NRG ONCOLOGY

RTOG 0526

A PROSPECTIVE PHASE II TRIAL OF TRANSPERINEAL ULTRASOUND-GUIDED BRACHYTHERAPY FOR LOCALLY RECURRENT PROSTATE ADENOCARCINOMA FOLLOWING EXTERNAL BEAM RADIOTHERAPY

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INSTITUTION MUST BE CREDENTIALED BEFORE ENROLLING PATIENTS ON THIS STUDY
(See Section 5.0)

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SCHEMA (3/10/10)

<table>
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<td>1 T E G S I R</td>
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*96 patients will receive either 125-iodine (I-125) 140 Gy minimum target dose or 103-palladium (Pd-103) 120 Gy minimum target dose. Treatment must begin within 8 weeks of registration.

Institutions must be credentialed by the Radiological Physics Center (RPC) for prostate brachytherapy and must demonstrate the ability to perform electronic data submission to the Image-Guided Therapy Center (ITC). (See Section 5.0 for details.)

Patient Population: (See Section 3.0 for Eligibility) (3/10/10)

- Biopsy-documented locally recurrent prostatic adenocarcinoma > 30 months after the completion of EBRT, biopsied ≤ 180 days prior to registration and with diagnosis confirmed by central pathology review (see Section 10.0).
- Disease-related characteristics at initial diagnosis (i.e., prior to EBRT) that fit the following criteria (Appendix III):
  - Stages T1-T2c, Gleason scores 2-7, and PSA ≤ 20 ng/mL
  - Baseline serum PSA value < 10 ng/mL performed with an FDA-approved assay (e.g., Abbott, Hybritech) within 8 weeks prior to registration. PSA should not be performed within 10 days of a prior prostate biopsy, and if the patient has been started on hormonal therapy, the PSA should be performed within 8 weeks prior to the commencement of hormonal therapy.

Required Sample Size: 96
1. Is there biopsy-documented locally recurrent prostatic adenocarcinoma > 30 months after the completion of EBRT, biopsied ≤ 180 days prior to registration?

2. Do disease-related characteristics at initial diagnosis (i.e., prior to EBRT) fit the following criteria?
   - Stages T1-T2c, Gleason scores 2-7, and PSA ≤ 20 ng/mL

3. Was there a history/physical with digital rectal examination of the prostate within 8 weeks prior to registration?

4. Were lymph nodes negative by imaging (pelvic ± abdominal CT or MR), or by nodal dissection (laparoscopy or laparotomy) within 8 weeks prior to registration?

5. Was there evidence of bone metastases (M0) on bone scan within 8 weeks prior to registration?

6. What is the Zubrod Performance Status?

7. What is the American Urological Association Symptom Index Score (AUA BPH)? Note: The use of alpha blockers is permitted when evaluating lower urinary tract symptoms, i.e., the AUA score with the patient on alpha blockers is acceptable.

8. Is this patient currently taking an alpha blocker?

9. Was the baseline serum PSA value < 10 ng/mL performed with an FDA-approved assay (e.g., Abbott, Hybritech) within 8 weeks prior to registration or 8 weeks prior to start of hormonal therapy and not within 10 days of a prior prostate biopsy?

10. Was the prostate volume as measured by transrectal ultrasound (TRUS) ≤ 45 cc or has pubic arch interference been ruled out?

11. Is the patient suitable for spinal or general anesthesia?

12. Has the patient had prior invasive cancer (except non-melanoma skin cancer) or hematological (e.g., acute leukemia, aggressive lymphoma, myeloma) malignancy within the past 3 years? (Previous diagnosis of low-grade lymphoma or chronic lymphocytic leukemia is allowed.)

13. Has the patient had prior EBRT to the prostate such that the minimum dose to the prostate exceeded 78 Gy (2 Gy fractions) or 79.8 Gy (1.9 Gy fractions) or 81 Gy (1.8 Gy fractions)?

14. Does the patient have gastrointestinal (GI) or genitourinary (GU) toxicity at the time of registration (for any reason) grade ≥ 2 as defined in Common Terminology Criteria for Adverse Events (CTCAE) version 3.0?
15. Does the patient have any of the following severe, active comorbidities?
   - Unstable angina and/or decompensated congestive heart failure
   - Myocardial infarction within the last 6 months
   - Bacterial or fungal infection requiring intravenous antibiotics at the time of registration
   - Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration
   - Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects
   - Acquired immune deficiency syndrome (AIDS) based upon current CDC definition

16. Does the patient have clinical and/or radiologic evidence of extraprostatic disease at initial diagnosis (i.e., prior to EBRT) or at time of local recurrence (i.e., prior to study registration)?

17. Has the patient had any of the following prior therapies?
   - Transurethral resection of the prostate (TURP)
   - Radionuclide (permanent or temporary implantation) prostate brachytherapy
   - Prostatectomy or prostatic cryosurgery
   - HIFU (high-intensity focused ultrasound)
   - Bilateral orchietomy
   - Chemotherapy for prostatic carcinoma

18. Did the patient start an LHRH agonist less than 2 months or more than 6 months before registration?

19. Did androgen suppression therapy (neoadjuvant, concurrent, or adjuvant) at the time of initial diagnosis and the initial external RT exceed a duration of 8 months?

(Y) If yes, is there documented evidence of a normal serum testosterone?
The following questions will be asked at study Registration:

1. Name of institutional person registering this case?
2. Has the Eligibility Checklist (above) been completed?
3. Is the patient eligible for this study?
4. Date the study-specific Consent Form was signed (must be prior to study entry).
5. Patient’s Initials (First Middle Last)
6. Verifying Physician
7. Patient’s ID Number
8. Date of Birth
9. Race
10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)
11. Gender
12. Patient’s Country of Residence
13. Zip Code (U.S. Residents)
14. Patient’s Insurance Status
15. Will any component of the patient’s care be given at a military or VA facility?
16. Calendar Base Date
17. Registration/randomization date: This date will be populated automatically.

(Continued on the next page)
(Y/N) 18. Have you obtained the patient's consent for his or her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer?

(Y/N) 19. Have you obtained the patient's consent for his or her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

(Y/N) 20. Have you obtained the patient's consent to allow someone from this institution to contact him or her in the future to take part in more research?

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by ______________________________  Date  ____________________

(Continued on the next page)
RTOG Institution # _________
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ELIGIBILITY CHECKLIST—STEP 2 (05/11/07)

Case # _________ (assigned in Step 1)

_________________ (Y) Was biopsy-documented locally recurrent prostatic adenocarcinoma > 30 months after the completion of EBRT, biopsied ≤ 180 days prior to registration confirmed by central pathology review?

The following questions will be asked at study Registration:

_________________ 1. Name of institutional person registering this case

_________________ 2. Report central pathology review biopsy status: 1) eligible; 2) ineligible

_________________ (Y/N) 3. Is the patient going to receive protocol treatment?

_________________ If no, the reason the patient cannot continue to Step 2: 1) disease progression; 2) patient refusal; 3) physician preference; 4) failure to submit tissue assay; 5) tumor is not a prostatic adenocarcinoma; 6) insufficient tissue submitted; 7) death; 8) other

_________________ 4. Patient's Initials

_________________ 5. Verifying Physician

_________________ 6. Patient's ID number

_________________ 7. Calendar Base Date (for Step 2) (DATE OF IMPLANT)

_________________ 8. Registration/randomization date (for Step 2): This date will be populated automatically.

Completed by ___________________________ Date _______________
1.0 INTRODUCTION

1.1 Background

For patients with clinical stage II prostate cancer,\textsuperscript{1} external beam radiation therapy (EBRT) is a commonly used primary treatment modality.\textsuperscript{2} Although conventional-dose EBRT may result in intermediate- to long-term clinical disease control,\textsuperscript{3} post-EBRT prostatic biopsy\textsuperscript{4} and serum prostate-specific antigen (PSA) determinations\textsuperscript{5} suggest that locally persistent tumor may exist in a certain proportion of patients. Furthermore, residual disease may serve as a source of tumor de-differentiation\textsuperscript{6} and systemic dissemination.\textsuperscript{7} As a result, additional medical intervention may be required to address the consequences of disease recurrence and cause-specific mortality may be increased due to uncontrolled local disease.

At present, patients with locally recurrent prostate cancer after EBRT are often managed with palliative intent, such as watchful waiting or androgen suppression. When curative therapy is considered, either radical prostatectomy or cryotherapy may be performed. However, EBRT-induced fibrosis tends to obliterate the usual tissue planes for surgical resection. This increases the degree of technical difficulty as well as the morbidity of the procedure, resulting in a general reluctance among surgeons to perform salvage surgery. The more common postoperative types and rates of complications described in the literature include urinary incontinence (mean, 32%; range, 15%-79%), bladder neck contracture/anastomotic stricture (mean, 18%; range, 7%-28%), and rectal injury (mean, 10%; range, 0%-19%).\textsuperscript{8,9} In more recent series, major complications have decreased significantly, especially rectal injury rates, which are reported in a series of 100 consecutive patients at 2% rather than the previously observed 5%.\textsuperscript{10} Incontinence rates are still high, with only about 39%-56% with full urinary continence.\textsuperscript{10,11} In a similar vein, salvage cryotherapy was associated with high rates of urinary incontinence (9%-73%), obstructive symptoms (3%-55%), erectile dysfunction (72%-100%), and severe perineal pain (5%-37%).\textsuperscript{12,13}

1.2 Prostate Brachytherapy

Transperineal ultrasound-directed prostate brachytherapy using permanently placed radioisotopes is an increasingly common modality for the primary treatment of clinical stage II prostate cancer. Compared with EBRT, it is possible to administer a high radiation dose to a tightly confined volume. Thus, it may be possible to use this radiotherapeutic modality to provide a second opportunity for tumor control in the patient with locally recurrent prostate cancer after EBRT.\textsuperscript{14-18} Perhaps the most substantial experience with this approach in contemporary practice was described by Grado et al.,\textsuperscript{18} who reported a retrospective cohort study that included 46 patients with local tumor recurrence after EBRT (median prescription dose: 66.2 Gy). Patients were treated with 125-iodine (I-125; median matched peripheral dose: 139 Gy, range: 70-157 Gy)\textsuperscript{19} or 103-palladium (Pd-103; median matched peripheral dose: 129 Gy, range: 86-194 Gy)\textsuperscript{20} transperineal permanent prostate brachytherapy. Ninety-eight percent of patients had local tumor control at last evaluation, with a 5-year cause-specific survival of 79%. Although acute adverse events were “common,” severe urinary and rectal complications were infrequent (6%). Quality-of-life endpoints were not described.

Beyer et al.\textsuperscript{17} also described their experience with 17 men treated with I-125 (median peripheral dose: 100 Gy)\textsuperscript{19} or Pd-103 (median peripheral dose: 97 Gy)\textsuperscript{20} transperineal permanent prostate brachytherapy for post-EBRT locally recurrent disease. These patients were carefully selected as most had low-grade (Gleason score 2-6) tumors with favorable (≤ 10 ng/mL) pre-implantation PSA levels. Overall, the 5-year overall survival and freedom from biochemical relapse\textsuperscript{21} estimates were 93% and 53%, respectively. Patients receiving pre-implantation androgen suppression therapy manifested a trend (72% vs. 37%) toward improved PSA-based outcome. Although initial tolerance was comparable to patients treated de novo with prostate brachytherapy, the most frequent adverse event was incontinence (of any degree) noted in one-quarter of patients. However, a formal quality-of-life assessment was not conducted.

Most recently, Lo et al.\textsuperscript{22} reported on 30 men treated with salvage Pd-103 brachytherapy (110-124 Gy), 26 of whom had prior EBRT (63-73.8 Gy, median 67.5 Gy). With a median follow-up of 5 years, the 8-year actuarial biochemical disease-free survival was 61.5%. Grade 1-2 rectal bleeding was seen in 17% of patients, and one patient with radioisotopes close to the rectum developed a recto-urethral fistula that required a colostomy. Grade 3 urinary obstruction was seen in 10% and was managed by transurethral resection.
The ideal prescribed dose has not been established for primary or salvage brachytherapy, and the published experience with salvage therapy includes a broad dose prescription range (I-125: 70-157 Gy; Pd-103: 86-194 Gy). Therefore, a “standard” dose prescription for salvage brachytherapy does not currently exist. In this trial, the dose prescribed to a planning target volume (PTV) that includes the prostate will be 140 Gy for I-125 and 120 Gy for Pd-103 to address the primary goal of the study in a multi-institutional setting. Given the variability in planning parameters for prostate brachytherapy as published in the multi-institutional analysis by Merrick et al., guidelines for V150, V200 and D90 will be taken from the lower end of the reported range. Extra controls, in the form of evaluated compliance criteria, have been added to this protocol to minimize dose to the critical structures.

2.0 OBJECTIVES

2.1 Primary
To evaluate the late treatment-related gastrointestinal (GI)/genitourinary (GU) adverse events of brachytherapy in patients with local tumor recurrence following EBRT for clinically localized prostate adenocarcinoma

2.2 Secondary
2.2.1 To evaluate acute treatment-related GI/GU adverse events
2.2.2 To determine:
- Overall survival
- Disease-free survival
- Disease-specific survival
- Clinical patterns of tumor recurrence (time to local tumor progression or distant failure)
- Time to biochemical failure
- The post-brachytherapy dosimetric coverage

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility (5/11/07) (3/10/10)
3.1.1 Biopsy-documented locally recurrent prostatic adenocarcinoma > 30 months after the completion of EBRT, biopsied ≤ 180 days prior to registration and confirmed by central pathology review (see Section 10.0).
3.1.2 Disease-related characteristics at initial diagnosis (i.e., prior to EBRT) that fit the following criteria (Appendix III):
- Stages T1-T2c, Gleason scores 2-7, and PSA ≤ 20 ng/mL
3.1.3 Staging, performed within 8 weeks prior to registration:
3.1.3.1 History/physical examination (to include a minimum digital rectal examination of the prostate and examination of the skeletal system and abdomen)
3.1.3.2 Negative lymph nodes by imaging (pelvic ± abdominal CT or MR), or by nodal dissection (laparoscopy or laparotomy)
3.1.3.3 No evidence of bone metastases (M0) on bone scan
3.1.4 Zubrod Performance Scale 0-1 (Appendix II)
3.1.5 American Urological Association Symptom Index Score (AUA BPH) < 15 (Appendix V; Note: The use of alpha blockers is permitted when evaluating lower urinary tract symptoms, i.e., the AUA score with the patient on alpha blockers is acceptable)
3.1.6 Age ≥ 18
3.1.7 Baseline serum PSA value < 10 ng/mL performed with an FDA-approved assay (e.g., Abbott, Hybritech) within 8 weeks prior to registration. PSA should not be performed within 10 days of a prior prostate biopsy, and if the patient has been started on hormonal therapy, the PSA should be performed within 8 weeks prior to the commencement of hormonal therapy.
3.1.8 Prostate volume as measured by transrectal ultrasound (TRUS) ≤ 45 cc or pubic arch interference ruled out
3.1.9 The patient must be suitable for spinal or general anesthesia
3.1.10 The patient must sign a study-specific informed consent form before study entry
3.2 Conditions for Patient Ineligibility (6/10/09) (3/10/10)

3.2.1 Prior invasive (except non-melanoma skin cancer) or hematological (e.g., acute leukemia, aggressive lymphoma, myeloma) malignancy unless disease-free for a minimum of 3 years. Previous diagnosis of low-grade lymphoma or chronic lymphocytic leukemia is allowed.

3.2.2 Prior EBRT to the prostate such that the minimum dose to the prostate exceeded 78 Gy (2 Gy fractions) or 79.8 Gy (1.9 Gy fractions) or 81 Gy (1.8 Gy fractions)

3.2.3 Baseline gastrointestinal (GI) or genitourinary (GU) toxicity (for any reason) grade $\geq$ 2 as defined in Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

3.2.4 Severe, active co-morbidity, defined as follows:

3.2.4.1 Unstable angina and/or decompensated congestive heart failure

3.2.4.2 Myocardial infarction within the last 6 months

3.2.4.3 Bacterial or fungal infection requiring intravenous antibiotics at the time of registration

3.2.4.4 Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration

3.2.4.5 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects

3.2.4.6 Acquired immune deficiency syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.

3.2.5 Clinical and/or radiologic evidence of extraprostatic disease at initial diagnosis (i.e., prior to EBRT) or at time of local recurrence (i.e., prior to study registration)

3.2.5.1 Histologic or radiologic evidence of tumor involvement of regional lymph nodes (N1) or the presence of metastatic disease (M1) (Appendix III)

3.2.6 Any of the following prior therapies:

- Transurethral resection of the prostate (TURP)
- Radionuclide (permanent or temporary implantation) prostate brachytherapy
- Prostatectomy or prostatic cryosurgery
- HIFU (high-intensity focused ultrasound)
- Bilateral orchiectomy
- Chemotherapy for prostatic carcinoma

NOTE 1: Androgen suppression therapy is permissible provided that the LHRH agonist was started at least 2 months and no more than 6 months before registration.

NOTE 2: Any combination of neoadjuvant, concurrent, or adjuvant androgen suppression therapy at the time of initial external radiotherapy is permissible provided the total duration was $\leq$ 8 months. If $> 8$ months, evidence of a normal serum testosterone must be documented.

4.0 ADDITIONAL PRETREATMENT EVALUATIONS/MANAGEMENT (3/10/10)

Note: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Additional Highly Recommended Pretreatment Evaluations/Interventions

4.1.1 Electrocardiogram and/or echocardiogram to ensure suitability for anesthesia

4.1.2 Serum creatinine and glucose, complete blood cell count, serum testosterone

5.0 REGISTRATION PROCEDURES

5.1 Preregistration Requirements

Institutions must be credentialied by the Radiological Physics Center (RPC) prior to registering any cases to this study. The credentialing materials may be found on the RPC web site at http://rpc.mdanderson.org under the credentialing tab.

5.1.1 In order to use brachytherapy on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements, or determining if they have already been met, are available at the RPC web site, http://rpc.mdanderson.org/rpc/ by selecting "Credentialing" and "RTOG."

5.1.2 All institutions must demonstrate the ability to perform electronic data submission to the Image-Guided Therapy Center (ITC) prior to enrolling patients on this study. Additional information can be found on the ATC website at http://atc.wustl.edu.
5.2 Regulatory Pre-Registration Requirements (4/12/12)

5.2.1 U.S. and Canadian institutions must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206), along with the completed CTSU-IRB/REB Certification Form, https://www.ctsu.org/public/CTSU-IRBcertif_Final.pdf. The study-related regulatory documentation also may be e-mailed to the CTSU at CTSURegulatory@ctsu.coccg.org. This must be done prior to registration of the institution’s first case:
- IRB/REB approval letter;
- IRB/REB approved consent (English and native language versions*)
  *Note: Institutions must provide certification/verification of consent translation to RTOG Headquarters (described below)
- IRB/REB assurance number

5.2.1.1 Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved RTOG will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational/letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

5.2.3 Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS

5.2.3.1 For institutions that do not have an approved LOI for this protocol: International sites must receive written approval of submitted LOI forms from RTOG Headquarters prior to submitting documents to their local ethics committee for approval. See http://www.rtog.org/Researchers/InternationalMembers.aspx

5.2.3.2 For institutions that have an approved LOI for this protocol: All requirements indicated in your LOI Approval Notification must be fulfilled prior to enrolling patients to this study.

5.3 Summary of Registration Procedures (6/10/09)

This study incorporates a two-step registration process.

**Step 1** of registration entails web registration as detailed in Section 5.4.
- Institutions will then submit the post-EBRT tissue to Dr. Amin for central pathology review, as detailed in Section 10.
- Dr. Amin will provide the results of the central review to institutions and RTOG Headquarters.

**Step 2** of registration entails a second web registration, at which time protocol treatment will begin. All cases must register to Step 2 regardless of eligibility.
- Once the patient has been enrolled in step 2 of the registration, a new data submission calendar will be provided to all eligible cases.

5.4 General Web Registration Instructions

Patients can be registered only after eligibility criteria are met. Institutions must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:
- The Investigator must have completed Human Subjects Training and been issued a certificate. (Training is available via http://phrp.nihtraining.com/users/login.php)
- The institution must complete the Password Authorization Form at http://www.rtog.org/LinkClick.aspx?fileticket=-BXerpB5u5AQ%3d&tabid=219 (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site (http://www.rtog.org), going to “Data Center Logon,” and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which
the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient’s record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study's database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

In the event the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters at (215) 574-3191 Monday through Friday, 8:30 a.m. to 5:00 p.m. ET.

6.0 RADIATION THERAPY

Brachytherapy will be performed within 8 weeks of Step 2 registration.

6.1 Dose Specifications (3/10/10)

6.1.1 Dosimetry

The dosimetry of I-125 and Pd-103 seeds will be performed in accordance with the formalism described by Rivard et al.23 in the Update of AAPM Task Group No. 43 Report.

The selection of needle and source placement should be performed to assure that the $V_{100}$ is ≥ 98% and the $D_{90}$ is ≤ 125% of the prescribed dose (see Sections 6.1.2.1 and 6.1.2.2) to the planning target volume (PTV).38 The volume (particularly in the central aspect) of the PTV that is expected to receive > 200% of the prescribed dose and the volume of rectal wall that receives the prescribed dose should be kept as small as possible.24 Suggested planning parameters for iodine implants are $V_{150}$ ≤ 45% and $V_{200}$ ≤ 10%. Because of the lower energy of palladium these suggested parameters are ≤ 55% and ≤ 15% for $V_{150}$ and $V_{200}$, respectively.

Note: If the site of local recurrence has been established with confidence through correlation of biopsy with imaging studies such as DCE (diffusion contrast enhanced) CT, MRI, and/or MR Spect, then the CTV and PTV may be defined as less than the whole prostate (see Section 6.4.1.1).

6.1.2.1 I-125 dose prescription: A modified peripheral loading pattern24,25 will be used so a planned (minimum) dose of 140 Gy will encompass the PTV.

6.1.2.2 Pd-103 dose prescription: A modified peripheral loading pattern24-26 will be used so a planned (minimum) dose of 120 Gy will encompass the PTV.

6.1.3 Post-Implantation Evaluation: Based on a CT scan obtained 3-5 weeks after the implant procedure. The CT scan will be performed in the supine position with or without a bladder catheter (which may serve as a conduit for instillation of contrast material and as a means to identify the urethra). Axial ≤ 3 mm thick contiguous images will be acquired from at least 2.0 cm superior to the base of the prostate to at least 2.0 cm inferior to the prostatic apex. This scan as well as the post-implant structures and dose distribution will be submitted to ITC and reviewed by RPC and/or the RTOG RTQA department.

6.1.3.1 Minimum Target Dose: The minimum dose to the evaluation target volume (ETV; $D_{100}$)

6.1.3.2 High-Dose Volume: The volume of the ETV enclosed by the > 150% isodose surface ($V_{150}$ of the ETV times the volume of the ETV) and the > 200% isodose surface ($V_{200}$ of the ETV times the volume of the ETV).

6.1.3.3 Low-Dose Volume: The volume of the ETV outside the ≥ 90% isodose surface (1-$V_{90}$ of the ETV times the volume of the ETV.)
6.2 Technical Factors

6.2.1 Seed Calibration and Handling

I-125 and Pd-103 seeds eligible to be used in this study must meet the AAPM criteria. The criteria may be summarized as follows:

- The vendor provides air-kerma strength calibrations that are directly or indirectly traceable to the air-kerma strength standards ($S_{KN99}$) for photon emitting brachytherapy sources maintained by the National Institute of Standards and Technology (NIST).
- A full set of TG-43 dosimetric parameters is available, supporting both calculation of the 2-D dose-rate distribution and, for seed models, the 1-D isotropic point source approximation. This set of dosimetric parameters must be based upon at least one experimental study and at least one Monte Carlo study of the source model's dosimetric parameters. These studies must be performed by independent investigators and must have been accepted for publication by a peer-reviewed journal.
- The vendor has assured that the calibration from NIST has been transferred to the Accredited Dosimetry Calibration Laboratories (ADCLs).
- The vendor has implemented a program of periodically comparing its air-kerma strength calibrations with the NIST primary standard and the secondary standards maintained by the ADCLs that is compliant with the CLA report.

A source strength of 0.29-0.46 U (0.23-0.36 mCi) may be used. As an alternative to I-125, Pd-103 seeds with an activity of 1.37-2.04 U (1.06-1.58 mCi/seed) that meet the AAPM criteria may be used.

The seeds will be received and inventoried according to each institution’s policy and procedures in a manner consistent with federal or state regulations. A random sampling of ≥ 10% of the seeds (at least 10 seeds) will be assayed using a method that provides direct traceability to either the NIST or an AAPM ADCL. The measured activity will be compared against the vendor’s statement of activity, and any discrepancy > 5% will be resolved before the seeds’ use. If seeds in sterile absorbable suture are used (e.g., Rapid Strand™), then a representative sample of such seeds shall be assayed. Assay performed by a third party, such as a third party vendor, is allowed provided the vendor meets the RPC’s requirements for credentialing.

6.3 Localization, Simulation, and Immobilization

6.3.1 Treatment Planning Ultrasound

Treatment planning will be based on a TRUS volume study of the prostate that is performed in a way that will reproduce the implant geometry. This study will be completed within 21 days before and/or at the time of the implant procedure.

6.3.1.1 The patient will be positioned in the dorsal lithotomy position with the spinal column centered on the table and the legs symmetrically elevated. The ultrasound probe and stepping device/stabilization unit will be secured relative to the patient, and the probe will be inserted into the rectum. The volume in the balloon (optional) will be adjusted to provide a satisfactory image without distorting the contour of the prostate. The ultrasound unit will be aligned so the grid (i.e., D column) bisects the prostate into equal right and left halves. Row #1 on the template matrix is positioned within the prostate on the axial image on which the prostate is most posteriorly situated and is anterior to the rectum at all levels.

6.3.1.2 The ultrasound probe will be advanced until the base of the prostate is visualized, and this level will be designated the zero plane. Contiguous serial axial images of the prostate at 0.5 cm increments beginning 0.5 cm cranial to the zero plane will be obtained and will extend ≥ 0.5 cm inferior (caudal) to the apex of the prostate. The prostate will be outlined on each axial image where it is present.

6.3.2 Pubic Arch Study

After serial imaging of the prostate (see Section 6.3.1), the pubic arch study may be performed by moving the probe caudally until the pubic arch shadow is visualized. The prostate is then traced from the image with the widest dimensions and superimposed over the pubic arch. The intersection of the pubic arch and the prostate cross-section is determined, and the amount of gland blocked by the pubic arch is estimated.

In addition to, or instead of, an ultrasound-based pubic arch study, pelvic CT may be used. The patient is positioned supine, hands on chest, feet together. Contiguous axial images ≤ 5 mm thick through the prostate and pubic arch are obtained. The largest prostate axial image
is laid over the narrowest portion of the pubic arch using CT reference points, and the amount of gland blocked by the pubic arch is estimated.29

6.3.3 Implantation Procedure
6.3.3.1 The implant procedure will be performed according to standard technique. The urethra will be localized using either a urinary catheter or aerated gel.
6.3.3.2 After all preplanned seeds have been placed, if additional needles and seeds are being considered, caution should be used because of the prior radiotherapy and great care must be taken particularly at the prostatic-rectal interface.
6.3.3.3 The patient will be monitored following the implant procedure to demonstrate compliance with appropriate state and federal release criteria.

6.4 Treatment Planning/Target Volumes (3/10/10)
6.4.1 The target volume definitions are largely based on those provided in ICRU Report 58, Dose and Volume Specification for Reporting Interstitial Therapy.
6.4.1.1 Clinical Tumor Volume (CTV): Pre-implantation TRUS-defined prostate volume. If the location of the biopsy-proven recurrence within the prostate has been identified using metabolic imaging, such as MR spectroscopy or SPECT, this volume will lie within the CTV and will be designated CTVi. The seed loading may be weighted preferentially such that the V150 to the CTVi is > 45% for I-125 and > 55% for Pd-103.
6.4.1.2 Planning Target Volume (PTV): This is an enlargement of the CTV by 2-3 mm in the lateral and anterior dimensions on each axial image. The posterior border is the same as the posterior border of the CTV. The CTV will be expanded 5 mm in cranial and caudal directions to create the PTV. The PTV will be used to establish the needle and seed coordinates necessary to achieve the desired dose specification. The PTV should be designed so as to limit dose to the critical structures as evaluated post operatively. In order to limit doses to the membranous urethra and the proximal penile structures, the caudal extent of the implant should be limited to 5 mm distal to the apex of the prostate after the implant has been performed. An expansion of CTVi according to the above parameters may be used to create PTVi which may be used as the basis of a partial prostate implant.
6.4.1.3 Evaluation Target Volume (ETV): The post-implantation CT-defined prostate volume.
6.4.1.4 Rectal Volume: The rectum will be contoured on each slice and include the outer rectal wall.
6.4.1.5 Urethra Volume: The urethra will be contoured on each slice where visible, starting at the bladder neck and continuing to the most inferior slice in the data set.
6.4.1.6 Bladder Volume: The outer wall of the bladder will be contoured on all slices where visible.
6.4.1.7 Dose and Volume Quantifiers: Dose and volume quantifiers will be obtained from the Dose-Volume Histogram for a particular structure. For this protocol “D” quantifiers will be listed as “Structure” + “D” + subscripted “Percent of Volume”. For instance, UrD90 = 170 Gy means that 90% of the urethral volume is covered by the surface described by the 170 Gy isodose (170 Gy is the minimum dose within this surface). “V” quantifiers refer to volume or percent volume which is covered by the subscripted dose usually written as a percentage of the prescription (reference) dose. For instance, RV100 = 2.0 cm3 means that 2.0 cm3 of the rectal volume was covered by the isodose surface described by 100% of the prescription dose (all doses within this surface are greater than or equal to the prescription dose). If the structure is omitted from the V or D quantifier, the quantifier refers to the ETV.

6.5 Critical Structures
The ETV, bladder, rectum, and urethra (if possible) will be defined on the CT scan. The following dosimetric analyses will be performed.24
- Two-dimensional dose distributions on images where the ETV is defined will display the following isodoses: 50%, 80%, 90%, 100%, 150%, and 200%.
- A dose volume histogram (DVH) for the ETV will be tabulated in 10 Gy increments to include doses ≤ 200% of the prescribed dose. The D80, D90, and D100 of the ETV will be tabulated.24
- The fractional volume (V) of the ETV that receives 200% (V200), 150% (V150), 100% (V100), 90% (V90), and 80% (V80) of the prescribed dose.24
- A DVH for the rectum (expressed in cm3) that extends from the level of the superior-most seed to the level of the inferior-most seed will be calculated and tabulated in 10 Gy increments.
A DVH for the bladder (expressed in cm$^3$) will be calculated and tabulated in 10 Gy increments.

The D5, D30 and V150 (cc) of the prostatic urethra will be calculated in patients with an indwelling urinary catheter at the time of post-implant CT.

The dose to the membranous urethra will be calculated at the center of the urethra, 10 mm caudal to the apex of the ETV. If no urethra is localized on the image set, the maximum dose in the plane 10 mm caudal to the apex of the ETV will be reported as the dose to the membranous urethra.

6.6 **Documentation Requirements (6/10/09)**

Dosimetric data to be digitally submitted to the ITC:

- A copy of the implant record generated during the procedure
- A copy of the post-implant CT scan; ETV, urethra, bladder, and rectum delineation; and dosimetry calculations (must be submitted electronically)
- A copy of the post-implant dosimetry report (T5 form) that contains the information required in Section 6.5 above (copy to RTOG Headquarters)

6.7 **Compliance Criteria (3/10/10)**

6.7.1 **Evaluation Criteria**

6.7.1.1 Per protocol: D90 for the ETV is ≥ 90% but < 130% of the prescription dose. If the implant has been designed as a partial prostate implant to cover the PTVt this must be indicated at the time of reporting. The ETV will still be defined as the whole prostate but the implant will be acceptable as “per protocol” provided the D90 for ETV is > 60%.

The following criteria for Organs at Risk apply to both whole and partial prostate implants.

- UrV$_{150}$ for the urethral volume is < 30%
- The maximum dose to the urethral volume is < 200% of the prescription dose
- The membranous urethra dose is < the prescription dose
- RV$_{100}$ for the rectal volume is < 1.0 cm$^3$.

6.7.1.2 Variation acceptable for whole prostate implant: D90 for the ETV is ≥ 80% but < 90% of the prescription dose, or is > 130% of the prescription dose.

- UrV$_{150}$ for the urethral volume is > 30% but < 50%
- The maximum dose to the urethral volume is > 200% but < 250% of the prescription dose
- RV$_{100}$ for the rectal volume is > 1.0 but < 2.0 cm$^3$.

6.7.1.3 Deviation unacceptable for whole prostate implant: D90 for the ETV is < 80% of the prescription dose.

- UrV$_{150}$ for the urethral volume is > 50%
- The maximum dose to the urethral volume is > 250% of the prescription dose
- The membranous urethra dose is > the prescription dose
- RV$_{100}$ for the rectal volume is > 2.0 cm$^3$.

6.8 **R.T. Quality Assurance Reviews**

The Physics Co-Chair, William Bice, PhD, and the Radiation Oncology Co-Chairs, Juanita Crook, MD, and Thomas Pisansky, MD, will perform a remote RT Quality Assurance Review of the dosimetry and contours respectively after complete data for the first 20 cases enrolled has been received at ITC. The next review will be performed remotely after complete data for the next 20 cases enrolled has been received at ITC. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled have been received at ITC, whichever occurs first.

6.9 **Radiation Toxicity (5/11/07)**

All patients will be seen at least at 1, 3, 6, 9, and 12 months post brachytherapy; then every 6 months for years 2-5; and then annually. Additional visits for symptom management are to be arranged as required. Any observations regarding radiation reactions will be recorded and should include attention toward the following potential adverse events as described in the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (see Section 6.10):

6.9.1 **Gastrointestinal:** Diarrhea, fistula, incontinence, necrosis, obstruction, perforation, proctitis, stricture/stenosis, ulcer

6.9.2 **Hemorrhage/bleeding:** Anus, rectum, bladder, prostate, urethra

6.9.3 **Pain:** Anus, rectum, bladder
6.9.4 Renal/genitourinary: Bladder spasms, cystitis, dysuria, fistula, incontinence, obstruction (bladder, prostate, urethra), perforation (bladder, prostate, urethra), stricture/stenosis (bladder, prostate, urethra), urinary frequency/urgency, urinary retention. Any incidence of urinary retention or need for catheterization should be documented and the American Urological Association Symptom Index (AUA BPH) questionnaire completed at each follow-up (Appendix V). Note: The AUA BPH questionnaire should only be completed through year 3.

6.9.5 Intraoperative injury: Anal sphincter, anus, rectum, bladder, prostate, urethra

6.10 Radiation Adverse Event Reporting (4/16/14)

6.10.1 Adverse Events (AEs) and Serious Adverse Events (SAEs) Reporting Requirements

Adverse events (AEs) as defined in the tables below and all serious adverse events (SAEs) will be reported to the Cancer Therapy Evaluation Program (CTEP) via the CTEP Adverse Event Reporting System (CTEP-AERS) application AND to NRG Oncology as directed in this section.

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. February 29, 2012; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm]

Definition of an SAE: Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:
- Death;
- A life-threatening adverse experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that do not result in death, are not life threatening, or do not require hospitalization may be considered an SAE experience, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

SAEs (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable, or definite) should be reported via CTEP-AERS.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. “On study” is defined as during or within 30 days of completing protocol treatment.

CTEP-AERS REPORTING REQUIREMENTS

CTEP-AERS provides a radiation therapy (RT)-only pathway for events experienced involving RT only, both with and without a drug component arm. Events that occur on the RT-only arm of a study with a drug component must be reported for purposes of comparison. Events that occur on an RT-only study without a drug component also must be reported. Events involving RT-only must be reported via the CTEP_AERS RT-only pathway.

Beginning April 1, 2011, this study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 for CTEP-AERS reporting of adverse events (AEs). All AE reporting on the study case report forms (CRFs) should follow grading criteria instructions on the specific CRF. The CTCAE version 4 is identified and located on the CTEP web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.

Adverse Events (AEs) and Serious Adverse Events (SAEs) that meet the criteria defined above experienced by patients accrued to this protocol must be reported to CTEP as
indicated in the following tables using the CTEP-AERS application. CTEP-AERS can be accessed via the CTEP web site (https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613). Use the patient’s case number without any leading zeros as the patient ID when reporting via CTEP-AERS. AEs and SAEs reported using CTEP-AERS must also be reported to NRG Oncology on the follow-up case report form (see Section 12.1). In addition, sites must submit CRFs in a timely manner after CTEP-AERS submissions.

Certain SAEs as outlined below will require the use of the 24 Hour CTEP-AERS Notification:

- **Phase II & III Studies:** All unexpected potentially related SAEs
- **Phase I Studies:** All unexpected hospitalizations and all grade 4 and 5 SAEs regardless of relationship

Any event that meets the above outlined criteria for an SAE but is assessed by the CTEP-AERS as “expedited reporting NOT required” must still be reported for safety reasons. Sites must bypass the “NOT Required” assessment and complete and submit the report. CTEP-AERS allows submission of all reports regardless of the results of the assessment.

**CRITERIA FOR CTEP-AERS REPORTING REQUIREMENTS FOR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS THAT OCCUR WITHIN 30 DAYS OF THE DATE OF THE LAST PROTOCOL TREATMENT**

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<thead>
<tr>
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<td>Unlikely</td>
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<td>Probable</td>
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<td>24 Hour: 5 Calendar Days</td>
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**CRITERIA FOR CTEP-AERS REPORTING REQUIREMENTS FOR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS THAT OCCUR > 30 DAYS AFTER THE DATE OF THE LAST PROTOCOL TREATMENT**

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<tr>
<td><strong>Unrelated</strong></td>
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<td>Unlikely</td>
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<td><strong>Possible</strong></td>
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<td>Probable</td>
<td>10 Calendar Days</td>
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<td><strong>Definite</strong></td>
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<td>24 Hour: 5 Calendar Days</td>
<td>10 Calendar Days</td>
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</table>

- Expedited AE reporting timelines defined:
  - “24 hours; 5 calendar days” – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
  - “10 calendar days” - A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
• Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following protocol treatment or procedure.
• Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

**NRG REPORTING REQUIREMENTS**
Beginning April 1, 2011, this study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 for CTEP-AERS reporting of adverse events (AEs). All AE reporting on the study case report forms (CRFs) should follow grading criteria instructions on the specific CRF. The CTCAE version 4 is identified and located on the CTEP web site at: [http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). All appropriate treatment areas should have access to a copy of the CTCAE version 4.

**Adverse Events (AEs) and Serious Adverse Events (SAEs)** that meet the criteria defined above experienced by patients accrued to this protocol must be reported via CTEP-AERS. SAEs must be reported to NRG Oncology within 24 hours of discovery of the event. Contact the CTEP Help Desk if assistance is required.

All supporting source documentation being faxed to NCI must be properly labeled with the RTOG (NRG) study/case numbers and the date of the adverse event and must be faxed to the NRG Oncology dedicated AE/SAE FAX, 215-717-0990, before the 5- or 10-calendar-day deadline. All forms submitted to NRG Oncology also must include the RTOG (NRG) study/case numbers; non-RTOG (NRG) intergroup study and case numbers must be included, when applicable. CTEP-AERS Reports are forwarded to NRG Oncology electronically via the CTEP-AERS system. Use the patient’s case number as the patient ID when reporting via CTEP-AERS.

Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported via CTEP-AERS within 24 hours of discovery. An expedited report, if applicable, will be required within 5 or 10 calendar days.

A 24-hour notification is to be made to CTEP by telephone at 301-897-7497 only when internet connectivity is disrupted. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS by the original submitter at the site.

**6.10.2 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)**
AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the CTEP-AERS system within 30 days of AML/MDS diagnosis. If you are reporting in CTCAE version 4, the event(s) may be reported as: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment-related secondary malignancy.

**7.0 DRUG THERAPY**
Not applicable to this study.

**8.0 SURGERY**
Not applicable to this study.

**9.0 OTHER THERAPY**

**9.1 Permitted Supportive Therapy**
All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site’s source documents as concomitant medication.

Clinical discretion may be exercised in the treatment of side effects. Rectal side effects such as diarrhea may be treated with psyllium, loperamide, or diphenoxylate. Bladder or rectal spasms can be treated with anticholinergics or tolterodine. Bladder/urethral irritation can be treated with phenazopyridine and/or alpha blockers. Sildenafil or similar agents may be used for erectile dysfunction.
9.2 Neoadjuvant Androgen Suppression

Neoadjuvant androgen suppression therapy is permitted if initiated between 2-6 months prior to registration. The duration may not exceed 6 months. Androgen suppression therapy is not allowed to begin on the date of the implant or as adjuvant therapy after the implant when there is no evidence of prostate cancer progression. It is important to document neoadjuvant androgen suppression therapy until its completion.

9.3 Salvage Therapy

Salvage therapy is not mandated or prescribed by this protocol but is at the discretion of the investigator. It is important to document salvage therapy on follow-up forms.

10.0 TISSUE/SPECIMEN SUBMISSION (6/10/09)

10.1 General Information

The RTOG Biospecimen Resource at the University of California San Francisco acquires and maintains high quality specimens from RTOG trials. Tissue from each block is preserved through careful block storage and processing. The RTOG encourages participants in protocol studies to consent to the banking of their tissue. The RTOG Biospecimen Resource provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions. The RTOG Biospecimen Resource also collects tissue for central review of pathology. Central review of tissue can be for eligibility and/or analysis.

In this study, tissue will be submitted for the purpose of post-EBRT central review of pathology during Step 1 Registration (mandatory for eligibility), post-brachytherapy biopsy for confirmation of local recurrence (strongly recommended but optional at physician discretion), and tissue banking (optional).

10.2 Specimen Collection of Step 1 Registration/Post-EBRT Biopsy for Central Review for Eligibility (required) (5/11/07) (6/10/09)

Central pathology review is mandatory to confirm eligibility. Central pathology review will be performed by Dr. Mahul B. Amin. All slides must be sent directly to Dr. Amin (see below).

The following material must be provided to Dr. Amin:

10.2.1 One H & E stained slide per positive biopsy site. If additional immunohistochemistry (IHC) was performed to confirm the diagnosis of cancer, this material should also be sent.

10.2.2 A Pathology Report documenting that the submitted slides contain tumor. The report must include the RTOG protocol number and the patient’s case number. The patient’s name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

10.2.2.1 A Pathology Report of the initial diagnostic biopsy results should also be provided, if available.

10.2.3 A Specimen Transmittal Form and a Pretreatment Pathology Submission Form (P4). These forms must include the RTOG protocol number and patient’s case number.

10.2.4 Central review will be performed for every case. Send materials by overnight mail directly to Dr. Amin at:

Mahul B. Amin, MD
Department of Pathology and Laboratory Medicine
Cedars-Sinai Medical Center
8700 Beverly Blvd., Suite 8728
Los Angeles, CA 90048
310-423-6631
FAX: 310-423-0170
aminm@cshs.org
(cc: ramirezdc@cshs.org)
 Include on the P4 form the name, telephone number, and fax number of the person to notify with the results of the tissue evaluation.
 Shipments must be made Monday through Friday.
 Notify Dr. Amin by email (cc: Dr. Amin's assistant: ramirezdc@cshs.org) on or before the day of submission: (1) that a case is being submitted for review; (2) the name of the contact person; (3) when to expect the sample; and (4) the overnight shipping carrier and tracking number.
 Dr. Amin will email the appropriate contact person from the submitting institution with the results and will fax a copy of the completed form to the institution and to RTOG Headquarters. Review will be completed within 24 to 48 hours.
 If the patient does not meet eligibility requirements, all tissue and forms will be returned to the participating submitting institution.

10.2.5 Dr. Amin will send all H & E slides to the RTOG Biospecimen Resource. If immunohistochemistry stains are submitted, they will be returned to the originating institution. For patients consenting to the tissue banking component of this study, slides will be kept at the Biospecimen Resource as part of the banking process (See Section 10.4). For patients not consenting to the tissue banking component of this study, the slides will be returned to the submitting institution.

10.3 Specimen Collection of Post-Brachytherapy Biopsy for Confirmation of Local Recurrence
(strongly recommended but optional at physician discretion) (6/10/09)
The following material is needed:

10.3.1 One H & E stained slide per positive biopsy site.
10.3.2 A Pathology Report documenting that the submitted slides contain tumor. The report must include the RTOG protocol number and the patient’s case number. The patient’s name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.
10.3.3 A Specimen Transmittal Form. This form must include the RTOG protocol number and patient’s case number.
10.3.4 Send materials to the RTOG Biospecimen Resource at the address listed in Section 10.7.
10.3.5 After the Biospecimen Resource has received the post-brachytherapy H & E slides, the slides will be forwarded to Dr. Amin for confirmation of local recurrence. Once Dr. Amin has completed his review, he will send all H & E slides back to the RTOG Biospecimen Resource. For patients consenting to the tissue banking component of this study, the slides will be kept at the Biospecimen Resource as part of the banking process (See Section 10.4). For patients not consenting to the tissue banking component of this study, the slides will be returned to the submitting institution.

10.4 Specimen Collection for Tissue Banking (6/10/09)
For patients who have consented to the tissue banking component of this study (See “About Using Tissue for Research” portion of Appendix I. Note: Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/specimen submission for banking.

10.4.1 Specimens from Step 1 Registration/Post-EBRT Biopsy (5/11/07)
10.4.1.1 After Dr. Amin has completed central review, he will send all H & E slides to the RTOG Biospecimen Resource. The Biospecimen Resource will retain these slides as part of the banking process. (For patients not consenting to the tissue banking component of this study, the slides will be returned to the submitting institution.) If additional immunohistochemistry stains are submitted, they will be returned to the submitting institution.
10.4.1.2 After eligibility has been confirmed, a paraffin-embedded tissue block of the tumor (preferred). If the block cannot be obtained, then 10-15 unstained slides (please use charged or “Plus” slides) from the block of the tumor. Tissue block or unstained slides must be clearly labeled with the pathology identification number that corresponds to the pathology report. Send specimens with a specimen transmittal form and an accompanying pathology report to the RTOG Biospecimen Resource at the address listed in Section 10.7.

10.4.2 Specimens from Post-Brachytherapy Biopsy for Confirmation of Local Recurrence
10.4.2.1 After Dr. Amin has completed his review for confirmation of local recurrence, he will send all H & E slides to the RTOG Biospecimen Resource. The Biospecimen Resource will retain these slides as part of the banking process. (For patients not consenting to the tissue banking component of this study, the slides will be returned to the submitting institution.)

10.4.2.2 Sites must also send a paraffin-embedded tissue block of the tumor (preferred). If the block cannot be obtained, then 10-15 unstained slides (please use charged or “Plus” slides) from the block of the tumor. Tissue block or unstained slides must be clearly labeled with the pathology identification number that corresponds to the Pathology Report. Send specimens with a specimen transmittal form and an accompanying pathology report to the RTOG Biospecimen Resource at the address listed in Section 10.7.

10.5 Reimbursement (3/29/11)

RTOG will reimburse institutions for submission of protocol specified biospecimen materials sent to the Biospecimen Resource at the University of California San Francisco and other protocol-specified collection repositories/laboratories. RTOG does not reimburse for central pathology review for eligibility. After confirmation from the RTOG Biospecimen Resource or other designated repository/laboratory that appropriate materials have been received, RTOG Clinical Trials Administration will authorize payment according to the schedule posted with the Reimbursement and Case Credit Schedule found on the RTOG web site (http://www.rtog.org/LinkClick.aspx?fileticket=Csxzt1v1hEk%3d&tabid=323). Biospecimen payments will be processed quarterly and will appear on the institution’s summary report with the institution’s regular case reimbursement.

10.6 Confidentiality/Storage (6/10/09)


10.6.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient’s case number only. The RTOG Biospecimen Resource database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.6.2 Specimens for central review will be retained until the study is terminated. Specimens for tissue banking will be stored for an indefinite period of time. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

10.7 Contact Information for RTOG Biospecimen Resource (4/12/12)

U. S. Postal Service Mailing Address: For Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu
### Specimens for Central Review

<table>
<thead>
<tr>
<th>Specimens taken from patient</th>
<th>Submitted as:</th>
<th>Shipped:</th>
</tr>
</thead>
<tbody>
<tr>
<td>One H&amp;E stained slide per positive biopsy site Submit IHC stains, if performed</td>
<td>H&amp;E stained slide IHC slide</td>
<td>Slide shipped ambient directly to Dr. Amin</td>
</tr>
</tbody>
</table>

### (B) Post-Brachytherapy Specimens (strongly recommended)

<table>
<thead>
<tr>
<th>Specimens taken from patient</th>
<th>Submitted as:</th>
<th>Shipped:</th>
</tr>
</thead>
<tbody>
<tr>
<td>One H&amp;E stained slide per positive biopsy site Submit IHC stains, if performed</td>
<td>H&amp;E stained slide IHC slide</td>
<td>Slide shipped ambient to RTOG Biospecimen Resource</td>
</tr>
</tbody>
</table>

### Specimens for Tissue Banking (optional)

<table>
<thead>
<tr>
<th>Specimens taken from patient</th>
<th>Submitted as:</th>
<th>Shipped:</th>
</tr>
</thead>
<tbody>
<tr>
<td>One H&amp;E stained slide per positive biopsy site Submit IHC stains, if performed</td>
<td>H&amp;E stained slide IHC slide</td>
<td>Slide shipped ambient directly to Dr. Amin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specimens taken from patient</th>
<th>Submitted as:</th>
<th>Shipped:</th>
</tr>
</thead>
<tbody>
<tr>
<td>A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or 10-15 unstained slides</td>
<td>Paraffin-embedded tissue block or 10-15 unstained slides (on “plus” slides)</td>
<td>Block or unstained slides shipped ambient to RTOG Biospecimen Resource</td>
</tr>
</tbody>
</table>

### (A) Step 1 Registration/Post-EBRT (after eligibility is confirmed)

<table>
<thead>
<tr>
<th>Specimens taken from patient</th>
<th>Submitted as:</th>
<th>Shipped:</th>
</tr>
</thead>
<tbody>
<tr>
<td>One H&amp;E stained slide per positive biopsy site Submit IHC stains, if performed</td>
<td>H&amp;E stained slide IHC slide</td>
<td>Slide shipped ambient directly to Dr. Amin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specimens taken from patient</th>
<th>Submitted as:</th>
<th>Shipped:</th>
</tr>
</thead>
<tbody>
<tr>
<td>A paraffin-embedded tissue block of the primary tumor removed after brachytherapy or 10-15 unstained slides</td>
<td>Paraffin-embedded tissue block or 10-15 unstained slides (on “plus” slides)</td>
<td>Block or punch shipped ambient to RTOG Biospecimen Resource</td>
</tr>
</tbody>
</table>
11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (3/29/11)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pre-Reg(^a)</th>
<th>Follow-up(^b)</th>
<th>At Disease Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>History, physical exam(^c)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Zubrod performance</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Tumor measurements</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Prostate biopsy with Gleason score</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>AUA BPH (Appendix V)</td>
<td>X(^d)</td>
<td>X(^d)</td>
<td></td>
</tr>
<tr>
<td>CBC, platelets</td>
<td>X(^e)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, glucose, serum testosterone</td>
<td>X(^e)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA</td>
<td>X(^d)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Prostate TRUS</td>
<td>X(^d)</td>
<td>X(^d)</td>
<td>X(^e)</td>
</tr>
<tr>
<td>Flexible cystoscopy</td>
<td>X(^e)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone scan</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph node assessment</td>
<td>X(^g)</td>
<td></td>
<td>X(^g)</td>
</tr>
<tr>
<td>Post-implant prostate CT</td>
<td>X(^i)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxicity evaluation</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EKG, ECHO</td>
<td>X(^e)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Within 8 weeks prior to registration, unless otherwise specified.
\(^b\) At 3-5 weeks after implant, then every 3 months for 1 year, then every 6 months for years 2-5, then annually.
\(^c\) To include, at a minimum, digital rectal examination of the prostate and examination of the skeletal system and abdomen.
\(^d\) PSA must be done:
  - Within 8 weeks prior to study entry and prior to prostate biopsy or
  - Within 8 weeks prior to study entry and at least 10 days after prostate biopsy
For those patients on hormones, PSA value must be obtained within 8 weeks prior to starting hormone therapy, and prior to biopsy or at least 10 days following biopsy.

**Note:** PSA obtained >8 weeks prior to study entry and/or within 10 days following prostate biopsy or > 8 weeks prior to starting hormone therapy must not be used for study entry PSA.

\(^e\) Optional, at physician discretion. Regarding serum testosterone: see Section 3.2.6 for details.
\(^f\) To determine prostatic volume and (lack of) extraprostatic disease; may be used for brachytherapy planning if done according to Section 6.3.1.
\(^g\) Pelvic ± abdominal CT or MRI and/or pelvic lymphadenectomy.
\(^h\) Post-implant prostate CT to be performed 3-5 weeks post-implant is meant to coincide with first follow-up.
\(^i\) In the event of bone pain or at physician’s discretion.
\(^j\) AUA BPH data to be collected through year 3.
\(^k\) See Section 3.1.5 for details.

11.2 Follow-up Schedule

11.2.1 Initial follow-up visit between 3 and 5 weeks after implant to coincide with post-implant CT.

11.2.2 After initial follow-up visit, follow-up will be done every 3 months for 1 year, then every 6 months for years 2-5, then annually.

11.2.3 A bone scan will be performed on any patient who presents with complaints of bone pain that cannot be attributed to any intercurrent disease. Discretionary plain films may be needed to evaluate lesions seen on bone scan to confirm the diagnosis of metastatic disease.

11.3 Measurement of Effect/Response

Prostate tumor dimensions in centimeters should be determined from physical exam (if possible) and should be recorded at entry to study.

11.3.1 No Evidence of Disease (NED): No clinical evidence of disease on digital rectal examination and no PSA failure (nadir + 2 definition).

11.3.2 Equivocal Disease (ED): This rating will be assigned under the following circumstances:
  - If abnormalities are present on the prostate digital rectal examination but are thought to be abnormal due to treatment and felt not to represent tumor.
  - If clinical evidence of residual tumor is present, but this has regressed from a previous examination (initial registration).
  - If PSA failure occurs (as described in Section 11.3.5) within 36 (see 11.3.5.1) months
post implant (due to possibility of “PSA bounce,” see 11.3.5.1).

11.3.3 Locally Progressive Disease (PD): This rating will be assigned when there is clinical evidence in the prostate gland of disease progression or recurrence. Only those patients with progressive disease on digital rectal examination or with a post-implant prostate biopsy showing carcinoma will be scored. The time of failure will be backdated to the first occurrence of equivocal disease after a prior normal examination or to the time of implant if a normal digital rectal examination was never achieved. Biopsy of the suspicious area must be done to document disease.

11.3.4 Disease-Free Survival: The disease-free survival duration will be measured from the date of registration to the date of documentation of disease progression or until the date of death from any cause. This endpoint will include all measures of disease status (examination, imaging studies, biopsy results, and PSA determinations).

11.3.5 Time to Biochemical (PSA) Failure: Failure occurs when the PSA is first noted to be 2 ng/mL or more than the current nadir value (PSA > current nadir + 2). If the rise in PSA to ≥ current nadir + 2 occurs during the first 36 months followed by a subsequent non-hormonal induced PSA decrease, patients will not be considered PSA failures. Starting hormones at any time after brachytherapy will be considered failure. The failure date is considered to be the date of the PSA reading that fulfills the criterion (nadir + 2), or the date of starting secondary intervention, whichever occurs first. Every effort should be made to withhold further therapy until clinical relapse is evident.

In the case of PSA failure, the site of failure should be ascertained before instituting further therapy. This would include bone scan and pelvic CT. Biopsy of the prostate should be performed to determine local control. Intervention depending upon the site(s) of recurrence will be left to the discretion of the individual investigator.

11.3.5.1 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).

11.3.6 Time to Local Progression: The time to progression will be measured from the date of registration to the date of documented local progression as determined by clinical exam.

11.3.6.1 Clinical criteria for local failure are progression (increase in palpable abnormality) at any time, failure of regression of the palpable tumor by 2 years, and redevelopment of a palpable abnormality after complete disappearance of previous abnormalities. Needle biopsy is recommended.

11.3.6.2 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. It is strongly encouraged that biopsies be reviewed centrally (see Section 10.3).

11.3.7 Time to Distant Failure: The time to distant failure will be measured from the date of registration to the date of documented lymphatic or hematogenous metastatic disease.

11.3.8 Survival: The survival time will be measured from the date of registration to the date of death. Every effort should be made to document the cause of death. Post-mortem examination will be carried out when feasible, and a copy of the final autopsy report sent to the RTOG.

11.3.9 Disease-Specific Survival: Disease-specific survival duration will be measured from the date of registration to the date of death due to prostate cancer. Causes of death may require review by the study chair or her designee. Death due to prostate cancer will be defined as:

11.3.9.1 Primary cause of death certified as due to prostate cancer.

11.3.9.2 Death in association with any of the following conditions:
   - Further clinical tumor progression occurring after initiation of "salvage" anti-tumor (e.g., androgen suppression) therapy.
   - A rise (that exceeds 1.0 ng/mL) in the serum PSA level on at least two consecutive occasions that occurs during or after "salvage" androgen suppression therapy.
   - Disease progression in the absence of any anti-tumor therapy.

11.3.9.3 Death from a complication of therapy, irrespective of disease status.
12.0 DATA COLLECTION

Data should be submitted to:

NRG Oncology
1818 Market Street, Suite 1600
Philadelphia, PA 19103

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission (5/11/07)

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment Pathology Submission Form (P4)</td>
<td>Within 1 week of step 1 registration</td>
</tr>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 weeks of study entry</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td>Within 2 weeks of study entry</td>
</tr>
<tr>
<td>Follow-up Form (F1)</td>
<td>1, 3, 6, 9, and 12 months following implant, then every 6 months for years 2-5, then annually</td>
</tr>
<tr>
<td>AUA BPH Scoring Form (PQ) (Appendix V)</td>
<td>Within 2 weeks of study entry; at 3-5 weeks after implant, then at 3, 6, 9, and 12 months, then every 6 months for years 2-3</td>
</tr>
<tr>
<td>Radiotherapy Form (T1) [copies to RTOG and ITC]</td>
<td>8 weeks post implant</td>
</tr>
<tr>
<td>Autopsy Report (D3)</td>
<td>As applicable</td>
</tr>
</tbody>
</table>

12.2 Digital Data Submission to Image-Guided Therapy Center (ITC) (6/10/09) (3/10/10)

The following forms are to be submitted to ITC via http://atc.wustl.edu.

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-implant evaluation CT scan</td>
<td>3-5 weeks post implant</td>
</tr>
<tr>
<td>Post-implant structure set</td>
<td></td>
</tr>
<tr>
<td>Post-implant plan</td>
<td></td>
</tr>
<tr>
<td>Post-implant dose distribution</td>
<td></td>
</tr>
<tr>
<td>Post-implant dosimetry data form (T5) [copy to RTOG HQ]</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy Form (T1)</td>
<td>8 weeks post implant</td>
</tr>
</tbody>
</table>

NOTE: Copies of simulation and port films and the complete RT daily treatment record for the previous original EBRT will be submitted to RTOG Headquarters ONLY if specifically requested.

12.2.1 Digital Data Submission to ITC
Digital data submission may be accomplished using magnetic tape or the Internet.
For network submission: The SFTP account assigned to the submitting institution by the ITC shall be used, and e-mail identifying the data set(s) being submitted shall be sent to:

itc@wustl.edu

For tape submission: Please contact the ITC about acceptable tape types and formats. Hardcopies accompanying digital data should be sent by mail or Federal Express and should be addressed to:

Image-Guided Therapy Center (ITC)
ATTN: Roxana Haynes
4511 Forest Park, Suite 200
St. Louis, MO 63108
314-747-5415
FAX 314-747-5423

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoint

To evaluate the late treatment-related GI/GU adverse events of brachytherapy in patients with local tumor recurrence following EBRT for clinically localized prostate adenocarcinoma. The dose level for brachytherapy is 140 Gy minimum target dose of I-125-iodine or 120 Gy minimum target dose of Pd-103. A late adverse event is defined as an adverse event occurring more than 270 days from the date of implantation and evaluated by the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. For the purposes of this study, late treatment-related adverse events will be evaluated between 271 days and 730 days from the implant. The treatment-related attribution includes definitely, probably, or possibly related to treatment.
Late treatment-related adverse events are defined as the following:

<table>
<thead>
<tr>
<th>Event</th>
<th>Grade(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal:</strong></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3-5</td>
</tr>
<tr>
<td>Fistula, GI–anus, rectum</td>
<td>3-5</td>
</tr>
<tr>
<td>Incontinence, anal</td>
<td>3-5</td>
</tr>
<tr>
<td>Necrosis, GI–anus, rectum</td>
<td>3-5</td>
</tr>
<tr>
<td>Obstruction, GI–rectum</td>
<td>3-5</td>
</tr>
<tr>
<td>Perforation, GI–rectum</td>
<td>3-5</td>
</tr>
<tr>
<td>Proctitis</td>
<td>3-5</td>
</tr>
<tr>
<td>Stricture/stenosis, GI–anus, rectum</td>
<td>3-5</td>
</tr>
<tr>
<td>Ulcer, GI–anus, rectum</td>
<td>3-5</td>
</tr>
<tr>
<td><strong>Hemorrhage/Bleeding:</strong></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage, GI–anus, rectum</td>
<td>3-5</td>
</tr>
<tr>
<td>Hemorrhage, GU–bladder, prostate, urethra</td>
<td>3-5</td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal–anus, rectum</td>
<td>3-4</td>
</tr>
<tr>
<td>Renal/genitourinary–bladder</td>
<td>3-4</td>
</tr>
<tr>
<td><strong>Renal/Genitourinary</strong></td>
<td></td>
</tr>
<tr>
<td>Bladder spasms</td>
<td>4</td>
</tr>
<tr>
<td>Cystitis</td>
<td>3-5</td>
</tr>
<tr>
<td>Fistula, GU–bladder, urethra</td>
<td>3-5</td>
</tr>
<tr>
<td>Incontinence, urinary</td>
<td>3-4</td>
</tr>
<tr>
<td>Obstruction, GU–bladder, prostate, urethra</td>
<td>3-5</td>
</tr>
<tr>
<td>Perforation, GU–bladder, prostate, urethra</td>
<td>3-5</td>
</tr>
<tr>
<td>Stricture/stenosis, GU–bladder, prostate, urethra</td>
<td>3-5</td>
</tr>
<tr>
<td>Urinary frequency/urgency</td>
<td>3</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>3-5</td>
</tr>
<tr>
<td><strong>Surgery/Intraoperative Injury</strong></td>
<td></td>
</tr>
<tr>
<td>Intraoperative injury–anal sphincter, anus, rectum, bladder, prostate, urethra</td>
<td>3-4</td>
</tr>
</tbody>
</table>

*Treatment-related grade 5 adverse event at any time*

### 13.1.2 Secondary Endpoints

**13.1.2.1** To evaluate acute treatment-related GI/GU adverse events.

An acute adverse event is defined as an adverse event occurring ≤270 days from the date of implantation and evaluated by the NCI CTCAE version 3.0 (see Section 13.1.1). The treatment-related attribution includes definitely, probably, or possibly related to treatment.

**13.1.2.2** To measure the following clinical outcomes: (see Section 11.3):

- Overall survival
- Disease-free survival
- Disease-specific survival
- Local failure
- Distant failure
- Biochemical failure

**13.1.2.3** To describe the distribution of the post-brachytherapy dosimetric coverage parameters

### 13.2 Sample Size

The primary goal of this study is to estimate the late treatment-related GI/GU adverse events (defined in 13.1.1) of prostate brachytherapy in patients with local tumor recurrence following EBRT for clinically localized prostate adenocarcinoma. We expect that ≤10% of patients will experience a late treatment-related GI/GU adverse event. A rate of ≥20% is considered unacceptable. Denote the rate of late treatment-related GI/GU adverse event as \( p_t \). The null hypothesis (\( H_0 \)) is that a dose level is not tolerable versus the alternative hypothesis (\( H_a \)) that a dose level is tolerable. The hypotheses are:
The sample size is calculated based on the above hypotheses with Fleming’s Multiple Testing Procedure at a significance level of 0.05 and 85% statistical power. At these type I and II error rates, 87 patients will detect a late treatment-related GI/GU adverse event rate of no more than 10% under the null hypothesis with an actual significance level of 0.029. Adjusting the number of cases for ineligible or unanalyzable cases by 10%, a maximum of 96 patients is required for this study.

13.3 Patient Accrual

Based on patient accrual in previous RTOG prostate studies, accrual will be negligible during the initial 6 months while institutions are obtaining IRB approval. The patient accrual is projected to be 3 patients per month considering the previous RTOG prostate studies, RTOG 0019 and 9805, and the characteristics of this patient population. The monthly accrual of RTOG 0019 and 9805 was 5 patients and 6 patients per month, respectively. However, the patient population for this study is more restricted than that in the two previous studies. We expect to complete accrual in 3 years. If at 21 months after study activation the average monthly accrual between months 16 and 21 is less than 2 patients, the feasibility of completing the study will be discussed with the study chairs, RTOG GU Cancer Committee chair, and RTOG Executive Committee. If the accrual rate is higher than the projected rate, we will amend the protocol to reflect the actual accrual rate.

13.4 Analysis Plan

13.4.1 Primary Endpoint

We expect that no more than 10% of patients will experience late treatment-related (grade ≥ 3) GI/GU adverse events. A rate of ≥ 20% is considered unacceptable. For the evaluation of late adverse events, analyzable patients are defined as eligible patients who received protocol treatment with at least 24 months of follow-up from the date of implantation. The stopping and continuation rules in the table below will be applied to the interim analyses. We are more concerned with a false negative decision (i.e., failure to detect an unacceptable rate if it exists) than we are with a false positive decision (i.e., a determination that the dose level is too toxic when in fact it is not). If at any stage we stop and reject the null hypothesis (H₀) and show that the late GI/GU adverse event rate may be no more than 10%, we will conclude that the current dose level is tolerable, stop the accrual for this dose level (if applicable), and consider escalation of the dose to that considered standard for primary brachytherapy. If we stop and reject the alternative hypothesis (Hₐ) at any stage, claiming that the late GI/GU adverse event rate may be at least 20%, we will stop the accrual for the current dose level (if applicable) and conclude that the current dose level is not tolerable. If we continue until the last stage, we will conclude either that the current dose level is tolerable or that it is not tolerable.

The rate of late treatment-related GI/GU adverse events, \( p_t \), will be calculated as the number of analyzable patients with late GI/GU adverse events divided by the total number of analyzable patients at the evaluation time point.

<table>
<thead>
<tr>
<th>Stopping and Continuation Rules for a Late GI/GU Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of analyzable patients</strong></td>
</tr>
<tr>
<td>( H_0: p_t \geq 0.2 )</td>
</tr>
<tr>
<td>44</td>
</tr>
<tr>
<td>73</td>
</tr>
<tr>
<td>87</td>
</tr>
</tbody>
</table>

*Analyzable patients are defined as eligible patients who received protocol treatment with at least 24 months follow-up from seed implant.
If at any time a grade 5 adverse event definitely, probably, or possibly related to treatment is reported, it will be reviewed by the study chairs, the study statistician, the RTOG GU Cancer Committee chair, and the RTOG Executive Committee. Case report forms (CRFs), source documentation, and a statistical report summarizing the study data will be reviewed as soon as possible. During this review, accrual will be suspended (if applicable). Following this review, the study chairs, the study statistician, the RTOG GU Cancer Committee chair, and the RTOG Executive Committee will discuss the findings and make a decision about amending the protocol and/or continuing the study.

Multivariate logistic regression\(^{32}\) will be used to model the association of factors with the occurrence of late treatment-related GI/GU adverse events. Both unadjusted and adjusted odds ratios and the respective 95% confidence interval will be computed. Time to late adverse events will be modeled by Cox-proportional hazards regression.\(^{33}\)

### 13.4.2 Secondary Endpoints

#### 13.4.2.1 Evaluation of Acute Treatment-Related GI/GU Adverse Events

An acute adverse event will be defined as an adverse event occurring no more than 270 days from the date of implantation. For the evaluation of acute adverse events, analyzable patients are defined as eligible patients who received any protocol treatment with at least 270 days of follow-up from implant. Treatment-related attribution includes definitely, probably, or possibly related to treatment. Patients will be tabulated by type, grade, and attribution of adverse event. Multivariate logistic regression\(^{32}\) will be used to model the distribution of acute treatment-related GI/GU adverse events. Both unadjusted and adjusted odds ratios and the respective 95% confidence interval will be computed.

#### 13.4.2.2 Analysis Plan for Clinical Outcomes

All eligible patients who received any protocol treatment will be included in the outcome analyses. For all secondary clinical outcome endpoints, all patients will be followed for a minimum of 5 years. The time to failure will be measured from the date of registration to the date of the event of interest (see Section 11.3). The secondary clinical outcomes disease-free survival and overall survival will be estimated using the Kaplan-Meier method.\(^{34}\) Disease-specific survival, local tumor progression, distant failure, and biochemical failure will be estimated using nonparametric estimation of cumulative incidence of the event of interest, taking into account the informative nature of censoring due to competing risks. Cumulative incidence, accounting for competing risk events, is estimated in a two-step process (Kalbfleisch and Prentice,\(^{35}\) Marubini and Valsecchi,\(^{36}\) Satagotan\(^{37}\)). Time to local, distant, and biochemical failure will be modeled by Cox proportional hazards regression.\(^{33}\) Both unadjusted and adjusted hazard ratios and the respective 95% confidence intervals will be computed. T-stage, PSA, Gleason score, and age (and other factors as appropriate) will be adjusted for in this analysis.

#### 13.4.2.3 Describing the Post-Brachytherapy Dosimetric Coverage

Post-brachytherapy dose coverage is evaluated by the evaluation target volume (ETV) parameters \(D_{90}, V_{100}, V_{90}, V_{150}, V_{200}\). The fractional volume of the ETV that receives \(p\)% of the prescribed dose is \(V_p\); \(D_q\) is the minimum dose in Gray delivered to \(q\)% of the prostate volume (see Section 6.5). The descriptive statistics of these variables will be tabulated.

### 13.4.3 Interim Reports

Interim reports will be prepared every 6 months until the final analysis. In general, the interim reports will include information about:

- Patient accrual rate with projected completion date
- Pretreatment characteristics of patients accrued
- The frequencies and grades of adverse events due to protocol treatment

### 13.4.4 CDUS Reporting

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

### 13.5 Inclusion of Minorities

In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, participation rates of men will be examined in the interim analyses. Based on the accrual statistics from RTOG prostate cancer trials 0019, 9805, and 9910, we project that 79% of the men in the study will be white, 15% will be African American, 3% will be Hispanic, 1% will be Asian, < 1% will be Pacific Islanders, and < 1%
will be American Indian or Alaskan Native. Table 2 lists the projected accrual for each ethnic and racial group.

**Table 2: Projected Distribution of Gender and Minorities**

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Gender</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
<td>Males</td>
<td>Total</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>N/A</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>N/A</td>
<td>93</td>
<td>93</td>
</tr>
<tr>
<td><strong>Ethnic Category: Total of all subjects</strong></td>
<td>N/A</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>Racial Category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
<td>N/A</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Asian</td>
<td>N/A</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Black or African American</td>
<td>N/A</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>N/A</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>White</td>
<td>N/A</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td>Others and Unknown</td>
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<td>3</td>
<td>3</td>
</tr>
<tr>
<td><strong>Racial Category: Total of all subjects</strong></td>
<td></td>
<td>96</td>
<td>96</td>
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</tbody>
</table>
REFERENCES


APPENDIX I

RTOG 0526

A PROSPECTIVE PHASE II TRIAL OF TRANSPERINEAL ULTRASOUND-GUIDED BRACHYTHERAPY FOR LOCALLY RECURRENT PROSTATE ADENOCARCINOMA FOLLOWING EXTERNAL BEAM RADIOThERAPY

Informed Consent Template for Cancer Treatment Trials
(English Language)

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have prostate cancer that has come back in your prostate after being treated with external beam radiotherapy.

Why is this study being done?
The purpose of this study is to evaluate the safety and effectiveness of brachytherapy (radiation seed implants) as treatment for prostate cancer that has come back in the prostate after external radiotherapy. The study will examine the side effects of the implants as well as the ability of the implants to get rid of the cancer.

It is important for you to realize that sometimes when prostate cancer comes back in the prostate after radiation it may be very slow growing and may not cause you symptoms or problems for years. Sometimes just monitoring your condition and not undergoing repeat treatment is appropriate. The treatment offered in this study may cause side effects. The side effects are discussed in this consent form, and you should read that section carefully and discuss it with your study doctor.

How many people will take part in the study?
About 96 men will take part in this study.

What will happen if I take part in this research study?
Before you begin the study… (3/10/10)

You will need to have the following exams, tests, or procedures to find out if you can be in the study. These exams, tests, or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.
Before starting any treatment, your study doctor needs to know that your prostate cancer grew back in your prostate gland and that it has not spread to other parts of your body. You will therefore need to have the following tests:

- A transrectal ultrasound (TRUS) will be done to measure the size of the prostate and see if cancer has spread to the nearby tissues. Small tissue samples will be taken by a needle biopsy done through the rectum into the prostate gland. If this shows prostate cancer, other tests will be done.
- About 2 tablespoons of blood will be taken from a vein. Tests will be done to determine the level of prostate-specific antigen (PSA) and may be done to check for low hemoglobin (anemia), the number of infection-fighting (white cells) and blood-clotting (platelets) cells, how well your kidneys are working, and testosterone (hormone) level.
- A bone scan will check for cancer spread to your bones.
- Computed tomography (CT) or magnetic resonance (MR) imaging of the pelvis and abdomen will be done to see if the cancer has spread.
- We may need to biopsy areas other than the prostate or do surgery to see if the cancer spread to certain lymph nodes.

In addition, your study doctor will need to send to a central study office a slide of the tumor tissue obtained at the time that you had surgery to find out if your prostate cancer came back. There, a pathologist will confirm that your tumor is the type of prostate cancer that the study doctors are evaluating in this study.

**During the study…**

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need these tests and procedures.

- A second TRUS may be done to measure the size of the prostate and to plan the prostate seed implantation. This may be done either at the time of the seed implant or within four weeks before the implant. This is done on either an inpatient (stay overnight) or outpatient (go home the same day) basis. The implantation will be done in the following way:
  - General or spinal anesthesia will be given before and during the implantation.
  - A tube (catheter) is inserted through the penis into the bladder, so urine can be drained.
  - Using TRUS for guidance, thin needles will be inserted through the skin between the anus and scrotum and positioned in the prostate.
  - The radioactive seeds will be put into the prostate as the needles are removed.
  - You will be taken to a recovery area after the seed implantation is done and may then go home, or you may stay overnight in the hospital.
  - The tube will be removed from the bladder either before you leave for home or within a day or two.

After the prostate seed implantation is complete… *(5/11/07)*

- Although the seeds are permanent, they release radiation only for a period of time. The amount of radiation you will give off following the implant is very low, so that you can leave the hospital immediately after the implant procedure. However, it is also recommended that you try to keep a 6-foot distance from babies, pregnant women, and small children for 3 weeks to 2 months after the procedure, depending on the type of
implant your study doctor uses. Your study doctor can tell you more details about the specific time period for which you should stay at a distance.

- You will come back to the study office three to five weeks later to have a CT scan of the prostate seed implantation area.

- You will have follow-up visits every three months for the first year, every six months for the next four years, and then every year for the rest of your life. Your study doctor will examine you and your prostate and will check your PSA (by a blood test) during these visits. Depending on the result of your PSA test, your study doctor may also see if other tests such as a bone scan or a biopsy of the prostate gland are needed at certain times.

- At each follow-up visit (until the end of the third year of the study), you will also be asked to answer a questionnaire that looks at urinary symptoms.

**How long will I be in the study?**  
After the prostate seed implantation, this study will follow you for life. You will visit your study doctor every three months for the first year after implantation, every six months for the next four years, and then every year for the rest of your life.

**Can I stop being in the study?**  
Yes. You can stop being in the study at any time. Tell the study doctor if you are thinking about stopping or you decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the treatment can be evaluated by him or her. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing would be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he or she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

**What side effects or risks can I expect from being in the study?**  
You may have side effects from this treatment. Everyone taking part in the study will be watched carefully for any side effects. However, researchers don’t know all the side effects that may happen. Side effects may be mild or very serious. You may not have any of these side effects. Your health care team may give you medicines to help lessen side effects. Many side effects go away within a few weeks of the seed implant. In some cases, side effects may be serious, long lasting, or may never go away. We may need to use drugs to help these problems, but they may not cure the problem. There is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Prostate seed implantation is done with anesthesia. Risks and side effects related to the anesthesia include those that are:

**Likely**
- Nausea
- Vomiting
- Headache
- Sore throat

**Rare but Serious**
- Blood pressure or heart rhythm problems
- Problems breathing
- Heart attack
- Allergic reaction
- Stroke
- Death

Risks and side effects related to the seed implant include those that are:

**Likely**
- Weak (slow) stream of urine
- Frequent urination
- Strong urges to urinate
- Pain when urinating

These problems are common, but they may improve or go away in many patients with time or the use of medicines.

**Less Likely**
- Need for use of a urinary catheter for an indefinite duration after the implant
- Blood in the urine shortly after brachytherapy (this usually clears up) or some months or years later
- Leakage of urine (incontinence)
- Pain in the implantation area (mild)
- Bladder infections that require antibiotics
- Injury to the rectum that may cause pain, bleeding, or leakage of stool
- Injury to the bladder, urethra, bowel, or other tissues in the pelvis
- Even though there may be no health risk, some radioactive seeds may travel to other parts of the body through a vein; however, the seeds release radiation only for a period of time

**Rare but Serious**
- Damage to the rectum requiring surgery or a colostomy (external bag to collect stool)

For more information about risks and side effects, ask your study doctor.

**Reproductive Risks**
Very small amounts of radiation from the radioactive seeds can reach other people. Talk to your study doctor if you are sexually active or are in close contact with small children and/or pregnant women. Exposure to radiation may be harmful to an unborn child. There is not enough medical information to know what the risks might be. You or your sexual partners must use one of the following birth control measures while you are in this study: condoms,
diaphragm, birth control pills or injections, intrauterine device (IUD), surgical sterilization, abstinence. In addition, you should use condoms during the first month following seed implantation due to the possibility that the seeds can be released during ejaculation.

**Are there benefits to taking part in this study?**

It is possible that this treatment will get rid of your prostate cancer. This could stop the cancer from spreading to other parts of your body. This may give you a healthier and longer life, but it is also possible this study may not make your health better.

We do know that the information from this study will help doctors learn more about prostate seed implants as a treatment for cancer that has come back in the prostate. This information could help future cancer patients.

**What other choices do I have if I don’t take part in this study?**

Your other choices may include:

- Surgical removal of the prostate (prostatectomy)
- Freezing the prostate (cryosurgery)
- Hormonal therapy
- Prostate seed implantation that is not as a part of this study
- Getting no treatment

Talk to your doctor about your choices before you decide if you will take part in this study.

**Will my medical information be kept private?**

Data are housed at RTOG Headquarters in a password-protected database. We will do our best to make sure that the personal information in your medical record will be kept private; however, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The Radiation Therapy Oncology Group (RTOG)
- Local institutional research boards
- The National Cancer Institute (NCI) and other government agencies, such as the Food and Drug Administration (FDA), involved in keeping research safe for people

**What are the costs of taking part in this study?**

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute’s Web site at:
http://www.cancer.gov/clinicaltrials/understanding/insurance-coverage

You can print a copy of the “Clinical Trials and Insurance Coverage” information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

**What happens if I am injured because I took part in this study?**

It is important that you tell your study doctor, __________________ [investigator’s name(s)], if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at __________________ [telephone number].

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

**What are my rights if I take part in this study?**

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

**Who can answer my questions about the study?**

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor __________________ [name(s)] at __________________ [telephone number].

For questions about your rights while taking part in this study, call the __________________ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at __________________ (telephone number).

![Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]
Consent Form for Use of Tissue for Research

[The following example of tissue consent has been taken from the NCI Cancer Diagnosis Program’s model tissue consent form found at http://www.cancerdiagnosis.nci.nih.gov/specimens/model.pdf]

About using tissue for research (3/29/11)

You have had a biopsy (or surgery) to see if you have cancer. Your doctor has removed some tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How Is Tissue Used for Research?" to learn more about tissue research. This information sheet is available to all at the following website: http://cdp.cancer.gov/humanSpecimens/ethical_collection/patient.htm

The research that may be done with your tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future. Reports about research done with your tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

For patients whose tumors come back after receiving prostate seed implantation:
If your study doctor recommends it and if you give your permission, you may have another biopsy to confirm that your tumor has come back. We would like to have this tissue sent to a central study office, so that a central pathologist can confirm that your tumor has come back. In addition, we would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases.

Things to think about

The choice to let us keep the leftover tissue for future research is up to you. No matter what you decide to do, it will not affect your care or your participation in the main part of the study.

If you decide now that your tissue can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue. Then any tissue that remains will no longer be used for research and will be returned to the institution that submitted it.

In the future, people who do research may need to know more about your health. Although the study doctor/institution may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.
Sometimes tissue is used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.

Your tissue will be used only for research and will not be sold. The research done with your tissue may help to develop new products in the future.

**Benefits**

The benefits of research using tissue include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

**Risks**

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

**Making your choice**

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. My tissue may be kept for use in research to learn about, prevent, or treat cancer.
   
   Yes  No

2. My tissue may be kept for use in research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

   Yes  No

3. Someone may contact me in the future to ask me to take part in more research.

   Yes  No

   **For patients whose tumors come back after receiving prostate seed implantation:**

4. My tissue may be sent to a central pathologist to confirm that my tumor has come back.

   Yes  No

5. My tissue may be kept for use in research to learn about, prevent, or treat cancer.

   Yes  No

6. My tissue may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
Where can I get more information? (4/12/12)

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at [http://cancer.gov](http://cancer.gov).

- For NCI’s clinical trials information, go to [http://cancer.govclinicaltrials](http://cancer.govclinicaltrials).
- For NCI’s general information about cancer, go to [http://cancer.gov/cancerinfo](http://cancer.gov/cancerinfo).

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature _________________________________________________

I have been given a copy of all _____ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant ________________________________

Date ____________________________
**APPENDIX II (6/10/09)**

**ZUBROD PERFORMANCE SCALE**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all predisease activities without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair 50% or more of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on self-care. Totally confined to bed</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>
APPENDIX III
AJCC STAGING SYSTEM PROSTATE, 6th Edition

DEFINITION OF TNM

Primary Tumor, Clinical (T)
TX Primary tumor cannot be assessed T0 No evidence of primary tumor

T1 Clinically inapparent tumor neither palpable or visible by imaging T1a Tumor incidental histologic finding in 5% or less of tissue resected T1b Tumor incidental histologic finding in more than 5% of tissue resected T1c Tumor identified by needle biopsy (e.g., because of elevated PSA)

T2 Tumor confined with prostate* T2a Tumor involves one-half of one lobe or less T2b Tumor involves more than one-half of one lobe but not both lobes T2c Tumor involves both lobes

T3 Tumor extends through prostate capsule** T3a Extraprostatic extension (unilateral or bilateral) T3b Tumor involves the seminal vesicle(s)

T4 Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles and/or pelvic wall

*Note: Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c

**Note: Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3, but as T2.

Regional Lymph Nodes (N)
NX Regional lymph nodes cannot be assessed N0 No regional lymph node metastasis N1 Metastasis in regional lymph node(s)

Primary Tumor, Pathologic (pT)
pT2* Organ confined pT2a Unilateral, involving one-half of one lobe or less pT2b Unilateral, involving more than one-half of one lobe but not both lobes pT2c Bilateral disease

pT3 Extraprostatic extension pT3a Extraprostatic extension** pT3b Seminal vesicle invasion

pT4 Invasion of bladder, rectum *Note: There is no pathologic T1 classification **Note: Positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease).
### Distant Metastasis (M)*

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Presence of distant metastasis cannot be assessed (not evaluated by any modality)</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

- M1a Nonregional lymph node(s)
- M1b Bone(s)
- M1c Other site(s) with or without bone disease

*Note: When more than one site of metastasis is present, the most advanced category is used; pM1c is most advanced.

### Histopathologic Grade (G)

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>GX</td>
<td>Grade cannot be assessed</td>
</tr>
<tr>
<td>G1</td>
<td>Well-differentiated (slight anaplasia [Gleason 2-4])</td>
</tr>
<tr>
<td>G2</td>
<td>Moderately differentiated (moderate anaplasia [Gleason 5-6])</td>
</tr>
<tr>
<td>G3-4</td>
<td>Poorly undifferentiated or undifferentiated (marked anaplasia [Gleason 7-10])</td>
</tr>
</tbody>
</table>

### Stage Grouping

<table>
<thead>
<tr>
<th>Stage</th>
<th>T1a</th>
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<th>M0</th>
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<tr>
<td>Stage IV</td>
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</tbody>
</table>

*Note: When more than one site of metastasis is present, the most advanced category is used; pM1c is most advanced.*
APPENDIX IV

GLEASON CLASSIFICATION^1

Histologic Patterns of Adenocarcinoma of the Prostate

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Margins Tumor Areas</th>
<th>Gland Pattern</th>
<th>Gland Size</th>
<th>Gland Distribution</th>
<th>Stromal Invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Well defined</td>
<td>Single, separate, round</td>
<td>Medium</td>
<td>Closely packed</td>
<td>Minimal, expansile</td>
</tr>
<tr>
<td>2</td>
<td>Less definite</td>
<td>Single, separate rounded but more variable</td>
<td>Medium</td>
<td>Spaced up to one gland diameter, average</td>
<td>Mild, in larger stromal planes</td>
</tr>
<tr>
<td>3</td>
<td>Poorly defined</td>
<td>Single, separate more irregular</td>
<td>Small medium, or large</td>
<td>Spaced more than one gland diameter, rarely packed</td>
<td>Moderate, in larger or smaller stromal planes</td>
</tr>
<tr>
<td>or 3</td>
<td>Poorly defined</td>
<td>Rounded masses of cribriform or papillary epithelium</td>
<td>Medium or large</td>
<td>Rounded masses with smooth sharp edges</td>
<td>Expansile masses</td>
</tr>
<tr>
<td>4</td>
<td>Ragged, infiltrating</td>
<td>Fused glandular masses or &quot;hypernephroid&quot;</td>
<td>Small</td>
<td>Fused in ragged masses</td>
<td>Marked, through smaller planes</td>
</tr>
<tr>
<td>5</td>
<td>Ragged, infiltrating</td>
<td>Almost absent, few tiny glands or signet ring</td>
<td>Small</td>
<td>Ragged anaplastic masses of epithelium</td>
<td>Severe between stromal fibers or destructive</td>
</tr>
<tr>
<td>or 5</td>
<td>Poorly defined</td>
<td>Few small lumina in rounded masses of solid epithelium central necrosis</td>
<td>Small</td>
<td>Rounded masses and cords with smooth sharp edges</td>
<td>Expansile masses</td>
</tr>
</tbody>
</table>

The Gleason Classification is a system of histologic grading based on over-all pattern of tumor growth at relatively low-magnification (40 to 100x). Five patterns of growth are recognized and numbered in order of increasing malignancy. Because of histologic variation in the tumor, two patterns are recorded for each case, a primary or predominate pattern and a secondary or lesser pattern.

The Gleason Score is the sum of the primary and secondary pattern, if only one pattern is present, the primary and secondary pattern receive the same designation.

(Primary = 2, Secondary = 1, Gleason = 3)

(Primary = 2, Secondary = 2, Gleason = 4)

APPENDIX V

Appendix 1-A: THE AMERICAN UROLOGICAL ASSOCIATION (AUA) SYMPTOM INDEX FOR BENIGN PROSTATIC HYPERPLASIA (BPH) AND THE DISEASE SPECIFIC QUALITY OF LIFE QUESTION

Note: Please see the form on the NRG Oncology/RTOG web site (http://www.rtog.org).