Official Title: A Phase I/II study of salvage high-dose-rate Brachytherapy, ExternAl beam COmbined and short-term hormonal therapy for the treatment of Node-positive locally recurrent prostate cancer after prior definitive radiotherapy.

NCT Number: NCT03553602

BEACON – A phase I/II study of high-dose-rate **B**rachytherapy and **E**xternal beam and short-term **A**ndrogen deprivation **CO**mbined for the treatment of Men with Fluciclovine PET Pelvic **N**odal Uptake in locally recurrent prostate cancer after prior definitive radiotherapy

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: _____

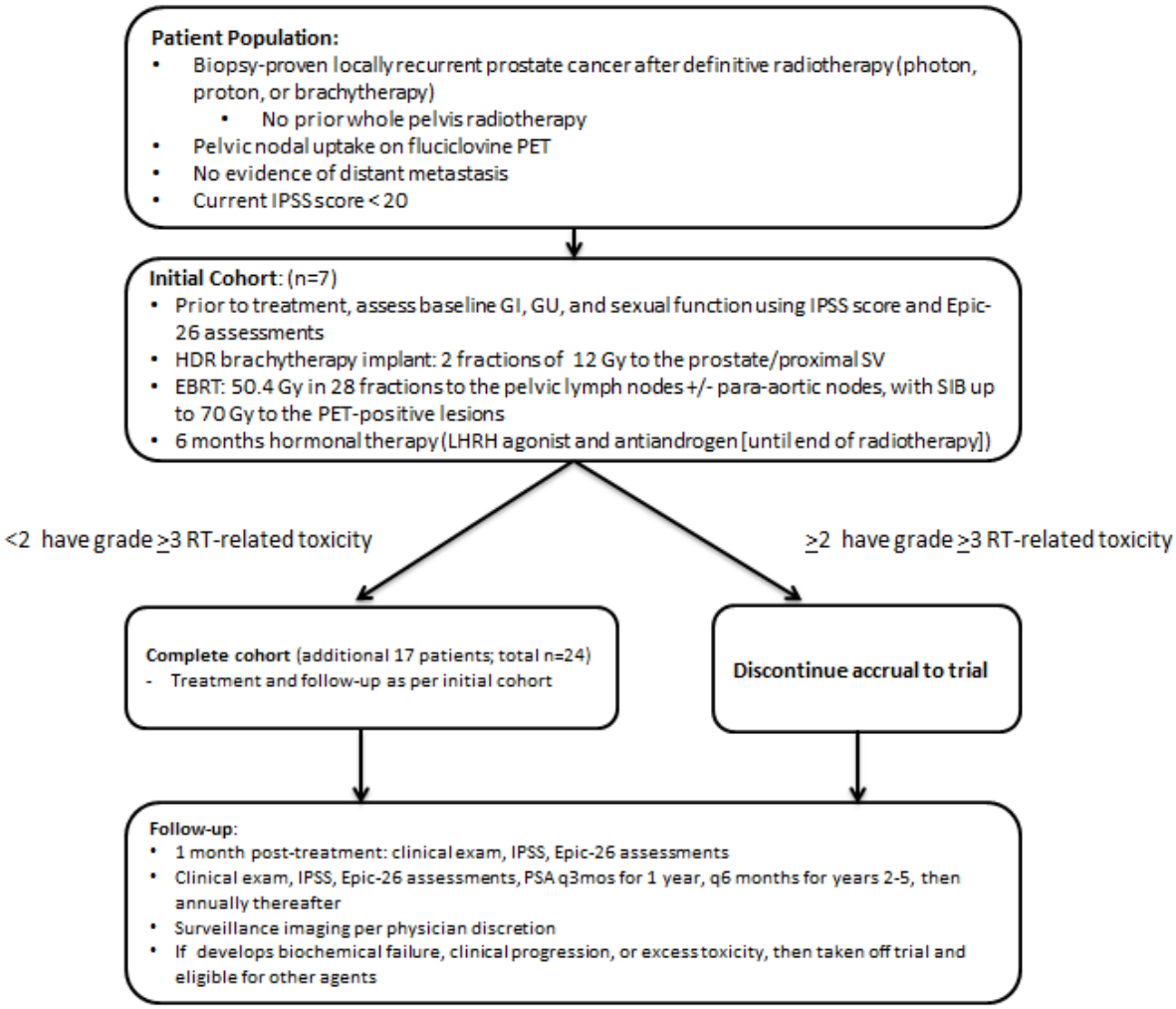
PI Signature: _____

Date: _____

STUDY SUMMARY	
Title	BEACON - A phase I/II study of high-dose-rate **B**rachytherapy and **E**xternal beam and short-term **A**ndrogen deprivation **CO**mbined for the treatment of Men with Fluciclovine PET Pelvic **N**odal Uptake in locally recurrent prostate cancer after prior definitive radiotherapy
Short Title	Combined salvage high dose rate brachytherapy, external beam and short-term hormonal therapy for local recurrent prostate cancer with fluciclovine PET uptake in pelvic nodes after radiotherapy
Protocol Number	***
Methodology	Phase I/II Non-randomized trial
Study Duration	5 years
Study Center(s)	Loyola University medical Center, Stritch School of Medicine, Loyola University Chicago
Objectives	1. To determine the 3 month grade ≥3 radiation-related genitourinary and gastrointestinal toxicity of this treatment approach (primary endpoint) 2. To describe the acute and late toxicity profile with this approach 3. To evaluate disease control efficacy outcomes (biochemical progression-free survival, local control, regional recurrence, cause-specific survival, overall survival, *etc.)* 4. To evaluate patient reported health related quality of life following this treatment approach 5. To describe the dosimetry in patients undergoing this approach
Number of Subjects	24

Diagnosis and Main Inclusion Criteria	• Biopsy-proven local recurrence of prostate adenocarcinoma (biopsy within 182 days) • Pathologic Fluciclovine uptake in pelvic lymph nodes without distant metastases • Current AUA International Prostate Symptom Score (IPSS) score <20 • Initial disease stage cT1-3a NX or N0 • Treated with prior definitive radiation therapy using any radiotherapeutic modality (prior whole pelvis RT ineligible)
Duration of Administration	2 brachytherapy implants, ~5-8 weeks of daily radiation, 6 months hormonal therapy
Statistical Methodology	This study is designed as a two stage Phase I/II, non-randomized study. In the first stage, 7 patients will be accrued. If there are 2 or more toxic responses in these 7 patients, the study will be stopped for safety reasons. Otherwise, 17 additional patients will be accrued for a total of 24 patients. Assuming that the true toxicity rate in the population is 10% or less, the study is powered to reject the null hypothesis that the toxicity rate is 33% or higher. A toxicity event is defined as an acute grade ≥3 radiation-related toxicity as assessed by the Common Toxicity Criteria for Adverse Events version 4. Standard non-parametric or parametric methods will be used to describe these patients' demographic and clinical information as well as their dosimetric information. The primary aim of the study is to estimate the toxicity rate of HDR brachytherapy among patients with recurrent prostate cancer. A one-tailed test for a difference in proportions will be used to determine whether the observed toxicity rate is lower than the hypothesized toxicity rate. The null hypothesis that the toxicity rate is 33% or higher will be rejected if more than 19 (non-toxic) responses are observed in 24 patients. When the true toxicity rate is 10.0%, this design yields a type I error rate of .046 and power of 81%. We also will describe the freedom from biochemical recurrence, relapse-free survival, local control, elsewhere-prostate control, freedom-from local failure, freedom from distant metastasis, freedom from hormonal therapy, disease-free survival, cause-specific survival, and overall survival.

Study Schema



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Abbreviations

ADT	androgen deprivation therapy
AE	adverse event
BR	biochemical recurrence
CRF	Case Report Form
CSS	cause specific survival
CTCAE v4.03	Common Toxicity Criteria for Adverse Events, version 4.03
CTV	clinical target volume
DM	distant metastasis
DFS	disease-free survival
DRE	digital rectal exam
DSMP	Data Safety Monitoring Plan
EBRT	external beam radiotherapy
EPC	elsewhere prostate control
EPF	elsewhere prostate failure
FDA	Food and Drug Administration
FFBR	freedom from biochemical recurrence
FFDM	freedom from distant metastasis
FFEPF	freedom from elsewhere prostate failure
FFHT	freedom from hormone therapy
FFLF	freedom from local failure
FFRF	freedom from regional failure
GCP	good clinical practice
GI	gastrointestinal
GS	Gleason score
GTV	gross tumor volume
GU	genitourinary
HDR	high-dose rate
HiFU	high intensity focused ultrasound
I-125	Iodine-125
IPSS	International Prostate Symptom Score
Ir-192	Iridium-192
IRB	Institutional Review Board
LC	local control
LDR	low-dose rate
LF	local failure
LRPC	locally recurrent prostate cancer
MP-MRI	multi-parametric MRI
OS	overall survival
PCA	patient controlled analgesia
Pd-103	Palladium-103

PSA	prostate specific antigen
PTV	planning treatment volume
RC	regional control
RF	regional failure
SAE	serious adverse event
UPR	unanticipated problems

1.0 BACKGROUND AND RATIONALE

1.1 *Disease Background and Lessons From Other Malignancies*

Prostate cancer is the most common cancer diagnosed in men and ranks second in cancer-related deaths among all men in the United States in 2012. In 2014, 177,489 men were diagnosed with prostate cancer, with 27,244 annual deaths.[1] Radiotherapy is a curative treatment option for these patients, yet a significant proportion of patients, particularly those with more aggressive disease, will go on to develop biochemical recurrence after curative treatment, and thereafter typically develop nodal and/or distant metastases from their progressed malignancy. For the patients who specifically present with nodal recurrence after curative radiotherapy, palliative androgen deprivation therapy (ADT) has been the primary treatment. However, ADT is not curative, and patients typically progress to castrate resistant disease over time and ultimately develop clinical progression of disease. In patients with a long life expectancy, identifying a way to salvage the patients who have local and regional disease alone could result in more durable disease outcomes and potential prevent morbidity and mortality.

In many disease sites, patients who had regional recurrence of disease are treated with aggressive salvage therapy in order to try for cure of the malignancy. An example of this includes patients who have mediastinal recurrence after SBRT or lobectomy for lung cancer. These patients are typically treated with definitive doses of concurrent chemoradiotherapy or sometimes with repeat SBRT in the setting of a local recurrence.[2–4] In head and neck cancer, patients are typically treated with regional chemoradiotherapy if they have had treatment of the primary but develop recurrence in the cervical lymph nodes. Additionally, reirradiation is an established treatment approach for patients with recurrence of disease.

Thus, an important question is whether the principles of all of these other malignancies can be applied to prostate cancer, as radiation has the potential to deliver curative treatment to regional disease in the definitive setting and brachytherapy can deliver curative treatment for local disease.[5–7]

Evidence for Salvage Local Therapy to the Prostate in Prostate Cancer

Even after initial treatment of prostate cancer with definitive radiation, biologic PSA failure can occur in up to 50% of patients.[8,9] However, in the patients who develop biochemical progression, up to 55% of those patients will have local recurrence alone, with the majority of those recurrences at the site of the dominant primary tumor.[10] For these men with local recurrence alone, treatment options include both palliative and definitive approaches. Often times, in this setting, men are treated with a palliative approach of continued PSA surveillance without intervention or androgen deprivation therapy (ADT). However, neither of these modalities is curative. Furthermore, the use of ADT is associated with side effects

of up to 80% of patients, including hot flashes, fatigue, gynecomastia and sexual dysfunction, leading to a 16.4% treatment cessation.[11,12]

Standard curative treatment options in the salvage setting after radiotherapy include salvage prostatectomy, cryosurgery, or brachytherapy to the prostate [13]

The decision of which salvage treatment modality to utilize is difficult, as there are no randomized data supporting one modality over another. Parekh, et al reported a systemic review comparing the oncologic benefits and toxicity profiles of radical prostatectomy, brachytherapy, cryotherapy, and high-intensity frequency ultrasound (HiFU) in the salvage setting after definitive external radiation. They found a similar rate of failure-free survival at 5 years across all salvage modalities, ranging from 52-56%. Salvage brachytherapy had a failure-free survival of 55.6%. Regarding toxicities, compared to the other modalities, brachytherapy had the lowest rate of incontinence (6.16%) and the second lowest rate of bladder neck stricture (7.48%). The rate of fistula formation was greatest in the HifU group, followed by brachytherapy, although this rate was still quite low at 3.09%. Prostatectomy carried the highest rates of incontinence (49.7%) and stricture (26.09%).[14]

1.2 *Salvage brachytherapy*

An additional treatment option in the setting of locally recurrent prostate cancer (LRPC) after definitive EBRT that has gained recent attention is the use of interstitial brachytherapy.[13] Brachytherapy is beneficial in the salvage setting due to its inherent ability to deliver a higher dose to a smaller area, thus sparing the previously irradiated surrounding normal tissues, and decreasing toxicity. This includes both low-dose-rate (LDR) and high-dose-rate (HDR) brachytherapy techniques, which have been studied in a variety of phase I/II trials and retrospective series, with the majority of available data reporting on LDR brachytherapy technique. Overall, the limited data on salvage brachytherapy show promising results, with both the achievement of biochemical disease control and the with treatment related toxicities, which are either comparable to or better than alternative salvage options.

There are limited retrospective data on the use of salvage LDR brachytherapy. Grado, et. al. describes a cohort of 46 men treated with LDR brachytherapy for LRPC after definitive EBRT, utilizing I-125 or Pd-103 radioactive seeds treating to 130-140Gy median matched peripheral dose. He reports a 5 year cause specific survival of 79%, a local control rate of 97% at latest follow-up with a low, 6% rate of severe urinary or rectal toxicities. [15] Another group, Beyer, et. al reported on a cohort of 17 men treated with LDR brachytherapy after definitive EBRT using I-125 or Pd-103, treated with a median peripheral dose of 97-100Gy. Their reported 5 year OS was 93% and freedom from biochemical relapse was 53%.[16] There is a current ongoing RTOG/NRG trial evaluating the use of salvage LDR brachytherapy in men treated with prior EBRT with initially diagnosed T1-T2c,

GS 2-7, PSA<20ng/mL, utilizing I-125 radioactive seeds treating to 140Gy minimum target dose or Pd-102 treating to minimum target dose of 120Gy.[17]

There is evidence supporting salvage HDR for patients with locally recurrent prostate cancer, primarily delivered to the whole prostate gland due to uncertainty about the geographic location of the local recurrence with older imaging techniques. Yamada, et al reported their results of a phase II study of 42 patients treating LRPC with salvage HDR brachytherapy after prior definitive external radiation. Their prescribed dose was 32Gy delivered in four fractions over 30 hours using a single implant. At a median follow-up up 26 months, they reported an actuarial 5-year biochemical recurrence free survival of 68.9% and a distant metastasis free survival of 81.5%. Regarding toxicities, acute genitourinary (GU) grade 1 and 2 toxicities rates were 38% and 40%, respectively, and 38% and 48% had late grade 1 or 2 GU toxicities. Only 1 of 42 patients developed late grade 3 toxicity of urinary incontinence, and 3 patients (7%) developed a late grade 3 urinary stricture corrected with urethral dilatation. Late grade 1-2 gastrointestinal (GI) toxicities occurred in 43% and 14% of patients, but there were no late grade 3+ GI toxicities.[18] Chen, et al reported a retrospective study of 52 patients receiving 36 Gy in six fractions given in two separate implants, 1 week apart. 5-year biochemical control was 51%, with a 2% incidence of grade 3 or higher late GU toxicity and no late grade 3+ GI toxicity.[19]

1.4 Rationale for Salvage Regional Therapy to the Pelvic Lymph Nodes in Prostate Cancer

There are emerging data that some patients who have recurrent disease in the pelvis may benefit from aggressive regional cancer-directed treatment with surgery or radiotherapy. Prospective studies have examined post-prostatectomy patients presenting with biochemical recurrence who underwent salvage pelvic lymph node dissection (PLND) of their [11C] choline PET/CT positive nodal disease. In a study by Rigatti et al 83.3% of patients with positive nodal metastases on [11C] choline PET/CT, had pathologic positive prostate cancer.[20] Following salvage lymph node dissection, a total of 41 patients (56.9%) had a subsequent biochemical response (defined as PSA <0.2). Ultimately, they found a 5-yr biochemical-free survival rate of 19% and concluded that salvage lymph node dissection in patients with nodal uptake on [11C] choline PET/CT can lead to a delay of clinical progression and a complete biochemical response can be achieved in a small proportion.

Another study by Suardi et al looked at the 5-yr results of patients following salvage PLND. They found that in their cohort of patients with a mean number of 29.5 nodes removed at the time of surgery, 47 patients (79.6%) had positive lymph nodes. Overall, 35 patients (59.3%) experienced biochemical response following surgery and this led to a 22.1% 8-yr biochemical-recurrence free survival. Therefore based on these results they concluded in patients with a small

volume of nodal recurrence a meaningful biochemical complete response after salvage LND can be achieved.[21]

With increasing use of imaging such as (18) F-fluciclovine PET/CT we are better able to detect occult nodal disease, even in those with low PSA levels.[22] Given that surgical series have shown improved biochemical response in patients with positive pelvic nodes detected on functional imaging, radiotherapy has a distinct advantage in that it can target gross disease as well as microscopic disease, and is non-invasive and an option for most patients.

The primary limitation to adding on radiotherapy to the pelvic nodes is the risks of reirradiation in areas of overlap. However, using modern sophisticated treatment planning methods such as intensity-modulated radiotherapy (IMRT) and volumetric arc therapy (VMAT), areas of overlap in critical structures can be minimized while delivering curative doses to target lesions.

1.5 *Rationale for current study*

Salvage regional and local radiation is frequently utilized across multiple disease sites in oncology for patients who have failed initial radiotherapy. However, in prostate cancer, due to the concern that nodal involvement is a manifestation of widespread distant disease, this type of approach has not typically been pursued. However, with newer imaging modalities such as fluciclovine PET, PSMA pet, and C11 PET, we are identifying nodal disease and excluding distant disease better than we ever have before. Thus, in this modern era regional control may translate to improved long-term biochemical control, and prevent the morbidity and mortality associated with clinical progression of biochemically recurrent prostate cancer

Thus, in patients who recur both in the prostate and in the pelvic lymph nodes, treating both with radiation could result in meaningful clinical efficacy for patients—similar to other disease sites. However, there are limited data exploring the feasibility and safety of this combination. Therefore, we propose this trial, combining salvage HDR brachytherapy to locally recurrent prostate cancer in the prostate and EBRT to the pelvis, both in the setting of short-term hormonal therapy, in patients who have developed local recurrence with regional pelvic nodal PET uptake after definitive radiation. We hypothesize that this approach can safely be performed without excess toxicity. Ultimately, we hope to use data from this Phase I/II study to create a multi-institutional phase III study in which we could analyze whether this treatment approach can improve disease control and survival outcomes when compared to standard palliative hormonal therapy.

2.0 STUDY OBJECTIVES

2.1 *Primary Objective*

2.1.1 To determine the incidence of acute grade ≥3 radiation-related genitourinary (GU) and gastrointestinal (GI) toxicity of this treatment approach

2.2 ***Secondary Objectives***

2.2.1 To describe the acute and late toxicity profile with this approach

2.2.2 To evaluate disease control efficacy outcomes (biochemical progression-free survival, local control, regional recurrence, cause-specific survival, overall survival, *etc.)*

2.2.3 To evaluate patient reported health related quality of life following this treatment approach

2.2.4 To describe the dosimetry in patients undergoing this approach

2.3 ***Endpoints***

2.3.1 Primary Endpoint:

2.3.1.1 3-month radiation-related grade ≥3 GU and GI toxicity as defined by Common Terminology Criteria for Adverse Events (CTCAE) v4.03 (Link available in Appendix A).

2.3.2 Secondary Endpoints:

2.3.2.1 All-grade acute and late toxicity as defined by CTCAE v4.03 criteria (see Appendix A)

2.3.2.2 Freedom from biochemical failure

2.3.2.3 Freedom from local failure

2.3.2.4 Freedom from elsewhere prostate failure

2.3.2.5 Freedom from regional failure

2.3.2.6 Freedom from distant metastasis

2.3.2.7 Freedom from hormone therapy

2.3.2.8 Disease-free survival.

2.3.2.9 Disease-specific survival

2.3.2.10 Overall Survival.

2.3.2.11 Patient reported Health-related quality of life as measured by the IPSS and EPIC-26 assessments (see Appendices B and C).

2.3.3 NCI CTCAE v4.03 toxicity criteria will be used to assess acute and late adverse events/toxicity endpoints (Appendix A). Disease specific endpoints will utilize a combination of laboratory values, multidisciplinary clinical decisions, radiographic imaging, functional imaging, and initiation of salvage therapy.

3.0 PATIENT ELIGIBILITY

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 *Inclusion Criteria*

3.1.1 Biopsy proven locally recurrent adenocarcinoma of the prostate after the completion of definitive radiation therapy for initially diagnosed prostate cancer.

3.1.1.1 Biopsy must be performed within 182 days of trial registration

3.1.1.2 Biopsy should be at least a standard sextant TRUS-guided biopsy

3.1.2 Initial cancer diagnosis that fits these specific criteria:

3.1.2.1 Stages cT1-T3a

3.1.2.2 Nx or N0

3.1.2.3 Mx or M0

3.1.3 Eligible initial definitive radiotherapy modalities include:

3.1.3.1 External beam radiotherapy, with photon or proton beam therapy

3.1.3.11 Conventional or moderately hypofractionated radiotherapy

3.1.3.12 Extremely hypofractionated external beam radiotherapy (Stereotactic body radiation therapy)

3.1.3.13 Treatment of the pelvic nodes with prior course of radiotherapy is not allowed.

3.1.3.14 No prior radiotherapy to the intended target for this course of radiotherapy other than prostate radiotherapy

3.1.3.2 Definitive Brachytherapy:

3.1.3.21 Low-dose rate

3.1.3.22 High-dose rate

3.1.3.23 Combined EBRT and brachytherapy

3.1.3.24 Treatment of the pelvic nodes with prior supplemental EBRT is not allowed.

3.1.4 Fluciclovine-positive pelvic nodes (as determined by an interpreting radiologist or nuclear medicine physician) in the pelvic nodal region (defined as the pelvic nodal regions up to the common iliac nodal region) without any evidence of lymph node involvement outside of this area or distant metastases

3.1.4.1 This will be based on the following imaging workup:

3.1.4.11 CT A/P or MRI Pelvis

3.1.4.12 Bone scan

3.1.4.13 Fluciclovine PET/CT

3.1.5 Candidate for hormonal therapy.

3.1.6 Current ECOG Performance status Scale 0-2 (Appendix D)

3.1.7 Current International Prostate Symptom Score (IPSS) < 20 (Appendix B)

3.1.8 Age $\geq$18

3.1.9 The patient must be medically suitable to receive general or spinal anesthesia.

3.1.10 AST, ALT, and alkaline phosphatase < 2 x upper institutional limit within 3 months of registration.

3.1.11 The patient must be able and willing to sign a study-specific written informed consent form before study entry.

3.2 ***Exclusion Criteria***

3.2.1 Preregistration GI or GU toxicity (for any reason) grade ≥ 3 as defined in CTCAE version 4.03. That is, grade ≥ 3 GU or GI toxicity after first course of radiotherapy

3.2.2 Treatment to a "whole pelvis" field with initial radiotherapy

3.2.3 Prior radiotherapy to the region of the body that is intended to be the target with the current course of RT.

3.2.4 Patients with distant metastases (such as to the bone, visceral organs, and lymph nodes other than the pelvic nodes including the common iliac nodes).

3.2.5 Patients receiving any other investigational agents.

3.2.6 Uncontrolled inter-current illness including, but not limited to, ongoing or active infection, severely symptomatic congestive heart failure, cardiac arrhythmia, recent myocardial infarction in last 6 months, or psychiatric illness/social situations that could limit compliance with study requirements.

3.2.7 Patients who have received chemotherapy or immunotherapy within one month prior to study enrollment, other than ADT.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

4.1 *Additional Mandatory Pretreatment Evaluations/Interventions*

4.1.1 Documentation of pharmacologic agents used by patient to treat urinary, bowel or erectile dysfunction.

4.1.2 Baseline Quality Of Life assessments, including IPSS, EPIC-26 assessments (Appendices B and C)

4.1.3 Eastern Cooperative Oncology Group (ECOG) performance assessment (Appendix D)

4.1.4 Any preoperative assessments needed for the brachytherapy implant operative procedure

4.1.5 AST, ALT, and alkaline phosphatase < 2 x upper institutional limit within 3 months of registration.

5.0 REGISTRATION PROCEDURES

Patients may not begin protocol treatment prior to registration. All patient registration will be centralized through the Department of Radiation Oncology Research Office. All

eligibility criteria must be met in order for a patient to be registered. To register a patient call (708) 216-2568, Monday-Friday 9:00am-5:00pm

5.1 *Access to Registration*

The Department of Radiation Oncology Research Office Study Coordinator, Beth Chiappetta, will coordinate all patient registrations. For any questions regarding patient registration please call: (708) 216-2568.

5.2 *Registering a Participant*

Obtain and file participant's signed and witnessed informed consent document in the Radiation Oncology Research Office.

5.3 *Other Relevant Clinical Trials*

At Loyola University Medical Center, there are no other clinical trials that will affect enrollment into this study, and this study will not affect enrollment into other clinical trials available at the institution.

6.0 RADIATION THERAPY

RT will start ~2 months after the start of ADT when possible (with RT starting earlier or later based on physician discretion). Either Brachytherapy or EBRT can be delivered first, or brachytherapy can be intercalated with EBRT course based on treating physician discretion.

6.1 Brachytherapy Implant procedure:

6.1.1 Patients will undergo 2 implants with 1 fraction of 12 Gy delivered with each implant, scheduled 1-2 weeks apart when possible, although longer or shorter intervals are acceptable with PI approval.

6.1.2 The implant procedure will be done under general anesthesia. The patient should be placed in the lithotomy position, generally after appropriate anesthesia. Then the perineum will be prepped and draped. A Foley catheter should be inserted for better visualization of the urethra and the bladder for the duration of the implant. Then, a single fiducial marker should be placed in the area of the target lesion as close to the lesion center as possible. Then, the brachytherapy loading catheters should be placed with the aid of a Liberty Medical template to allow for at least adequate coverage of the target lesion. Once adequate placement is confirmed by transrectal ultrasound (TRUS), the template will be sutured to the perineum. The patient's legs should be returned to a neutral position. After the patient is awoken from anesthesia and has stabilized, he will then be transferred to the Radiation Oncology Department for CT simulation, treatment planning, and radiation delivery.

6.1.3 Patient controlled analgesia (PCA), IV, or PO pain medications may be used during the post-operative period for pain control and throughout the day of the procedure as needed.

6.1.4 After completion of each of the brachytherapy treatments (upon completion of MRI and Treatment planning), all catheters should be removed.

6.2 Brachytherapy Treatment Planning

6.2.1 CT Simulation: CT simulation will be performed per standard protocol for evaluation of catheter position and treatment planning.

6.2.2 Diagnostic MRI: When possible, patient will undergo a diagnostic MRI after the implant with the catheters in position to aid in treatment planning. This will be registered to the CT image set.

6.2.3 Volume delineation: Target volumes and organs at risk (OARs) will be contoured using brachytherapy planning software. The patient's prior multi-parametric MRI and the fiducial placed during the procedure can be used to help define the target.

6.2.4 Source Loading: The HDR treatment will be delivered on the day of the catheter placement, after visual inspection of the catheters prior to delivery of the treatment is performed, and any necessary catheter adjustments are made prior to the treatment. If the catheters cannot be satisfactorily repositioned and cannot be corrected by a new plan with appropriate coverage of the target and sparing of the OARs, then we will consider postponing or aborting the treatment

6.3 Brachytherapy Volume Delineation:

6.3.1 Target Volume: The target volume will consist of the prostate and proximal seminal vesicles encompassing the area of local recurrence. The Planning Target Volume (PTV) will be defined as the GTV, plus a 0-5 mm margin, restricted to adjacent OARs applicable.

6.3.2 Critical Structures: Critical structures to be contoured include the bladder, Foley bulb, rectum, and urethra. Critical structures must be contoured on every CT slice that contains a target volume and in at least 3 slices (9 mm) above and below the CTV

6.4 Brachytherapy Dose Specifications:

6.4.1 For each brachytherapy procedure, the prescription dose to the PTV and GTV will be the highest deliverable dose up to 12 Gy in one fraction. Priority will be given to the normal tissue dose constraints over the

prescription dose. That is, the maximum dose will be that which is achievable without violating the normal tissue dose constraints. Priority will be given to GTV coverage first and then CTV coverage. If necessary, treatment to areas of the prostate/seminal vesicles judged to be at low risk of involvement can be omitted if it is felt that delivering full dose to these areas would result in unacceptable significant risk of toxicity.

In general, the volume of the GTV getting 100% of the prescription dose should be ≥95% when possible (V100 ≥ 95%) and, again, when possible, prescription dose should be delivered to at least 90% of the GTV (D90 ≥ 100%).The same coverage goals apply to the PTV, although this is less of a priority and can also be a lower dose than that prescribed to the GTV due to normal tissue constraints.

The normal tissue dose constraints will be as follows:

Bladder: D 0.1 cc ≤ 95%

D 1 cc ≤ 75%

V75% ≤ 1 cc

Foley Bulb: D 0.1 cc ≤ 80%

Rectum: D 1 cc ≤ 75%

V75% ≤ 1 cc

Urethra: Max point dose ≤ 120%

D 1 cc ≤ 110%

6.5 External Beam Radiotherapy Treatment Planning

6.5.1 Patients will undergo CT simulation prior to treatment planning.

6.5.2 The GTV will be any nodes in the pelvis (up to the common iliac nodes) felt by the treating physician to be involved with the cancer based on radiographic, pathologic, or fluciclovine PET. The prostate and SV will not be treated with EBRT.

6.5.3 The CTV_5040 will include the GTV with 5 mm margin as well as the pelvic lymph nodes as defined by RTOG guidelines. If patients have common iliac involvement or if the treating physician deems it necessary, the para-aortic nodes will be included in the CTV up to the level of the renal vessels. This CTV will be expanded by 0.6 cm to create PTV_5040. This will be treated to 5040 cGy in 28 fractions of 180 cGy.

6.5.4 A simultaneous integrated boost (SIB) to the involved nodes will be created. The GTV will receive up to 7000 cGy in 28 fraction of 250 cGy as part of this SIB.

6.5.5 Of note, normal tissue tolerances will typically take priority over total dose to the GTV, and PTV_5040. It is encouraged that the target volumes be restricted in areas of overlap with prior the prior RT based on treating physician discretion while ensuring adequate coverage of gross disease. This PTV will be the PTV_high_risk. For example, if the lower obturator nodes received ≥50 Gy with the prior radiotherapy plan, then in areas of this nodal region that do not have gross disease treatment can be omitted to avoid overlap between the current field and prior field in the rectum and bladder and femoral heads. If the treating physician and PI feel it is necessary to violate the normal tissue constraints, this is acceptable.

6.5.6 Normal Tissue Constraints:

Minimize areas of overlap with prior radiotherapy, particularly areas of cumulative doses > 80 Gy in the rectum, bladder, and femoral heads.

Bowel space: V55 < 1 cc, V60 < 0.1 cc.

Rectum: V70 < 10%, Max dose < 7350

Sigmoid: V70 < 10%, Max dose < 7350

Bladder: V70 < 10%, Max dose < 7350

Femoral Heads: V50 < 10%

Guidelines for PTV and GTV coverage (can be violated based on normal tissue goals): V100 > 95%, V95 > 99%

6.5.7 Daily CBCT will be performed setting up to the GTV lesions, with priority of coverage of these lesions. Second priority will be set up to the bony anatomy.

7.0 HORMONE THERAPY

Other than androgen deprivation therapy, patients must not receive other cancer-directed therapy (including standard fractionated radiotherapy, chemotherapy, biological therapy, and surgery) while on-study except at disease progression.

Standard institutional practices for neoadjuvant/concurrent and adjuvant short-term (6 months) androgen deprivation hormonal therapy will be used with the salvage

radiotherapy regimen. When possible, radiotherapy will begin approximately 2 months after the start of hormonal therapy. Some patients may have received prior hormonal therapy, but still require 6 months with the trial.

7.1 Anti-Androgen Therapy: Casodex (Bicalutamide)

For further information, consult the package insert.

7.1.1 Timing: Oral anti-androgen therapy will begin approximately within 10 days of the start of the LHRH agonist. It should continue until the completion of radiotherapy.

7.1.2 Bicalutamide 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, (+,-). Bicalutamide is a racemic mixture with the antiandrogen activity residing exclusively in the (-) or R-enantiomer. Bicalutamide has a long half-life compatible with once-daily dosing.

7.1.3 Supply: Commercially available.

7.1.5 Administration: Bicalutamide is administered orally at a dose of one 50 mg tablet per day. Bicalutamide will begin approximately within (before, same day as, or after) 10 days of the date of the first LHRH agonist administration, and continue until the end of the radiation therapy. Administration will be suspended only if there is an apparent or suspected reaction to the drug. During RT interruptions, bicalutamide will be continued.

7.1.6 Toxicity: Consult the package insert for comprehensive toxicity information. In animal experiments, birth defects (abnormal genitalia, hypospadias) were found in male offspring from female animals dosed with bicalutamide during pregnancy. Although offspring from male animals dosed with bicalutamide did not show any birth defects, patients enrolled in this trial are advised not to cause pregnancy nor donate sperm while receiving protocol therapy or during the first 3 months after cessation of therapy. The use of barrier contraceptives is advised. The most frequent adverse events reported among subjects receiving bicalutamide therapy are breast tenderness, breast swelling, and hot flashes. When bicalutamide 50 mg was given in combination with an LHRH analog, the LHRH analog adverse event profile predominated with a high incidence of hot flashes (53%) and relatively low incidences of gynecomastia (4.7%) and breast pain (3.2%). Other side effects include impotence and loss of libido, fatigue, and rarely, photosensitivity and diarrhea.

7.1.7 Dose Modifications: AST and ALT will be measured pretreatment and during the first week of EBRT. If the AST or ALT rises to $\geq$ 2x the institutional upper limit of normal, bicalutamide must be discontinued.

Elevated AST/ALT values to < 2x the institutional upper limit of normal are subject to dose modifications or discontinuation of anti-androgen at the discretion of the treating physician.

7.2 LHRH Agonist Therapy (leuprolide, goserelin)

For additional information, consult the package inserts.

7.3.1 Timing: The first LHRH administration will occur together with the start of anti-androgen treatment ~8 weeks prior to the start of RT. The total duration of LHRH therapy will be 6 months. The total administered duration as well as the specific agent used must be documented.

7.3.2 Description: LHRH agonists are long-acting analogs of the native LHRH peptide and are effective at reducing serum testosterone. Analogs approved by the FDA (or by Health Canada for Canadian institutions) can be used in this study.

7.3.3 Supply: Commercially available.

7.3.4 Storage: LHRH analogs should be stored as directed by the commercial supplier.

7.3.5 Administration: LHRH analogs are administered with a variety of techniques, including subcutaneous insertion of a solid plug in the abdominal wall (Zoladex), intramuscular injection (Lupron), subcutaneous injection (Eligard), or insertion of a long-acting cylinder that slowly releases the agent (Viadur). The manufacturer's instructions should be followed.

7.3.6 Toxicity: Consult the package insert for comprehensive toxicity information. Class-related toxicity is generally a manifestation of the mechanism of action and related to low testosterone levels. In the majority of patients testosterone levels increase above normal in 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 LHRH analogs is vasomotor hot flashes; edema, gynecomastia, bone pain, thrombosis, and gastrointestinal 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. Other side effects include impotence and loss of libido, weight gain, depression, dizziness, loss of bone density, anemia, increased thirst and urination, unusual taste in the mouth, skin redness or hives, pain at injection site, and muscle mass and strength loss, hair changes, penile length and testicular volume loss, increased cholesterol, hypertension, diabetes exacerbation, emotional lability, nausea, vomiting, and rarely, allergic generalized rash and difficulty breathing.

8.0 STUDY PROCEDURES

8.1 *Screening/Baseline Procedures*

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 3 months prior to registration unless otherwise stated. The screening procedures include:

8.1.1 Informed Consent

8.1.2 Medical History

Complete medical, surgical, and oncologic history including previous radiotherapy history.

8.1.3 Demographics

Age, gender, race, ethnicity.

8.1.4 Review subject eligibility criteria

8.1.5 Review previous and concomitant medications

8.1.6 Physical exam

8.1.7 Performance status

ECOG performance status evaluated prior to study entry according to Appendix D.

8.1.8 Adverse event assessment

Baseline adverse events from prior radiotherapy regimen will be assessed. See section 10.0 for adverse event monitoring and reporting.

8.1.9 Tumor assessment

To be performed with at least a PSA, DRE, multi-parametric MRI of the prostate, bone scan and functional imaging (Fluciclovine PET is encouraged).

8.1.10 Baseline quality of life assessment

Documentation of patient's AUA IPSS score, and completion of EPIC-26 instrument; documentation of medication used to treat urinary, bowel, or erectile dysfunction

8.1.11 Labs

AST, ALT, Alkaline Phosphatase, and any labs required for the brachytherapy procedure as part of usual care.

8.2 *Follow-up Procedures*

Patients will be followed as described in Section 8.3.

8.3 *Study Parameters*

	Pre-study	Start of EBRT	Week 4 post-treatment	Month 3 & 6	Month 12	Follow-up Q 6 months*	Time of Biochemical Recurrence
Informed Consent	X						
History and PE, including DRE	X		X	X	X	X	
Medication Assessment	X		X	X	X	X	
Performance Status	X		X	X	X	X	
Toxicity Assessment			X	X	X	X	
PSA	X			X	X	X	
Bone scan	X						X
MP-MRI	X						X¥
PET/CT	X						
IPSS score	X		X	X	X	X	
EPIC-26	X		X	X	X	X	
AST/ALT/ALK PHOS	X	X					

* Until disease progression, death, or follow up period is complete

¥If MP-MRI reveals any suspicious lesions, then biopsy is encouraged.
DRE – Digital Rectal Exam
PE – Physical Exam
MP – Multi-parametric
EBRT – External Beam Radiotherapy

8.4 *Removal of Subjects from Study*

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral, or administrative reasons. The reason(s) for discontinuation will be documented and may include:

8.4.1 Patient voluntarily withdraws prior to treatment;

8.4.2 Patient withdraws consent (termination of treatment and follow-up);

8.4.3 Patient is unable to comply with protocol requirements;

8.4.4 Patient develops interval co-morbidity that makes continuation in the protocol unsafe;

8.4.5 Treating physician(s) judge(s) the study would not be in the patient's best interest;

8.4.6 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;

8.4.7 If a research subject cannot be located to document survival after a period of 2 years; the subject may be considered "lost to follow-up". All attempts to contact the subject during the two years must be documented and approved by the Data Monitoring Committee.

9.0 MEASUREMENT OF EFFECT

9.1 *Antitumor Effect- Solid Tumors*

9.1.1 Definitions:

Evaluable for toxicity: All patients will be evaluable for toxicity immediately following brachytherapy.

Evaluable for disease control assessment: All patients with at least 2 follow-up PSAs will be evaluable for disease control. After brachytherapy, these patients will have their disease status classified according to the definitions stated below.

Biochemical (PSA) recurrence (BR): Based on RTOG Phoenix definition: an increase of the PSA level at least 2 ng/ml greater than the minimum level after therapy (REF: phoenix paper)

> All patients with BR should undergo at least MP-MRI of the prostate and bone scan. Biopsy of any suspicious lesions within the prostate gland on MP-MRI is encouraged.

Freedom from Biochemical (PSA) Recurrence (FFBR):
The time to PSA failure will be measured from the date of treatment to the date of a rise by 2 ng/mL or more above the nadir PSA. The time of failure will be the date of the first PSA that is 2 ng/mL or more above the lowest prior post-treatment PSA value. If the rise in PSA to > nadir + 2 occurs during the first 36 months followed by a subsequent non-hormonal induced PSA decrease, patients will **not** be considered PSA failures.

> As a benign "spike" or "bounce" in the PSA value has been described in as many as 35% of patients 12-36 months following brachytherapy, intervention for a PSA failure should be based on a positive prostate biopsy at least 24 months post-treatment and/or clinical evidence of
> distant relapse (i.e., bone scan, CT scan, etc).

Local Failure (LF): This rating will be assigned when there is biopsy-proven disease progression or recurrence at the lesion within the prostate treated with protocol therapy. Histologic criterion for local failure is the presence of prostatic carcinoma upon biopsy more than 2 years after the start of treatment. Residual carcinoma on biopsy should show minimal radiation effect and should be in clinical scenario of increasing PSA.

Local Control (LC): Absence of local failure. This will be assumed in patients with a controlled PSA and for those with PSA failure but no radiographic, clinical, or biopsy-proven disease at the lesion treated with protocol therapy.

Freedom from Local Failure (FFLF): The time to local progression will be measured from the date of treatment to the date of local failure.

Elsewhere Prostate Failure (EPF): This rating will be assigned when there is biopsy-proven disease progression/recurrence at outside the lesion treated with protocol therapy but within the prostate or seminal vesicles.

Elsewhere Prostate Control (EPC): Absence of EPF. Will be assumed in patients with a controlled PSA and in patients with PSA failure but no radiographic, clinical, or biopsy-proven disease at the site treated with protocol therapy.

Freedom from Elsewhere Prostate Failure (FFEPF): The time to elsewhere prostate failure will be measured from the date of treatment to the date of EPF.

Regional Failure (RF): Visible disease on imaging that occurs in lymph nodes within the usual regional spread pattern of prostate cancer

Regional Control (RC): Absence of regional/nodal recurrence.

Freedom from Regional Failure (FFRF): The time to regional failure will be measured from the date of treatment to the date of RF.

Distant Metastasis (DM): Visible disease on imaging that occurs elsewhere in the body including non-regional lymph nodes.

Freedom from Distant Metastasis (FFDM): The time to distant metastasis will be measured as the date of treatment to the date of DM.

Freedom from hormone therapy (FFHT): The time from the date of treatment to first administration of androgen deprivation therapy

Disease-free Survival (DFS): Defined as the duration of time from the date of completion of treatment to either BR, LF, EPF, RF, DM, or death.

Cause-specific Survival (CSS): Defined as the duration of time from the date of completion of treatment to death from prostate cancer.

Overall Survival (OS): Defined as the duration of time from the date of completion of treatment until death from any cause.

10.0 ADVERSE EFFECTS

10.1 *Data Safety Monitoring Plan*

This trial will be conducted in accordance with the Data Safety Monitoring Plan (DSMP) of the Cardinal Bernardin Cancer Center of Loyola University Medical Center.

10.2 *Adverse Event Monitoring*

All patients experiencing an adverse event, regardless of its relationship to study therapy, will be monitored until:

- The adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- Any abnormal laboratory or imaging results have returned to baseline;

- There is a satisfactory explanation other than the study treatment for the changes observed; or
- Death.

10.3 *Definitions*

10.3.1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

An adverse event will be determined to be radiation-related or non-radiation-related based on review by the treating physician and principle investigator.

10.3.2 Severity of Adverse Events

All non-hematologic adverse events will be graded according to the NCI CTCAE version 4.03. The link to CTCAE version 4.03 is available in Appendix A**.**

If no CTCAE grading is available, the severity of an AE is graded as follows:

Mild (grade 1): The event causes discomfort without disruption of normal daily activities

Moderate (grade 2): The event causes discomfort that affects normal daily activities or requires pharmacologic intervention to treat.

Severe (grade 3): The event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status or requires an operative procedure to treat.

Life-threatening (grade 4): The patient was at risk of death at the time of the event.

Fatal (grade 5): The event caused death.

10.3.3 Serious Adverse Events (SAE)

A serious adverse event is defined in regulatory terminology as any untoward medical occurrence that:

10.3.3.1 *Results in death.*

If death results from (progression of) the disease, the disease should be reported as the event itself.

10.3.3.2 *Is life-threatening.*

If the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

10.3.3.3 *Requires in-patient hospitalization or prolongation of existing hospitalization for ≥24 hours.*

10.3.3.4 *Results in persistent or significant disability or incapacity.*

10.3.3.5 *Is an important medical event.*

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".

10.4 *Steps to Determine if an Adverse Event Requires Expedited Reporting*

Step 1: Identify the type of AE using the NCI CTCAE v4.03.

Step 2: Grade the AE using CTCAE v4.03.

Step 3: Determine whether the AE is related to radiation therapy.

Attribution categories are as follows:

- Definite: The AE *is clearly related* to the radiation treatment.
- Probable: The AE *is likely related* to the radiation treatment.
- Possible: The AE *may be related to* the radiation treatment.
- Unrelated: The AE *is clearly NOT related* to the radiation treatment.

Step 4: Determine the prior experience of the AE.

Expected events are those that have been previously identified as resulting from administration of a similar radiotherapy treatment delivery. An AE is

considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- The current known AE's listed in this protocol.
- The consent form.
- The current Investigator's Brochure

10.5 *Exceptions to AE and SAE Definitions*

For the purposes of this study, neither the condition, prolonged hospitalization, nor surgery are reported as AEs or SAEs under the following circumstances:

- Hospitalization or prolonged hospitalization is for a diagnostic or elective surgical procedure for a preexisting condition. Surgery should not be reported as an outcome of an AE if the purpose of surgery is elective or diagnostic and the outcome is uneventful.

- Hospitalization or prolonged hospitalization is due to social reasons (e.g. awaiting transport home)

10.6 *Reporting Requirements for Adverse Events*

10.6.1 Expedited Reporting

- The Principal Investigator must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the administration of radiation therapy.

- The institutional officials must be notified within 10 business days of "any unanticipated problems involving risk to subjects or others" (UPR/UPIRSO).

  The following events meet the definition of UPR:

  1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.

  2. Any serious accidental or unintentional change to the Institutional Review Board (IRB) approved protocol that alters the level of risk.

  3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.

  4. Any new information (e.g., publication, safety monitoring report updated sponsor safety report), interim result or other finding that

indicates an unexpected change to the risk/benefit ratio for the research.

5. Any breach in confidentiality that may involve risk to the subject or others

6. Any complaint of a subject that indicates an unanticipated risk that cannot be resolved by the Principal Investigator.

10.6.2 Routine Reporting

All other adverse events such as those that are expected, or are unlikely or definitely not related to the study participation are to be reported annually as part of routine data submission.

10.7 *Stopping Rules*

Grade 3 or 4 toxicities will be evaluated by the primary investigator, and if radiation therapy is thought to contribute to the toxicity, the institutional officials will review it in detail. The nature of the toxicity will undergo a thorough review and determine if the study should be stopped for fear of excessive risk to future patients. Grade 5 toxicities (death) will be evaluated by the primary investigator and the institutional officials for review. If radiotherapy is felt to directly contribute to death then the institutional officials will determine if the study should be stopped.

11.0 DATA COLLECTION

11.1 *Online Database*

Data collection will utilize the REDCap database. REDCap is a secure web-based application designed for building and collecting data sets.

12.0 STATISTICAL CONSIDERATIONS

12.1 *Study Design/Study Endpoints*

The primary outcome will be any radiotherapy-related acute or chronic grade 3-5 toxicity as defined previously in the document. The study is designed as a two stage Phase II study as described below.

12.2 *Sample Size and Accrual*

Primary Aim

In this single-arm oncology trial evaluating the safety and efficacy of HDR brachytherapy for recurrent prostate cancer, one goal is to determine the toxicity

of single fraction focal treatment. Simon's two-stage [23] design is used to power this aim. The primary hypothesis is that the acceptable toxic response rate is less than or equal to 10.0% (p_1). The unacceptable toxic rate is set at 33% (p_o).

More concisely:

$$H_o: p_o \geq .33$$

$$H_A: p_1 \leq .10$$

The null hypothesis is that the unacceptable toxic response rate is at least 33%. This will be tested against a one-sided alternative that the toxicity rate is 10% or less.

In the first stage, 7 patients will be accrued. If there are 2 or more toxic responses (radiation-related acute grade >=3 GU or GI toxicity) in these 7 patients, the study will be stopped for safety reasons. Otherwise, 17 additional patients will be accrued for a total of 24 patients. Note that, under these conditions, the probability of stopping early is 73% if the toxic response rate is truly higher than 10.0%.

At the end of the second stage, the null hypothesis that the toxicity rate is 33% or higher will be rejected if more than 19 (non-toxic) responses are observed in 24 patients. When the true toxicity rate is 10.0%, this design yields a type I error rate of .046 and power of 81%.

Secondary Aim

We also will describe the freedom from biochemical recurrence, relapse-free survival, local control, elsewhere-prostate control, freedom-from local failure, freedom from distant metastasis, freedom from hormonal therapy, disease-free survival, cause-specific survival, and overall survival.

12.3 *Data Analyses Plans*

For this single group trial, summary frequencies and statistics will be provided for all relevant patient characteristics and clinical measures, including demographics (e.g., age, cancer stage, educational attainment, etc) as well as clinical outcomes (e.g., laboratory monitoring, adverse event monitoring, etc.). These include valid counts with percentages for categorical and ordinal variables as well as median with interquartile range or mean with standard deviation or standard error for continuous variables.

For the primary aim, a one-tailed one-sample test for proportions will be used to test whether the observed toxicity rate is lower than the hypothesized toxicity rate. For relapse-free survival, death will *not* be considered a competing event.

Instead, a two-sided one-sample log-rank test will be used to estimate the probability of being relapse free 24 months following treatment.

The instantaneous risk of relapse or death may be estimated as a function of age, cancer stage, and other covariates using semi-nonparametric Cox proportional hazards models. For these models, the number of covariates used for the adjustment will be determined by the number of events. Approximately one predictor for every 10 relapse or mortality events may be used to determine adjusted survival probabilities as described by Peduzzi et al. [24] For all Cox proportional hazards models, the proportional hazards assumption will be evaluated using Martingale residuals as described by Lin, Wei, and Ying.[25] If the proportional hazards assumption is violated, parametric accelerated failure time models may be used assuming the true underlying hazard distribution is identified.

13.0 STUDY MANAGEMENT

13.1 *Conflict of Interest*

13.1.1 Any investigator who has a conflict of interest (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must properly disclose this conflict of interest per the University conflict of interest policy. All investigators will follow the institutional conflict of interest policy.

13.2 *IRB Approval and Consent*

13.2.1 It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

13.2.2 In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirements, and should adhere to Good Clinical Practice (GCP) guidelines and to ethical principles that are outlined in the Declaration of Helsinki.

13.2.3 Prior to recruitment and enrollment onto this study, the patient will be provided with a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the Food and Drug Administration (FDA) regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participation in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

13.2.4 Prior to a patient's participation in the study, the written informed consent form should be signed and personally dated by the patient and by the individual who conducted the informed consent discussion.

13.3 *Informed Consent*

The investigator is responsible for ensuring that no patient participates in any study-related examination or activity before that patient has given informed consent. The informed consent will be provided both through the written informed consent document and through verbal review of all information contained therein. Information provided in this way is to include potential benefits, aims of the study, potential harms or side effects and methods of the study. The patient will be given opportunity to ask questions about any aspect of the information and will be given time to review the information on their own. The patient may, after having been provided with this detailed written and verbal information, provide written consent. The patient will then be provided a copy of the executed informed consent for their reference. The patient is free to withdraw consent at any time and for any reason. The only consequence of consent withdrawal is that the patient is no longer able to participate in the study.

13.4 *Protected Health Information*

In accordance with the Health Information Portability and Accountability Act (HIPAA), patients who have provided written informed consent must also sign a subject authorization to release medical information to the study sponsor and allow a regulatory authority, or the IRB access to the subject's medical information relevant to the study. This authorization may be combined with the informed consent form in accordance with the institutional practice.

13.5 *Data Management and Monitoring/Auditing*

Study-specific instructions regarding the entry and submission of data using CRFs is available through the Radiation Oncology Research Office. The Internal and Affiliate Data Compliance Policies of the Cardinal Bernardin Cancer Center's DMC will be strictly enforced.

13.5.1 Study Chart

In addition to the regular hospital chart, a separate patient folder will be kept which will include the patient's signed and dated informed consent document.

13.5.2 Patient Registration (please refer to Sections 3.0 & 5.0)

Please refer to Sections 3.0 & 5.0 for more extensive instructions. Before a patient can be treated on study, please complete and submit the following

items to confirm patient eligibility and receive a subject registration number:

1. Eligibility CRF.
2. Signed and dated informed consent document.
3. Clinical, laboratory and imaging workup, as well as baseline quality of life assessment

13.6 *Data Submission Guidelines*

Once a subject is confirmed and enrolled to the study, the following CRFs should be submitted to the Radiation Oncology Research Office. Specific timeframes will be defined according to the study parameters table (Section 8.3), but in general, on-study data should be submitted no later than 5 business days after the date of subject registration. Accrual on a trial may be suspended if data is not submitted within 90 days after the data's due date (as it is defined by the protocol)

13.6.1 All patient data will be entered into our brachytherapy REDCap database, including baseline information, all follow-up information, including but not limited to disease control parameters as detailed in section 9.0, and patient reported and physician graded toxicity. Additionally, adverse events and survival status will be reported in the database as well.

13.7 *Adherence to the Protocol*

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

13.7.1 Emergency Modifications

Investigators may implement a deviation from, or a change of the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within five (5) business days of making the change.

13.7.2 Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs

- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants
- Has damaged the scientific integrity of the data collected for the study
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, state laws, or university policies

If a deviation or violation occurs without prior approval from the Principal Investigator, please follow the guidelines below:

Protocol Deviations: Personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Study personnel should report violations within one (1) week of the Primary Investigator becoming aware of the event.

13.8 *Amendments to the Protocol*

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

13.9 *Record Retention*

Study documentation includes all data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. Study documents should be kept on file until three (3) years after the completion and final study report of this investigational study.

13.10 *Obligations of Investigators*

The Principal Investigator is responsible for the conduct of the clinical trial at this site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator will be responsible for assuring all the required data will be collected and entered into the REDCap database. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all data entry will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

13.11 *Study recruitment*

Electronic letters describing the trial design and eligibility criteria will be sent to regional physicians treating prostate cancer in order to notify them and their patients of potential of this trial. An initial consultation with the treating Loyola radiation oncologist will be required.

References:

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Appendix A:

NCI-CTCAE version 4.03 available at

(http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-4_QuickReference_5x7.pdf)

Appendix B:

AUA SYMPTOM SCORE (AUASS)

PATIENT NAME: _____ **TODAY'S DATE:** _____

(Circle One Number on Each Line)	Not at All	Less Than 1 Time in 5	LessThan Half the Time	About Half the Time	More Than Half the Time	Almost Always
Over the past month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
During the past month or so, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5
During the past month or so, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
During the past month or so, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
During the past month or so, how often have you had a weak urinary stream?	0	1	2	3	4	5
During the past month or so, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
	None	1 Time	2 Times	3 Times	4 Times	5 or More Times
Over the past month, how many times per night 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 the score for each number above and write the total in the space to the right. **TOTAL:** _____

SYMPTOM SCORE: 1-7 (Mild) 8-19 (Moderate) 20-35 (Severe)

QUALITY OF LIFE (QOL)

	Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
How would you feel if you had to live with your urinary condition the way it is now, no better, no worse, for the rest of your life?	0	1	2	3	4	5	6

Appendix C:

The following questions are about urinary, bowel, sexual, and hormonal concerns:

1. Over the PAST 4 WEEKS, how often have you leaked urine?

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

2. Which of the following best describes your urinary control DURING THE LAST 4 WEEKS? (Please select only one)

1 ☐ No urinary control whatsoever
2 ☐ Frequent dribbling
3 ☐ Occasional dribbling
4 ☐ Total control

3. How many pads or adult diapers per day did you usually use to control leakage DURING THE LAST 4 WEEKS? (Please select only one)

1 ☐ None
2 ☐ One pad per day
3 ☐ Two pads per day
4 ☐ Three or more pads per day

4. How big a problem, if any, has each of the following been for you DURING THE LAST 4 WEEKS? (Please select one answer in each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a. Dripping or leaking urine.....	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
b. Pain or burning on urination.....	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
c. Bleeding with urination.....	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
d. Weak urine stream or incomplete emptying..	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
e. Need to urinate frequently.....	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

5. Overall, how big a problem has your urinary function been for you DURING THE LAST 4 WEEKS? (Please select only one)

1 ☐ No Problem
2 ☐ Very small Problem
3 ☐ Small Problem
4 ☐ Moderate Problem
5 ☐ Big Problem

6. How big a problem, if any, has each of the following been for you? (Select one answer in each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a. Urgency to have a bowel movement.....	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
b. Increased frequency of bowel movements...	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
c. Losing control of your stools.....	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
d. Bloody stools.....	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
e. Abdominal/ Pelvic/ Rectal pain.....	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

7. Overall, how big a problem have your bowel habits been for you DURING THE LAST 4 WEEKS? (Please select only one)

1 ☐ No Problem
2 ☐ Very small Problem
3 ☐ Small Problem
4 ☐ Moderate Problem
5 ☐ Big Problem

8. How would you rate each of the following DURING THE LAST 4 WEEKS? (Please select only one)

	Very Poor to None	Poor	Fair	Good	Very Good
a. Your ability to have an erection?.....	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
b. Your ability to reach orgasm (climax)?.....	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

9. How would you describe the usual QUALITY of your erections DURING THE LAST 4 WEEKS? (Please select only one)

1 ☐ None at all
2 ☐ Not firm enough for any sexual activity
3 ☐ Firm enough for masturbation and foreplay only
4 ☐ Firm enough for intercourse

10. How would you describe the FREQUENCY of your erections DURING THE LAST 4 WEEKS? (Please select only one)

1 ☐ I NEVER had an erection when I wanted one
2 ☐ I had an erection LESS THAN HALF the time I wanted one
3 ☐ I had an erection ABOUT HALF the time I wanted one
4 ☐ I had an erection MORE THAN HALF the time I wanted one
5 ☐ I had an erection WHENEVER I wanted one

11. Overall, how would you rate your ability to function sexually DURING THE LAST 4 WEEKS? (Please select only one)

1 ☐ Very poor
2 ☐ Poor
3 ☐ Fair
4 ☐ Good
5 ☐ Very good

12. Overall, how big a problem has your sexual function or lack of sexual function been for you DURING THE LAST 4 WEEKS? (Please select only one)

1 ☐ No Problem
2 ☐ Very small Problem
3 ☐ Small Problem
4 ☐ Moderate Problem
5 ☐ Big Problem

13. How big a problem DURING THE LAST 4 WEEKS, if any, has each of the following been for you?

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a. Hot flashes.....	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
b. Breast tenderness/enlargement.....	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
c. Feeling depressed.....	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
d. Lack of energy.....	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
e. Change in body weight.....	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

Appendix D:

ECOG Performance Scale

ECOG PERFORMANCE STATUS*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:

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