Department of Radiation Oncology

[Redacted]

CO-INVESTIGATOR(S):

Matthew Abramowitz, M.D.
Assistant Professor
Department of Radiation Oncology

[Redacted]

Aaron Wolfson, M.D.
Professor and Vice-Chair of Radiation
Oncology
Department of Radiation Oncology

[Redacted]

SUB-INVESTIGATORS

Laura Freedman, M.D.
Assistant Professor of Radiation Oncology
Sylvester Comprehensive Cancer Center

[Redacted]

Radka Stoyanova, Ph.D.
Research Assistant Professor
Department of Radiation Oncology

[Redacted]

Stuart Samuels, MD
Assistant Professor of Radiation Oncology
Sylvester Comprehensive Cancer Center

[Redacted]

Alan L. Dal Pra, MD
Assistant Professor of Radiation Oncology
Sylvester Comprehensive Cancer Center

[Redacted]

Arnold Markoe, M.D., Sc.D.
Professor and Chairman Emeritus of
Radiation Oncology
Department of Radiation Oncology

[Redacted]

Eric Mellon, MD, PhD
Assistant Professor of Radiation Oncology
Sylvester Comprehensive Cancer Center

[Redacted]

Roberto J. Manzano, MD
Sr. Research Associate 1
Department of Radiation Oncology
Sylvester Comprehensive Cancer Center



STATISTICIAN:

Isildinha Reis
Biostatistician
Division of Biostatistics

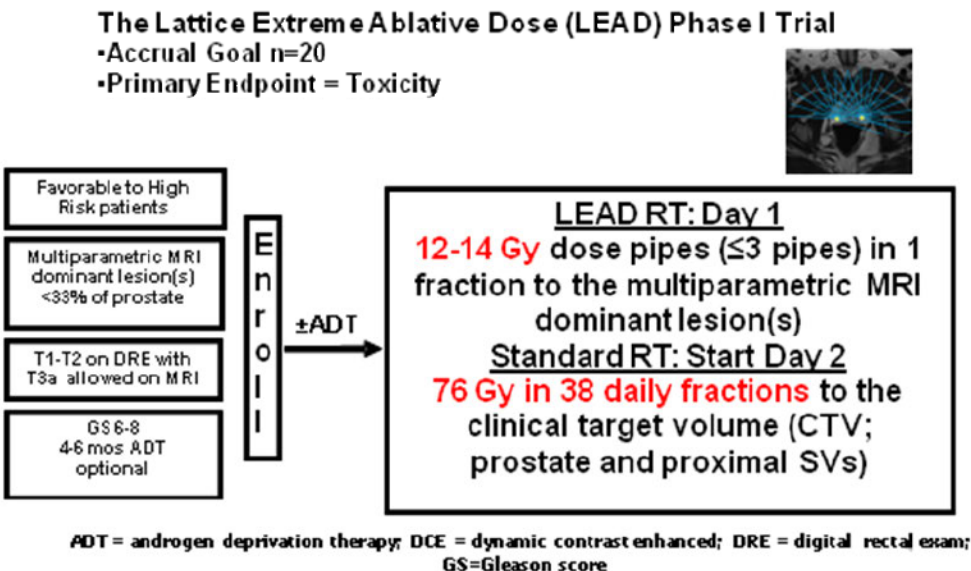


TABLE OF CONTENTS

SCHEMA	6
ELIGIBILITY CHECKLIST	9
HYPOTHESIS.....	11
1.0 BACKGROUND	11
1.1 Study Disease.....	11
1.2 Study Agent/Technique	11
1.3 Other Agent(s)	12
1.4 Rationale.....	12
1.5 Quality of Life.....	20
1.6 Age, Gender and Ethnicity	21
2.0 OBJECTIVES	21
2.1 Primary Objective	21
2.2 Secondary Objectives.....	21
3.0 PATIENT SELECTION.....	21
3.1 Inclusion Criteria.....	21
3.2 Exclusion Criteria	22
3.3 Enrollment Procedures	23
4.0 TREATMENT PLAN.....	23
4.1 Pre-enrollment Multiparametric MRI	23
4.2 Assessment of Protocol Eligibility and Enrollment	24
4.3 Prostate Biopsy and Gold Seed Fiducial Marker Placement	24
4.4 Prostate Cancer Upgrading and Change of Treatment	25
4.5 Prostate Biopsy Tissue Handling	25
4.6 MRI and CT-Simulation	25
4.7 Risk Assessment for RT and ADT Planning.....	26
4.8 LEAD Dose Distribution, Planning and Constraints	26
4.9 Normal tissue contouring guidelines	27
4.10 Prostate PTV Planning and Constraints	28
4.11 Distal seminal vesicle CTV2 and PTV2 for high risk patients.....	28
4.12 Protein biomarkers and immune activation markers in the serum/whole blood.....	29
4.13 Proteomic and Genomic Analyses of Blood and Urine	29
4.14 Supportive Care Guidelines	30
4.15 Duration of Therapy.....	30
5.0 CLINICAL AND LABORATORY EVALUATIONS	31
6.0 DOSING DELAYS/DOSE MODIFICATIONS	33

6.1	Study Agent	33
6.2	Other Agent(s)	33
7.0	AGENT FORMULATION AND PROCUREMENT.....	34
8.0	CORRELATIVE/SPECIAL STUDIES.....	37
9.0	MEASUREMENT OF EFFECT.....	37
10.0	MEASUREMENT OF TOXICITY.....	39
11.0	ADVERSE EVENT REPORTING.....	40
12.0	CRITERIA FOR DISCONTINUATION OF THERAPY.....	43
13.0	DATA REPORTING.....	43
14.0	STATISTICAL CONSIDERATIONS.....	43
15.0	INVESTIGATOR’S RESPONSIBILITIES.....	45
16.0	REFERENCES.....	47
APPENDIX I	54
	STUDY CALENDAR	54
APPENDIX II	56
	NATIONAL CANCER INSTITUTE (NCI) COMMON TOXICITY CRITERIA (CTC).....	56
APPENDIX III	57
	DATA AND SAFETY MONITORING PLAN.....	57
APPENDIX IV	58
	DATA SUBMISSION SCHEDULE.....	58
APPENDIX V	59
	ADDITIONAL ITEMS.....	59
APPENDIX VI	60
	PERFORMANCE SCALES	60
APPENDIX VII	61
	The Modified 18-Item Memorial Anxiety Scale for Prostate Cancer	61
APPENDIX VIII	63
	EPIC-SF12	63
APPENDIX IX	85
	INTERNATIONAL PROSTATE SYMPTOM SCORE (IPSS): Page 1 of 2.....	85

Schema



1. Eligibility screening: Includes MultiparametricMRI of prostate and pelvis

- A. Biopsy confirmed adenocarcinoma of the prostate.
- B. T1-T3a disease based on digital rectal exam.
 - a. T3a disease based on MRI only is acceptable (no evidence of frank (clear-cut) SV involvement or invasion of bladder or rectum).
- C. Gleason score 6-10. Gleason ≥8 patients must have <40% of the tissue overall involved with Gleason 8-10 in the biopsy specimen to be eligible.
- D. All patients may receive 4-6 months (+/- 2 months) of ADT at the discretion of the treating physician, if the patient agrees. Patients with Gleason score ≥8 must be offered long term androgen deprivation therapy (ADT) and refuse such treatment because only 4-6 months (+/- 2 months) (short term ADT) is permitted (not required) on this protocol. The ADT is recommended to begin after fiducial marker placement; however, is permitted to have been started up two months prior to the signing of consent.
- E. PSA ≤30 ng/mL within 3 months of enrollment.
- F. No previous pelvic radiotherapy.
- G. No previous history of radical/total prostatectomy (suprapubic prostatectomy is acceptable).
- H. 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.
- I. Identifiable multiparametric MRI-defined tumor lesion or lesions, that total in volume <33% of the prostate.
- J. Ability to understand and the willingness to sign a written informed consent document.
- K. Zubrod performance status <2.

- L. Patients must agree to fill out the psychosocial questionnaires.
- M. Bone scan negative if PSA >15 ng/mL or Gleason \geq 8 disease. A questionable bone scan is acceptable if plain x-rays and/or MRI are negative for metastasis.
- N. 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 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.
- O. Serum liver function tests (LFTs) are taken within 3 months of enrollment.
- P. Complete blood counts are taken within 3 months of enrollment.
- Q. Age \geq 35 and \leq 85 years.

2. After Enrollment and Prior to Treatment

- A. Transrectal research prostate biopsies and gold seed fiducial marker placement:
 - 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 multiparametric 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.

3. Treatment Technique

- A. LEAD RT: 12-14 Gy dose pipes on day 1.

The LEAD dose distribution may be planned and delivered by the Cyberknife, an image-guided robotic SBRT system, or on a standard LINAC,. The LEAD RT dose plan will involve the placement of 1 to 3 dose pipes of 7-12 mm diameter the length of the multiparametric MRI GTV volume; but, may extend up to 6 mm above and 6 mm below the GTV. The GTV will include the multiparametric MRI-defined suspicious lesions defined by either early phase contrast enhancing lesion on dynamic contrast enhanced (DCE)-MRI or water restriction on the Apparent Diffusion Coefficient (ADC) maps, considered with the abnormality on T2-weighted imaging. For anterior lesions in the transition zone an abnormality based on only DCE-MRI is not enough and must be accompanied by, restricted water motion on diffusion weighted imaging (DWI) via an ADC point value of <1000 and/or increased choline + creatinine relative to citrate (\geq 0.9 ratio) on MR spectroscopy (MRS). The LEAD RT region(s) will be centered in the GTV region(s), but may extend out of the GTV to avoid being too close to the vital structures (rectum, urethra, bladder or penile bulb. The LEAD regions should be positioned \geq 2 mm from the vital structures to avoid excessive dose to these structures. Up to three dose pipes spaced by approximately 1.5 – 2.0 cm may be used, with no more than two per side of the prostate. The LEAD RT dose pipes will be covered by 12-14 Gy with a maximum of 20 Gy. The

maximum dose for each dose pipe shall be <20 Gy. A variation will be maximum doses ≥ 20 Gy to 23 Gy, with a protocol violation above this limit. The Vprescription (12-14 Gy) is expected to be <20% and >10% of the tumor, but this is not a constraint. The V(3 Gy) for the rectum, bladder, and penile bulb will be <8% (4.0 Gy Dmax). Protocol variations will be a V(3 Gy) of 8-10% with a Dmax of 4.5 Gy. A protocol violation will be anything above these limits. For the urethra, the V(3 Gy) will be <10%. A protocol primary variation will be a V(3 Gy) of 10-20% with a Dmax of 6.0 Gy. A secondary protocol variation will be for any dose above the limits; there will not be any protocol deviations for the urethral dose. The urethra is more resistant to higher radiation doses; hence, the more relaxed constraints.

B. IMRT: Start of 76 Gy in 2 Gy fractions on day 2 (within 32 hr of LEAD RT).

There shall be no gap of more than 30 hours between the first three 2 Gy fractions; the LEAD RT treatment will therefore be done on a Monday, Tuesday, or Wednesday, unless special arrangements are made to treat on the weekend. In-tempo image-guided technique will be used to deliver both the LEAD and the fractionation treatments to minimize the dosimetric error from intra-fractional prostate movement. The primary Clinical Target Volume (CTV1) will include the prostate (with GTV) and the proximal seminal vesicles (usually about 10 mm and/or $\leq 50\%$). The CTV1 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 (PTV1) will be 3-5 mm around the CTV1 in all dimensions. For tumors at the base, a margin of 5 mm on the proximal seminal vesicles is recommended.

The pelvic lymph nodes may be treated in high risk patients (CTV2) to 56 Gy in the planned 38 fractions. There is no expansion for the PTV2.

IMRT plans will be evaluated by dose-volume histogram analysis. Less than or equal to 17% and 35% of the rectum should receive ≥ 65 Gy and ≥ 40 Gy, respectively, in calculated 2 Gy equivalent doses.¹ Less than or equal to 25% and 50% of the bladder should receive ≥ 65 Gy and ≥ 40 Gy, respectively, in calculated 2.0 Gy equivalent doses. At least 95% of the PTVs should receive the prescription dose (a minor variation will be <95% to $\geq 90\%$ of the prescription dose). Assuming an α/β ratio of 3.0, the biologically equivalent dose in 2.0 Gy fractions to the LEAD RT region would be 149 Gy.

Eligibility Checklist

- _____ 1. Biopsy confirmed adenocarcinoma of the prostate.
- _____ 2. All must be within limits:
- _____ Palpable Stage T1a-T3a (AJCC 2002 staging system) (Y/N).
- _____ T1a is permitted if peripheral zone biopsies are positive (Y/N).
- _____ MRI-defined \leq T3a disease (Y/N).
- _____ PSA \leq 30 ng/ml within 3 months of enrollment. If PSA was above 20 and dropped to \leq 20 with antibiotics, this is acceptable for enrollment. (_____) **Fill In Value**
- _____ If PSA is >15 ng/ml or Gleason 8 disease, has a bone scan been obtained \leq 4 months before enrollment that is negative for metastasis (Y/N vs. **N/A**)? A questionable bone scan is acceptable if plain x-rays and/or MRI are negative for metastasis.
- _____ Gleason score 6-10. (_____) **Fill In Value**
- _____ If Gleason score \geq 8: Refused long term androgen deprivation therapy (ADT) (Y/N)?
- _____ If Gleason score \geq 8: Is there <40% Gleason 8-10 tumor, over the total tissue including other tumor and normal tissue (Gleason 8 tumor length/other biopsy tissue length]*100 = <40%) (Y/N)?
- _____ Is ADT for 4-6 months (+/- 2 months) planned (Y/N)?
- _____ If yes, for how many months? (4, 5 or 6 mo)
- _____ Multiparametric MRI abnormality of <33% of the prostate volume.
- _____ If no contrast for multiparametric MRI, was ADC map point dose in T2W abnormality <1000 (Y/N)?
- _____ 3. Is the patient currently on ADT? (Y/N)
- _____ If Yes, was the ADT started \leq 2 months prior to signing the consent (Y/N)
- _____ 4. Zubrod performance status of 0-1.(Y/N) (Karnovsky or ECOG performance status may be used to estimate Zubrod) Performance status is (_____) **Fill In Value**.

- _____ 5. Was the serum testosterone level, drawn as a baseline study in patients not started on androgen deprivation therapy prior to signing consent (Y/N)? Note that serum testosterone is only required for study entry for those not previously started on ADT and should be obtained in applicable patients ≤ 4 months before signing consent. (_____) **Fill In Value.** Serum testosterone is within 40% of normal assay limits for those not started on ADT (a serum testosterone level is still recommended prior to fiducial pmarker placement in those started on ADT prior to signing consent).
- _____ 6. No prior pelvic radiotherapy (Y/N).
- _____ 7. No prior or planned radical prostatectomy (Y/N).
- _____ 8. No concurrent, active malignancy, other than non-metastatic skin cancer or early stage chronic lymphocytic leukemia (well-differentiated small cell lymphocytic lymphoma) (Y/N).
- _____ 9. Is patient willing to fill out psychosocial questionnaires (Y/N)?
- _____ 10. Ability to understand and willing to sign a written informed consent document. (Y/N)
- _____ 11. Serum liver function tests (LFTs) are taken within 3 months of enrollment. (Y/N)
- _____ 12. Complete blood counts are taken within 3 months of enrollment. (Y/N)
- _____ 13. Age ≥ 35 and ≤ 85 years. (Y/N)

Signature

Date

HYPOTHESIS

1. Delivery of single fraction Lattice Extreme Ablative Dose (LEAD) RT to the dominant tumor lesion(s) in the prostate as identified by multiparametric functional Magnetic Resonance Imaging is safe and feasible.
2. Biomarker expression levels differ in the functional MRI identified suspicious and unsuspected tumor regions. We hypothesize that a significant source of variation in biomarker levels is due to tumor heterogeneity and that it is molecular abnormalities in the dominant tumor areas that are angiogenic and determine outcome.

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, in the same year failure rates continue to remain high (27,360 deaths). Local persistence of prostate cancer treated with radiotherapy (RT) is underappreciated. 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.²⁻⁴ There is some evidence to support 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 Magnetic Resonance Imaging (MRI), and in particular Dynamic Contrast Enhanced MRI (DCE-MRI) is very promising for the *in vivo* 3D localization of the dominant tumor area.⁵ Delivery of ablative spatially fractionated radiation to the DCE-MRI defined tumor volume may induce significant tumor endothelial cell death and possibly bystander effects including reduced tumor interstitial fluid pressure in densely populated tumors due to rapid cell kill.

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-67,⁶p53,^{7,8} MDM2,^{9,10} bcl-2 and bax,¹¹ p16,^{12,13}cox-2,¹⁴ and PKA¹⁵ in which abnormal expression using immunohistochemistry (IHC) has been associated with worse patient outcome after radiotherapy. However, 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 are hypervascular on MRI (from angiogenesis) that determine outcome. 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 unsuspected regions.

1.2 Study Agent/Technique

We propose to use a novel method for delivery of ablative spatially fractionated radiation to the multiparametric functional MRI defined tumor volume in the framework of a single-arm phase I clinical trial. The technique, deemed Lattice Extreme Ablative Dose (LEAD) RT, involves the creation of high doses shaped in cylinders through the DCE and/or DWI-MRI defined region(s) and adjacent apparently normal prostate in a lattice framework. The LEAD RT delivery will be in a single fraction of 12-14 Gy prior to standard fractions (2.0 Gy per day) for an additional 76 Gy (total dose for all treatments of 88-90 Gy and 149 Gy_{3.0} in 2.0 Gy equivalents).

In this protocol we also aim to examine biomarkers obtained from ultrasound-guided prostate biopsies. The patients will have the option of refusing the pre-RT prostate biopsies that

are planned to be done when the patient has fiducial markers placed. Emphasis will be placed on biopsying regions in which the multiparametric MRI shows enhancement with or without DWI indicated water restriction. 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. At the present time, Eigen has made available to us the MRI-ultrasound (MRIus) fusion software, which 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 Eigen Artemis® system 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. In this protocol, the MRIus fusion software may be used to obtain research biopsies and the results of the biopsies (e.g., in terms of Gleason score) will not be used for diagnosis (the patients already have a diagnosis) or influence treatment in any way. The patient is free to withdraw from the protocol at any time, including 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 during the ultrasound-guided biopsies to enhance the probability of obtained biomarkers more representative of patient outcome. A third option that will become available in 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.

1.3 Other Agent(s)
N/A

1.4 Rationale

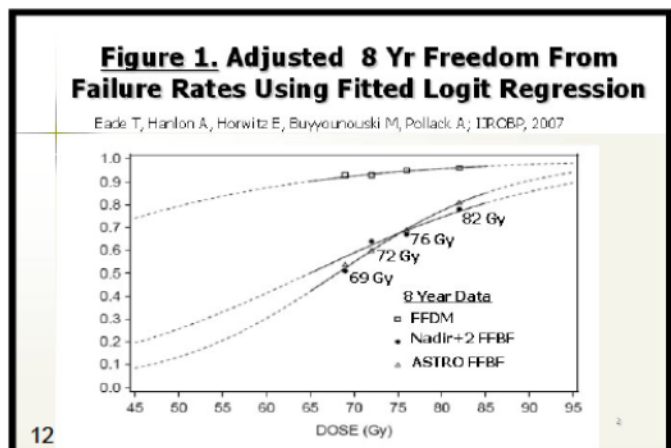
1.4.1 Radiotherapy Dose Escalation for Prostate Cancer

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

Table 1. Prostate Cancer PSA Era Randomized Dose Escalation Trials

Author(yr)	n	Dose(Gy)	FFBF	p-value
Kuban(2007)*	151	78	73%(10yr)	0.004
	150	70	50%(10yr)	
Zietman(2005)	195	79.2	80%(5 yr)	<0.001
	197	70.2	61%(5 yr)	
Peeters(2006)	333	78	64%(5 yr)	0.02
	331	68	54%(5 yr)	
Deamaley(2007)*	422	74	71%(5 yr)	0.0007
	421	64	60%(5 yr)	

FFBF = freedom from biochemical failure
*Nadir+2 FFBF; * Neoadjuvant AD 3-6 mo.



inadequate, leaving behind residual disease in the prostate in the majority. There are several non-randomized studies showing that radiotherapy dose is an important determinant of patient outcome.¹⁶ A Phase III randomized dose escalation trial lead by Dr. Alan Pollack, the principal investigator of this protocol, at M.D. Anderson Cancer Center (MDACC) comparing 70 to 78 Gy^{2,3} confirms the retrospective analyses. With a median follow-up of 8.7 years, the MDACC randomized trial showed a Phoenix definition¹⁷ of freedom from biochemical failure (FFBF) at 10 years of 50% for the 70 Gy group versus 73% for the 78 Gy group (**Table 1**). Similar results have been reported for three other contemporary PSA era randomized RT dose escalation trials (**Table 1**).^{4,18,19}

The most compelling reason for further escalating dose is that failure rates are still unacceptable. **Figure 1** shows a recent analysis of the dose-response of patients treated at Fox Chase Cancer Center (FCCC) in the PSA era.¹⁶ The curves shown are adjusted for pretreatment initial PSA (iPSA), Gleason score and T-stage. Patients were separated into 4 dose groups ranging from < 70 Gy to ≥ 80 Gy and the dose-response curves for freedom from biochemical failure (ASTRO and nadir + 2) and freedom from distant metastases were calculated. The dose-response biochemically between 76 and 82 Gy was estimated to be 2.2% for every 1 Gy added, suggesting that doses of ≥80 Gy would be most effective at limiting local persistence of disease. Thus, it is clear that significantly greater doses are needed to sterilize high tumor burden areas of 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.²⁰⁻²² The most comprehensive series were reported by Crook *et al*²³ and divided patients into three groups: biopsy negative (no tumor), indeterminate (containing adenocarcinoma cells with severe radiation treatment effect) or positive (adenocarcinoma cells without treatment effect). Most patients had 6 biopsies (range 4-7), but it was unclear how many had sextant biopsies since more than one biopsy was routinely obtained from the original region of positivity. Serial biopsies were obtained, beginning at 12 months after RT. They found that 30% who had tumor present on their initial biopsy converted to negative and remained disease free. Likewise, the proportion of indeterminate biopsies decreased over time. In multivariate analyses, biopsy status at 24-36 months was the most significant independent predictor of biochemical failure identified. Another observation pertinent to this grant was that when the proliferation markers PCNA and Ki-67 were seen in indeterminate biopsies, eventual failure was significantly more likely. Recent analyses by Crook *et al*²⁴ and Zelefsky *et al*²⁵ confirm the prior results of Crook and colleagues.^{26,27}

In our analysis of the biopsies from FCCC protocol 02-602, we have preliminary data indicating 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.²⁸ Such an association has implications in how to approach the treatment of prostate cancer with radiotherapy. High tumor burden areas could be given higher RT doses to reduce local persistence.

1.4.3 Molecular Biomarkers in Biopsies Obtained from Different Areas of the Prostate

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. The biomarker studies proposed will provide the foundation for biomarker collection and analysis in larger Phase II/III clinical trials that build on the proposed protocol.

We have been investigating the expression of proteins related to apoptosis and the cell cycle, and have found a number of prostate cancer tissue biomarkers (e.g., Ki-67, p53, MDM2, bcl-2, bax, p16, cox-2 and PKA) measured by immunohistochemistry (IHC) that are predictive of outcome in patients enrolled in Radiation Therapy Oncology Group (RTOG) clinical trials, 86-10 and 92-02. The power of the clinical trials performed by the RTOG is that substantial numbers of men have been treated with standard techniques. Each of the biomarkers has been tested individually with the standard clinical factors of PSA, Gleason score and T-stage, and assigned protocol treatment.

DCE-MRI measures hypervascularity, which may be related to angiogenesis. DWI measures water motion and is mapped on an Apparent Diffusion Coefficient (ADC) map. MRS measures the metabolites choline+creatine and citrate, the ratios of which are indicative of malignancy. The hypothesis is that these and other biomarkers will be different in the dominant tumor areas defined by functional MRI and that directing biopsies to these areas biomarker models will become more accurate. Abnormal blood vessel formation may in turn lead to the development of hypoxia, culminating in a cycle of hypoxia and angiogenesis. VEGF expression will be examined, as this has also recently been shown by Vergis *et al*²⁹ to predict biochemical failure in men treated with radiotherapy. In addition, we will measure androgen receptor (AR) and hypoxia markers. A main tenet of the proposed trial is that hypoxia is causing resistance to high radiation doses and is a main determinant of outcome in men with prostate cancer. To better understand the role of hypoxia, Hif-1 α ,²⁹ CA-9,^{30,31} BNIP3³⁰, GLUT1^{30,32} and EGR1³³ will be measured in all of the ultrasound-guided prostate biopsies. The distribution of hypoxia, angiogenesis and apoptotic biomarkers in uninvolved and involved prostate will be better understood as a result.

1.4.4 The Role of Spatially Fractionated Radiation.

High-dose GRID radiotherapy, sometimes termed spatially-fractionated GRID radiotherapy (SFGRT), is a treatment modality that was introduced in 1909 and commonly used through the 1930's.³⁴⁻³⁶ In 1909, Kohler in Germany described radiation with regularly spaced blocked areas through a metallic screen or sieve that created an effect similar to treatment with multiple small pencil beams.³⁷ Subsequently, Liberson in the United States used this technique for the successful treatment of deep-seated tumors.³⁸ Spatially fractionated radiation, in contradistinction to standard approaches, does not attempt to treat the total tumor volume with a uniform dose. Instead, GRID involves the delivery of high doses of radiation in clusters of small areas without producing prohibitive normal tissue damage to skin and subcutaneous tissues. In its early applications, two-dimensional grid fields were used, typically with orthovoltage beams allowing spatially alternated dose distributions. The grids were usually composed of open/shield circular or square shapes ranging in size from 0.5 to 1.5 cm. The application was mainly for the treatment of advanced bulky tumors.

With the development of megavoltage radiation, GRID radiotherapy has been less commonly used and considered obsolete as a clinical method for delivering high dose radiation. The use of more modern technology to deliver spatially fractionated radiation with superior dosimetry to GRID has not been explored. As a result, other potential advantages of high dose spatially fractionated GRID radiotherapy also remain unexplored. Nonetheless, dramatic clinical responses have been reported with GRID radiotherapy.³⁹⁻⁴³

Published results employing GRID radiotherapy clinically have largely focused on its use in the palliative setting. A report of 22 patients with large or recurrent tumors treated with GRID radiotherapy using doses of 10-15 Gy described palliative relief of symptoms and objective regression in 20 of 22 patients.⁴⁰ A second study of 71 patients with advanced or bulky tumors of varying histologies demonstrated a 78% response rate for pain palliation and 72.5% objective clinical response rate after GRID radiation of 10-20 Gy with or without additional external beam radiation.⁴¹ Neither of these studies demonstrated significant toxicity with treatment. In the primary treatment setting, 28 patients with non-metastatic stage IV head and neck cancers were treated with GRID radiotherapy to 15-20 Gy, followed by conventional doses of external beam radiation either as definitive treatment or in the pre-operative setting. Neck control was reportedly 96%, with a pathologic complete response rate of 85% in those patients that underwent neck dissection. There were no grade 4 toxicities.⁴³ Most recently, an evaluation of 14 patients with bulky head and neck squamous cell carcinomas, which employed a single fraction of GRID radiotherapy followed by standard concurrent chemo-radiation demonstrated similar toxicity profile to standard chemo-radiation alone, with an excellent control rate of the gross tumor volume of 79%.⁴² These promising clinical results have generated a renewed interest in the spatially fractionated radiation approach at many centers in the US and internationally, and the radiobiology of this approach is now being explored.

When large doses of radiation are delivered to only a portion of the target volume, as in the case of spatially fractionated RT, radiation dose to adjacent normal tissues is lower, yet many of the radiobiologic principles associated with high-dose-per-fraction radiation to the tumor target remain applicable. These include the bystander effect within the GRID irradiated tumor volume that occurs in the tumor cells that fall directly under shielded regions (low-dose regions) of the grid. Bystander factors, such as TNF- α shown by Sathishkumar *et al*⁴⁴ and Shareef *et al*⁴⁵, TRAIL shown by Shareef *et al*⁴⁶ and ceramide shown by Sathishkumar *et al*⁴⁷ are induced in cells that are under the open field of the high-dose GRID areas and are hypothesized to be responsible for initiating the cell death cascade both in the epithelial and endothelial compartments of the tumor micro-environment. In addition to this bystander effect within the grid-irradiated tumor, Peters *et al* reported that there is robust abscopal effect in distant tumors or metastatic lesions that are not irradiated or treated.⁴⁸ Garcia-Barros *et al*⁴⁹ in a recent communication have postulated that "high dose" radiation of 15 Gy causes an environment of Potential Lethal Damage that makes these cells sensitive to further doses of radiation, especially the endothelial cells of the tumor microvasculature and this effect is the primary cause of tumor cell death. These bystander effects are not observed with conventionally fractionated radiation. The data strongly suggest that GRID therapy would induce a more rapid rate of tumor cell apoptosis in bulky, hypoxic, tumors than conventional dosimetric approaches.

1.4.5 LEAD, a Technique to Deliver Dosimetrically Superior Spatially Fractionated Radiation.

While spatially fractionated radiation delivered by GRID technique has the potential to be effective in conjunction with standard therapies in patients with bulky prostate tumors, the technique of GRID radiotherapy has not evolved significantly since its inception in the early 1900's, and is not the optimal method of delivering spatially fractionated radiation in the modern era. GRID has the limitation of delivering relatively high doses of

15

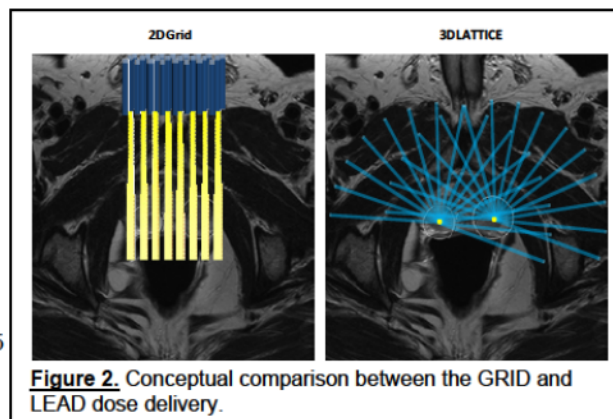


Figure 2. Conceptual comparison between the GRID and LEAD dose delivery.

radiation to normal tissues, depending on tumor location, as it is delivered via a single beam that must pass through normal tissues to reach its target. Most importantly, the highest-dose regions of the grid are superficial, and often are outside of the tumor target itself. Unnecessary high dose exposure to the surrounding normal tissue can be significantly reduced by reconfiguring the grid treatment into a 3D dose LATTICE, a new approach to spatially fractionated radiation which takes advantage of modern-era technology. This technique can be used to place high-dose islands within the tumor target only, not outside of the target. Using this technique, high doses of radiation are concentrated cylinders within the tumor volume, with drastically lower dose in-between (peak-to-valley effect) and leaving anything outside of tumor volume minimally exposed. Because more pronounced radiation dose peaks and valleys are generated using LEAD technique compared to GRID, it may be more radiobiologically effective, with significantly less radiation dose to adjacent normal tissues, and therefore should confer less additional toxicity. A conceptual comparison between the two techniques as applied to the prostate is shown in **Figure 2**.

Despite the existing data from radiobiological investigations of spatially fractionated radiotherapy, its use in the clinical setting is limited. As described above, none of the publications on this technique involve patients followed in a prospective fashion, and links between biology and clinical outcome have been inadequately studied.

Based on this background information, the central hypothesis of this proposal is that a single fraction of high-dose radiation delivered via LEAD technique will mediate induction of TNF- α , TRAIL, PAR-4, and ceramide, potentially synergizing the effect of conventional fractionated radiation, without adding toxicity above that expected with standard intensity modulated radiotherapy (IMRT). Single fraction priming high dose LEAD radiation is proposed to enhance tumor cell kill via bystander (local) and abscopal (distant) effects on non-irradiated tumor cells. We anticipate that LEAD RT in combination with a subsequent clinically standard fractionation and dose of radiation will improve control of bulky prostate cancers locally and possibly impact occult micro-metastatic disease thereby leading to gains in patient survival.

1.4.6 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.⁵⁰ 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 the 6-12 regions is routinely performed in addition to biopsy of suspicious hypoechoic areas. The technique misses up to 23% of cancers at the time of first biopsy.⁵¹

Multiparametric Magnetic Resonance Imaging (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.⁵² 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.⁵² 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.⁵³ Utilizing an endorectal coil in detecting cancer in the prostate improves MRI's sensitivity (78%) but the specificity still remains poor (55%).⁵⁴

DCE-MRI combined with T2w-MRI detection of prostate cancers have shown accuracies of over 80% in the detection of prostate cancer.^{55,56} DCE-MRI of prostate cancer patients has demonstrated potential for discriminating between normal and cancerous tissues.^{57,58} In general, higher and faster enhancement in cancer vs. normal tissue is found due to tumor vascularity, which has been related more to aggressive tumor behavior.

There are varying sensitivity and specificity assessments of DCE-MRI, depending upon what is used as the 'gold standard', biopsies or prostatectomy samples, and how many partitions (bilateral, quadrants, sextants, etc) of the prostate are correlated. For example, Jager *et al*⁵⁹ report a sensitivity and specificity of 73.5% and 81% respectively, in defining prostate cancer based on 4 sections (quadrants) comparisons. Kim *et al*⁶⁰, using a semi-automated analysis, achieved sensitivity and specificity of 96% and 65%, respectively (prostate was partitioned in 18 segments). The same group reported an improved specificity (77%), but a lower sensitivity (73%) for DCE-MRI acquired on a higher field (3T) MR magnet.⁶⁰ In this report, the DCE data were read by two genitourinary radiologists. Higher specificity values (91.5–97.4%) and a lower sensitivity (46.0–60.3%) were reported by Girouin *et al*⁶¹, who also used visual inspection by three radiologists (prostate was divided into 20 sections).

There is a plethora of approaches for interpretation of DCE-MRI data, ranging from 1) fitting parameters in theoretical models^{57,62-64} to 2) simpler contrast to time parameters (onset time, slope of enhancement, time to peak, peak enhancement, washout)^{65, 66} to 3) visual assessment for early enhancing lesions.^{60,61} Visual diagnostic inspection by an experienced radiologist has proven to be in some cases superior to the automatic parameter estimation. However, this method cannot produce the visualization of the tumor for the purposes of RT.

We have developed software, which combines the intuitiveness of the visual inspection with the automatic depiction of the tumor location on the anatomical images. The approach is based on an unsupervised pattern recognition technique called constrained non-negative matrix factorization (cNMF).^{65,66} The technique assumes each image to be a mixture of k tissue components with individually associated basic temporal behavior. k is estimated from application of Principal Component Analysis (PCA)^{67,68} and is the number of significant Principal Components. As a result, one can explain the observed DCE-MRI data-matrix as a product of identified basic temporal curves $S(t)$ and their corresponding weights W , amplitudes at each spatial location. W represents images and thus it is non-negative. In addition, since the basic 'contrast-to-time' curves $S(t)$ represent positive quantities, they must also be non-negative. Therefore, the decomposition of the data matrix is constrained by $W \geq 0$ and $S \geq 0$. A major advantage of cNMF is that the identified temporal patterns have direct physical interpretation

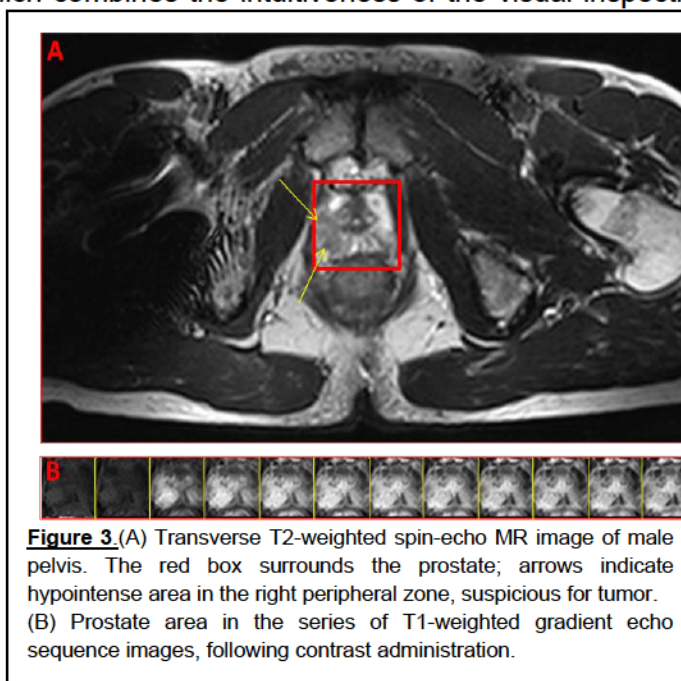


Figure 3. (A) Transverse T2-weighted spin-echo MR image of male pelvis. The red box surrounds the prostate; arrows indicate hypointense area in the right peripheral zone, suspicious for tumor. (B) Prostate area in the series of T1-weighted gradient echo sequence images, following contrast administration.

(fast, slow, constant) and thus, we can relate their corresponding weights (amplitudes, strengths) to a particular tissue. After visual inspection of the curves in \mathbf{S} , the presence/absence of the tumor tissue's temporal signature S_T is determined. S_T is characterized by a relatively fast contrast uptake and wash-out.⁶⁹ cNMF is based on the non-negative matrix factorization algorithm⁷⁰ and it is quite fast.

1.4.7 Preliminary Data

1.4.7.1 Prostate Imaging for Radiation Treatment Planning at the University of Miami

MRI simulation of the prostate is routinely performed. T2, T1 non-contrast, T1 DCE and DWI MRI sequences are obtained with size and spacing suitable for fusion with the CT for treatment planning. The MRI exam of the prostate is performed at the University of Miami on a 1.5T or 3.0T MR scanner with a body coil. In **Figure 3** an axial T2w MRI of a male pelvis is shown: resolution $0.7 \times 0.7 \times 2.5$ mm; Rectangular Field of View: 360×264 mm; slice thickness - 2.5 mm (no gap); 72 slices; repetition time (TR) 6300 ms/echo time (TE) 112 ms; flip angle 120° . The arrows point to a hypointense area in the right peripheral zone suspicious for tumor (**Figure 3A**). The prostate, centered in the red box, is presented in the series of T1-weighted gradient echo sequence MR images (**Fig 3B**), acquired with identical spatial resolution, spacing and image size as the T2w MRI. Prior to contrast material injection, one set of MR images were acquired as a pre-contrast image T1 data set. The rest of the data were acquired following intravenous bolus injection of a paramagnetic gadolinium chelate - 0.1 mmol of gadopentetate dimeglumine per kilogram of body weight. The contrast is administered with a power injector at 2.5 mL/s and followed by a 15-mL saline flush. The image sequence parameters were: TR/TE 5.1/2.3 ms; flip angle 10° . Eleven post-contrast imaging datasets (37 sec each) were collected.

1.4.7.2 Delineation and Visualization of Prostate Cancer in DCE-MRI

Our software co-registers the DCE data with the T2-weighted MRI. The Region of Interest (ROI) is manually outlined on each axial slice. Let I_{ij} denote the ROI on the i^{th} axial slice at j^{th} time point and let \mathbf{D} be the

matrix of the DCE-MRI data: $\mathbf{D} = \begin{pmatrix} I_{1,1} & \dots & I_{1,m} \\ \vdots & \ddots & \vdots \\ I_{n,1} & \dots & I_{n,m} \end{pmatrix}$ where

n is the number of slices within the ROI and m is the number of acquired time series. Principal Component Analysis (PCA) is applied to \mathbf{D} to determine k – the number of significant Principal Components (PCs). The data is further analyzed with the constrained non-negative matrix factorization (cNMF)⁴ method, which assumes each image to be a mixture of k tissue

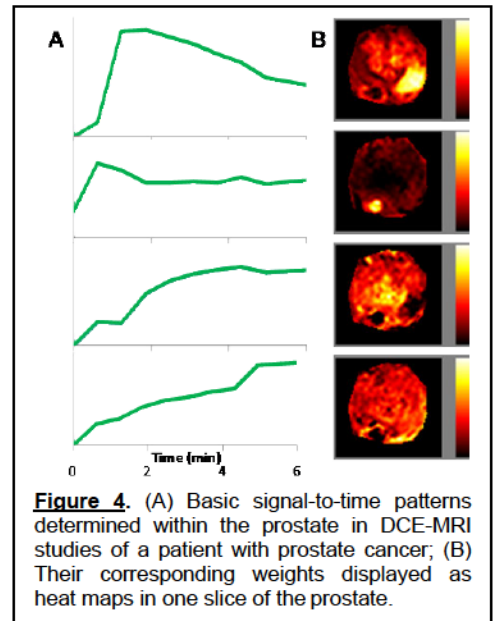
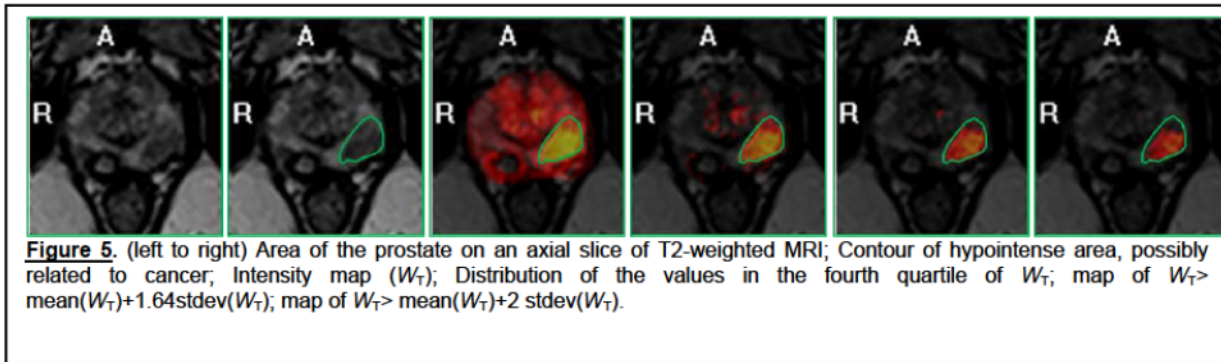


Figure 4. (A) Basic signal-to-time patterns determined within the prostate in DCE-MRI studies of a patient with prostate cancer; (B) Their corresponding weights displayed as heat maps in one slice of the prostate.



components with individually associated basic contrast-to-time curves. cNMF determines representation of D as a product of k basic contrast signatures (S) and their weights (W), i.e.

$$D \approx W \times S, \text{ where } W = \begin{pmatrix} W_{1,1} & \dots & W_{1,k} \\ \vdots & \ddots & \vdots \\ W_{n,1} & \dots & W_{n,k} \end{pmatrix} \text{ and } S = \begin{bmatrix} S_1 \\ \vdots \\ S_k \end{bmatrix}$$

under the constraint that all elements of W

and S are non-negative. When PCA is applied to D , four of the higher order PCs contained structural information (data not shown). Further, cNMF was applied to D seeking 4 solutions ($k=4$). The identified four temporal curves (S) and their corresponding weights are shown in **Figure 4**. The first curve in **Figure 4** shows the characteristic tumor tissue's temporal signature: relatively fast contrast uptake and wash-out (S_T). The highest intensities of its corresponding weight W_T (**Figure 4B**, top image) indicate that the location of this pattern coincides with the hypointensity on the T2w (**Figure 5**). The second curve is almost constant throughout the experiment and its spatial location indicates that it is associated with a nodule, possibly a cyst. The last two patterns are related to tissues with a relatively slow contrast uptake.

We investigated several schemes for thresholding the tumor pattern map (W_T) so that the target for radiation is clearly depicted on the anatomical image. In **Figure 5** three thresholded maps are presented: (1) All values in W_T larger than the lower limit of the fourth quartile; (2) $W_T > \text{mean}(W_T) + 1.64\text{stdev}(W_T)$; and (3) $W_T > \text{mean}(W_T) + 2\text{stdev}(W_T)$. The thresholded maps are overlaid with the corresponding T2w image and the green contour depicts the area of hypointensity suspicious for tumor. All methods for thresholding performed quite well with the last being the most conservative. For this project we will use the second method resulting in a display of values from the 95th percentile and higher, assuming that W_T is normally distributed. The last image in **Figure 5** depicts the area of the tumor with a rhomboid-like structure (3-5 mm sides) formed by the highest intensities in W_T . This area potentially could guide the placement of one high-dose cylindrical LEAD region of and it is clearly depicted in all displays of the thresholded W_T .

1.4.7.3. LEAD Dose Delivery

To affirm deliverability and accuracy of the desired radiation dose we carried out the following experiment: a Cyberknife-based LEAD RT dose plan was delivered to a 3D phantom with five small dose cylinders, and a maximum dose of 15 Gy at the center of each dose cylinder (**Figure 6A, B**). The plan was

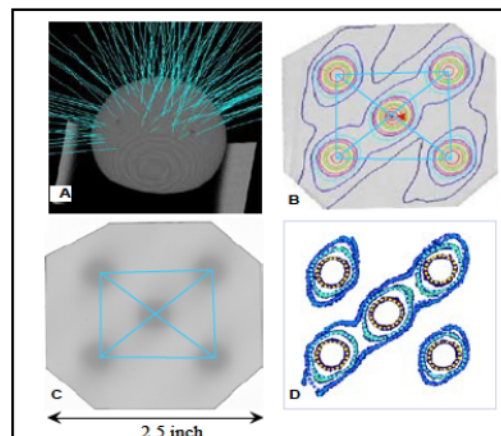


Figure 6.(A-B) Cyberknife-based LEAD dose plan, delivered to a 3D phantom. (C) Dosimetric verification, using Gafchromic films. (D) Computational (dash) and measured (color bands) dose.

developed on a clinically commissioned commercial planning system without any software or hardware modification. Wide-range Gafchromic films were employed for dosimetric verification (**Figure 6C**). Good agreement (3% and <1 mm) between the measurements and the plans was obtained, as shown in **Figure 6D** (computation in dash vs. measurement in color bands). Only a small amount of the “surrounding normal tissue/critical structures” received 2-3 Gy or less.

The results show that it is feasible to deliver the desired cylindrical high dose LEAD RT dose distributions with “peak-to-valley” characteristics, the key to triggering the expected bystander effects.

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.⁷¹⁻⁷⁶ Reports by Zelefsky et al^{77,78} indicate that treatment with IMRT reduces the incidence of late grade 2 rectal toxicity compared to 3DCRT. The 8 year risk of \geq grade 2 rectal bleeding was 1.6%. The 8-year rate of \geq grade 2 urinary toxicity was 12%. The impact of IMRT has been greatest on the reduction in rectal toxicity, as compared to 3DCRT.

In the study proposed here all patients will receive IMRT. The Quality of Life (QOL) assessments will provide unique data on the effects of LEAD RT on QOL. We have selected a group of measures that have been used extensively in prostate cancer populations.

As an index of Prostate Cancer-Specific Anxiety we will administer the Memorial Anxiety Scale for Prostate Cancer patients (MAX-PC). The MAX-PC is an 18-item instrument designed to detect symptoms of anxiety in prostate cancer patients. It is designed to evaluate three separate aspects of prostate cancer specific anxiety on 3 subscales: anxiety related to prostate cancer in general (prostate cancer anxiety subscale), anxiety specifically centered 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.⁸⁰

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)⁸¹ 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 $\alpha > .91$) across sexual function and sexual bother composites. The EPIC-SF12 questionnaire will be used to measure changes in QOL over time.^{82,83}

All participants will be assessed at baseline (prior to initial biopsy), during the last week of RT, at 6 weeks, 3 months, 9 months, 15 months and then yearly to 5.25 years. Psychosocial assessments will be conducted by a trained and fully-bilingual clinical coordinator/research nurse with experience in conducting psychosocial assessments in prostate cancer populations. We will make every effort to pair our psychosocial assessment visits with scheduled clinic appointments to reduce participant burden. The psychosocial battery will last between 30-40 minutes. All assessments will be conducted in private rooms in our clinics. All psychosocial data will be deidentified and only coded by participant number. Should a participant display any

significant signs of distress (e.g. high levels of anxiety, depressed mood or spontaneous comments suggesting a need for psychosocial care), we will refer participants to appropriate psychosocial resources within our medical center.

Another measure of urinary function is the International Prostate Symptom Score (IPSS).⁸⁴ This scoring system has been established as a measure of radiation morbidity in patients treated for prostate cancer⁸⁵⁻⁸⁸ and will be administered prior to treatment, at the end of radiotherapy and at each follow-up visit. 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. It is estimated that approximately 40% of patients are White, 24% are African American, 35% are Hispanic and 1% are other based upon standard NIH definitions.

2.0 OBJECTIVES

2.1 Primary Objective

- To determine the feasibility and toxicity of LEAD RT in a Phase I clinical trial.

2.2 Secondary Objectives

- To measure the risk of leaving tumor cells in the prostate after LEAD RT by obtaining serial post-RT MRI's (3 months and 9 months, and within 2 months of the post-treatment prostate biopsy).
- To quantify biomarker expression in different prostate tumor regions, comparing specifically the multiparametric suspicious and unsuspecting regions.
- To determine the proportion of study patients with positive prostate biopsies at 2-2.5 years after completion of therapy as a preliminary indication of the efficacy.
- To report failure-free (biochemical and clinical progression) and overall survival.
- To assess Health-Related Quality of Life (HRQOL) in the study patients.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

- A. Biopsy confirmed adenocarcinoma of the prostate.
- B. T1-T3a disease based on digital rectal exam (DRE).
 - a. T3a disease based on MRI is acceptable (no evidence of frank (clear-cut) SV involvement or invasion of bladder or rectum).
- C. Gleason score 6-10.
- D. Patients with Gleason score ≥ 8 must be offered long term androgen deprivation therapy (ADT) and refuse such treatment because only 4-6 months (+/- 2 months) (short term ADT) is permitted (not required) on this protocol. The ADT is recommended to begin after fiducial marker placement; however, ADT is permitted to have been started up to two months prior to the signing of consent. All patients in this protocol may (not required) be treated with 4-6 months (+/- 2 months) of ADT, at the discretion of the treating physician.
 - a. Gleason ≥ 8 must have <40% of the tissue involved with Gleason 8 in the biopsy specimen.

- E. PSA \leq 30 ng/mL within 3 months of enrollment. If PSA was above 30 and dropped to \leq 30 with antibiotics, this is acceptable for enrollment.
- F. No previous pelvic radiotherapy.
- G. No previous history of radical/total prostatectomy (suprapubic prostatectomy is acceptable).
- H. 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 \geq 5 years then the patient is eligible.
- I. Identifiable multiparametric-MRI tumor lesion or lesions, that total in volume $<$ 33% of the prostate
 - a. Multiparametric MRI of prostate and pelvis is required prior to protocol consideration.
 - b. If contrast not given, the point dose on the ADC map should be $<$ 1000.
- J. Ability to understand and the willingness to sign a written informed consent document.
- K. Zubrod performance status $<$ 2.
- L. Willingness to fill out quality of life forms.
- M. Bone scan negative if PSA $>$ 15 ng/mL or Gleason \geq 8 disease. A questionable bone scan is acceptable if other imaging tests are negative for metastasis.
- N. 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), and 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.
- O. Serum liver function tests (LFT) are taken within 3 months of enrollment.
- P. Complete blood counts are within taken within 3 months of enrollment.
- Q. Age \geq 35 and \leq 85 years.

3.2 Exclusion Criteria

- A. $>$ T3a disease on digital rectal exam or $>$ T3a disease clearly identified by MRI.
- B. Gleason score $<$ 6.
- C. \geq 40% Gleason 8-10 tumor, over the total tissue including other tumor and normal tissue. For example: (Gleason 8-10 tumor length/other biopsy tissue length)*100 = \geq 40%.
- D. Androgen deprivation therapy longer than 8 months. Androgen deprivation timing is for the Luteinizing hormone-releasing hormone (LHRH) agonist portion only and not when anti-androgen is started beforehand with the purpose of counteracting the surge in testosterone from the LHRH agonist
- E. PSA $>$ 30 ng/mL within 3 months of enrollment.
- F. Unable to obtain a 1.5T or 3.0T multiparametric MRI of the pelvis and prostate with or without contrast.
- G. Unidentifiable multiparametric MRI tumor lesion.
- H. Identifiable multiparametric-MRI tumor lesions, that total in volume \geq 33% of the prostate.
- I. Previous pelvic radiotherapy.
- J. Previous history of radical prostatectomy.

- K. 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.
- L. Zubrod performance status ≥ 2 .
- M. Inability to understand or unwilling to sign a written informed consent document
- N. Unwilling to fill out quality of life/psychosocial forms.
- O. Bone scan is positive and other imaging tests confirm a suspicion of metastasis from prostate cancer.
- P. Serum testosterone is not within 40% of normal assay limits taken within 4 months of enrollment (only applicable to patients not started on ADT prior to signing consent).
- Q. Serum liver function tests (LFTs) are not taken within 3 months of enrollment.
- R. Complete blood counts are not taken within 3 months of enrollment.
- S. Age <35 and >85 years.

3.3 Enrollment Procedures

To enter a patient, the investigator or study team will contact the CRS representative. All eligibility requirements must be reviewed prior to the patient entering the study. The following information must be provided to the CRS representative:

- 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.
- 4) To assure compliance with early stopping for toxicity, the monitor will inform the study team when the forth patient may be enrolled.

3.3.1 Cancellation Guidelines

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

3.3.2 Emergency Registration

If an emergency registration takes place after business hours the SCCC completed Protocol Enrollment Form, completed eligibility checklist and a copy of the signed informed consent must be submitted to the QMO by the next business day.

4.0 TREATMENT PLAN

4.1 Pre-enrollment Multiparametric MRI

T2, T1 non-contrast, T1 DCE and DWI MRI scans are being done routinely, when possible, in all patients being planned for external beam radiotherapy for prostate cancer. The

DCE-MRI scans are obtained pre-contrast and at 30-40 sec intervals post-contrast, for a minimum of 10 scans. If renal function does not permit contrast and there are distinct lesions on T2 and DWI, and a point dose of <1000 is seen on the ADC map, the patient is eligible. These sequences are routinely obtained at 2.5 mm intervals to include the pelvis and prostate. An enema is recommended to be self-administered by the patient within 2.0 hr of multiparametric MRI to empty the bowel. A diet designed to reduce bowel gas will be recommended the day before the MRI and CT scans for simulation. The patient is instructed not to void before the scan, to mimic bladder position during treatment. MRI exclusions include ferromagnetic metal in body/eye, pacemaker, defibrillator, other mechanical device, or extreme claustrophobia (medication with anti-anxiety agents, such as Ativan, may be used). Since the multiparametric 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.

4.2 Assessment of Protocol Eligibility and Enrollment

Patients who have a suspicious lesion (or lesions) on multiparametric MRI that involves <33% of the prostate will be eligible. A suspicious lesion is defined as distinct early enhancement on DCE-MRI or significant water motion restriction by DWI reflected as a point value of <1000 on an Apparent Diffusion Coefficient (ADC) map. Thus, patients who unable to receive contrast for the MRI are still eligible. The DCE-MRI would be expected to show early washin and delayed washout. For DCE-MRI early enhancing anterior lesions in the transition zone that meet these criteria, there is also the requirement for a point value of ≤ 1000 on the ADC map in that region or a high choline + creatinine to citrate ratio (≥ 0.9 ratio) on MR spectroscopy. MRS is being added to our current standard multiparametric assessment algorithm. Eligible patients will be screened by the treating physicians and dedicated protocol nursing staff for fulfillment of eligibility criteria. If the patient is deemed eligible, protocol consent will then be obtained. The treating protocol physician will explain the risks and procedures to the patient, along with the Clinical Research Coordinator. The patient will be entered into the

4.3 Prostate Biopsy and Gold Seed Fiducial Marker Placement

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. 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 includes using standard ultrasound-guidance, the Eigen Artemis® system (MRI-ultrasound fusion guided biopsies), or MRI-guided prostate biopsies. The MRI ultrasound fusion method is preferred. 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. 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 per the discretion of the urologist, antibiotic treatment before, during and after fiducial marker placement may be administered. Also, prior to fiducial marker implantation/biopsy collection, antibiotic prophylaxis may be prescribed (e.g., Levaquin 500 mg daily, Ciprofloxacin 500 mg twice daily, or a similar antibiotic depending on allergy history and physician preference), may be prescribed/administered.

4.4 Prostate Cancer Upgrading and Change of Treatment

In the event that the protocol obtained transrectal prostate research 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 biopsies at the time of fiducial marker placement is higher, the patient must agree to be treated in accordance with the initial treatment plan, based on the pathologic parameters in the original diagnostic prostate biopsies and not the protocol obtained 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 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, including T2w, T2*-weighted gradient echo sequence (for clear visualization of the gold markers⁸⁹) or other sequence(s) that visualize the fiducial markers, and T1 sequences will be obtained at 1.5 mm cuts at least 1 week after fiducial marker placement to facilitate fusion with CT based on the markers. This limited MRI of the prostate will be fused to the original diagnostic MRI to ensure that the LEAD RT is accurately targeted as close to the center of the multiparametric MRI-defined region as possible, with consideration of nearby normal structures. The limited planning MRI will be fused to the CT-simulation scan based on the fiducial markers.

CT-simulation will then be obtained under the same conditions with typical pelvic immobilization. Images will be taken at 1.5 mm intervals from the top of the sacrum to at least 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.

A rectal air balloon, by Radiadyne® or another vendor, may be used for both MRI and CT acquisitions, as well as for the treatment delivery, per the company's recommendations. Briefly, patients are instructed to use a rectal enema prior to coming into the department for simulation, which is part of the routine. A rectal balloon may be used protocol, but is not required. The balloon is commercially available and is commonly used in patients who are being treated for prostate cancer and are not on clinical trials. The rationale for the rectal balloon is that it may assist in stabilizing the prostate and limiting the radiation dose to the healthy surrounding critical structures. Under physician direction, the therapists will monitor the placement of the rectal balloon, if used, relative to the patient's anatomy, and adjust the depth stopper, and fill volume accordingly.

4.7 Risk Assessment for RT and ADT Planning

- *Favorable Risk:* Clinical and MRI T1-T2, Gleason 6 with low tumor burden (<20% of tumor in the biopsied tissue, average adjusted by biopsy region). The percent tumor per region will be averaged such that if 10 regions are biopsied and three show 40%, 50% and 60% involvement, the total percentage of tumor is 15%.
- *Intermediate Risk:* Clinical and MRI T1-T2, Gleason 7 with low (<20% average adjusted by region) or high tumor ($\geq 20\%$ average adjusted by region). Questionable *extracapsular extension* (T3a disease) on MRI remains eligible as an intermediate risk patient and patients may refuse ADT, or accept up to 6 months of ADT, starting up to 2 months prior to signing consent, and still participate.
- *High Risk:* cT3a or MRI T3a with obvious extracapsular extension or Gleason ≥ 8 : These patients must be offered and refuse long term ADT. They may receive 4 to 6 (+/- 2 months) months of ADT (6 months preferred). ADT may begin up to 2 months prior to signing the consent. If the patient accepts long term ADT, the patient may not be enrolled on the study. The pelvic lymph nodes may be treated during the 38 standard fractionation treatments if desired by the treating physician.

4.8 LEAD Dose Distribution, Planning and Constraints

Dose Pipe Distribution: 12-14 Gy dose pipes on day 1.

The LEAD dose distribution may be planned and delivered by the Cyberknife or a standard LINAC, if the dose distributions are deemed acceptable. The LEAD RT dose plan will involve the placement of 1 to 3 dose pipes of 7.5 mm diameter the length of the multiparametric MRI-defined GTV volume with roughly 50 non-coplanar focused beams for each dose cylinder planned using the Cyberknife. The GTV will include the early phase contrast enhancing lesion on DCE-MRI, considered with the abnormality on T2-weighted imaging and for transition zone lesion the ADC map and/or the MRS choline+creatine to citrate ratio. The LEAD RT region(s) will be positioned as close to the center of GTV region(s) as possible (should be positioned ≥ 2 mm from the rectum to avoid excessive dose to the rectum).

LEAD Planning: To provoke a bystander effect, we propose to deliver 1-3 LEAD dose cylinders in the prostate gland, no more than 2 per side. Ideally, the GTVs will be covered by the 10 Gy isodose envelop, with the maximum prescribed dose ranging from 12 Gy to 14 Gy. The separation between the dose cylinders should be such that the dose between should decrease to 20-30% of the maximum dose, while the dose to critical structures such as rectum, bladder and urethra are controlled under known tolerance constraints.⁹⁰

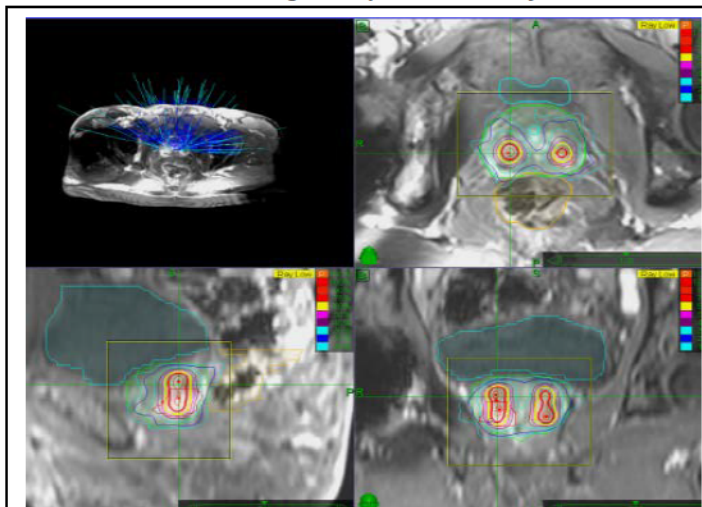


Figure 7. Theoretical treatment model generating a LEAD dose distribution in 3-D using a robotic radiosurgery system. Two high dose vertexes are simulated in parallel to one another. The diameter of each one is 7.5 mm and its length (up to 20 mm) is determined by the size of the tumor.

Techniques that can be applied to achieve such dose distribution include non-coplanar focused photon beam with a Cyberknife or an aperture modulated arc (AMAT) with a DMLC linear accelerator. Image-guidance and

real time target tracking is preferred, but not required in the LEAD boost portion of the treatment. The Cyberknife may be used for both the LEAD RT single fraction treatment as well as the whole prostate standard fractionation treatments that follow for 38 fractions. The 38 standard dose and fractionation treatments are to the prostate and proximal seminal vesicles, and may also involve the simultaneous treatment of the distal SVs and pelvic lymph nodes in high risk patients, as desired by the treating physician. In summary, the LEAD RT and following 38 standard dose per fraction treatments may be done on the Cyberknife or a standard LINAC with image guidance for alignment prior to treatment delivery (real-time tracking is not required).

LEAD Timing: The LEAD treatment will be delivered and within 32 hr, the conventional fractionation treatment will follow. There shall be no gap between the first three daily 2 Gy fractions each delivered within 30 hr of each other; the LEAD RT treatment will therefore be done on a Monday, Tuesday, or Wednesday unless special arrangements are made to treat on the first Saturday.

LEAD Constraints: One to three pipes will be used to treat the larger lesions, with up to two on one side of the prostate; they will be spaced by 1.5 – 2.0 cm, if possible. The LEAD RT dose pipes will be covered by 12-14 Gy with a maximum of 20 Gy. The maximum dose for each dose pipe shall be <20 Gy. A variation will be maximum doses ≥ 20 Gy to 23 Gy, with a protocol violation above this limit. The Vprescription (12-14 Gy) is expected to be <20% and >10% of the tumor, but this is not a constraint. The V(3 Gy) for the rectum and bladder will be <8% (4.0 Gy Dmax). Protocol variations will be a V(3 Gy) of 8-10% with a Dmax of 4.5 Gy. A protocol violation will be anything above these limits. For the urethra, the V(3 Gy) will be <10%. A protocol primary variation will be a V(3 Gy) of 10-20% with a Dmax of 6.0 Gy. A secondary protocol variation will be for any dose above the limits; there will not be any protocol deviations for the urethral dose. The urethra is more resistant to higher radiation doses; hence, the more relaxed constraints.

As described below, a conformal dose plan with the Cyberknife or a more standard LINAC for conventional fractionation of 2 Gy x 38 will be subsequently applied. The LEAD and conventional fractionation plans will be summed to assure that the combined dose distributions to the critical structures do not exceed tolerance. In this evaluation the biological equivalent dose (BED) will be computed to convert the LEAD dose to the conventional fractionation dose.

In **Figure 7** a theoretical treatment model has been created whereby a LEAD dose in 3-D was generated using a robotic radiosurgery system. Two high dose cylinders are simulated in parallel to one another. The diameter of each dose pipe is 7.5 mm and its length (up to 20 mm) is determined by the size of the tumor. The dose cylinders are spaced 1.5-2 cm apart. The dose cylinders should preferably be situated at the center of the GTV. Preliminary dosimetric studies indicate that it is feasible to introduce up to three LEAD RT dose cylinders in the prostate without excessive dose to the surrounding critical structures such as bladder, rectum and urethra. For example, in a 50.9 cc prostate with a 4.0 cc dominant enhancing tumor (GTV1) in the peripheral zone on one side and a 1.6 cc secondary enhancing lesion (GTV2) on the other side, approximately 2 cm distant, two dose rods were placed covered by 15 Gy with a maximum of 20 Gy. The V(15 Gy) values for GTV1 and GTV2 were 13.4% and 15.0%, with the V(3 Gy) (Dmax) for the rectum, bladder and urethra of 5.8% (4.0 Gy), 1.0% (3.9 Gy), and 47% (4.0 Gy).

4.9 Normal tissue contouring guidelines

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

and contents will be contoured. The femoral heads should be outlined down to the region between the greater and lesser trochanters.

The potential bowel space within 5 cuts of the CTV (CTV1 or CTV2, whichever is most superior) should be outlined to minimize dose to the bowel. The potential bowel space includes the areas on either side of the bladder medially.

4.10 CTV/PTV Planning and Constraints

Primary CTV1/PTV1 Planning: The CT and MRI simulation scans will be loaded into a planning computer and fused based on the fiducial markers. At each slice level, the pelvic bones, bladder, rectum, prostate, and seminal vesicles will be outlined. The rectum will be outlined from the anterior flexion of the rectosigmoid superiorly to the ischial tuberosities inferiorly. The entire bladder will be outlined. The femoral heads should be outlined down to the region between the greater and lesser trochanters. As described above, the GTV will include the multiparametric MRI-defined lesion(s). The LEAD RT region will be located as close to the center of the GTV region and should be positioned ≥ 2 mm from the rectum to avoid excessive dose to the rectum.

The primary Clinical Target Volume (CTV1) will include the prostate (with GTV) and the proximal seminal vesicles (usually about 10 mm and/or $\leq 50\%$). The CTV1 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 (PTV1) will be 3-5 mm around the CTV1 in all dimensions. For tumors at the base, a margin of 5 mm on the proximal seminal vesicles is recommended.

Constraints: The plans will be evaluated by dose-volume histogram analysis based on prior established criteria.⁹¹ The goal is to obtain these constraints for the combined LEAD plus standard fractionation treatments.

- *Rectum:* Less than or equal to 17% and 35% of the rectum should receive ≥ 65 Gy and ≥ 40 Gy, respectively, in calculated 2 Gy equivalent doses.¹
- *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 violation 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.
- *PTV:* At least 95% of the PTV should receive the prescription dose of 76 Gy in 38 fractions (a minor variation will be $< 95\%$ to $\geq 90\%$ of the prescription dose); a violation would be $< 90\%$. Assuming an α/β ratio of 3.0, the biologically equivalent dose in 2.0 Gy fractions to the LEAD RT region would be 149 Gy.

The maximum dose heterogeneity in PTV1 will be affected substantially by LEAD RT. High dose gradients are acceptable as long as the normal tissue constraints are met.

4.11 Distal seminal vesicle and pelvic lymph node CTV2 and PTV2 for selected high risk patients

A secondary Clinical Target Volume (CVT2) may be treated in selected high risk patients at the discretion of the treating physician. The CTV2 will include the distal seminal vesicles and the pelvic lymph nodes. The PTV2 will be 0 mm. The recommended volumes are on the RTOG website under the "Core Lab/Contouring Atlases" menu (<http://www.rtog.org/CoreLab/ContouringAtlases/ProstatePelvicLymphNodes.aspx>). PTV2 should receive 56.24 Gy at 1.48 Gy per fraction over the 38 fractions of the standard

fractionation treatment. At least 95% of the PTV should receive the prescription dose (a minor variation will be <95% to \geq 90% of the prescription dose); a violation would be <90%. The maximum dose heterogeneity in the PTV2 will be affected by the proximity of CTV1 and possibly LEAD RT. Therefore, no heterogeneity limits are defined.

4.12 Protein biomarkers and immune activation markers in the serum/whole blood

We will assess protein biomarkers and immune activation markers in the serum/whole blood samples of patients receiving high-dose LEAD RT. Samples taken from subjects will be analyzed for activation of peripheral immunity; we will analyze B and T cell activation-specific cell surface markers (CD19, B220, CD40, CD27, CD28, CD30, CD37, CD38, CD43, and surface IgG, IgM, and IgD; CD4, CD8, HLA-DR, CD11b, CD25, CD38, CD45RO, CD134, CD150, CRTAM, FOXP3, Ly-m22 by FACS), transcription (AID, I κ B α ; granzyme, perforin, HLA-DRA by RT-PCR) and secreted cytokines (IgG, IgM; sIL2R, neopterin, sCD4, sCD8, TNF α , IL-1b, IL-2, IL-6 by ELISA) before and after irradiation. To this end, an additional 10 cc of peripheral blood will be collected after the LEAD RT treatment at about 24 hr. (\pm 12 hr.) following the procedure. One tube of whole blood from patients will be collected into an anticoagulant tube (EDTA). Buffy coat and plasma will be isolated by centrifugation. Plasma will be frozen at -80°C until analysis. PBMCs will be isolated from buffy coat on a ficoll gradient and frozen in RPMI (+40% FBS, 10% DMSO) until analysis. The second tube will be the 7-mL Vacutainer SST Gel & Clot Activator Plus Plastic (BD). Blood collected tubes will be gently inverted to evenly mix the clot activator and will be kept at room temperature for 1 hr for serum separation and will be shipped to Dr. Pollack's lab for ELISA. The whole blood will be shipped to Dr. Pollack's laboratory. The results of the biomarker confirmation will be correlated with clinical response.

4.13 Proteomic and Genomic Analyses of Blood and Urine

The objectives are 1) to examine protein in pretreatment serum, hypermethylated DNA in urine for patterns that predict for biochemical failure and 2) to determine if the profiles from serum and urine in men treated with radiotherapy may be used as an adjunct to PSA in identifying failure at an earlier point in time. For the second objective, serum and urine samples will be collected during the last week of RT at 6 weeks, 3 months, at 9 months and within 2 months prior to the 2-year prostate biopsy.

To summarize, we plan to collect plasma and serum, as well as red cells and lymphocytes (buffy coat) before treatment and at the designated follow-up times to determine if the protein changes observed are useful in predicting the outcome of men treated with radiotherapy. We anticipate that the research biosamples will be obtained from all 25 cases. 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.⁹²Promoter 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. *GSTP1* hypermethylation is well established as "early," frequent and cancer specific and can be detected by the sensitive MSP test. The hypermethylation of *GSTP1* is found in >90% of primary prostate cancers, but not in normal prostatic tissue or other normal tissues. *GSTP1* was detected in the urine of 79% of men with PC. *GSTP1* and *RAR β* gene hypermethylation in voided urine DNA will be assayed with the aim of 100% diagnostic coverage for molecular detection of recurrent prostate cancer. The diagnostic utility of *GSTP1*

and *RARβ* hypermethylation will be determined. Further genes will be added to the detection panel to provide molecular prognostic information.

4.14 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.
- Antispasmodics: Antispasmodics, 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.

4.15 Duration of Therapy

- Within 4 weeks of enrollment, patients will be biopsied (patient may refuse) and fiducial markers placed.
- LHRH agonist androgen deprivation therapy: 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 (preferred) in men with intermediate or high (optional) risk prostate cancer. All patients may receive 4-6 months (+/- 2 months) LHRH agonist therapy.
- Anti-androgen treatment should begin 1-14 days prior to LHRH agonist injections. Anti-androgen will be continued four 4 months.
- .
- Standard fraction RT: Day 2 of radiotherapy will start within 32 hr of LEAD RT and will consist of 38 fractions at 2.0 Gy over 7.5 weeks
- Treatment will be stopped for grade 4 acute toxicity (according to the current version of Common Terminology Criteria for Adverse Events (CTCAE version 4), but may be resumed per protocol if the treatment break is less than 10 working days. Since we have never observed grade 4 toxicity acutely using IMRT (conformal CyberKnife treatment is an IMRT-like treatment),

such an event is unlikely. If grade 4 toxicity resolves beyond the 10 days the treating physician will decide whether to give additional RT.

- Treatment will be stopped if metastasis is detected by radiographic or pathologic evidence and the patient will be removed from the study, but not from intent-to-treat analysis. A work-up for metastasis during treatment will only be carried out if the treating physician deems necessary.
- Multiparametric MRI exams of the prostate/pelvis will be carried out after RT at 3 months, 9 months, and within 2 months of the post-treatment prostate biopsies.
- Prostate biopsies will be taken at 2-2.5 years post completion of all therapy.

5.0 CLINICAL AND LABORATORY EVALUATIONS

5.1 Baseline/pretreatment Evaluations

- History and physical and evaluation of patient's ability to perform daily activities (Zubrod performance status; Karnovsky or ECOG performance status may be used to estimate Zubrod) ≤ 8 weeks prior to signing consent.
- Blood tests: 4 tubes of blood will be drawn ≤ 3 month prior to protocol entry unless otherwise indicated:
 - PSA Level
 - Testosterone level - Serum testosterone will be drawn ≤ 4 months before signing consent or after enrollment but before the first radiation treatment and is within 40% of normal assay limits using the formula $x=0.4*\text{lower assay limit}$ and $x=0.4*\text{upper assay limit} + \text{upper assay limit}$). 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.
 - Liver function tests are within 40% of normal assay limits, as defined by the equation for testosterone.
 - Complete blood cell counts are within 40% of normal assay limits, as defined by the equation for testosterone.
 - Lipid profile (no assay limit)
- Bone scan (depending on PSA level and Gleason score) ≤ 4 months prior to signing of consent. A questionable bone scan is acceptable if other imaging studies are negative for metastasis.
- Multiparametric MRI of prostate/pelvis at 1.5T or 3.0T MRI scan ≤ 3 months prior to protocol entry.
- Gold marker placement and prostate biopsies (if patient opts to have biopsies) within 4 weeks after enrollment.
- A pathology review at the University of Miami of prostate biopsies.
- Prior to fiducial marker placement, research fluids including plasma and serum (4 tubes), and 50 ml urine will be obtained.
- CT and MRI simulation.
- Quality of Life surveys will be administered after enrollment and prior to fiducial marker placement:
 - 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 administered pre-treatment.

5.2 Evaluations During Treatment

- High dose boost will be started on a Monday, Tuesday or Wednesday.
- Plasma and serum (up to 4 tubes) and urine (50 mL) will be collected for research (research fluids) at 24 hr post-LEAD RT and during the last week of RT.
- Weekly history and physical, evaluation of patient's ability to perform daily activities (Zubrod performance status; Karnovsky or ECOG performance status may be used to estimate Zubrod), and evaluation of toxicity.
- Blood (up to 4 tubes) will be drawn at RT completion during the last week of RT from a vein for the following tests:
 - Serum Testosterone.
 - Liver function tests (only if on ADT)
 - Complete cell counts
 - Lipid profile
- Quality of Life surveys will be administered 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 Index (IPSS) questionnaire during the last week of RT.

5.3 Post-treatment Evaluations (after RT) *Measurements and follow-up visits should occur ± 2 weeks up to the 3 month visit and ± 4 weeks for subsequent measurements/visits*

- History and physical, evaluation of patient's ability to perform daily activities (Zubrod performance status; Karnovsky or ECOG performance status may be used to estimate Zubrod), and evaluation of side effects at 6 weeks, 3 months, and then every 6 months for 5.25 years.
- Blood work (tubes of blood will be drawn at each follow-up as described below):
 - PSA at 6 weeks, 3 months and then every 6 months for 5.25 years.
 - Testosterone at 6 weeks, 3 months, and 9 months after radiotherapy. If testosterone remains abnormally low after ADT, tests will continue to be done at each follow-up visit.
 - BUN and creatinine to evaluate kidney function prior to MRIs at 3 months, 9 months and within 2 months prior to the 2-year prostate biopsy.
 - Liver function tests at 6 weeks and 3 months after radiotherapy (only at 3 months if not receiving ADT).
 - Complete blood counts at 3 months.
 - Lipid profile at 6 weeks, 3 months, 9 months, and within 2 months prior to the 2-year prostate biopsy.
- Plasma and serum (up to 4 tubes), and urine (50 mL) for research fluid tests will be obtained at 6 weeks, 3 months, 9 months and within 2 months prior to the 2-year prostate biopsy.
- Multiparametric MRI's of prostate/pelvis with timed contrast (if possible) at 3 months, 9 months, and within 2 months prior to the post-treatment prostate biopsies at 2 – 2.5 years post-completion of all therapy. 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.

- Bone scan at the discretion of treating physician.
- Quality of Life surveys:
 - The Expanded Prostate Cancer Index Composite Questionnaire-SF12 (EPIC-SF12) at 6 weeks, 3 months, 9 months, 15 months, and then yearly to 5.25 years
 - Memorial Anxiety Scale for Prostate Cancer patients (MAX-PC) at 6 weeks, 3 months, 9 months, 15 months, and yearly to 5.25 years
- International Prostate Symptom Index (IPSS) questionnaire at 6 weeks, 3 months, and then every 6 months for 5.25 years.

Note: Measurements and follow-up visits should occur \pm 2 weeks up to the 3 month visit and \pm 4 weeks for subsequent measurements/visits with the exception of the post-LEAD RT lipids and blood and urine collection for research, which is 24 hr \pm 12 hr.

5.4 Early Discontinuation of Therapy

See early stopping rules in Section 12.0

6.0 DOSING DELAYS/DOSE MODIFICATIONS

6.1 Study Agent

The study agent in this protocol is radiation, to be delivered in an innovative and investigational manner. The experimental component of the treatment is a single high-dose fraction of LEAD radiation, a dose of 12-14 Gy to be delivered to the multiparameter MRI identified tumor lesion(s). As described above, a standard radiation dose used for treatment of prostate cancer is 76 Gy at 2.0 Gy per day. This will be begun the day after the LEAD RT treatment (total dose for all treatments of 88-90 Gy and 149 Gy_{3.0} in 2.0 Gy equivalents).

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 months (+/- 2 months) may be administered to some patients as described in sections 3.1 and 4.7. This timing is based on LHRH agonist injections (not the bicalutamide).

STAD will consist of oral antiandrogen administration and LHRH agonist injections to begin within the aforementioned timeframe. The antiandrogen will be either flutamide at 250 mg p.o. TID or bicalutamide at 50 mg p.o. QD. Antiandrogen therapy should begin at approximately the same time as LHRH agonist injection but may be started up to two weeks earlier. Antiandrogen 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 months (+/- 2 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), four to six 1-month injections, or a 6-month injection.

7.0 AGENT FORMULATION AND PROCUREMENT

7.1 Agents

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

7.1.1 Other names

- **Lupron** - leuprolide acetate
- **Zoladex** - goserelin
- **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.
- **Casodex** is a nonsteroidal antiandrogen which has no androgenic or progestational properties. The chemical name is Propanamide, N-[4-cyano-3(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulphonyl]-2-hydroxy-2- methyl, (+,-).
- **Eulexin** is a substituted anilide. It is a fine, light, yellow powder, insoluble in water but soluble in common organic solvents such as aromatic or halogenated hydrocarbons. Its concentration in plasma can be determined by gas chromatography.

7.1.3 Mode of action

- **Lupron** possesses greater potency than the natural hormone. Leuprolide acetate, a LHRH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Human studies indicate that following an initial stimulation, chronic administration of leuprolide acetate results in suppression of ovarian and testicular steroidogenesis. This effect is reversible upon discontinuation of drug therapy. Administration of leuprolide acetate has resulted in inhibition of the growth of certain hormone dependent tumors (prostatic tumors in Noble and Dunning male rats and DMBA-induced mammary tumors in female rats) as well as atrophy of the reproductive organs. In humans, administration of leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in premenopausal females). However, continuous administration of leuprolide acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to castrate levels. These decreases occur within two to four weeks after initiation of treatment, and castrate levels of testosterone in prostatic cancer patients have been demonstrated for more than five years with continuous drug administration.
- **Zoladex** is a LHRH analog with substitutions for the L-amino acid Glycine in positions 6 and 10. These substitutions produce analog with 50-100 times the potency and longer duration of action than the naturally occurring peptide when assessed in acute animal tests.

- **Casodex** is a racemic mixture with the anti-androgen activity residing exclusively in the (-) or (R) enantiomer.
- **Eulexin** Flutamide is a non-steroid anti-androgen that is metabolized into a hydroxylated derivative, which effectively competes with the hydrotestosterone for androgen receptor sites.

7.1.4 Storage and stability

The agents are commercially available and received in manufacturer's packaging. If administered 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 temperatures 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.

7.1.5. 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.
- **Casodex** 50 mg has the status of an approved new drug. Casodex has a long half-life compatible with once-daily dosing. Anti-androgen will be given for a maximum of four months.
- **Eulexin** is supplied as 125 mg capsules and is commercially available. Anti-androgen 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.

- **Lupron** is administered by intramuscular injection. Each kit contains a vial of sterile lyophilized microspheres, which is leuprolide incorporated in a biodegradable polymer of polylactic acid. Any formulation may be used. Product does not contain preservative and should be discarded if not used immediately.
- **Zoladex** 10.8-mg depot is supplied with a 14-gauge needle. Being sterile, the syringe should be removed from its package only by the physician/nurse immediately before use. Zoladex will be injected subcutaneously using an aseptic technique. The needle should be inserted to its full length, pulled back 1cm and then injected. The manufacturer recommends inserting the needle into the subcutaneous fat then changing the direction of the needle so that it parallels the abdominal wall before inserting the needle to its full length. This will create a little pocket for the Zoladex plug so that it does not extend when the needle is withdrawn. After rechecking to ensure that the depot has been discharged, the used syringe will be discarded in a safe manner. One can ensure that the depot has been discharged by ensuring the tip of the plunger is visible within the tip of the needle.

- **Casodex** is administered orally at a dose of one 50 mg tablet per day. Casodex will be started from two weeks to one day prior to LHRH administration and continued throughout radiotherapy. Administration will be suspended only if there is an apparent or suspected reaction to the drug. Bicalutamide will be terminated on the last day of radiotherapy. During radiotherapy interruptions, Casodex will be continued.

- **Eulexin** is administered orally at a dose of two 125 mg capsules three times a day for a total daily dose of 750 mg (six capsules).

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 anti-androgen therapy. If the AST or ALT rises $\geq 2x$ 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 anti-androgen therapy. If AST or ALT increases $\geq 2x$ the upper institutional limit of normal, flutamide must be discontinued.

7.1.9 Availability

The agents are commercially available and will not be dispensed by the Sylvester pharmacy.

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.

- **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.⁹³ 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.⁹³ 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 markers placement, patients who choose to have biopsies will undergo needle biopsy of the prostate. 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 needle biopsy of the prostate, unless clinically contraindicated or the patient refuses. . A total of 12-14 biopsy cores, are preferred; although the number could be less if the physician thinks it is not appropriate to continue. Biopsies may be obtained from any suspicious functional MRI areas and/or the original site of biopsy confirmation of prostate cancer at diagnosis. 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 Eigen Artemis® system fusion software (not 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.

If the research biopsies contain prostate tumor cells, the results will be discussed with the patient and additional management considerations (e.g., rebiopsy) 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 rebiopsy a year later to look for clearance of the tumor cells. The strategy to rebiopsy 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

- *Feasibility*: The proportion of enrolled patients for whom LEAD RT dose can be successfully administered following MRI-guided planning.
- *Acute toxicity*: Grade 2 or higher treatment-related acute GU/GI toxicity occurring during treatment and within 30 days of completing treatment. The severity of the reactions to the treatment is scored according to the criteria outlined in Appendix II.
- *Late toxicity*: Delayed toxicities are usually related to urinary, rectal, and sexual function. The anticipated urinary and rectal toxicities and severity criteria are shown in Appendix II.
- *Biopsy failure rate*: The proportion of positive biopsy findings among patients without clinical or biochemical failure 2-2.5 years after completing study treatment.
- *Biochemical failure-free interval (BFFI)*: The elapsed time from study enrollment to first documented evidence of biochemical failure ($PSA \geq \text{nadir}+2$). In the absence of biochemical failure, follow-up time will be censored at the date of last documented biochemical failure-free status.
- *Biochemical failure (BF) rate*: The cumulative incidence of BF allowing for competing risk as needed.
- *Biochemical failure-free survival (BFFS)*: The elapsed time from study enrollment to first documented evidence of biochemical failure or death from any cause, whichever occurs first. In the absence of any event defining biochemical failure, follow-up time will be censored at the date of last documented biochemical failure-free status.
- *Failure-free interval (FFI)*: The elapsed time from study enrollment to first documented evidence of biochemical or clinical failure. Clinical failure is defined as 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). In the absence of any event defining failure, follow-up time will be censored at the date of last documented failure-free status.
- *Failure rate*: The cumulative incidence of biochemical or clinical failure allowing for competing risk as needed.
- *Failure-free Survival (FFS)*: The elapsed time from study enrollment 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 study enrollment to death from any cause. For surviving patients, follow-up will be censored at the date of last contact.
- *Biomarker expression*: Quantification of the amount of the biomarker specific immunohistochemical staining in the area of tumor
- *QOL*: Two contemporary instruments will be utilized to assess patient function and bother (Expanded Prostate Cancer Index Composite-SF12 (EPIC-SF12)), and prostate cancer-specific anxiety (Memorial Anxiety Scale for Prostate Cancer patients (MAX-PC)).

9.2 Guidelines for Evaluation of Measurable Disease

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

- Pretreatment: A qualitative description of the pretreatment tumor status on DRE, if palpable, will be recorded in the patient's 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.¹⁷ 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 during the last week of RT, at 6 weeks, 3 months, 9 months, 15 months, and then yearly to 5.25 years after radiotherapy.

9.3 Response Criteria

No evidence of rising PSA and negative biopsies

9.4 Confirmatory Measurement/Duration of Response

N/A

9.5 Progression-Free Survival

N/A

9.6 Response Review

N/A

10.0 MEASUREMENT OF TOXICITY

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

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

11.0 ADVERSE EVENT REPORTING

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

11.1 Definitions

11.1.1 **Adverse events** (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. FDA

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 investigational 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 more timely monitoring of patient safety and care. The following sections provide information about expedited reporting.

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

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

11.2.1 Determination of Reporting Requirements

Reporting requirements may include the following considerations:

- 1) whether the patient has received an investigational or commercial agent;

2) the characteristics of the adverse event including the grade (severity), the relationship to the study therapy (attribution), and the prior experience (expectedness) of the adverse event;

3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

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

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

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

Step 2: Grade the event using the NCI CTC.

Step 3: Determine whether the adverse event is related to the protocol therapy (investigational or commercial).

Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: Determine the prior experience of the adverse event.

11.3 Reporting Methods – n/a

11.3.5 FDA Reporting

N/A

11.3.6 IRB Reporting

11.3.6.1 All adverse events that are serious adverse events **and** are unexpected **and** are related or possibly related IRB within ten (10) working days of being made known to the Principal Investigator. Events that are more frequent than anticipate 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.

11.3.7 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 will 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 submission schedule, may be found in Appendix IV.

14.0 STATISTICAL CONSIDERATIONS

14.1 Sample Size/Accrual Rate

Twenty five (25) patients will be enrolled over a two-year period, subject to early stopping rules for safety (grade 3 or higher treatment-related acute GU/GI toxicity) and feasibility (LEAD eligibility). Study size is intended to provide initial evidence of safety and feasibility of the proposed treatment as a basis for planning Phase II efficacy trial.

14.2 Analysis Plan

Study findings will include descriptive statistics summarizing patient baseline characteristics, RT planning parameters and treatment received⁹⁴. A detailed safety profile will be provided consisting of lists and tabulations of all adverse events indicating type, grade, attribution to treatment and time of onset relative to treatment according to CTCAE standards. This will be done separately for acute and late toxicity (see Section 9.1). Patient level summaries will include worst grade toxicity and the number and duration of treatment delays attributable to toxicity.

Feasibility will be assessed by reporting the proportion of enrolled patients who are administered LEAD dose following successful MRI-guided planning and corresponding 95% confidence interval (CI) using the exact binomial method. The same method will be used to estimate the two-year positive biopsy rate defined as the proportion of positive biopsy findings among patients without clinical or biochemical failure two years after completing study treatment.

Clinical outcome will be further assessed by estimating the rate of biochemical failure, as defined in Section 9.1, using the method of cumulative incidence allowing for competing risk of death without biochemical failure. Biochemical failure free survival will be estimated by the Kaplan Meier method. Similar analysis will be provided for the combined rate of biochemical and clinical failure (cumulative incidence) and failure free survival (Kaplan Meier). Although death of study patients during the planned follow up period is expected to be rare and not attributable to prostate cancer, we include these survival endpoints (biochemical failure-free, failure-free, and overall survival) for completeness.

We will summarize the scores of QOL assessments with descriptive statistics and apply mixed effects modeling to evaluate changes over time.

Finally, to the extent permitted by available data from baseline biopsies, exploratory analysis will be performed to investigate the relationship between the level of biomarker expression in tumor tissue within vs. outside the DCE-MRI determined region and the correlation between these measures and Gleason score. Analysis of the sequential imaging studies will correlate the presence/absence of DCE enhancing area and its volume with biopsy positivity at 2 – 2.5 years. We will attempt to establish the ability of MRI for early assessment of RT outcome.

14.3 Stratification Factors
N/A

14.4 Interim Monitoring

We propose the following guidelines for the Sylvester Data and Safety monitoring Committee (DSMC) (see also Appendix III) in its review of accumulating data on toxicity and feasibility 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, or response, at the time such assessments are made.^{95,96}

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, and likewise for the true feasibility rate. As data on treated patients become available, each of these probability

Number of Patients With acute treatment Related Grade 3+ GI/GU Toxicity	Total Patients Evaluated	Observed Rate
2	3 to 6	≥33% (2 of 6)
3	7 of 11	≥27% (3 of 11)
4	12 to 16	≥25% (4 of 16)
7	17 to 25	≥25% (7 of 25)

distributions is revised and the resulting posterior probability becomes the basis for recommending either early termination or continuation of the study. In the sections that follow, we provide specific stopping guidelines based on posterior probabilities for monitoring toxicity and efficacy over the course of this trial. Underlying assumptions for the prior distributions are also presented.

Stopping rules for safety: The following early stopping guidelines, which are based on a Bayesian method, will be

applied to ensure safety of this Phase I trial. Safety monitoring will be based on the occurrence of treatment related (possible, probable, or definite) grade 3 or higher GI or GU toxicity occurring during study treatment or within 30 days 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%. **Table 2** shows specific instances where this guideline is met, thus suggesting early termination due to evidence of excessive toxicity.

As an additional safeguard, the first three patients enrolled on study will be observed for 30 days following treatment completion of the third patient before enrollment is continued (fourth patient). If two or three of the first three study patients have grade 3 or higher GI/GU toxicity within 30 days of treatment completion, enrollment will be suspended pending DSMC review. If none or one of the first three patients enrolled on study have grade 3 or higher GI/GU toxicity

within 30 days of treatment completion, enrollment will continue without restriction on the interval between successive enrollments.

Posterior probabilities used to derive the preceding table are calculated under a prior beta distribution with parameters $\beta_1 = 0.2$ and $\beta_2 = 1.8$, which corresponds to an expected rate of 15% based on prior information roughly equivalent to having studied 2 patients^{96,97}. 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.

Table 3. Stopping Rules For Lack of Feasibility

Number of Patients ineligible For LEAD	Total Patients enrolled and completed CT simulation	Observed LEAD ineligibility rate
2	3	67%
3	4 to 6	≥50% (3 of 6)
4	7 to 10	≥40% (4 of 10)
5	11 to 13	≥38% (5 of 13)
6	14 to 17	≥35% (6 of 17)
9	18 to 25	≥35% (9 of 25)

Stopping rules for lack of feasibility

Similarly, for purposes of monitoring the feasibility of delivering LEAD RT, we consider the proportion of patients enrolled on study for whom it is not possible to deliver LEAD RT as determined from CT/MRI simulation and planning, referred to as the *LEAD ineligibility rate*. The LEAD treatment will not be delivered if the summed dose of LEAD and conventional treatment to critical structures exceeds tolerance. Early stopping due to infeasibility of the proposed study treatment will be considered if there is evidence that the rate of LEAD ineligibility exceeds

20%. Specifically, we suggest as a guideline for early termination a posterior probability of 90% or higher that the rate of unacceptable toxicity exceeds 20%. **Table 3** shows specific instances where this guideline is met, thus suggesting early termination due to early evidence of LEAD infeasibility.

Posterior probabilities used to derive the preceding table are calculated under a prior beta distribution with parameters $\beta_1 = 0.4$ and $\beta_2 = 1.6$, which corresponds to an expected rate of 20% based on prior information roughly equivalent to having studied 2 patients. Furthermore, this prior distribution assigns a small a priori chance (36%) to the possibility that the true rate of unacceptable toxicity is 20% or greater.

14.5 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 research team 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 any CRFs. Subject clinical source documents would include hospital/clinic patient records; physician's and nurse's notes; original laboratory, radiology, pathology, and Quality of Life surveys; signed informed consent forms. When the CRF or any form is used as the source document, this must be clearly stated in the investigator study file.

At a minimum the following source documents will be collected:

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

15.5 Recording and Processing of Data

If using hard copies of CRFs, study center personnel will complete individual CRFs 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 CRFs 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

16.0 REFERENCES

1. Storey MR, Pollack A, Zagars G, Smith L, Antolak J, Rosen I: Complications from radiotherapy dose escalation in prostate cancer: preliminary results of a randomized trial. *Int J Radiat Oncol Biol Phys* 48:635-42, 2000
2. Pollack A, Zagars GK, Starkschall G, Antolak JA, Lee JJ, Huang E, von Eschenbach AC, Kuban DA, Rosen I: Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys* 53:1097-105, 2002
3. Kuban DA, Tucker SL, Dong L, Starkschall G, Huang EH, Cheung MR, Lee AK, Pollack A: Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys* 70:67-74, 2008
4. Zietman AL, Bae K, Slater JD, Shipley WU, Efstathiou JA, Coen JJ, Bush DA, Lunt M, Spiegel DY, Skowronski R, Jabola BR, Rossi CJ: Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95-09. *J Clin Oncol* 28:1106-11, 2010
5. Bigler SA, Deering RE, Brawer MK: Comparison of microscopic vascularity in benign and malignant prostate tissue. *Hum Pathol* 24:220-6, 1993
6. Li R, Heydon K, Hammond ME, Grignon DJ, Roach M, 3rd, Wolkov HB, Sandler HM, Shipley WU, Pollack A: Ki-67 staining index predicts distant metastasis and survival in locally advanced prostate cancer treated with radiotherapy: an analysis of patients in radiation therapy oncology group protocol 86-10. *Clin Cancer Res* 10:4118-24, 2004
7. Grignon DJ, Caplan R, Sarkar FH, Lawton CA, Hammond EH, Pilepich MV, Forman JD, Mesic J, Fu KK, Abrams RA, Pajak TF, Shipley WU, Cox JD: p53 status and prognosis of locally advanced prostatic adenocarcinoma: a study based on RTOG 8610. *J Natl Cancer Inst* 89:158-65, 1997
8. Che M, DeSilvio M, Pollack A, Grignon DJ, Venkatesan VM, Hanks GE, Sandler HM: Prognostic value of abnormal p53 expression in locally advanced prostate cancer treated with androgen

deprivation and radiotherapy: a study based on RTOG 9202. *Int J Radiat Oncol Biol Phys* 69:1117-23, 2007

9. Khor LY, Desilvio M, Al-Saleem T, Hammond ME, Grignon DJ, Sause W, Pilepich M, Okunieff P, Sandler H, Pollack A: MDM2 as a predictor of prostate carcinoma outcome: an analysis of Radiation Therapy Oncology Group Protocol 8610. *Cancer* 104:962-7, 2005

10. Khor LY, Bae K, Paulus R, Al-Saleem T, Hammond ME, Grignon DJ, Che M, Venkatesan V, Byhardt RW, Rotman M, Hanks GE, Sandler HM, Pollack A: MDM2 and Ki-67 predict for distant metastasis and mortality in men treated with radiotherapy and androgen deprivation for prostate cancer: RTOG 92-02. *J Clin Oncol* 27:3177-84, 2009

11. Khor LY, Moughan J, Al-Saleem T, Hammond EH, Venkatesan V, Rosenthal SA, Ritter MA, Sandler HM, Hanks GE, Shipley WU, Pollack A: Bcl-2 and Bax expression predict prostate cancer outcome in men treated with androgen deprivation and radiotherapy on radiation therapy oncology group protocol 92-02. *Clin Cancer Res* 13:3585-90, 2007

12. Chakravarti A, Heydon K, Wu CL, Hammond E, Pollack A, Roach M, Wolkov H, Okunieff P, Cox J, Fontanesi J, Abrams R, Pilepich M, Shipley W: Loss of p16 expression is of prognostic significance in locally advanced prostate cancer: an analysis from the Radiation Therapy Oncology Group protocol 86-10. *J Clin Oncol* 21:3328-34, 2003

13. Chakravarti A, DeSilvio M, Zhang M, Grignon D, Rosenthal S, Asbell SO, Hanks G, Sandler HM, Khor LY, Pollack A, Shipley W: Prognostic value of p16 in locally advanced prostate cancer: a study based on Radiation Therapy Oncology Group Protocol 9202. *J Clin Oncol* 25:3082-9, 2007

14. Khor LY, Bae K, Pollack A, Hammond ME, Grignon DJ, Venkatesan VM, Rosenthal SA, Ritter MA, Sandler HM, Hanks GE, Shipley WU, Dicker AP: COX-2 expression predicts prostate-cancer outcome: analysis of data from the RTOG 92-02 trial. *Lancet Oncol* 8:912-20, 2007

15. Pollack A, Bae K, Khor LY, Al-Saleem T, Hammond ME, Venkatesan V, Byhardt RW, Asbell SO, Shipley WU, Sandler HM: The importance of protein kinase A in prostate cancer: relationship to patient outcome in Radiation Therapy Oncology Group trial 92-02. *Clin Cancer Res* 15:5478-84, 2009

16. Eade TN, Hanlon AL, Horwitz EM, Buyyounouski MK, Hanks GE, Pollack A: What dose of external-beam radiation is high enough for prostate cancer? *Int J Radiat Oncol Biol Phys* 68:682-9, 2007

17. Roach M, 3rd, Hanks G, Thames H, Jr., Schellhammer P, Shipley WU, Sokol GH, Sandler H: Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys* 65:965-74, 2006

18. Peeters ST, Heemsbergen WD, Koper PC, van Putten WL, Slot A, Dielwart MF, Bonfrer JM, Incrocci L, Lebesque JV: Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. *J Clin Oncol* 24:1990-6, 2006

19. Dearnaley DP, Sydes MR, Graham JD, Aird EG, Bottomley D, Cowan RA, Huddart RA, Jose CC, Matthews JH, Millar J, Moore AR, Morgan RC, Russell JM, Scrase CD, Stephens RJ, Syndikus I, Parmar MK: Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 8:475-87, 2007

20. Cox JD, Stoffel TJ: The significance of needle biopsy after irradiation for the stage C adenocarcinoma of the prostate. *Cancer* 40:156-160, 1977

21. Herr HW, Whitmore WF, Jr.: Significance of prostatic biopsies after radiation therapy for carcinoma of the prostate, *The prostate*, vol. 3. New York, Alan R. Liss, Inc., 1982

22. Cox JD, Kline RW: The lack of prognostic significance of biopsies after radiotherapy for prostatic cancer. *Semin Urol* 1:237-42, 1983

23. Crook J, Malone S, Perry G, Bahadur Y, Robertson S, Abdoell M: Postradiotherapy prostate biopsies: what do they really mean? Results for 498 patients. *Int J Radiat Oncol Biol Phys* 48:355-67, 2000
24. Crook JM, Malone S, Perry G, Eapen L, Owen J, Robertson S, Ludgate C, Fung S, Lockwood G: Twenty-four-month postradiation prostate biopsies are strongly predictive of 7-year disease-free survival: results from a Canadian randomized trial. *Cancer* 115:673-9, 2009
25. Zelefsky MJ, Reuter VE, Fuks Z, Scardino P, Shippy A: Influence of local tumor control on distant metastases and cancer related mortality after external beam radiotherapy for prostate cancer. *J Urol* 179:1368-73; discussion 1373, 2008
26. Crook J, Robertson S, Esche B: Proliferative cell nuclear antigen in postradiotherapy prostate biopsies. *International Journal of Radiation Oncology Biology Physics* 30:303-308, 1994
27. Crook JM, Raymond Y, Salhani D, Yang H, Esche B: Prostate motion during standard radiotherapy as assessed by fiducial markers. *Radiother Oncol* 37:35-42, 1995
28. Buyyounouski MK, Li T, Al-Saleem T, Horwitz E, Konski A, Feigenberg S, Uzzo R, Greenberg R, Pollack A: Predicting local persistence of intermediate and high-risk prostate cancer using percentage of adenocarcinoma in pretreatment biopsy tissue. *International Journal of Radiation Oncology Biology Physics* 72:S321-S322, 2008
29. Vergis R, Corbishley CM, Norman AR, Bartlett J, Jhavar S, Borre M, Heeboll S, Horwich A, Huddart R, Khoo V, Eeles R, Cooper C, Sydes M, Dearnaley D, Parker C: Intrinsic markers of tumour hypoxia and angiogenesis in localised prostate cancer and outcome of radical treatment: a retrospective analysis of two randomised radiotherapy trials and one surgical cohort study. *Lancet Oncol* 9:342-51, 2008
30. Shaida N, Launchbury R, Boddy JL, Jones C, Campo L, Turley H, Kanga S, Banham AH, Malone PR, Harris AL, Fox SB: Expression of BNIP3 correlates with hypoxia-inducible factor (HIF)-1alpha, HIF-2alpha and the androgen receptor in prostate cancer and is regulated directly by hypoxia but not androgens in cell lines. *Prostate* 68:336-43, 2008
31. Anai S, Shiverick K, Medrano T, Nakamura K, Goodison S, Brown BD, Rosser CJ: Downregulation of BCL-2 induces downregulation of carbonic anhydrase IX, vascular endothelial growth factor, and pAkt and induces radiation sensitization. *Urology* 70:832-7, 2007
32. Farrall AL, Whitelaw ML: The HIF1alpha-inducible pro-cell death gene BNIP3 is a novel target of SIM2s repression through cross-talk on the hypoxia response element. *Oncogene* 28:3671-80, 2009
33. Sperandio S, Fortin J, Sasik R, Robitaille L, Corbeil J, de Belle I: The transcription factor Egr1 regulates the HIF-1alpha gene during hypoxia. *Mol Carcinog* 48:38-44, 2009
34. Jolles B, Koller PC: The role of connective tissue in the radiation reaction of tumours. *Br J Cancer* 4:77-89, 1950
35. Marks H: A new approach to the roentgen therapy of cancer with the use of a grid. *J Mt Sinai Hosp N Y* 17:46-8, 1950
36. Marks H: Clinical experience with irradiation through a grid. *Radiology* 58:338-42, 1952
37. Kohler H: Zur Rontgentiefentherapie mit Massendosen. . *MMW* 56:2314-2316, 1909
38. Liberson F: Value of multiperforated screen in deep x-ray therapy. . *Radiology* 20:186-195, 1933
39. Mohiuddin M: Overcoming the barrier of radiation resistance in advanced cancer by using high dose spatially fractionated radiation., *International Journal of Radiation Oncology Biology Physics*, 1997, pp S329

40. Mohiuddin M, Curtis DL, Grizos WT, Komarnicky L: Palliative treatment of advanced cancer using multiple nonconfluent pencil beam radiation. A pilot study. *Cancer* 66:114-8, 1990
41. Mohiuddin M, Fujita M, Regine WF, Megooni AS, Ibbott GS, Ahmed MM: High-dose spatially-fractionated radiation (GRID): a new paradigm in the management of advanced cancers. *Int J Radiat Oncol Biol Phys* 45:721-7, 1999
42. Penagaricano JA, Moros EG, Ratanatharathorn V, Yan Y, Corry P: Evaluation of Spatially Fractionated Radiotherapy (GRID) and Definitive Chemoradiotherapy with Curative Intent for Locally Advanced Squamous Cell Carcinoma of the Head and Neck: Initial Response Rates and Toxicity. *Int J Radiat Oncol Biol Phys*, 2009
43. Huhn JL, Regine WF, Valentino JP, Meigooni AS, Kudrimoti M, Mohiuddin M: Spatially fractionated GRID radiation treatment of advanced neck disease associated with head and neck cancer. *Technol Cancer Res Treat* 5:607-12, 2006
44. Sathishkumar S, Dey S, Meigooni AS, Regine WF, Kudrimoti MS, Ahmed MM, Mohiuddin M: The impact of TNF-alpha induction on therapeutic efficacy following high dose spatially fractionated (GRID) radiation. *Technol Cancer Res Treat* 1:141-7, 2002
45. Shareef MM, Cui N, Burikhanov R, Gupta S, Sabapathi S, Mohiuddin M, Rangnekar VM, Ahmed MM: Role of TNF α and TRAIL in high dose radiation induced bystander signaling in lung adenocarcinoma. *Cancer Research*, 2007
46. Shareef MM, Cui N, Burikhanov R, Gupta S, Sathishkumar S, Shajahan S, Mohiuddin M, Rangnekar VM, Ahmed MM: Role of tumor necrosis factor-alpha and TRAIL in high-dose radiation-induced bystander signaling in lung adenocarcinoma. *Cancer Res* 67:11811-20, 2007
47. Sathishkumar S, Boyanovsky B, Karakashian AA, Rozenova K, Giltiy NV, Kudrimoti M, Mohiuddin M, Ahmed MM, Nikolova-Karakashian M: Elevated sphingomyelinase activity and ceramide concentration in serum of patients undergoing high dose spatially fractionated radiation treatment: implications for endothelial apoptosis. *Cancer Biol Ther* 4:979-86, 2005
48. Peters ME, Shareef MM, Gupta S, Zagurovskaya-Sultanov M, Kadhim MA, Mohiuddin M, Ahmed MM: Potential Utilization of Bystander / Abscopal-Mediated Signal Transduction Events in the Treatment of Solid Tumors. *Current Signal Transduction Therapy* 2:129-143, 2007
49. Garcia-Barros M, Paris F, Cordon-Cardo C, Lyden D, Rafii S, Haimovitz-Friedman A, Fuks Z, Kolesnick R: Tumor response to radiotherapy regulated by endothelial cell apoptosis. *Science* 300:1155-9, 2003
50. Shinohara K, Wheeler TM, Scardino PT: The appearance of prostate cancer on transrectal ultrasonography: correlation of imaging and pathological examinations. *J Urol* 142:76-82, 1989
51. Roehl KA, Antenor JA, Catalona WJ: Serial biopsy results in prostate cancer screening study. *J Urol* 167:2435-9, 2002
52. Hom JJ, Coakley FV, Simko JP, Qayyum A, Lu Y, Schmitt L, Carroll PR, Kurhanewicz J: Prostate cancer: endorectal MR imaging and MR spectroscopic imaging--distinction of true-positive results from chance-detected lesions. *Radiology* 238:192-9, 2006
53. Coakley FV, Kurhanewicz J, Lu Y, Jones KD, Swanson MG, Chang SD, Carroll PR, Hricak H: Prostate cancer tumor volume: measurement with endorectal MR and MR spectroscopic imaging. *Radiology* 223:91-7, 2002
54. Hricak H, White S, Vigneron D, Kurhanewicz J, Kosco A, Levin D, Weiss J, Narayan P, Carroll PR: Carcinoma of the prostate gland: MR imaging with pelvic phased-array coils versus integrated endorectal-pelvic phased-array coils. *Radiology* 193:703-709, 1994

55. Futterer JJ, Heijmink SW, Scheenen TW, Veltman J, Huisman HJ, Vos P, Hulsbergen-Van de Kaa CA, Witjes JA, Krabbe PF, Heerschap A, Barentsz JO: Prostate cancer localization with dynamic contrast-enhanced MR imaging and proton MR spectroscopic imaging. *Radiology* 241:449-58, 2006
56. Mazaheri Y, Shukla-Dave A, Muellner A, Hricak H: MR imaging of the prostate in clinical practice. *MAGMA* 21:379-92, 2008
57. Padhani AR, Gapinski CJ, Macvicar DA, Parker GJ, Suckling J, Revell PB, Leach MO, Dearnaley DP, Husband JE: Dynamic contrast enhanced MRI of prostate cancer: correlation with morphology and tumour stage, histological grade and PSA. *Clin Radiol* 55:99-109, 2000
58. Turnbull LW, Buckley DL, Turnbull LS, Liney GP, Knowles AJ: Differentiation of prostatic carcinoma and benign prostatic hyperplasia: correlation between dynamic Gd-DTPA-enhanced MR imaging and histopathology. *J Magn Reson Imaging* 9:311-6, 1999
59. Jager GJ, Ruijter ET, van de Kaa CA, de la Rosette JJ, Oosterhof GO, Thornbury JR, Ruijs SH, Barentsz JO: Dynamic TurboFLASH subtraction technique for contrast-enhanced MR imaging of the prostate: correlation with histopathologic results. *Radiology* 203:645-52, 1997
60. Kim CK, Park BK, Kim B: Localization of prostate cancer using 3T MRI: comparison of T2-weighted and dynamic contrast-enhanced imaging. *J Comput Assist Tomogr* 30:7-11, 2006
61. Girouin N, Mege-Lechevallier F, Tonina Senes A, Bissery A, Rabilloud M, Marechal JM, Colombel M, Lyonnet D, Rouviere O: Prostate dynamic contrast-enhanced MRI with simple visual diagnostic criteria: is it reasonable? *Eur Radiol* 17:1498-509, 2007
62. van Dorsten FA, van der Graaf M, Engelbrecht MR, van Leenders GJ, Verhofstad A, Rijpkema M, de la Rosette JJ, Barentsz JO, Heerschap A: Combined quantitative dynamic contrast-enhanced MR imaging and (1)H MR spectroscopic imaging of human prostate cancer. *J Magn Reson Imaging* 20:279-87, 2004
63. Buckley DL, Roberts C, Parker GJ, Logue JP, Hutchinson CE: Prostate cancer: evaluation of vascular characteristics with dynamic contrast-enhanced T1-weighted MR imaging--initial experience. *Radiology* 233:709-15, 2004
64. Ocak I, Bernardo M, Metzger G, Barrett T, Pinto P, Albert PS, Choyke PL: Dynamic contrast-enhanced MRI of prostate cancer at 3 T: a study of pharmacokinetic parameters. *AJR Am J Roentgenol* 189:849, 2007
65. Du S, Sajda P, Brown T, Stoyanova R: Recovery of Metabolomic Spectral Sources using Non-negative Matrix Factorization. *Conf Proc IEEE Eng Med Biol Soc* 2:1095-8, 2005
66. Sajda P, Du S, Brown TR, Stoyanova R, Shungu DC, Mao X, Parra LC: Nonnegative matrix factorization for rapid recovery of constituent spectra in magnetic resonance chemical shift imaging of the brain. *IEEE Trans Med Imaging* 23:1453-65, 2004
67. Brown TR, Stoyanova R: NMR spectral quantitation by principal-component analysis. II. Determination of frequency and phase shifts. *J Magn Reson B* 112:32-43, 1996
68. Stoyanova R, Brown TR: NMR spectral quantitation by principal component analysis. III. A generalized procedure for determination of lineshape variations. *J Magn Reson* 154:163-75, 2002
69. Alonzi R, Padhani AR, Allen C: Dynamic contrast enhanced MRI in prostate cancer. *Eur J Radiol* 63:335-50, 2007
70. Lee DD, Seung HS: Learning the parts of objects by non-negative matrix factorization. *Nature* 401:788-91, 1999
71. Namiki S, Ishidoya S, Tochigi T, Kawamura S, Kuwahara M, Terai A, Yoshimura K, Numata I, Satoh M, Saito S, Takai Y, Yamada S, Arai Y: Health-related quality of life after intensity modulated radiation therapy for localized prostate cancer: comparison with conventional and conformal radiotherapy. *Jpn J Clin Oncol* 36:224-30, 2006

72. Yoshimura K, Kamoto T, Nakamura E, Segawa T, Kamba T, Takahashi T, Nishiyama H, Ito N, Takayama K, Mizowaki T, Mitsumori M, Hiraoka M, Ogawa O: Health-related quality-of-life after external beam radiation therapy for localized prostate cancer: intensity-modulated radiation therapy versus conformal radiation therapy. *Prostate Cancer Prostatic Dis*, 2006
73. Junius S, Haustermans K, Bussels B, Oyen R, Vanstraelen B, Depuydt T, Verstraete J, Joniau S, Van Poppel H: Hypofractionated intensity modulated irradiation for localized prostate cancer, results from a phase I/II feasibility study. *Radiat Oncol* 2:29, 2007
74. Lips I, Dehnad H, Kruger AB, van Moorselaar J, van der Heide U, Battermann J, van Vulpen M: Health-related quality of life in patients with locally advanced prostate cancer after 76 Gy intensity-modulated radiotherapy vs. 70 Gy conformal radiotherapy in a prospective and longitudinal study. *Int J Radiat Oncol Biol Phys* 69:656-61, 2007
75. Lips IM, van Gils CH, van der Heide UA, Kruger AE, van Vulpen M: Health-related quality of life 3 years after high-dose intensity-modulated radiotherapy with gold fiducial marker-based position verification. *BJU Int* 103:762-7, 2009
76. Marchand V, Bourdin S, Charbonnel C, Rio E, Munos C, Campion L, Bonnaud-Antignac A, Lisbona A, Mahe MA, Supiot S: No Impairment of Quality of Life 18 Months After High-Dose Intensity-Modulated Radiotherapy for Localized Prostate Cancer: A Prospective Study. *Int J Radiat Oncol Biol Phys*, 2009
77. Zelefsky MJ, Chan H, Hunt M, Yamada Y, Shippy AM, Amols H: Long-term outcome of high dose intensity modulated radiation therapy for patients with clinically localized prostate cancer. *J Urol* 176:1415-9, 2006
78. Zelefsky MJ, Fuks Z, Hunt M, Lee HJ, Lombardi D, Ling CC, Reuter VE, Venkatraman ES, Leibel SA: High dose radiation delivered by intensity modulated conformal radiotherapy improves the outcome of localized prostate cancer. *J Urol* 166:876-81, 2001
79. Lebeau T, Perrotte P, Valiquette L, Benard F, McCormack M, Saad F, Karakiewicz PI: Validation of prostate cancer index and SF-12 short forms. *Can J Urol* 12:2873-9, 2005
80. Dale W, Bilir P, Han M, Meltzer D: The role of anxiety in prostate carcinoma: a structured review of the literature. *Cancer* 104:467-78, 2005
81. Wei JT, Dunn RL, Litwin MS, Sandler HM, Sanda MG: Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. *Urology* 56:899-905, 2000
82. Schulz MW, Chen J, Woo HH, Keech M, Watson ME, Davey PJ: A comparison of techniques for eliciting patient preferences in patients with benign prostatic hyperplasia. *J Urol* 168:155-9, 2002
83. Konski A, Watkins-Bruner D, Feigenberg S, Hanlon A, Kulkarni S, Beck JR, Horwitz EM, Pollack A: Using decision analysis to determine the cost-effectiveness of intensity-modulated radiation therapy in the treatment of intermediate risk prostate cancer. *Int J Radiat Oncol Biol Phys* 66:408-15, 2006
84. Barry MJ, Fowler FJ, Jr., O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK: Correlation of the American Urological Association symptom index with self-administered versions of the Madsen-Iversen, Boyarsky and Maine Medical Assessment Program symptom indexes. Measurement Committee of the American Urological Association. *J Urol* 148:1558-63; discussion 1564, 1992
85. Desai J, Stock RG, Stone NN, Iannuzzi C, DeWyngaert JK: Acute urinary morbidity following I-125 interstitial implantation of the prostate gland. *Radiat Oncol Investig* 6:135-41, 1998

86. Merrick GS, Butler WM, Lief JH, Dorsey AT: Temporal resolution of urinary morbidity following prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 47:121-8, 2000
87. Egawa S, Shimura S, Irie A, Kitano M, Nishiguchi I, Kuwao S, Hayakawa K, Baba S: Toxicity and health-related quality of life during and after high dose rate brachytherapy followed by external beam radiotherapy for prostate cancer. *Jpn J Clin Oncol* 31:541-7, 2001
88. Merrick GS, Butler WM, Wallner KE, Lief JH, Galbreath RW: Prophylactic versus therapeutic alpha-blockers after permanent prostate brachytherapy. *Urology* 60:650-5, 2002
89. van Lin EN, Futterer JJ, Heijmink SW, van der Vicht LP, Hoffmann AL, van Kollenburg P, Huisman HJ, Scheenen TW, Witjes JA, Leer JW, Barentsz JO, Visser AG: IMRT boost dose planning on dominant intraprostatic lesions: gold marker-based three-dimensional fusion of CT with dynamic contrast-enhanced and 1H-spectroscopic MRI. *Int J Radiat Oncol Biol Phys* 65:291-303, 2006
90. Eade TN, Horwitz EM, Ruth K, Buyyounouski MK, D'Ambrosio DJ, Feigenberg SJ, Chen DY, Pollack A: A comparison of acute and chronic toxicity for men with low-risk prostate cancer treated with intensity-modulated radiation therapy or (125)I permanent implant. *Int J Radiat Oncol Biol Phys* 71:338-45, 2008
91. Pollack A, Hanlon AL, Horwitz EM, Feigenberg SJ, Konski AA, Movsas B, Greenberg RE, Uzzo RG, Ma CM, McNeeley SW, Buyyounouski MK, Price RA, Jr.: Dosimetry and preliminary acute toxicity in the first 100 men treated for prostate cancer on a randomized hypofractionation dose escalation trial. *Int J Radiat Oncol Biol Phys* 64:518-26, 2006
92. Cairns P, Esteller M, Herman JG, Schoenberg M, Jeronimo C, Sanchez-Cespedes M, Chow NH, Grasso M, Wu L, Westra WB, Sidransky D: Molecular detection of prostate cancer in urine by GSTP1 hypermethylation. *Clin Cancer Res* 7:2727-30, 2001
93. Schellhammer P, Sharifi R, Block N, Soloway M, Venner P, Patterson AL, Sarosdy M, Vogelzang N, Jones J, Kolvenbag G: A controlled trial of bicalutamide versus flutamide, each in combination with luteinizing hormone-releasing hormone analogue therapy, in patients with advanced prostate cancer. Casodex Combination Study Group. *Urology* 45:745-52, 1995
94. Armitage P, Berry G, Matthews JNS: *Statistical Methods in Medical Research* (ed 4th), Blackwell Scientific, 2002
95. Spiegelhalter DJ, Freedman LS, Parmar MK: Bayesian approaches to randomized trials (with discussion). *J Royal Stat Soc Ser A* 157:357-416, 1994
96. Fayers PM, Ashby D, Parmar MK: Tutorial in biostatistics Bayesian data monitoring in clinical trials. *Stat Med* 16:1413-30, 1997
97. Spiegelhalter DJ, Freedman LS, Parmar MK: Bayesian approaches to randomized trials. *Journal of the Royal Statistical Society Series-a-Statistics in Society* 157:357-387, 1994

APPENDIX I
STUDY CALENDAR

Assessment	Prior to RT	24 hr Post-LEAD RT	Weekly during RT	Follow-up				
				During last week of RT	6 Weeks	3 Mo	Every 6 months thereafter up to 5.25 years post-RT	Other
History & Physical Exam*	X		X	X	X	X	X	
Multiparametric MRI of prostate/pelvis ^a	X					X		At 9 mo, and within 2 mo of 2 yr prostate biopsy
Bone Scan or PET Bone Scan ^b	X							As needed
Prostate Biopsy ^c	X							2 – 2.5 years post completion of all therapy
CT and MRI simulation	X							As needed
PSA ^a	X				X	X	X	
Serum-Testosterone ^d	X			X	X	X		At 9 months after RT
BUN and creatinine						X		At 9 months and within 2 mo of 2 yr prostate biopsy
Liver function tests ^a	X			X	X	X		
Complete blood cell counts ^a	X			X		X		
Lipid Profile ^a	X	X		X	X	X		At 9 months and within 2 mo of 2 yr prostate biopsy
EPIC-SF12 ^e	X			X	X	X		At 9 months, 15 mo and yearly to 5.25 years
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	At each follow-up visit
Start of ADT ^g	X							
Plasma and serum, and urine collection for research ^h	X	X		X	X	X		At 9 months and within 2 mo of 2 yr prostate biopsy

*Toxicity and performance status (Zubrod score) will be assessed at each scheduled history and physical exam visit. Interval history will be obtained during following RT at these visits. On-treatment and follow-up physical exams are focused per routine.

- ^aObtained \leq 3 months of signed consent and complete blood count and liver function tests (LFTS). If ADT is not administered, only pretreatment and 3 month LFTs are required. Lipid panels are preferred to be fasting (not required).
- ^bObtained \leq 4 months of enrollment if PSA >15 ng/mL or Gleason score $8 \geq$ disease. A questionable bone scan is acceptable if other imaging is negative for metastasis. For all others, to be obtained at the discretion of the treating physician.
- ^c The initial biopsy will be carried out during fiducial markers placement (if patient opts to have biopsy), within 4 weeks after enrollment (registration). In follow-up, prostate biopsy will be obtained at 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 no evidence of failure.
- ^dSerum testosterone will be drawn as part of routine workup ≤ 4 months before signed consent or after enrollment but prior to the first radiation treatment and must be within 40% of normal assay limits, defined as $x=0.4$ *lower assay limit and $x=0.4$ *upper assay limit + upper assay limit. 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. Serum testosterone will be drawn at the end of RT, 6 weeks, 3 months, and 9 months after radiotherapy. If testosterone remains abnormally low, tests will continue to be done at each follow-up visit.
- ^eAfter enrollment (registration) and prior to fiducial marker placement.
- ^f International Prostate Symptom Score will be administered pretreatment, at the end of treatment and at each follow-up visit.
- ^gAndrogen deprivation therapy (ADT) for applicable patients: ADT is recommended to be initiated after fiducial marker placement. Anti-androgen treatment is recommended to begin 1-14 days before LHRH agonist start. ADT may occur up to 2 months prior the signing of consent (timing is relative to LHRH agonist injection). If not started prior to consent, ADT is recommended to start after fiducial marker placement and prior to radiotherapy start.
- ^hAfter enrollment and prior to fiducial marker placement 2-4 tubes of blood and 50 mL of urine will be collected, as described in Sections 4.11, 4.12 and 5.0 for research studies.

Note: Measurements and visits during treatment should occur \pm 3 days; measurements and visits during follow-up should occur \pm 2 weeks up to the 3 month visit and \pm 4 weeks for subsequent measurements/visits, with the exception of the post-LEAD RT lipids and blood & urine collection for research, which is 24 hr \pm 12 hr.

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:

[http://10.64.1.160/eForm///Clinical%20Research%20Services/Data%20and%20Safety%20Monitoring%20Committee%20\(DSMC\)/DSMC%20Plan_120407.pdf](http://10.64.1.160/eForm///Clinical%20Research%20Services/Data%20and%20Safety%20Monitoring%20Committee%20(DSMC)/DSMC%20Plan_120407.pdf)

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 during the last week of RT, 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

ECOG / WHO / Zubrod	Karnofsky	Activity
Zubrod 0	Karnofsky 90-100	Normally Active
Zubrod 1	Karnofsky 70-80	Symptoms but ambulatory where strenuous physical activity is restricted
Zubrod 2	Karnofsky 50-60	In bed less than 50 percent of the time. Capable of all self-care
Zubrod 3	Karnofsky 30-40	In bed more than 50 percent of the time. Capable of only limited self-care.
Zubrod 4	Karnofsky 10-20	Completely disabled and bedridden.
Death		

APPENDIX VII

The Modified 18-Item Memorial Anxiety Scale for Prostate Cancer

We would like to better understand how patients cope with aspects of their treatment for prostate cancer and the medical tests frequently involved in their care.

Below is a list of comments made by men about prostate cancer. Please indicate by circling the number next to each item how frequently these comments were true for you *during the past week* using the following scale: not at all=0, rarely=1, sometimes=2, often = 3.

1. Any reference to prostate cancer brought up strong feelings in me. ____
2. Even though it's a good idea, I found that getting a PSA test scared me. ____
3. Whenever I heard about a friend or public figure with prostate cancer, I got more anxious about my having prostate cancer. ____
4. When I thought about having a PSA test, I got more anxious about my having prostate cancer. ____
5. Other things kept making me think about prostate cancer. ____
6. I felt kind of numb when I thought about prostate cancer. ____
7. I thought about prostate cancer even though I didn't mean to. ____
8. I had a lot of feelings about prostate cancer, but I didn't want to deal with them. ____
9. I had more trouble falling asleep because I couldn't get thoughts of prostate cancer out of my mind. ____
10. I was afraid that the results from my PSA test would show that my disease was getting worse. ____
11. Just hearing the words "prostate cancer" scared me. ____

For the next three questions, please indicate how frequently these situations have *EVER*

been true for you using the following scale: not at all=0, rarely=1, sometimes=2, often = 3.

12. I have been so anxious about my PSA test that I have thought about delaying it. ____

13. I have been so worried about my PSA test result that I have thought about asking my doctor to repeat it. ____

14. I have been so concerned about my PSA test result that I have thought about having the test repeated at another lab to make sure they were accurate. ____

Listed below are a number of statements concerning a person's beliefs about their own health.

In thinking about the *past week*, please indicate how much you agree or disagree with each statement: strongly agree =0, agree =1, disagree =2, or strongly disagree =3. Please circle the number of your answer.

15. Because cancer is unpredictable, I feel I cannot plan for the future. ____

16. My fear of having my cancer getting worse gets in the way of my enjoying life. ____

17. I am afraid of my cancer getting worse. ____

18. I am more nervous since I was diagnosed with prostate cancer. ____

APPENDIX VIII

EPIC-SF12

SF-12 & EPIC

This questionnaire is designed to measure Quality of Life issues in patients with Prostate Cancer. To help us get the most accurate measurement, it is important that you answer all questions honestly and completely.

Remember, as with all medical records, information contained within this survey will remain strictly confidential.

Today's Date (please enter date when survey completed): Month ____ Day ____ Year ____

1. In general, would you say your health is:

(Circle one number)

Excellent1

Very good2

Good.....3

Fair.....4

Poor.....5

2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(Circle 1, 2, or 3 on each line)

Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
--------------------------	-----------------------------	------------------------------

a. **Moderate activities**, such as moving a table, pushing a vacuum cleaner,

bowling, or playing golf.....	1	2	3
-------------------------------	---	---	---

b. Climbing several flights of stairs.....	1	2	3
---	---	---	---

3. During the **PAST 4 WEEKS**, have you had any of the following problems with your work or other regular daily activities as a result of your **PHYSICAL HEALTH?**

(Please answer YES or NO for each question by circling 1 or 2 on each line.)

	Yes	No
a. Accomplished less than you would like	1	2
b. Were limited in the kind of work or other activities.....	1	2

4. During the **PAST 4 WEEKS**, have you has any of the following problems with your work or other regular daily activities as a result of any **EMOTIONAL PROBLEMS**, such as feeling depressed or anxious?

(Please answer YES or NO for each question by circling 1 or 2 on each line.)

	Yes	No
a. Accomplished less than you would like	1	2

b. Didn't do work or other activities as **carefully** as usual..... 1 2

5. During the **past 4 weeks**, how much did pain interfere with your normal work (including both work outside the home and housework)?

(Circle one number)

Not at all1

Slightly2

Moderately.....3

Quite a bit.....4

Extremely.....5

6. These questions are about how you feel and how things have been with you during the **PAST 4 WEEKS**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

(Circle one number on each line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
a. Have you felt calm and peaceful?	1	2	3	4	5	6
b. Did you have a lot of energy?	1	2	3	4	5	6
c. Have you felt downhearted and blue?	1	2	3	4	5	6

7. During the **past 4 weeks**, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

(Circle one number)

- All of the time1
- Most of the time2
- Some of the time.....3
- A little of the time.....4
- None of the time5

URINARY FUNCTION

This section is about your urinary habits. Please consider **ONLY THE LAST 4 WEEKS**.

8. Over the **past 4 weeks**, how often have you leaked urine?
(Circle one number)

- More than once a day..... 1
- About once a day..... 2
- More than once a week..... 3
- About once a week..... 4
- Rarely or never..... 5

9. Over the **past 4 weeks**, how often have you urinated blood?
(Circle one number)

- More than once a day..... 1
- About once a day..... 2
- More than once a week..... 3
- About once a week..... 4

Rarely or never..... 5

10. Over the past 4 weeks, how often have you had pain or burning with urination?
(Circle one number)

More than once a day..... 1

About once a day..... 2

More than once a week..... 3

About once a week..... 4

Rarely or never..... 5

11. Which of the following best describes your urinary control during the last 4 weeks?
(Circle one number)

No urinary control whatsoever1

Frequent dribbling.....2

Occasional dripping.....3

Total control.....4

12. How many pads or adult diapers per day did you use to control leakage during the last 4 weeks?
(Circle one number)

None..... 0

1 pad per day..... 1

2 pads per day..... 2

3 or more pads per day..... 3

13. How big a problem, if any, has each of the following been for you during the last 4 weeks?
(Circle one number)

No Very Small Small Moderate Big

Problem Problem Problem Problem Problem

a. Dripping or leaking urine.....0	1	2	3	4
Pain or burning on urination.....0	1	2	3	4
Bleeding with urination.....0	1	2	3	4
b. Weak urine stream or incomplete emptying.....0	1	2	3	4
c. Waking up to urinate.....0	1	2	3	4
d. Need to urinate frequently during the day.....0	1	2	3	4

14. Overall, how big a problem has your urinary function been for you during the last 4 weeks?
 (Circle one number)

- No problem..... 1
- Very small problem... ..2
- Small problem..... 3
- Moderate problem... ..4
- Big problem..... 5

URINARY SYMPTOMS

(Circle one number on each line)

	Less	Less	About	More
Not	than	than	half than	
at	1 time	half the	the	half the Almost
<u>all</u>	<u>in 5</u>	<u>time</u>	<u>time</u>	<u>time</u> <u>Always</u>

15. **Incomplete emptying**
 Over the past month, how often have
 you had a sensation of not emptying

your bladder completely after you

finished urinating?..... 0 1 2 3 4 5

16. Frequency

Over the past month, how often have

you had to urinate again in less than

two hours after you finished urinating?... 0 1 2 3 4 5

17. Intermittency

Over the past month, how often have

You found you stopped and started

Again several times when you urinated?... 0 1 2 3 4 5

18. Urgency

Over the past month, how often have

you found it difficult to postpone

urine?..... 0 1 2 3 4 5

19. Weak Stream

Over the past month, how often have

you had a weak urinary system?..... 0 1 2 3 4 5

20. Straining

Over the past month, how often have

you had to push or strain to begin

urination?..... 0 1 2 3 4 5

21.Nocturia

Over the past month, how many times

did you most typically get up to urinate **(none)** **(1x)** **(2x)** **(3x)** **(4x)** **(5x or more)**

from the time you went to bed at night

until the time you got up in the morning?... 0 1 2 3 4 5

BOWEL HABITS

The next section is about your bowel habits and abdominal pain.

Please consider **ONLY THE LAST 4 WEEKS.**

22. How often have you had rectal urgency (felt like I had to pass stool, but did not) during the last 4 weeks?

(Circle one number)

More than once a day..... 1

About once a day..... 2

More than once a week..... 3

About once a week..... 4

Rarely or never5

23. Often have you had uncontrolled leakage of stool or feces?

(Circle one number)

More than once a day..... 1

- About once a day..... 2
- More than once a week..... 3
- About once a week..... 4
- Rarely or never5

24. How often have you had stools (bowel movements) that were loose or liquid (no form, watery, mushy) during the last 4 weeks?

(Circle one number)

- Never..... 1
- Rarely..... 2
- About half the time..... 3
- Usually..... 4
- Always5

25. How often have you had bloody stools during the last 4 weeks?

(Circle one number)

- Never..... 1
- Rarely..... 2
- About half the time..... 3
- Usually..... 4
- Always5

26. How often have your bowel movements been painful during the last 4 weeks?

(Circle one number)

- Never..... 1

- Rarely..... 2
- About half the time..... 3
- Usually..... 4
- Always5

27. How many bowel movements have you had on a typical day during the last 4 weeks?

(Circle one number)

- Two or less..... 1
- Three to four..... 2
- Five or more..... 3

28. How often have you had crampy pain in your abdomen, pelvis or rectum during the last 4 weeks?

(Circle one number)

- More than once a day..... 1
- About once a day..... 2
- More than once a week..... 3
- About once a week..... 4
- Rarely or never..... 5

29. How big a problem, if any, has each of the following been for you?

(Circle one number on each line)

No Very Small Small Moderate Big
Problem Problem Problem Problem Problem

- a. Urgency to have a bowel..... 0 1 2 3 4

movement

b. Increased frequency of..... bowel movements	0	1	2	3	4
c. Watery bowel movements.....	0	1	2	3	4
d. Losing control of your stools.....	0	1	2	3	4
e. Bloody stools.....	0	1	2	3	4
f. Abdominal/Pelvic/ Rectal pain.....	0	1	2	3	4

30. Overall, how big a problem have your bowel habits been for you during the last 4 weeks?

(Circle one number)

- No problem..... 1
- Very small problem...2
- Small problem..... 3
- Moderate problem...4
- Big problem..... 5

SEXUAL FUNCTION

The next section is about your **current** sexual function and sexual satisfaction. Many of the questions are very personal, but they will help us understand the important issues that you face every day. Remember, **THIS SURVEY INFORMATION IS COMPLETELY CONFIDENTIAL**. Please answer honestly about **THE LAST 4 WEEKS ONLY**.

31. How would you rate each of the following during the last 4 weeks?

(Circle one number on each line)

		Very Poor to		Very	
	None	Poor	Fair	Good	Good
a. Your level of sexual desire.....	1	2	3	4	5
b. Your ability to have an erection...	1	2	3	4	5
c. Your ability to reach orgasm.....	1	2	3	4	5

32. How would you describe the usual QUALITY of your erections during the last 4 weeks?

(Circle one number)

- None at all..... 1
- Not firm enough for any sexual activity..... 2
- Firm enough for masturbation and foreplay only3
- Firm enough for intercourse.....4

33. How would you describe the FREQUENCY of your erections during the last 4 weeks?

(Circle one number)

- I NEVER had an erection when I wanted one..... 1
- I had an erection LESS THAN HALF the time I wanted one...2
- I had an erection ABOUT HALF the time I wanted one.....3
- I had an erection MORE THAN HALF the time I wanted one4

I had an erection WHENEVER I wanted one..... 5

34. How often have you awakened in the morning or night with an erection during the last 4 weeks?

(Circle one number)

- Never..... 1
- Less than once a week..... 2
- About once a week..... 3
- Several times a week..... 4
- Daily..... 5

35. During the last 4 weeks, how often have you had any sexual activity?

(Circle one number)

- Not at all..... 1
- Less than once a week..... 2
- About once a week..... 3
- Several times a week..... 4
- Daily..... 5

36. During the last 4 weeks, how often did you have sexual intercourse?

(Circle one number)

- Not at all..... 1
- Less than once a week..... 2
- About once a week..... 3
- Several times a week..... 4

Daily..... 5

37. Overall, how would you rate your ability to function sexually during the last 4 weeks?

(Circle one number)

Very poor..... 1

Poor..... 2

Fair..... 3

Good..... 4

Very good..... 5

38. How big a problem, if any, has each of the following been for you?

(Circle one number on each line)

	No	Very Small	Small	Moderate	Big
	<u>Problem</u>	<u>Problem</u>	<u>Problem</u>	<u>Problem</u>	<u>Problem</u>
a. Your level of sexual desire.....	0	1	2	3	4
b. Your ability to have an erection..	0	1	2	3	4
c. Your ability to reach an orgasm..	0	1	2	3	4

39. Overall, how big a problem has your sexual function or lack of sexual function been for you during the last 4 weeks?

(Circle one number)

No problem..... 1

Very small problem... ..2

Small problem..... 3

Moderate problem.....4

Big problem..... 5

HORMONAL FUNCTION

The next section is about your hormone function. Please consider **ONLY THE LAST 4 WEEKS.**

40. Over the last 4 weeks, how often have you experienced hot flashes?

(Circle one number)

More than once a day..... 1

About once a day..... 2

More than once a week..... 3

About once a week..... 4

Rarely or never..... 5

41. How often have you had breast tenderness during the last 4 weeks?

(Circle one number)

More than once a day..... 1

About once a day..... 2

More than once a week..... 3

About once a week..... 4

Rarely or never..... 5

42. During the last 4 weeks, how often have you felt depressed?

(Circle one number)

- More than once a day..... 1
- About once a day..... 2
- More than once a week..... 3
- About once a week..... 4
- Rarely or never..... 5

43. During the last 4 weeks, how often have you felt a lack of energy?

(Circle one number)

- More than once a day..... 1
- About once a day..... 2
- More than once a week..... 3
- About once a week..... 4
- Rarely or never..... 5

44. How much change in your weight have you experienced during the last 4 weeks, if any?

(Circle one number)

- Gained 10 pounds or more..... 1
- Gained less than 10 pounds..... 2
- No change in weight..... 3
- Lost less than 10 pounds..... 4
- Lost 10 pounds or more..... 5

45. How big a problem during the last 4 weeks, if any, has each of the following been for you?

(Circle one number on each line)

	No	Very Small	Small	Moderate	Big
	<u>Problem Problem Problem Problem Problem</u>				
a. Hot flashes.....	0	1	2	3	4
b. Breast tenderness/enlargement..	0	1	2	3	4
c. Loss of body hair.....	0	1	2	3	4
d. Feeling depressed.....	0	1	2	3	4
e. Lack of energy.....	0	1	2	3	4
f. Change in body weight.....	0	1	2	3	4

Overall Satisfaction

46. Overall, how satisfied are you with the treatment you received for your prostate cancer?

(Circle one number)

Extremely dissatisfied.....	1
Dissatisfied.....	2
Uncertain.....	3
Satisfied.....	4
Extremely satisfied.....	5

FINAL SECTION

These last questions are about your household and your general medical history. These items are very important for our research. Please answer honestly.

1a. With which of the following racial groups do you identify?

Caucasian/ White/ Non-Hispanic White.....	1
---	---

Black.....	2
Asian.....	3
Mixed (If mixed, select as many as apply from above).....	4

1b. How do you describe your ethnicity?

White/ European background (not Latino/Hispanic).....	1
Black/African-American (not Latino/Hispanic).....	2
Latino/Hispanic.....	3

If Latino/Hispanic, are you:

- | | |
|-------------------------------------|---|
| Mexican..... | a |
| Puerto Rican..... | b |
| Cuban..... | c |
| Colombian..... | d |
| Venezuelan..... | e |
| Argentinean..... | f |
| Nicaraguan..... | g |
| Other Caribbean country..... | h |
| Other South American country..... | i |
| Other Central American country..... | j |
| Other: Please specify _____ | k |

Asian/Oriental/Pacific Islander.....	4
American Indian/ Native Alaskan.....	5

Other: Please specify _____

6

2. Which of the following best describes your current relationship?

(Circle one number)

- | | |
|---|---|
| Living with spouse or partner..... | 1 |
| In a significant relationship, but not living together..... | 2 |
| Not in a significant relationship..... | 3 |

3. What is your current marital status?

(Circle one number)

- | | |
|--------------------|---|
| Never married..... | 1 |
| Married..... | 2 |
| Separated..... | 3 |
| Divorced..... | 4 |
| Widowed..... | 5 |

4. Are you now working at a paying job?

(Circle one number)

- | | |
|--------------------------------|---|
| Yes, full-time..... | 1 |
| Yes, part-time | 2 |
| No, but looking for a job..... | 3 |
| No, retired..... | 4 |

5. Do you currently smoke cigarettes?

(Circle one number)

No..... 1
Yes..... 2

6. Have you EVER had any of the following treatments for prostate cancer?

(Please circle YES or NO for every item and fill in the month/year during which therapy was started)

a. Radical prostatectomy (surgery to remove the prostate through the abdomen)

1= No (Skip to item b)

2=Yes, Month & year of surgery: ____/____

b. External beam radiation

1= No (Skip to item c)

2=Yes, Month & year completed: ____/____

c. Radioactive seed implantation (Brachytherapy)

1= No (Skip to item d)

2=Yes, Month & year of surgery: ____/____

d. Expectant Management (Watchful Waiting)

1= No (Skip to item e)

2=Yes, Month & year of diagnosis: ____/____

e. Orchiectomy (surgical removal of the testes)

1= No (Skip to item f)

2=Yes, Month & year of surgery: ____/____

f. Hormone deprivation therapy shots

1= No (Skip to item g)

2=Yes, Month & year of started: ____/____

g. Hormone pills (Flutamide, Nilandron, or Casodex)

1= No (Skip to item h)

2=Yes, Month & year of surgery: ____/____

h. Other

1= No

2=Yes, Specify: _____

7. Which therapy, if any, do you **currently** use to improve your erections?

(Circle one number)

- | | |
|---|---|
| Not at all..... | 0 |
| Vacuum erection device (Erect-aid)..... | 1 |
| Penile injection therapy..... | 2 |
| Penile prosthesis..... | 3 |
| Muse (intra-urethralalprostadil)..... | 4 |
| Viagra (Sildenafil)..... | 5 |
| Other _____ | 6 |

8. Have you **EVER** had any of the following medical conditions?

(Please circle YES or NO for every item)

	<u>No</u>	<u>Yes</u>
a. Diabetes.....	1	2
b. Heart attack, chest pain.....	1	2
c. Stroke.....	1	2
d. Amputation.....	1	2

e. Circulation problems in your legs or feet.....	1	2
f. Asthma, emphysema, or breathing problems.....	1	2
g. Stomach ulcer, irritable bowel.....	1	2
h. Kidney disease.....	1	2
i. Major depression.....	1	2
j. Seizures.....	1	2
k. Alcoholism or alcohol problem.....	1	2
l. Drug problems.....	1	2

9. How much school did you complete?

(Circle one number)

Grade school or less.....	1
Some high school or technical school.....	2
High school or technical school graduate	3
Some college.....	4
College graduate.....	5
Graduate or professional school after college...	6

10. What is your approximate annual combined household income?

(Circle one number)

Less than \$10,000.....	1
\$10,000 - \$30,000.....	2
\$30,001 - \$100,000.....	3
More than \$100,000.....	4

**APPENDIX IX
 INTERNATIONAL PROSTATE SYMPTOM SCORE (IPSS): Page 1 of 2**

Patient Name _____

Patient Number _____

(Please circle your response)

	Not at all	Less than 1 in 5 times	Less than half the time	About half the time	More than half the time	Almost always
1. Incomplete Emptying: Over the past month, how often have you had the sensation of not emptying your bladder completely, after you have urinated?	0	1	2	3	4	5
2. Frequency: Over the past month, how often have you had to urinate again in less than two hours after you finished urinating?	0	1	2	3	4	5
3. Intermittency: Over the past month, how often have you found you stopped and started again several times when you urinate?	0	1	2	3	4	5
4. Urgency: Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. Weak Stream: Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5
6. Straining: Over the past month, how often have you had to push to begin urination?	0	1	2	3	4	5
Note: Question 7 is scored differently						
7. Nocturia: Over the past month, <u>how many times</u> did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5

ADD YOUR TOTAL SCORE: _____

IPSS Questionnaire Page 2 of 2

	Delighted	Pleased	Satisfied	Mixed	Dissatisfied	Unhappy	Terrible
Quality of life due to urinary symptoms: If you were to spend the rest of your life with your urinary condition, just the way it is now, how would you feel about that?	0	1	2	3	4	5	6

 Patient Signature

 Physician Signature

 Date

 Date