Ultra-hypofractionated, image-guided, intensity-modulated radiation therapy in combination with brachytherapy for clinically localized, intermediate risk prostate cancer

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

OneMSK Sites	
Manhattan	All Protocol Activities
Basking Ridge	Follow Up Only
Commack	Follow Up Only
Rockville Centre	Follow Up Only
Westchester	Follow Up Only
Nassau	Follow Up Only

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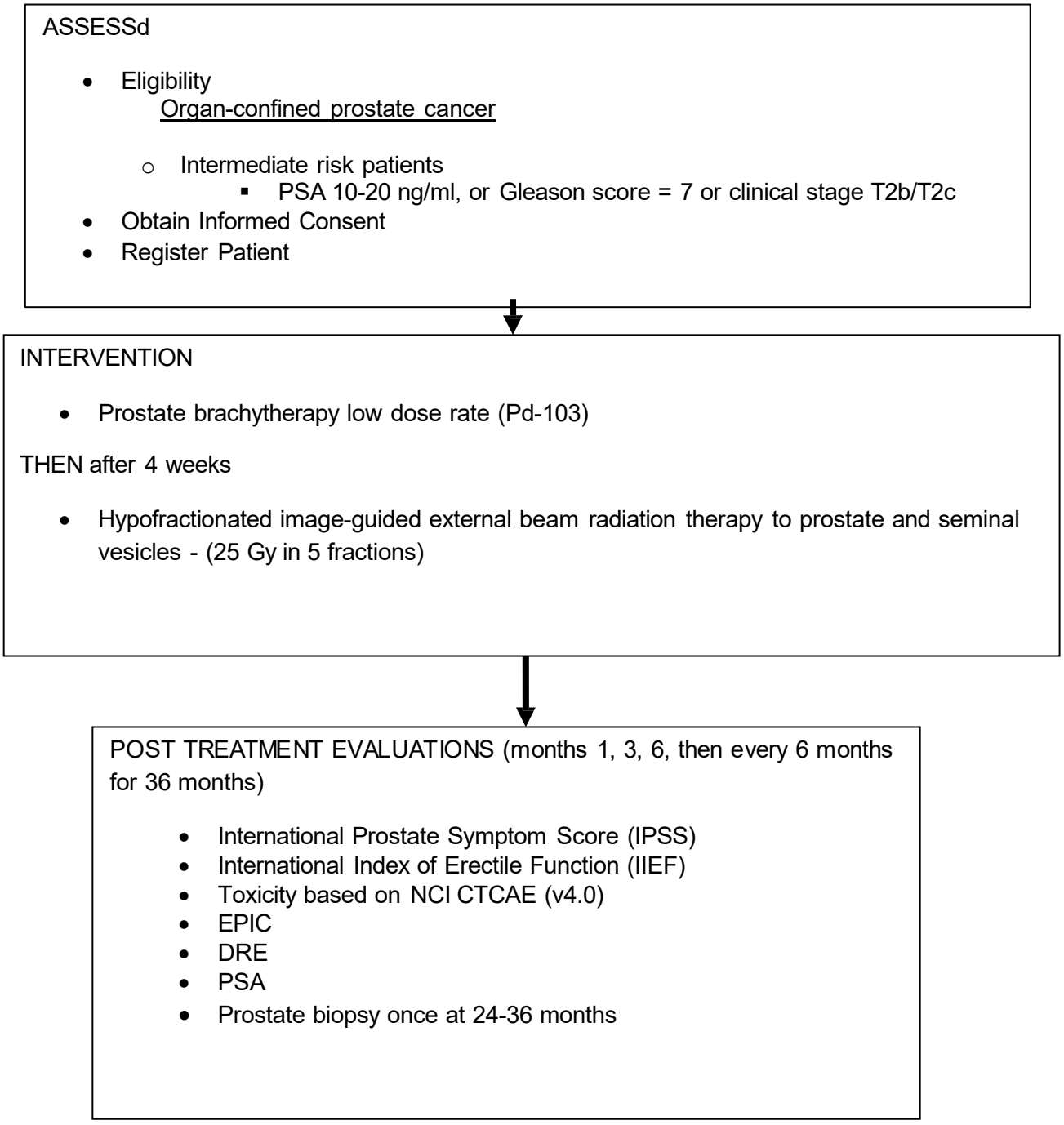
1.0 PROTOCOL SUMMARY AND/OR SCHEMA



This study will enroll participants with localized, intermediate risk prostate cancer (T2b/c or Gleason 7 or PSA 10-20 ng/mL). Patients enrolled in the study will undergo low dose rate (LDR) prostate brachytherapy using Pd-103 followed approximately 4 weeks later with hypofractionated image-guided external beam radiation therapy (25Gy in 5 fractions; 5Gy x 5 fractions every other day) to the prostate and seminal vesicles. Both brachytherapy as well as external beam will be performed according to our current standards of practice using the same equipment, techniques, and treatment planning procedures.

Patients will be followed post-treatment at 1, 3, 6 (+/- 4 weeks) and every 6 months (+/- 4 weeks) thereafter until 36 months. During the post-treatment followup, patients will be evaluated for urinary, bowel/rectal and sexual toxicity. Toxicity will be assessed according to CTCAE v4.0, IPSS, IIEF and EPIC validated instruments. Baseline measures of these domains will be obtained prior to treatment at the time of enrollment. Serum PSA levels will be drawn on the same schedule as clinical followup. Post-treatment prostate biopsies will be obtained once between 24-36 months post-treatment to evaluate pathologic response to therapy.

The total number of participants enrolled will be 45 to be accrued in approximately 3 years.

2.1 OBJECTIVES AND SCIENTIFIC AIMS

.Primary Objective:

- Evaluate late urinary toxicity as assessed by CTCAE v4.0 at approximately 12 months of hypofractionated radiation therapy in combination with brachytherapy for the treatment of intermediate risk prostate cancer.

Secondary Objectives:

- Assess IPSS changes
- Evaluate late rectal and erectile toxicity
- Evaluate PSA relapse-free survival
- Evaluate local control based on post-treatment prostate biopsy at 24-36 months

3.0 BACKGROUND AND RATIONALE

The goal of radiation therapy for prostate cancer is to deliver high doses to the target (i.e. prostate +/- seminal vesicles) while reducing dose to normal surrounding tissue. Brachytherapy is a particularly effective way to achieve this goal as radiation sources are placed directly into target tissue with very rapid dose fall off. Dose escalation strategies include a combination of brachytherapy and conformal external beam radiation therapy and outcomes using this treatment appear to compare favorably to external beam radiation therapy approaches. [1, 2] Typical external beam radiation therapy courses in this setting are 4-5 weeks of daily radiotherapy using fraction sizes of 1.8-2 Gy. An emerging body of literature suggests that hypofractionated schedules may

be superior to conventional fractionation schemes in terms of both tumor control and toxicity for prostate cancer. The use of hypofractionated radiation therapy combined with brachytherapy has not been investigated; however in addition to a potential radiobiologic benefit, this approach may also be more convenient for patients and reduce the burden of therapy as well.

Radiobiology of Prostate Cancer

To maximize the therapeutic ratio, a fractionation schedule of radiotherapy should optimize the dose per fraction with respect to the sensitivity of the tumor relative to normal tissues. In most cancers, adjacent late responding tissues are more sensitive to increased fraction dose than tumors. For this reason most radiation regimens utilize small daily fraction sizes (1.8-2Gy) to maximize the therapeutic ratio. Radiobiologic research however suggests that prostate cancer may not optimally respond to these standard fraction sizes and may benefit from deliver of higher doses per fraction.

The suggestion that prostate cancer may have a unique radiobiology was suggested by Brenner and Hall who observed that biochemical control was similar for 70 Gy given in 1-2Gy fractions and I-125 brachytherapy using a prescription dose of 144Gy. [3] Subsequent studies by others have demonstrated that the α/β (ratio of intrinsic radiosensitivity to repair capacity) for prostate cancer ranges between 1.5-1.85. [4, 5] This low α/β ratio predicts a greater capacity for repair between fractions, with an accompanying greater relative sparing with smaller fraction sizes. Therefore, a higher dose per fraction may be particularly beneficial for prostate cancer cell death.

BED calculations for current study:

Using the BED equation:

$$\mathbf{nd(1+d/\ \alpha/\beta)}$$

where:
n=number of fractions
d=dose per fraction
α/β= 1.5, 3, and 10

	45Gy/1.8Gy	**25Gy/5Gy**
BED (α/β=1.5)	99	108
BED (α/β=3)	72	68
BED (α/β=10)	53	37.5

Similar BEDs are expected to be isoeffective or have the same biologic effect. An α/β of 10 is assumed for early-responding tissues and 3 for late-responding tissues. An α/β of 1.5 is used for prostate cancer).

Safety of Hypofractionation for Prostate Cancer

Hypofractionated radiotherapy for prostate cancer has been studied since the 1960s. [6] Early experience using 36Gy delivered in 6Gy fractions reported minimal acute and long term toxicity with this approach. This early experience utilized relatively crude planning techniques as compared with more modern approaches, however despite this; hypofractionated therapy

appeared to be safe. Since this early experience, many subsequent studies have demonstrated that toxicity of hypofractionated regimens using brachytherapy or external beam radiation appear at least comparable if not more favorable to conventionally fractionated regimens. [7, 8, 9, 10] Katz et al reported toxicity outcomes in patients receiving up to 36.25Gy in 7.25Gy fractions at a median followup of 60 months. In this group, acute grade 3-4 toxicity was noted in 0% and late grade 3 urinary toxicity in 2% of patients. In a study by Bhattasali et al, 228 predominantly low- and intermediate-risk prostate cancer patients were treated with 35-36.25Gy in 5 fractions. [11] With a minimum followup of 24months, EPIC urinary and bowel bother scores were transiently elevated at 1 month following treatment and declined to near-baseline by 2 years. Moderate to severe urinary or bowel bother was noted in 8% and 2.5% of patients respectively. Several studies are ongoing to determine the optimal duration and dose using hypofractionated regimens. Our group is currently conducting a dose escalation hypofractionated approach (IRB protocol #09-035), which will help establish the optimal dose delivered in a 5 fraction regimen.

Brachytherapy combined with external beam radiation therapy for prostate cancer

LDR brachytherapy combined with conventional external beam radiotherapy for patients with intermediate risk prostate cancer addresses not only a need for dose escalation but also addresses concerns of dose coverage of extracapsular disease extension and is an accepted standard of care approach for intermediate risk disease (www.nccn.org). Long term outcomes using either LDR brachytherapy have been reported.[12, 13, 15] We recently reported 7-year PSA relapse-free survival of 92% for patients with intermediate risk prostate cancer treated with prostate brachytherapy combined with 50.4Gy of external beam radiotherapy. [14] With regards to toxicity, acute and late grade 3 or higher GU toxicity was noted in 2.3% and 3.1% respectively. Grade 2 late GU and GI toxicity were 21% and 4% respectively.

Although hypofractionated regimens for the definitive treatment of prostate cancer are considered part of a standard approach, the integration of a hypofractionated approach combined with brachytherapy has not yet been studied. To date, two ongoing studies are examining this in a Phase I setting (www.clinicaltrials.gov). The purpose of this study is to establish the toxicity associated with brachytherapy combined with hypofractionated radiation therapy.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

Patients enrolled in this study will undergo LDR prostate brachytherapy followed approximately 4 weeks later with hypofractionated, image-guided intensity modulated radiation therapy to a dose of 25Gy in 5 fractions of 5Gy delivered every other day. Radiobiologically, as indicated in the BED calculations in Section 3, the dose of hypofractionated radiotherapy is expected to have less acute toxicity and equivalent late toxicity as standard fractionated treatment. Both brachytherapy and hypofractionated external beam radiation therapy will be delivered using the same equipment, techniques and treatment planning procedures as currently practiced at MSKCC.

Patients will be followed post-treatment at 1, 3, 6 (+/- 4 weeks) and every 6 months (+/- 4 weeks) thereafter until 36 months. During the post-treatment followup, patients will be evaluated for urinary, bowel/rectal, and sexual toxicity. Baseline measures of these domains will be obtained prior to treatment. The primary endpoint will be urinary toxicity as assessed by CTCAE v4.0 at 12 months. Bowel and sexual function will also be assessed at followup as

secondary endpoints. Serum PSA levels will be drawn on the same schedule as clinical followup. Post-treatment prostate biopsies will be obtained once at 24-36 months post-treatment to evaluate pathologic response to therapy.

4.3 Intervention

Patients enrolled in this study will undergo LDR prostate brachytherapy followed approximately 4 weeks later with hypofractionated, image-guided intensity modulated radiation therapy to a dose of 25Gy in 5 fractions of 5Gy delivered every other day. Both brachytherapy and hypofractionated external beam radiation therapy will be delivered using the same equipment, techniques and treatment planning procedures as currently practiced at MSKCC.

Patients will undergo a prostate brachytherapy procedure as currently practiced at MSKCC. The prescribed radiation dose will remain our standard prescription dose of 100Gy using Pd-103. The dose constraints for brachytherapy treatment planning will remain the same. For patients with large prostate volumes (>60cc), cytoreductive androgen deprivation will be allowed for a maximum duration of 6 months prior to brachytherapy. For patients with a prostate volume between 50-60ccs, homone therapy will be at the discretion of the physician.

Approximately 4 weeks following brachytherapy, the patient will undergo hypofractionated image-guided intensity modulated radiation therapy (25Gy in 5 fractions delivered every other day). Dose constraints for treatment planning are presented in Section 9 and were modeled based on our current standard guidelines for hypofractionated therapy and our constraints for standard fractionation external beam radiotherapy post-brachytherapy. Radiation therapy will be delivered every other day, Monday through Friday until 5 treatments are completed. Daily target motion will be monitored and corrected, using fiducial markers implanted at the time of brachytherapy as per the routine standard in our Department for patients who receive external beam radiotherapy.

5.1 THERAPEUTIC/DIAGNOSTIC AGENTS

No investigational devices, new agents, new equipment, nor new radiation techniques will be used in the protocol. The brachytherapy procedure is performed using our current standard procedures, equipment, treatment planning and dosing. A detailed step-by-step account of the procedures for simulation, planning and treatment are detailed in Section 9.0. Radiation will be delivered every other day, Monday through Friday until 5 treatments are completed. Daily target motion will be monitored and corrected using fiducial markers implanted at the time of brachytherapy. All treatment is given on an outpatient basis.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

Intermediate risk prostate cancer patients will be eligible for this study. Intermediate risk grouping will be assessed per NCCN guidelines as:

- Pathologically-proven diagnosis of prostate adenocarcinoma

- PSA 10-20ng/mL or
- Gleason =7 or
- Clinical stage T2b/c

Additionally, patients will be required to meet the following criteria

- Age ≥18
- KPS≥70
- Prostate volume ≤ 60cc (cytoreductive androgen deprivation therapy prior to brachytherapy of ≤ 6 months duration will be allowed to achieve this goal). For patients with a prostate volume between 50-60ccs, hormone therapy will be at the discretion of the physician.
- International Prostate Symptom Score ≤15

6.3 Subject Exclusion Criteria

- Prior prostate surgery (including TURP)
- Prior history of chronic prostatitis or urethral stricture
- Inflammatory bowel disease
- Prior history of pelvic radiotherapy
- Unable to give informed consent
- Metastatic disease.

7.0 RECRUITMENT PLAN

Potential research subjects will be identified by a member of the patient"s treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC). If the investigator is a member of the treatment team, s/he will screen their patient"s medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

We expect that the study population will be fully representative of the range of patients seen at MSKCC without exclusion to age (≥ 18 years) or ethnic background. Given the limited patient number to be entered onto the study, no specific outreach efforts are planned. It is expected that approximately 5 potentially eligible patients will be seen weekly in consultation amongst the 4 consenting physicians. If stopping rules are not met, it is anticipated that this protocol will take approximately 3 years to accrue.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of

the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

8.1 PRETREATMENT EVALUATION

- MSKCC prostate biopsy or pathology review of prostate biopsy material
- Full history and physical examination *within 6 weeks of enrollment*
- *Digital Rectal Exam (DRE) within 3 months of enrollment*
- Pretreatment PSA *within 6 weeks of enrollment*
- Pelvic MRI or CT (MRI preferred) *within 6 months of enrollment*
- Bone scan if there is suspicion of bone metastases *within 6 months of enrollment*
- Baseline IPSS, IIEF, and EPIC survey *within 6 weeks of enrollment* (*repeated within 4 weeks prior to brachytherapy for patients undergoing cytoreductive hormone therapy*)

9.1 TREATMENT/INTERVENTION PLAN

Brachytherapy Procedure (all steps as per current departmental procedure):

- Patients undergo general anesthesia for outpatient interstitial brachytherapy
- Transrectal guidance of implanted fiducial markers into the prostate
- Transrectal ultrasound utilized to guide needles/seeds into the prostate gland
    - LDR procedure:
        - Pd103 radioactive seeds inserted according to intraoperative plan using MICK applicator and ultrasound/fluoroscopic guidance.
        - Prescription dose= 100Gy to the prostate
        - Postoperative CT-based dosimetry following procedure
- Following completion of brachytherapy treatment, Foley catheter removal and voiding trial
- Discharge home

Hypofractionated Radiation Therapy:

Simulation (all steps as per current departmental procedure):

- Approximately 2 weeks following interstitial brachytherapy, a simulation for hypofractionated external beam radiation therapy will take place.
- A bowel preparation will be performed the night before simulation.
- Patients will be instructed to maintain a full bladder during simulation and treatment.
- Patients will be supine and positioned in a thermoplastic mold.
- A Foley and rectal catheter will be placed for simulation only.
- CT images will be obtained as per existing department protocols and used for treatment planning purposes.

Treatment Planning:

- The gross tumor volume (GTV) will be defined as the prostate gland.
- The clinical tumor volume (CTV) will be defined as the prostate and seminal vesicles.

- The planning target volume (PTV) will be defined as a non-uniform expansion around the CTV: 0.5cm in all directions except posteriorly at the rectal interface which will be 0.3cm.
- Normal tissues to be contoured include:
  - Bladder wall (inner and outer)
  - Rectal wall (inner and outer)
  - Urethra
  - Bilateral femoral heads/neck
  - Large bowel
  - Small bowel

- The following dose constraints will be used for treatment planning:

PTV D95% [Dose to 95% volume]		90%
Rectal wall max	106% of Rx	2650 cGy
Rectal wall D1cc [Dose to 1cc]	103% of Rx	2575 cGy
Rectal wall mean dose		1550 cGy
Urethra max	100% of Rx	2500 cGy
Urethra D1cc [Dose to 1cc]	90% of Rx	2250 cGy
Bladder wall max	106% of Rx	2650 cGy
Bladder wall D5cc [Dose to 5cc]	103% of Rx	2575 cGy
Bladder wall mean dose		1650 cGy
Small/Large Bowel max		2500/2650 cGy
Femur max		2000 cGy

Treatment delivery:

- Patients will be treated every other day (as per standard hypofractionated treatment) Monday- Friday
- Patient set up will be according to simulation parameters (immobilization, full bladder)
- Daily pretreatment in-room imaging will localize target as per department routine
- Any necessary translational shifts will be made and approved prior to treatment.
- Treatment will be delivered as per routine.

10.1 EVALUATION DURING TREATMENT/INTERVENTION

Patients who cannot meet the necessary dosimetric constraints will not be eligible for participation in the study and will be withdrawn from study, since they will already be enrolled at this time

- There will be at least one status check visit during the course of hypofractionated external beam radiotherapy.
- Participants will have clinic follow-up visits at 1, 3, and 6 months (+/- 4wks) posttreatment.
- Then at 6 month intervals (+/- 4wks) post treatment.
- Follow-up scheduling is based on the last day of hypofractionated treatment.
- At each followup visit, patients will undergo standard DRE and serum PSA. Patients will also be asked to complete sexual quality of life questionnaires (EPIC), and urinary and rectal quality of life questionnaires (IPSS and IIEF), which will be captured per standard of care and be assessed for toxicity using CTCAE 4.0. If patient is unable to come in for a followup appointment, a telephone followup will suffice and the PSA and DRE will be deferred. IPSS, IIEF, and EPIC questionnaires can be completed over the phone or sent to patients via mail, fax, or electronic mail by the physician or the physician"s office assistant if the patient is unable to come in for a follow-up appointment. If the patient cannot be reached by phone or prefer to complete the questionnaires personally, the questionnaires will be sent via mail, fax or electronic mail. The questionnaires sent directly to patientsmust be blank forms with no patient identifiers, only study ID numbers.If questionnaires are sent via mail, the patient must be provided with a pre-filled business enevelop that will allow patients to return it with no expense. Patients must also have the option of returning questionnaires by electronic mail or fax. If a patient is unable to come in for a follow-up appointment or complete the questionnaires over the phone, the method by which questionnaires are sent to patients and the method by which questionnaires are returned will be determined based on the patient"s preference or if they are unable to be contacted by phone, the contact information on file for the patient as some patients may not have access to a phone, fax or electronic mail.A repeat prostate biopsy will be completed between months 24 and 36 for pathologic response assessment. This is a standard assessment tool.

After 36 months, patients will be encouraged and have the option of continued followup through our Prostate Survivorship Clinic for as long as feasible. Continued quality of life (IPSS, IIEF) and disease (PSA, DRE) assessment will be as per standard practice in the Prostate Survivorship Clinic.

	Prior to brachy therapy start unless otherwise indicated	During RT	Month 1, 3, and 6 (+/- 4 weeks)	Month 12-36 (every 6 months +/- 4 weeks)	Once during year 2-3
Pathology review	X				
History and PE	X[1]				
DRE	X[1]		X	X	
PSA	X[1]		X	X	
Prostate biopsy	X (if				X

	applicable)				
Pelvic MRI or CT	X[2]				
Bone scan (if deemed necessary)	X[2]				
Toxicity assessment (CTCAE 4.0, IPSS, IIEF, EPIC)	X[1, 3, 4]		X[4]	X[4]	X[4]
LDR Brachytherapy		X (Once)			
IG-IMRT (every other day)		X			
Status check		X (Once)			
Followup			X	X	X

1 Within 6 weeks of enrollment; comorbidities are captured at baseline

2 Within 6 months of enrollment

3 IPSS, IIEF, and EPIC repeated within 4 weeks prior to brachytherapy for patients undergoing cytoreductive hormone therapy

4 Standard of care IIEF and IPSS Questionnaires will be used

11.1 TOXICITIES/SIDE EFFECTS

The toxicities associated with radiation therapy to the prostate can be classified as either early (occurring within 90 days of treatment) or late (after 90 days). For the purpose of this study, the CTCAE v4.0 will be used as the primary endpoint to assess treatment-related toxicity. We expect that based on our prior studies[14, 15], 20% of patients of patients with have grade 2 or higher GU toxicity. The treatment will be considered to have significantly higher toxicity if ≥40% of patients in this study have ≥grade 2 at 12 months.

DEFINITIONS:

1. Adverse Event (AE)
    a. An AE is defined by the GCP (Guide to Good Clinical Practice) as any undesirable experience occurring to a subject during a clinical trial, whether or not it is considered related to the investigational product(s).
2. Serious Adverse Event (SAE)
    a. An SAE is an adverse experience that:
        i. Is fatal or life-threatening
        ii. Is disabling
        iii. Results in hospitalization or prolongation of hospitalization
        iv. Results in a congenital anomaly or occurrence of malignancy
        v. Any urinary or rectal toxicity that is grade 3 or higher
3. Unexpected Adverse Event (UAE)
    a. A UAE is an experience not previously reported (in nature, severity, or incidence) in the current Investigator"s Brochure or general investigational plan.

Toxicities associated with radiation treatment include increased urinary frequency, urgency, weak stream, and nocturia. Other toxicities that may be related to radiation are fatigue, dysuria, hematuria, erectile dysfunction, urinary obstruction (due to edema or stricture), proctitis, bowel

injury or secondary cancers. Urinary, rectal, and erectile toxicities will be measured using IPSS, CTCAE v 4.0, and EPIC validated instruments (appendix).

The probability of severe (grade 3 or higher) urinary or rectal toxicity is expected to be ≤5% which is currently observed rate of severe toxicity reported using standard combined brachytherapy and conventionally fractionated external beam radiation at MSKCC. [14]

To insure that unexpected significant toxicity is identified as early as possible with this treatment, we will observe the first 6 patients for a minimum of 3 months before enrolling any additional patients. If more than one patient has a grade 3 toxicity, we will wait 12 months before resuming accrual. If 4 or more patients of the first 6 patients have grade 3 or higher toxicity at 3 months we will terminate the study.

Evaluation of SAE:
Review of the patient record including treatment dosimetry (brachytherapy and external beam radiation) will be undertaken by the principal investigator and investigators of the study. The PI in conjunction with the investigators may decide to continue the protocol without modification, discontinue the study altogether, or modify the protocol prior to enrolling more patients pending the results of the review based on the criteria state in section 14.0.

12.1 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The primary objective of this study is to assess toxicity associated with combined LDR brachytherapy and hypofractionated radiation therapy for intermediate risk prostate cancer at 12 months via CTCAE v4.0. Both acute and late toxicity associated with radiation therapy will be evaluated in a fashion similar to those used in prior studies of radiation therapy in prostate cancer patients. All grade 2 or higher toxicities will be evaluated and attributed to radiation therapy or not. Evaluation will be carried out prior to treatment to serve as a baseline. During each subsequent followup visit, patients will be asked to complete questionnaires (IPSS, IIEF, and EPIC) and asked about symptoms. The primary expected toxicities are genitourinary and gastrointestinal (rectal). Sexual function assessment is included but is not considered an SAE.

The following instruments will be used in the evaluation of toxicities:
Appendix 1-NCI CTCAE v 4.0
Appendix 2-International Prostate Symptom Score
Appendix 3-International Index of Erectile Function-6
Appendix 4- EPIC urinary, bowel and sexual domain

a. NCI Common Toxicity Criteria. The NCI scales are simple to complete and provide a means for assessing patient symptoms. Only the CTCAE v 4.0 will be used in toxicity grading.

b. International prostate symptom score index (IPSS). This validated and widely used instrument is a patient administered questionnaire that is currently part of routine patient evaluation. The IPSS index is a seven item questionnaire designed to assess urinary functioning, specifically urinary frequency, nocturia, weak urinary stream, hesitancy, intermittence, incomplete emptying, and urgency. Questions are rated on a six point Likert scale with higher scores indicating more difficulty in urinary functioning. This measure demonstrated a high internal consistency (Cronbach's alpha = 0.84) with excellent test-retest reliability (r = 0.92). The IPSS index also demonstrated good validity with strong associations with other measures of urinary difficulties. The IPSS index also showed appropriate sensitivity to change. This measure has been widely used

in clinical practice and research protocols (See appendix 2). It will be used as part of pretreatment evaluation and in follow-up and will be summarized using descriptive statistics.

c. Sexual function will be assessed before treatment and at each follow up appointment with the International Index of Erectile Function (IIEF) (See appendix 3). The IIEF short form is a 6 item questionnaire which measures participants' responses on a 5 and 6 point Likert Scale. A principal components analysis identified five distinct factors (i.e., erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall sexual satisfaction). The IIEF demonstrated a high degree of internal consistency for the overall scale (Cronbach's alpha = 0.91) as well as the five factors (Cronbach's alpha values greater than 0.73). Test-retest reliability was also strong for the total score and the five domain scores. The IIEF demonstrated adequate construct validity, and all five domains showed a high degree of sensitivity and specificity to the effects of treatment. Significant (P values = 0.0001) changes between baseline and post-treatment scores were observed across all five domains in the treatment responder cohort as compared to the nonresponder cohort in the original validation study. This questionnaire takes approximately 3 minutes to complete.

d. EPIC is a 32 item questionnaire for patients with prostate cancer assessing urinary function, bowel habits, sexual function, hormonal function, and overall satisfaction. The grading scales vary per question (in some cases, a high score indicates more severe symptoms, but in others a lower score indicates worse symptoms).

We plan to use the assessment scores which are part of our standard followup to describe trends in scores over time. We plan to summarize and present all 14 scores for the EPIC at all 9 assessment times. Only the total scores from the IPSS and IIEF will be used. We will consider a clinically significant change if there is a change of 5 or more in the total score of the IPSS, IIEF, or EPIC questionnaires.

Post-treatment PSA relapse-free survival will be studied using serial PSA measurements after treatment as detailed above. PSA relapse free survival will be defined as the time from the end of radiation therapy to PSA relapse or last follow-up. PSA relapse will be defined according to the revised American Society for Therapeutic Radiology and Oncology consensus and Houston definition (absolute nadir plus 2ng/mL dated at the time of failure).

Post-treatment biopsy results will be analyzed using the current MSKCC institutional standard developed and published by the Departments of Pathology and Radiation Oncology. Specifically, pathologic response rates from biopsies will be divided into 3 categories:

1) Prostate adenocarcinoma without typical radiation-induced changes
2) Prostate adenocarcinoma with radiation-induced changes
3) No evidence of prostate adenocarcinoma

13.1 CRITERIA FOR REMOVAL FROM STUDY

The study subject will be removed from the study for any of the following reasons after review by the PI:

1) A change in patient"s medical status unrelated to study treatment results in patient unable to comply with protocol
2) Patient is unable to meet dosimetric constraints in Section 9
3) Patient is unable to comply with followup schedule.
4) Patient request.
5) If ineligible for protocol as designated by Section 6, the patient will be removed.

14.0 BIOSTATISTICS

The primary objective is to assess the toxicity of hypofractionated radiation therapy in combination with brachytherapy for the treatment of intermediate risk prostate cancer. To set up a decision rule we will focus on the CTCAE v 4.0 (see appendix) grade 2 or higher GU toxicity observed at the 1-year follow-up time (+/- 4 weeks). We will enroll 40 evaluable patients, and if 12 or more patients have a CTCAE v4.0 grade 2 or higher toxicity at 1 year, this treatment will be deemed too toxic and the study will be stopped. Otherwise it will be declared safe. This decision rule has the following probabilities of declaring treatment unsafe

True toxicity rate	0.15	0.20	0.25	0.30	0.35	0.40	0.45
Probability of declaring unsafe	1%	8%	28%	56%	79%	92.9%	98.2%

Patients who withdraw, die due to reasons other than toxicity, or fail to provide the 1-year CTCAE v4.0 GU toxicity status will be replaced by new patients. To this end we may need to enroll an additional 4 patients (10%).

For the secondary objectives, all toxicities will be tabulated by type and grade. Post-treatment PSA values will be summarized numerically and graphically. Time to PSA relapse will be analyzed by Kaplan-Meier estimation. The pathologic response rates at 24-36 months will be calculated as sample proportion based on the available patients and confidence intervals will be provided. Erectile function evaluated by IIEF will be summarized by descriptive statistics.

It is expected that it will take approximately 3 years to accrue the total of 45 patients.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.3 Randomization

NA

16.1 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into CRDB. Source documentation will be available to support the computerized patient record. All research material from this study will be handled with the same confidentiality as patient"s other medical data. Data collected will include toxicity data (CTCAE v 4.0 toxicity, IPSS, IIEF, and EPIC) as well as PSA and biopsy information.

16.2 Quality Assurance

An assigned RSA will work with the PI to ensure proper adherence to the protocol, eligibility verification, informed consent, and data accuracy.

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and accuracy of evaluations and followup will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of twice per year or more frequently if indicated.

16.3 Data and Safety Monitoring

Eligibility of patients will be verified with the principal investigator. Only the designated investigators can obtain informed consent.

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center"s Research Council and Institutional Review Board (see section 16.2).

During the protocol development and review process, each protocol will be assessed for the level of risk and the degree of required monitoring. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) is reviewed and monitoring procedures are established at the time of protocol activation.

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the

new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: *http://cancertrials.nci.nih.gov/researchers/dsm/index.html*. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb2.mskcc.org/irb/index.htm*.

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17.1 PROTECTION OF HUMAN SUBJECTS

Patient Confidentiality: Patient/subject privacy and confidentiality will be maintained according to MSKCC guidelines and all data derived from this study will be kept in a secure database. All data and results will be anonymously reported with regard to individual subjects.

Voluntary nature of the study: Subjects will be made aware of the voluntary nature of the study as part of the informed consent process. They will be allowed to withdraw participation at any time without the risk of alteration in the quality of their medical care.

17.2 Privacy

MSKCC"s Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant"s last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 „Reporting of Serious Adverse Events", the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant"s condition
    - Indication if the participant remains on the study

- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

For IND/IDE protocols: The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

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20.0 APPENDICES

Appendix 1. NCI CTCAE version 4.0
Appendix 2. International Prostate Symptom Score
Appendix 3. International Index of Erectile function- Item 6
Appendix 4. EPIC urinary, bowel and sexual domains