RADIATION THERAPY ONCOLOGY GROUP

RTOG 0321

PHASE II TRIAL OF COMBINED HIGH DOSE RATE BRACHYTHERAPY AND EXTERNAL BEAM RADIOTHERAPY FOR ADENOCARCINOMA OF THE PROSTATE

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SCHEMA

R
E
C
O
R
D

PSA
1. ≤ 10
2. > 10 to ≤ 20

Combined Gleason Score
1. 2-6
2. 7
3. 8-10

T Stage
1. T1c- -T2c
2. T3a, T3b

Hormonal Therapy
1. No
2. Yes

Timing of HDR Brachytherapy
1. Before XRT
2. After XRT

R
E
G
I
S
T
E
R

Patients will receive 45 Gy external beam radiation therapy and HDR brachytherapy boost 19 Gy in 2 fractions

Institution must be pre-credentialed (Section 5.0)

Patient Population: (See Section 3.0 for complete eligibility) (3/23/05)
Histologically-confirmed, adenocarcinoma of the prostate
One of the following combinations
- Clinical stage T1c - T2c, Gleason score 2-6 and PSA > 10 but ≤ 20
- Clinical stage T3a, T3b, Gleason score 2-6 and PSA ≤ 20
- Clinical stage T1c - T3b, Gleason score 7-10 and PSA ≤ 20

Zubrod Performance Status 0-1
No prior pelvic or prostate radiation
No distant metastases (M0)
No clinically involved lymph nodes

Required Sample Size: 110

RTOG Institution # _____

RTOG 0321 **ELIGIBILITY CHECKLIST (7/30/04) (3/23/05) (4/25/06)**

Case # _____

_____(Y) 1. Is there histologically confirmed, locally confined adenocarcinoma of the prostate?

_____(Y) 2. Does the patient meet all criteria of one of the combinations of factors listed in section 3.1.6?
- Clinical stage T1c - T2c, Gleason score 2-6 and PSA > 10 but ≤ 20
- Clinical stage T3a, T3b, Gleason score 2-6 and PSA ≤ 20
- Clinical stage T1c - T3b , Gleason score 7-10 and PSA ≤ 20

_____(T1c-T3b) 3. What is the T stage?

_____(Y) 4. Are nodes clinically negative by imaging (pelvic CT, MRI)?

_____(M0) 5. Is the patient clinically M0?

_____(0-1) 6 What is the performance status?

_____(≤20) 7. What is the PSA level (prior to hormone therapy, if applicable)?

_____(N) 8. Has the patient had pelvic or prostate radiation?

_____(Y/N) 9. Has the patient had any hormone therapy?

_____(Y) 10. If yes, did it begin ≤ 120 days prior to study entry?

_____(N) 11. Has the patient had radical surgery for prostate carcinoma?

_____(N) 12. Has the patient had prior chemotherapy for prostate cancer?

_____(Y/N) 13. Has the patient had a prior invasive malignancy (except non-melanomatous skin cancer)?

_____(Y) If yes, has the patient been disease free for a minimum of 3 years prior to study entry?

_____(N) 14. Are there any major medical or psychiatric illnesses that would prevent completion of treatment or interfere with follow-up?

_____(N) 15. Has the patient had a TURP?

_____(N) 16. Has the patient had a hip replacement?

_____(≤20) 17. How many patients have you registered to this study?

(Continued on the next page)

The following questions will be asked at Study Registration:

_____ 1. Name of institutional person registering this case?

_____(Y) 2. Has the Eligibility Checklist (above) been completed?

_____(Y) 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. Patient's Country of Residence

_____ 12. Zip Code (U.S. Residents)

_____ 13 Patient's Insurance Status

_____ 14. Will any component of the patient's care be given at a military or VA facility?

_____ 15. Radiotherapy start date

_____ 16. Combined Gleason Score of tumor (2-6, 7, 8-10)

_____ 17. Has the patient had hormonal therapy within 120 days of study registration?

(Continued on the next page)

_____ 18. Pretreatment PSA (pre hormone, if given) [≤10 vs. >10 to ≤20]

_____ 19. T Stage (T1c-T2c vs., T3a-T3b)

_____ 20. HDR brachytherapy given before or after XRT? (Before XRT vs. After XRT)

The Eligibility Checklist must be completed in its entirety prior to calling RTOG. 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 _____

1.0 INTRODUCTION

1.1 Background

The goal of radiotherapy is to deliver a high dose of radiation to the target volume while minimizing the dose to the surrounding normal tissue. Using CT based three-dimensional treatment planning system and multiple field technique, the three dimensional conformal radiotherapy (3DCRT) has become the standard of care for external beam radiotherapy for prostate cancer. Multiple institutional studies and prospective randomized trials have been done documenting the safety and efficacy of this modality. Brachytherapy is an alternative method of delivering conformal radiotherapy for treatment of prostate cancer. The technique of HDR prostate brachytherapy has been in clinical practice since the 1980's.[1-13] Kovacs et al reported one of the earliest experiences using HDR brachytherapy boost at University of Kiel.[10, 11, 13] Patients treated were mostly T2b-T3, G3. They used a combination of split course external beam radiotherapy and two 15 Gy HDR treatments. They reported 18% positive biopsy rate 18 months post treatment. The result was updated at 10 years and 78 percent of 171 patients remained free of disease at median follow-up of 55 months. Mate et al at Swedish Medical Center reported their experience with HDR brachytherapy.[9] They used a more moderated hypofractionated schema with four treatments of 3-4 Gy fractions of HDR treatments combined with 45-50 Gy of external beam radiotherapy. They recommended routine cystoscopy at the end of the implant procedure to ensure the catheters are placed at the proper depth and to avoid injuring the urethra. Pretreatment patient characteristics were stage T1b to T3c, mean initial PSA was 12.9 and Gleason grade ranges 3 to 9. They reported 84% 5-year biochemical disease free survival. Martinez et al at the William Beaumont Hospital reported the only on-going prospective dose escalation trial using HDR brachytherapy as a boost. There have been multiple updates of their results.[5-7, 12, 14] They have continued to dose escalate using increasingly larger fractions of HDR treatment range from 5.5-6.5 Gy x 3 to 8.25-11.5 Gy x 2 combined with 46 Gy of external beam radiotherapy. As of their most recent update, they have shown acceptable toxicity levels using 9.5 Gy x 2 treatments. Patients with a PSA level ≥ 10, T stage ≥ T2b, and Gleason score ≥ 7 were selected for the trial. Despite a high frequency of poor prognostic factors, the actuarial biochemical control rate was 89% at 2 years and 63% at 5 years. The 5-year actuarial rates of local failure and distant metastasis were 16% and 14%, respectively. Borghede et al. at Goteborg University in Sweden reported their experience using 50 Gy of external beam radiotherapy combined with 2 fractions of 10 Gy HDR boost.[1, 2] They used ultrasound to target tumor nodules within the prostate and gave an additional 5 Gy boost during each HDR treatment. They reported a 4% positive biopsy rate at 18-months post treatment. Patients included in the study were T1-3, and grade 1-3. No hormonal therapy was used in the study. After a median follow-up of 45 months, a post-treatment PSA level of ≤ 1 was obtained in 84% of the patients. Dinges et al. at University of Berlin reported their experience combining 40-45 Gy of external beam radiotherapy with a 9-10 Gy HDR boost.[3, 4] Out of 82 patients with a median follow-up of 24 months, the local control rate was 79.5% at 2 years. The results from these single institutional clinical trials have shown the technique of HDR brachytherapy for prostate cancer is feasible with minimal morbidity. However, the excellent results of institutional studies must be validated in multi-institutional setting, and should be compared with other treatment techniques in multi-institutional, prospective trials.

1.2 Technical aspects of HDR brachytherapy

There are many reasons why HDR brachytherapy may be useful in the delivery of conformal radiotherapy to the prostate. Modern HDR brachytherapy systems use computer planning programs and robotic delivery systems. During the treatment, a single, high-activity iridium-192 source is moved through the implant catheters at 2.5-5 mm intervals. The programmable delivery system controls the amount of time the source stops at a particular location. This is also called the "dwell time". By changing the combination of dwell times, an infinite variety of isovolume dose distributions can be generated. The brachytherapy treatment planning systems can optimize the dwell times based on their location in the implant using computer algorithms. This allows a more homogenous dose within the implant volume and better coverage of the target volume.[15] Recent advances in treatment planning may provide further refinement of dosimetry by using inverse planning algorithms.[16, 17] Hsu et al compared the dosimetry data generated from 3D conformal external beam radiotherapy with HDR brachytherapy and showed significantly less rectal and bladder volume irradiated using HDR brachytherapy boost compared with conformal external beam radiotherapy.[18] Beside the dosimetric advantages, there are other practical advantages of HDR brachytherapy compared with traditional LDR brachytherapy. Since the HDR source has high activity (typically 10 Curie), a treatment is delivered in a few minutes,

similar to external beam radiotherapy, and it is always carried out in the shielded controlled environment of the HDR treatment room. Between treatments the patient does not need to be isolated and can stay in an unshielded room with other patients. There is no radiation exposure to hospital personnel or to the patient's family members. Since HDR implant is a closed system, there is no risk of seed migration. The effect of post-implant edema can be accounted for by performing dose calculation after the implant. Finally, by treating multiple patients with a single radioactive source there is the potential for cost saving compared to permanent seed implant boost.

1.3 Radiobiology of HDR brachytherapy

Clinical gain has been predicted and reported using alternative fractionation schemes in radiotherapy.[19, 20] The linear-quadratic model represents the basis for estimating the clinical effects of alternative fractionation schemes. In this model, the response of tissue to altered fractionation is determined by the tissue's alpha-beta ratio. Tissue with a higher alpha-beta ratio is less sensitive to a high dose per fraction or hypofractionated radiotherapy. In clinical practice, most tumors have a high alpha-beta ratio; therefore, these tumors are treated with standard fractionated or hyperfractionated radiotherapy. Conversely, tumors with a lower alpha-beta ratio can be treated effectively with a higher dose per fraction radiotherapy or hypofractionated radiotherapy.

The alpha-beta value commonly used for acute responding tissue and tumor is 10-12 Gy. Brenner et al estimated the alpha-beta ratio for prostate carcinoma based on mature clinical data and has shown that prostate cancer has an exceptionally low alpha-beta ratio of 1.5 Gy.[21] Recent studies have supported this finding.[22-24] If this is true, then prostate cancer's alpha-beta ratio is significantly lower than the alpha-beta ratio of dose limiting structures around the prostate (3-5 Gy). This suggests there is a potential gain for treating prostate cancer using hypofractionated radiotherapy.[25-27] Hsu et al calculated this potential biological dose gain based on the linear quadratic model and comparison of HDR dosimetry with conformal external beam radiotherapy.[18] They showed a potential increase of 7-64% in the biological dose delivered to the prostate without an increase in the biological dose delivered to the rectum using HDR boost. It is clear from this study that if the radiobiological hypothesis is correct, the hypofractionation radiotherapy may indeed be a more effective form of radiotherapy for prostate cancer and may have fewer side effects. However, the feasibility of delivering high quality HDR prostate brachytherapy and the actual toxicity of treatment must be documented in further multi-institutional trials.

2.0 OBJECTIVES

2.1 Primary Objectives

2.1.1 The primary goal of this study is to estimate the rate of late Grade 3 or greater genitourinary and gastrointestinal toxicity following treatment with external beam radiation therapy and high dose rate brachytherapy.

2.2 Secondary Objectives

2.2.1 Secondary goals of this study include an estimation of:

- Acute grade 3 or greater genitourinary and gastrointestinal toxicity
- Freedom from biochemical failure
- Overall survival
- Disease-specific survival
- Clinical relapse, local and/or distant

2.2.2 Develop a quality assurance process for HDR prostate brachytherapy

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility (3/23/05)

3.1.1 Histologically confirmed, adenocarcinoma of the prostate, clinical stage T1c-T3b, N0, M0 (Appendix III).

3.1.2 Patient will have clinically negative nodes as established by imaging (pelvic CT, MR).

3.1.3 The patient will be clinically M0.

3.1.4 Zubrod status 0-1 (Appendix II).

3.1.5 No prior pelvic or prostate radiation or chemotherapy for prostate cancer; induction hormonal therapy beginning $\leq$ 120 days prior to registration is acceptable.

3.1.6 One of the following combinations of factors:

- Clinical stage T1c-T2c, Gleason score 2-6 and PSA >10 but $\leq$ 20

Clinical stage T3a-T3b, Gleason score 2-6 and PSA ≤ 20
Clinical stage T1c-T3b, Gleason score 7-10 and PSA ≤ 20

3.1.7 Patients must sign a study-specific consent form prior to registration.

3.2 Conditions for Patient Ineligibility (3/23/05) (4/26/06)

3.2.1 Stage T4 disease.
3.2.2 Lymph node involvement (N1).
3.2.3 Evidence of distant metastases (M1).
3.2.4 Radical surgery for carcinoma of the prostate.
3.2.5 Previous hormonal therapy beginning > 120 days prior to registration.
3.2.6 Major medical or psychiatric illness which, in the investigator's opinion, would prevent completion of treatment and would interfere with follow-up.
3.2.7 Prior TURP.
3.2.8 Prior invasive malignancy(except non-melanomatous skin cancer) unless disease free for a minimum of 3 years (For example, carcinoma *in situ* of the oral cavity or bladder are permissible).
3.2.9 Hip prosthesis.

4.0 PRETREATMENT EVALUATIONS (3/23/05)

4.1 History and physical (to include tumor measurements) and Zubrod performance status (Appendix II).
4.2 Lymph node evaluation must be performed within 90 days prior to registration by at least one of the following: CT or MRI.
4.3 Cystoscopy, if advised by the urologist, may be performed to check for urethral strictures, bladder pathology, or a large median prostate lobe.
4.4 Prostate specific antigen (PSA) prior to treatment (pre-hormone therapy, if given).

5.0 REGISTRATION PROCEDURES

5.1 Pre-Registration Requirements

5.1.1 HDR Brachytherapy Credentialing Only institutions that have completed the Knowledge Assessment Questionnaire, the Facility Inventory, and the Benchmark Cases, as described in RTOG HDR Prostate Implant Quality Assurance Guidelines (see ATC web site and link to http://atc.wustl.edu/) may enter patients into this study. The sample clinical case with complete Post Implant Data Form and other materials are to be sent to the Radiological Physics Center (RPC). Upon review and successful completion, the Radiological Physics Center will notify both the registering institution and RTOG Headquarters that the institution is eligible to enter patients onto this study. Notification will then be given to the institution from the RTOG RT Quality Assurance Department.

5.1.2 As part of the credentialing process, 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 on electronic data submission can be found on the ATC web site at http://atc.wustl.edu.

5.1.3 A maximum of 20 patients from each institution may be registered.

5.2 Registration

5.2.1 Online Registration

Patients can be registered only after eligibility criteria are met. The RA will register the patient by logging onto the RTOG Web site (http://www.rtog.org), going to "Data Center Log in" and selecting the link for new patient registrations. A user name and password is required. The system triggers a program to verify that all regulatory (OHRP assurance, IRB approval) and credentialing requirements 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 and credentialing 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 RTOG Headquarters 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 and/or credentialing 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 that the RTOG Web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters.

6.0 RADIATION THERAPY

Note: Intensity Modulation Radiation Therapy (IMRT) is not allowed.

6.1 External Beam Radiation Therapy

The clinical target volume (CTV) for the external beam treatment is the prostate and seminal vesicles or whole pelvis depending on the lymphatic risk. If 2/3 PSA + [(GS-6) x 10] is > 15%, whole pelvis radiation is required.

6.1.1 Technical Factors

Megavoltage equipment is required with effective photon energies of ≥ 6 MV. Minimum source to axis distance is 100 cm. Any treatment technique (field arrangement) capable of producing the required dose distribution will be acceptable, with the exception of perineal boost. IMRT is not allowed on this protocol. A minimum of four fields (AP:PA:R:L) is required. Typical field arrangements will be four-field technique for regional lymphatic volume, and 4 or 6 field technique for the prostate and seminal vesicles.

6.1.2 Target Volume - Whole Pelvis (3/23/05)

6.1.2.1 The superior border of the regional lymphatic volume will be at the bottom of the L5. Lateral borders will be at least 2 cm lateral to the pelvic brim. Inferior borders will be generally near the inferior border of the ischial tuberosity. If CT treatment planning is used, the border should be set at least 2 cm below the most inferior aspect of the prostate. If urethrogram is used, the border should be set at least 1.5 cm below the apex of the urethrogram.

6.1.2.2 In the lateral fields care should be made to adequately cover the internal and external iliac lymph nodes below the L5 and to include the posterior extension of the seminal vesicles. The anterior border should include the pubic symphysis and the posterior border should include the S2 vertebral body

6.1.2.3 The use of the CT treatment planning is highly recommended. When using CT treatment planning, there should be a 1-1.5 cm margin around the posterior border of the prostate and seminal vesicles. A representation of the prostate and the seminal vesicles should be identified on the simulation films or on the digital reconstructed radiographs (DRR).

6.1.3 Target Volume – Prostate and Seminal Vesicles (3/23/05)

6.1.3.1 Prostate and seminal vesicles target volume must be obtained based on a pre-treatment CT. The PTV is a 1-1.5 cm margin around the prostate gland and the seminal vesicles (CTV). A representation of the prostate and the seminal vesicles must be identified on the simulation film or on the DRR.

6.1.4 Critical Structures

The bladder and part of the rectum will receive the same dose as the regional lymphatics. An effort should be made to keep the bladder distended.

6.1.5 Dose Specifications

6.1.5.1 For conventional (non-CT based) treatment planning: the prescribed dose is defined on the central axis at the projected center of the target volume. All patients will require isodose plans at the central axis.

6.1.5.2 For conformal (CT based) treatment planning: the dose should be prescribed to the minimum target dose (i.e. to the highest isodose line which encompasses the PTV).

6.1.5.3 Daily doses will be 1.8 Gy given five times per week for a total dose of 45 Gy.

6.1.6 Data Submission

External Beam Radiation Therapy data to be submitted only upon request.

6.2 Brachytherapy

6.2.1 Timing **(4/25/06)**

Brachytherapy may be performed before or after the external beam radiotherapy. The overall treatment course (external beam radiotherapy and brachytherapy) should be limited to no longer than 8 weeks.

6.2.2 Implant Procedure (3/23/05)

6.2.2.1 Afterloading catheters must be placed with TRUS guidance. The implant catheters must be CT compatible, do not use metal catheters. The implant procedure may be done under epidural, spinal or general anesthesia. Epidural or patient controlled analgesia (PCA) may be used during the post-op period for pain control. During the implant, attention should be given to keep

the catheters in the prostate without perforating the urethra. A Foley catheter should be inserted to allow visualization of the urethra. Posterior rows of catheters may be advanced into the seminal vesicles under TRUS guidance.

6.2.2.2 No fewer than 14 catheters must be in the clinical target volume for adequate coverage without excessive hot spots.

6.2.2.3 Flexible cystoscopy should be done to ensure that no implant catheter is left in the prostate Evaluation of the depth of insertion should be done by retroflexing the cystoscope 180 degrees in the bladder until the bladder neck is visualized. Advance the tip of the implant catheter until bladder mucosa is tenting. Efforts should be made to minimize accidental perforation of the bladder mucosa.

6.2.2.4 To facilitate with the identification of target and normal structures, fiducial marker seeds must be placed under TRUS guidance at the base (1-2 seeds) and the apex of the prostate (1 seed). A 14-16 Fr. Foley catheter should be inserted in the urethra at the conclusion of the implant procedure.

6.2.3 Brachytherapy Treatment Planning (Electronic data submission required)

6.2.3.1 3D CT based brachytherapy treatment planning is required.

6.2.3.2 The treatment planning CT scan must be performed with the patient in the supine position with the Foley catheter in place. Metallic obturators or non-CT compatible dummy ribbons must be removed prior to the CT scan. The scan must include the all of the CTV with at least 9 mm superior and inferior margin, and the scan must include the tips of all the implanted catheters. The scan thickness must be ≤ 0.3 cm and the slices must be contiguous. The brachytherapy target volume and critical structures must be outlined on all CT slices (see Section 6.2.4)

6.2.3.3 Dwell Selection and Dwell Time Optimization The dwell time in dwell positions located outside of the PTV must be turned down or off to minimize normal tissue irradiated. A dwell time optimization program based on geometric or inverse planning algorithm may be used. Manual optimization is also accepted.

6.2.4 Brachytherapy Target Volume

6.2.4.1 The definition of volumes will be in accordance with ICRU Report 58: Dose and Volume Specification for reporting interstitial therapy.[28] The Clinical Target Volume (CTV) is defined by the physician on the treatment planning CT scan. For T1c-T2b, the brachytherapy CTV includes the prostate only and for T3a-T3b, the brachytherapy CTV includes the prostate and extra-capsular extension.

6.2.4.2 The brachytherapy Planning Target Volume (PTV) is identical to the CTV.

6.2.5 Critical Structures

Critical structures to be contoured include the bladder, rectum, and urethra. When contouring the bladder and rectum, the outer most border of the mucosa must be contoured. For the urethra, the outer surface of the Foley catheter must be contoured. Critical structures must be contoured on every CT slice that contains a target volume and in at least 3 slices (9 mm) above and below the CTV.

6.2.6 Dose Specifications

The prescription dose of 19 Gy in two fractions will be given only to the CTV. The brachytherapy dose will be prescribed to the periphery of the PTV. The goal is to deliver the prescription dose to at least 90% of the PTV. However, the dose to critical normal structures must be kept to a minimum. The volume of bladder and rectum receiving 75% of the prescription dose must be kept to less than 1 cc (V75 rectum and V75 bladder < 1 cc) and the volume of urethra receiving 125% of the prescription dose must be kept to less than 1 cc (V125 urethra < 1 cc). If the dose to critical normal structures cannot be kept below the specified level, we recommend readjusting the implant or repeating the implant procedure until a more optimal implant is obtained.

6.2.7 Source Loading

The first HDR treatment will be delivered on the day of the catheter placement. The second treatment will be delivered within 24 hours after the first treatment, but no less than 6 hours between implants.

6.2.8 Catheter Position Verification

Visual inspection of the catheters prior to delivery of each treatment is required. Fluoroscopy or CT may be also used to verify the position of the catheters. The physician may adjust the catheters if catheter displacement is identified prior to the treatment. If the physician feels the catheters cannot be satisfactorily repositioned and cannot be corrected by a new plan, then the treatment should be postponed until a satisfactory implant may be done. If the planning process is repeated, then a second set of data should be submitted.

6.2.9 Catheter Removal
After completion of the treatment all catheters should be removed.

6.2.10 Data Submission (See Section 12.2)
All data must be submitted digitally to ITC:

Image-Guided Therapy Center (ITC)
Washington University School of Medicine
4511 Forest Park, Suite 200
St. Louis MO 63110
Phone: 314-747-5415
Fax: 314-747-5423

6.2.10.1 HDR Treatment plan This includes the overall treatment time, source activity, and dwell times of each fraction delivered should be submitted electronically to ITC.

6.2.10.2 Treatment planning CT The scan must include the entire prostate and the area at least 3 slices (9 mm) above and below the prostate. The tips of all the catheters must be included. The patient's external body contours should not be included in the field of view (FOV) in order to maximize the image quality. The scan should be transmitted in DICOM form to ITC electronically.

6.2.10.3 Contours and Isodose Distributions Isodose distributions of 75%, 100%, 125%, 150%, 200% of the prescription dose, with contours of the PTV and critical structures with at least 9 mm in the cephalad and caudal directions must be submitted digitally to ITC (unless ITC requests hard copies). Electronic data transmission will be used after the institution has successfully completed a practice run with the Image Guided Therapy Center [ITC].

6.2.10.4 Dose Volume Histograms The number of sample points used in these calculations should be stated. A minimum of 5000 points should be sampled for the calculation of each DVH. A post implant data form that describes the volumes, the dose description, and the dose volume histograms of the PTV, rectum, bladder, and urethra will be completed. The post implant data form will be attached to the above material. These data will be submitted electronically to ITC.

6.2.11 Compliance Criteria
Unacceptable deviation is any dose to bladder, rectum or urethra greater than the prescription guideline (section 6.2.6)

Per Protocol: ≥ 90% of the PTV receives the prescription dose.
Minor variation: ≥ 80% to < 90% of the PTV receives the prescription dose.
Major variation: < 80% of the PTV receives the prescription dose.

6.2.12 R.T. Quality Assurance Reviews
The principal investigator, Dr. Hsu, will perform an RT Quality Assurance Review after complete digital data for the first 20 cases enrolled have been received at ITC. Dr. Hsu will perform the next review after complete data for the next 20 cases enrolled have been received. 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. These reviews will be ongoing.

6.3 Radiation Toxicity

6.3.1 All patients will be seen weekly by their radiation oncologist during radiation therapy. Any observations regarding radiation reactions will be recorded and should include attention toward the following potential side effects:

6.3.2 Small bowel or rectal irritation manifesting as abdominal cramping, diarrhea, rectal urgency, proctitis, or hematochezia

6.3.3 Bladder complications including urinary frequency, urgency, dysuria, hematuria, urinary tract infection, and incontinence

6.3.4 Clinical discretion may be exercised to treat side effects from radiation therapy. Rectal side effects such as diarrhea may be treated with drugs such as diphenoxylate or loperamide or similar drugs. Bladder or rectal spasms can be treated with anticholinergic or tolterodine. Bladder irritation can be managed with phenazopyridine and/or an alpha blocker. Erectile dysfunction can be treated with sildenafil or similar drugs.

6.4 Radiation Adverse Event Reporting

6.4.1 Adverse Events (AEs) and Serious Adverse Events (SAEs) Reporting Requirements (4/25/06)

Adverse events (AEs) and serious adverse events (SAEs) will be reported to the Cancer Therapy Evaluation Program (CTEP) via the Adverse Event Expedited Reporting System (AdEERS) application AND to the Radiation Therapy Oncology Group (RTOG) 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: Expedited Adverse Event Reporting Requirements*. December 2004.]

Definition of an SAE: Any adverse experience occurring at any dose 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.

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.

AdEERS REPORTING REQUIREMENTS

AdEERS 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 AdEERS RT-only pathway.

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for grading of all adverse events. A copy of the CTCAE v3.0 can be downloaded from the Cancer Therapy Evaluation Program (CTEP) home page (http://ctep.info.nih.gov) or the RTOG web site (http://www.rtog.org/members/toxicity/main.html).

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 AdEERS application. AdEERS can be accessed via the CTEP web site (https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup). Use the patient's case number as the patient ID when reporting via AdEERS. AEs and SAEs reported using AdEERS **must also be reported to RTOG on the AE case report form** (see Section 12.1).

Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System 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. The AdEERS System allows submission of all reports regardless of the results of the assessment.

CRITERIA FOR AdEERS REPORTING REQUIREMENTS FOR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS THAT OCCUR WITHIN 30 DAYS OF THE DATE OF THE LAST PROTOCOL TREATMENT

	3		3		4 & 5	4 & 5
	Unexpected		Expected		Unexpected	Expected
	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization		
Unrelated Unlikely	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24 Hour: 5 Calendar Days	10 Calendar Days

CRITERIA FOR AdEERS REPORTING REQUIREMENTS FOR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS THAT OCCUR > 30 DAYS AFTER THE DATE OF THE LAST PROTOCOL TREATMENT

	3		3		4 & 5	4 & 5
	Unexpected		Expected		Unexpected	Expected
	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization		
Unrelated Unlikely	Not required	Not required	Not required	Not Required	Not required	Not required
Possible Probable Definite	10 Calendar Days	Not required	Not required	Not Required	24 Hour: 5 Calendar Days	10 Calendar Days

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete AdEERS 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 AdEERS 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.

RTOG REPORTING REQUIREMENTS

AdEERS 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 AdEERS RT-only pathway.

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for grading of all adverse events. A copy of the CTCAE v3.0 can be downloaded from the Cancer Therapy Evaluation Program (CTEP) home page (http://ctep.info.nih.gov) or the RTOG web site (http://www.rtog.org/members/toxicity/main.html).

Adverse Events (AEs) and Serious Adverse Events (SAEs) that meet the criteria defined above experienced by patients accrued to this protocol **must be reported as indicated in the following tables to: RTOG AE/SAE PHONE: 215-717-2762; 800-227-5463 ext. 4189**

(available 24 hours/day). SAEs must be reported to RTOG within 24 hours of discovery of the event.

Outside of regular business hours (8:30-5:00 EST), leave a message that includes the study/case numbers and the caller's contact information. A Data Manager will return the call the next business day requesting details of the event. The Data Manager will also inform the caller whether the AdEERS report must be submitted within 5 or 10 days of the initial phone report.

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

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

6.4.2 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS) (4/25/06)

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the **NCI/CTEP Secondary AML/MDS Report Form** available at http://ctep.cancer.gov/forms/index.html. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification (RTOG study/case numbers). This form will take the place of a report via the AdEERS system and **must be faxed to the Investigational Drug Branch, FAX 301-230-0159, and mailed to RTOG Headquarters (address below) within 30 days of AML/MDS diagnosis.**

RTOG Headquarters
AML/MDS Report
1818 Market Street, Suite 1600
Philadelphia, PA 19103

7.0 DRUG THERAPY

Does not apply to this study

8.0 SURGERY

8.1 Prostate Rebiopsy

8.1.1 A biopsy will be performed for all patients with evidence of biochemical failure or growth of a palpable abnormality. A PSA failure is defined as a consistent and significant rise in the PSA. The ASTRO definition of PSA failure will be used. Thus, when the PSA rises on three consecutive occasions, biochemical failure has occurred and the date of the failure is midway between the last non-rising PSA and the first rise in PSA.

8.1.2 Biopsies are strongly recommended for patients with evidence of distant failure to assist in accurately determining the "true" local control rate. In the absence of a biopsy, such patients will be considered local failure if their exam is abnormal. If their exam is normal or if they are post orchiectomy they will be censored at the last point in time they were considered locally controlled and considered "inevaluable" for further assessment of local control.

9.0 OTHER THERAPY (3/23/05)

9.1 Neoadjuvant androgen suppression (nonsurgical) is permitted for protocol patients if clinically indicated. The following conditions apply:

Must begin ≤ 120 days prior to registration to this study.

PSA prior to hormonal therapy must be available.

9.2 Adjuvant androgen suppression (non surgical) is permitted for protocol patients if clinically indicated. The following conditions apply:
Must begin during the radiotherapy.
Must not continue ≥ 2 years from completion of radiotherapy.

9.3 Diphenoxylate, loperamide or similar drugs may be used for diarrhea.

9.4 Tolterodine or anticholinergic drugs may be used to treat bladder or rectal spasms.

9.5 Phenazopyridine and or an alpha blocker may be used to treat bladder irritation.

9.6 Sildenafil, or similar drugs, may be used to treat erectile dysfunction.

10.0 TISSUE/SPECIMEN SUBMISSION

Does not apply to this study

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (3/23/05) (9/8/05)

Assessments	Pre-Study Entry	XRT/ Implant RT[e]	At 3 months from start of treatment, then at 6, 9 and 12 months; then every 6 months x 3 years. Annually thereafter.
History/Physical Exam (DRE[f])	X	X[e]	X
Zubrod Performance Status	X		X
Tumor Measurement	X		X
Status of hormonal therapy (duration of treatment, if given)	X		X
PSA (Pre-HT, if given)	X[a]		X
Pelvic CT or MRI	X[b]		X[d]
Bone Scan			X[d]
TRUS	X		
Flexible Cystoscopy	X[c]		
Prostate Biopsy	X		X[d]
Toxicity Evaluation	X	X[g]	X

a. PSA must be done prior to initiation of hormones for patients receiving neoadjuvant hormonal therapy
b. Within 90 days prior to registration
c. Optional
d. At time of PSA failure, and as indicated
e. Per institutional standards.
f. DRE not required to be done weekly
g. Weekly during XRT

11.2 Follow-up Schedule (3/23/05)

11.2.1 Initial follow-up visit at 3 months from start of treatment.

11.2.2 After initial follow-up visit, follow-up will be done at 6, 9, and 12 months post therapy.

11.2.3 Then every six months until five years post-implant.

11.2.4 Then annually thereafter.

11.2.5 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 Criteria for Toxicity

11.3.1 All acute and late adverse events from protocol radiation therapy will be reported and scored for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov). **Please note that this study will not be using separate toxicity scales for acute and late radiation adverse events.**

11.4 Measurement of Response

11.4.1 Prostate tumor dimensions in centimeters and PSA values must be recorded on the data collection forms for the initial and follow-up evaluations of the patient.

11.4.2 After study entry, disease evaluations will be made and recorded using the following criteria:

11.4.2.1 No Evidence of Disease (NED): No clinical evidence of disease on digital rectal examination and no PSA failure.

11.4.2.2 Equivocal Disease (ED): This rating will be assigned under the following circumstances:

1) 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.
2) If clinical evidence of residual tumor is present but this has regressed from a previous examination (initial registration).
3) PSA 2.1 - 4 ng/mL. Rebiopsy is required, before starting hormone therapy, in any patient with PSA failure but with negative bone scan and CT scans. If the biopsy is negative, then they will be scored as NED.

11.4.2.3 Progressive Disease (PD): Progressive disease will be declared if one or more of the following criteria are met:

1) Clinical evidence in the prostate gland of disease progression or recurrence.
2) Clinical or radiographic evidence of tumor recurrence within the pelvic lymphatics or soft tissue beneath the bifurcation of the common iliac arteries,
3) Clinical or radiographic evidence of hematogenous (osseous, hepatic, etc.) and/or extrapelvic lymphatic of soft tissue relapse.

11.5 Other Response Parameters

11.5.1 Disease-Free Interval: The disease-free interval will be measured from the date of accession to the date of documentation of progression or until the date of death (from other causes).

11.5.2 Time to Biochemical Failure: PSA failure is defined according to the ASTRO consensus guidelines. The PSA nadir will be defined as the lowest PSA value reached immediately before a biochemical failure. Biochemical failure is defined as a consistent and significant rise in the PSA level. When the serum PSA rises on three consecutive occasions from the nadir value, biochemical failure has occurred and the date of failure is midway between the last non-rising PSA and the first rise in PSA.

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

11.5.4 Time to Distant Failure: The time to distant failure will be measured from the date of study entry to the date of documented regional nodal recurrence or distant disease relapse. Patients with evidence of biochemical failure, but a negative prostate biopsy, will be considered as distant failure only.

11.5.5 Overall Survival: The survival time will be measured from the date of accession to the date of death. All patients will be followed for survival. Every effort should be made to document the cause of death.

11.5.6 Disease-Specific Survival Disease-specific survival will be measured from the date of study entry to the date of death due to prostate cancer. The following will be considered as failure events in assessing disease specific survival:

Death certified as due to prostatic cancer.

Death from other causes with active malignancy (clinical or biochemical progression).

Death due to complications of treatment, irrespective of the status of malignancy.

Death from other causes with previously documented relapse (either clinical or biochemical) but inactive at the time of death will not be considered in disease-specific survival, but will be analyzed separately.

12.0 DATA COLLECTION

Data should be submitted to:

Data Management Department
RTOG Headquarters
American College of Radiology
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 to RTOG HQ (3/23/05, 4/25/06)

Item	Due
Demographic Form **(A5)**	Within 2 weeks of study entry
Initial Evaluation Form **(I1)**	
Pathology Report **(P1)**	
External Beam Dosimetry	
Radiotherapy Form (**T1**)* (copy to RTOG HQ and ITC)	Within 1 week post radiotherapy to RTOG
Follow-up Form **(F1)**	Post RT follow-up at 3 months from start of treatment, then at 6, 9 and 12 months; then every 6 months x 5 years. Annually thereafter.
Adverse Event Form **(AE)**	Post RT follow-up every 3 months from start of treatment x 1 year; then, if applicable.

12.2 Summary of Data Submission to Image-Guided Therapy Center (ITC) (9/8/05)

Brachytherapy Dosimetry	
Digital Protocol Treatment Form (DDSI)	Within 1 week post radiotherapy to ITC
Digital Data (DD)	
• HDR Treatment Plan	Within 1 week post radiotherapy to ITC
• Contours and Isodose Distribution	Within 1 week post radiotherapy to ITC
• Color DVH	Within 1 week post radiotherapy to ITC

***NOTE:** Copies of external beam simulation and port films and the complete external beam RT daily treatment record for the site will be submitted to RTOG Headquarters ONLY if specifically requested.

12.2.1 Digital Data Submission to ITC (4/25/06):

- CT treatment planning images, dosimetry information (in 3-D according to RTOG guidelines);
- Digital data submission form
- Digital data submission may be accomplished using magnetic tape or the internet. For network submission , the FTP account assigned to the submitting institution by the ITC shall be used, and the email identifying the data set(s) being submitted shall be sent to: **itc@castor.wustl.edu**. For tape submission, please contact the ITC about acceptable tape types and formats.

- Hardcopy to accompany digital data to be sent by mail or Federal Express should be addressed to:

Image-Guided Therapy Center (ITC)
Washington University School of Medicine
4511 Forest Park, Suite 200
St. Louis MO 63108
Phone: 314-747-5415
Fax: 314-747-5423

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 *Primary Endpoint*

- Late severe GU and GI toxicity is defined as grade 3-5 GU and GI toxicity more than nine months from the start of the protocol treatment. It is graded based on CTCAE v3.0.

13.1.2 *Secondary Endpoints*

- Acute severe GU and GI toxicity is defined as grade 3-5 toxicity within nine months from the start of protocol treatment. It is graded based on CTCAE v3.0.
- Biochemical failure
- Overall survival
- Disease-specific survival
- Clinical progression including local/regional and distant relapse

13.2 Sample Size

13.2.1 *Overview*: The primary goal of this study is to estimate the rate of late grade 3-5 genitourinary and gastrointestinal toxicity following treatment with external beam radiation therapy and high dose rate (HDR) brachytherapy. Late toxicity will be defined as toxicity occurring more than nine months from the start of radiotherapy. It is graded based on CTCAE v 3.0.

13.2.2 *Sample Size Derivation*: The study is designed to test whether the 18-month late GU/GI toxicity following the protocol treatment is above 10%. The sample size is determined so that the probability of rejecting the treatment because of excessive late toxicity is 90% if the true late toxicity rate is 20%. Assuming exponential distribution for time from the end of the acute period *(9 months from the start of protocol treatment)* to the occurrence of late toxicity, the hazard rate for the expected 10% toxicity rate and the unacceptable 20% toxicity rate is 0.012/month and 0.025/month, respectively. Following the asymptotic property of the observed hazard and using Z-test for logarithm of the hazard, we require 16 cases with severe late GU/GI toxicity. Thus, 98 patients are required to be accrued within a year and be followed for an additional 18 months to have a statistical power of 90% with one-sided significance level of 0.05. Considering 10% ineligible cases and lack-of-data cases, **the total sample size of the study is 110 patients**.

13.3 Patient Accrual and Study Duration

It is expected that it will take approximately a year to complete the study. The analysis for late toxicity will be carried out after each patient has had at least 18 months of follow-up. For the secondary endpoint of biochemical failure, an additional two years of follow-up are needed to estimate the 3-year failure rate.

13.4 Analysis Plan

13.4.1 *Interim Reports*: Interim reports will be prepared every six months until the RTOG meeting after the last patient has been entered to the study. In general, the interim reports will contain information about patient accrual rate with projected completion dates of the trial, status of QA review and compliance rate of treatment per protocol, the frequencies and severity of toxicity.

13.4.2 *The Analysis of Severe Late GU/GI Toxicity*: This analysis will be carried out when each patient has had at least 18 months of follow-up. The time to the occurrence of severe late GU/GI toxicity is defined as the time interval from the tenth month after start of protocol treatment to the date of onset of grade 3-5 GU/GI toxicity. If no such toxicity is observed till the time of the analysis, the patient will be censored at the time of the analysis. The hazard rate will be estimated by life table approach with time span of 18 months. Then the one-sided Z-test will be performed to test the significance of the difference between the logarithm of the observed hazard rate and the logarithm of the hypothesized hazard rate of 0.012/month with the variance equal to the reciprocal of the number of cases with late toxicity observed. Because of the lead time of 9 months for the acute period, the 18-month late toxicity will be estimated by the 9-month toxicity rate using the cumulative incidence approach[29] to the defined time to severe late GU/GI toxicity.

13.4.3 *Estimation of Secondary Endpoints Related to the Efficacy*: Cumulative incidence approach[29] will be used to estimate the failure rate for biochemical, disease-specific, local-regional and distant failures. Kaplan-Meier method[30] will used to estimate the overall survival rate.

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, we address this issue here, as we will also analyze treatment differences in this male cohort by ethnicity. Based on previous RTOG P0019 data, the ethnicity enrollment for this study is expected as follows:

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	N/A	4	4
Not Hispanic or Latino	N/A	106	106
Ethnic Category: Total of all subjects*	N/A	110	110
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	N/A	1	1
Asian	N/A	1	1
Black or African American	N/A	10	10
Native Hawaiian or other Pacific Islander	N/A	1	1
White	N/A	97	97
Racial Category: Total of all subjects*	N/A	110	110

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APPENDIX I

RTOG 0321

SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE

PHASE II TRIAL OF COMBINED HIGH DOSE RATE BRACHYTHERAPY AND EXTERNAL BEAM RADIOTHERAPY FOR ADENOCARCINOMA OF THE PROSTATE

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, "Taking Part in Clinical Trials: What Cancer Patients Need To Know," is available from your doctor.

You are being asked to take part in this study because you have prostate cancer.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to test the safety of a high dose rate (HDR) radiation therapy delivered via a temporary implant (brachytherapy) with external beam radiation therapy and to see what effects (good and bad) it has on you and your prostate cancer.

This research is being done because although the use of brachytherapy for prostate cancer is not new, using a high dose rate temporary implant with external beam radiation therapy is a more recent combination which needs more investigation.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

About 110 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY? (3/23/05, 6/3/05, 4/25/06)

If you take part in this study, you will have the following tests and procedures:

Work-up	Treatment	Follow-up
Physical Exam PSA Prostate Biopsy CT or MRI Scan	External Beam Radiotherapy and High Dose Rate Brachytherapy	3 months from start of treatment, then at 6, 9 and 12 months; then every 6 months x 5 years. Annually thereafter.

External Radiation Therapy:

External radiation therapy to the prostate or the pelvis will be given once a day, five days a week for five weeks. A typical radiation treatment lasts about 15 minutes. External radiation therapy treatments will be given on an outpatient basis at your institution.

Internal Radiation Therapy (Brachytherapy)

You will be admitted to the hospital for an overnight stay. A temporary implant will be inserted into your prostate and high dose rate brachytherapy (radiation therapy) will be given via the implant. This procedure will be done under anesthesia at your institution. Under the guidance of ultrasound, thin catheters will be inserted through the skin between the anus and scrotum into the prostate. After the implant a pelvic CT scan will be done to identify the location of the catheters, the prostate and normal structures (rectum, bladder, urethra). A typical brachytherapy treatment takes 5-30 minutes. You will receive a total of 2 treatments within a 24 hour period. Each treatment will be given in a treatment room protected with lead walls, like with a regular x-ray. You will not be radioactive while you wait for the treatment in your hospital room. After the last treatment is completed the implant will be removed before you are discharged.

• Procedures that are part of regular cancer care and may be done even if you do not join the study.

Procedure	Schedule
History and Physical Exam Tumor Measurements PSA Blood Test	Prior to study entry and at follow-ups
Prostate Biopsy Pelvic CT or MRI Scan	Prior to study entry
Cystoscopy (bladder exam)	As medically indicated

• Standard procedures being done because you are in this study.

Procedure	Schedule
External Beam Radiotherapy	25 treatments, Monday to Friday for five weeks
Hormonal Therapy	May be given prior to radiotherapy starting ≤ 120 days prior to registration and during the radiotherapy and possibly for up to 2 years after the radiotherapy as medically indicated.

Extra procedures being done because you are in this study:

Procedure	Schedule
High Dose Rate Brachytherapy	Twice, either before or after the external beam radiotherapy
TRUS (Transrectal ultrasound)	During the implant
Cystoscopy (bladder exam)	During the implant
Pelvic CT Scan	After the implant
Prostate Biopsy	If there is a treatment failure

HOW LONG WILL I BE IN THE STUDY?

We think you will be in the treatment part of the study for eight weeks.

Follow up visits with your physician will be scheduled for three months after you start treatment, then every three months for one year, then every six months for five more years, and then annually for the rest of your life.

The researcher may decide to take you off this study if it is in your best medical interest, your condition worsens, or new information becomes available and this information suggests the treatment will be ineffective or unsafe for you. It is unlikely, but the study may be stopped early due to lack of funding or participation.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Drugs may be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the treatment is stopped, but in some cases side effects can be serious or long-lasting or permanent.

Risks Associated with External Radiation Therapy

Very Likely

Tanning or redness of skin in treatment area
Rash, itching or peeling of skin
Temporary hair loss in the treatment area
Temporary fatigue, nausea or diarrhea
Abdominal cramps or bladder irritation

Less Likely, But Serious

Injury to the bladder, urethra, bowel or other tissues in the pelvis or abdomen
Rectal bleeding, intestinal or urinary obstruction, and impotence (may not be reversible)

Risks Associated with Brachytherapy

Very Likely

Infection that can be treated with antibiotics
Soreness in the implant area
Temporary fatigue, nausea or diarrhea
Abdominal cramps
Bladder irritation with some bleeding
Impotence (may not be reversible)
Urinary tract infection (UTI)

Less Likely, But Serious

Injury to the bladder, urethra, bowel or other tissues in the pelvis or abdomen
Rectal bleeding, intestinal or urinary obstruction, and incontinence (may not be reversible)
Serious infection

Risks Associated with Anesthesia

Less Likely

Nausea, vomiting
Headache
Sore throat

Less Likely, But Serious
Blood pressure problems
Heart rhythm problems
Breathing changes
Drug reactions
Heart attack
Stroke
Death

If you are a man able to father children, the treatment you receive may risk harm to an unborn child unless you use a form of birth control approved by your doctor. The treatment may cause sterility, however, adequate birth control measures must still be used. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study. If you suspect you have caused anyone to become pregnant while you are on this study, you must tell your doctor immediately.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with prostate cancer in the future.

WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: (1) radiation therapy; (2) hormone therapy; (3) surgery; or (4) no treatment except medications to make you feel better. With the latter choice, your tumor may continue to grow and your disease would spread. These treatments could be given either alone or in combination with each other.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments.

Another option may be to get the treatment plan described in this study at this center and other centers even if you do not take part in the study.

Please talk to your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include the Radiation Therapy Oncology Group (RTOG) and groups such as the Food and Drug Administration (FDA), the National Cancer Institute (NCI) or its authorized representatives.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization. Medicare should be considered a health insurance provider.

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. If you choose to stop participating in the study, you should first discuss this with your doctor. In order to provide important information that may add to the analysis of the study, he/she may ask your permission to submit follow-up data as it relates to the study. You may accept or refuse this request. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

For information about your disease and research-related injury, you may contact:

Name	Telephone Number

For information about this study, you may contact:

Name	Telephone Number

For information about your rights as a research subject, you may contact:
(OHRP) suggests that this person not be the investigator or anyone else directly involved with the research)

Name	Telephone Number

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's Cancer Information Service at **1–800–4–CANCER (1–800–422–6237)** or **TTY: 1–800–332–8615.**

Visit the NCI's Web sites for comprehensive clinical trials information at **www.cancer.gov/clinicaltrials** or for accurate cancer information including PDQ (Physician Data Query) visit **www.cancer.gov/cancerinfo/pdq**

SIGNATURE

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (full study plan).

Patient's Name	Signature	Date
Name of Person Obtaining Consent	Signature	Date

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

ZUBROD PERFORMANCE SCALE

0	Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).

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 Extracapsular 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).

APPENDIX III (continued)

AJCC STAGING SYSTEM
PROSTATE, 6th Edition

Distant Metastasis (M)*

MX	Presence of distant metastasis cannot be assessed (not evaluated by any modality)	
M0	No distant metastasis	
M1	Distant metastasis	
	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)

GX	Grade cannot be assessed
G1	Well-differentiated (slight anaplasia [Gleason 2-4])
G2	Moderately differentiated (moderate anaplasia [Gleason 5-6])
G3-4	Poorly undifferentiated or undifferentiated (marked anaplasia [Gleason 7-10])

Stage Grouping

Stage I	T1a	N0	M0	G1
Stage II	T1a	N0	M0	G2, G3-4
	T1b	N0	M0	Any G
	T1c	N0	M0	Any G
	T1	N0	N0	Any G
	T2	N0	M0	Any G
Stage III	T3	N0	M0	Any G
Stage IV	T4	N0	M0	Any G
	Any T	N1	M0	Any G
	Any T	Any N	M1	Any G

APPENDIX IV

GLEASON CLASSIFICATION

Histologic patterns of adenocarcinoma of the prostate

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

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)

1. Gleason, D.F. et al: Prediction of prognosis for prostatic carcinoma by combined histologic grading and clinical staging. J Urol 111:58, 1974.