RADIATION THERAPY ONCOLOGY GROUP

RTOG 0232

A PHASE III STUDY COMPARING COMBINED EXTERNAL BEAM RADIATION AND TRANSPERINEAL INTERSTITIAL PERMANENT BRACHYTHERAPY WITH BRACHYTHERAPY ALONE FOR SELECTED PATIENTS WITH INTERMEDIATE RISK PROSTATIC CARCINOMA

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(2/15/05;10/11/05; 2/16/06; 1/11/08; 9/23/08)

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INSTITUTION MUST BE PRE-CREDENTIALED (See Section 5.0) (10/11/05)

This study is supported by the NCI Cancer Trials Support Unit (CTSU) [1/24/07]

Institutions not aligned with the RTOG will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix.

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at http://members.ctsu.org
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.
- Data management will be performed by the RTOG. **Case report forms** (with the exception of patient enrollment forms)**, clinical reports, and transmittals** must be sent to RTOG Headquarters unless otherwise directed by the protocol. Do not send study data or case report forms to CTSU Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by the RTOG. Please send query responses and delinquent data to the RTOG and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and RTOG Headquarters.

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SCHEMA

S
T
R
A
T
I
F
Y

Stage
1. T1c
2. T2a – T2b

Gleason Score
1. ≤ 6
2. 7

PSA
1. 0 - < 10
2. 10-20

Neoadjuvant Hormonal Therapy
1. No
2. Yes

R
E
C
0
R
D

Isotope
1. I-125
2. Pd-103

R
A
N
D
O
M
I
Z
E

Arm 1: 45 Gy EBRT
Partial pelvis (1.8 Gy/fraction M-F for five weeks) followed 2-4 weeks later by Pd-103 (100 Gy) or I-125 (110 Gy)*

or

Arm 2 Pd-103 (125 Gy) or I-125 (145 Gy)*

***** Protocol treatment must begin within four weeks after study entry.

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

Eligibility: (See Section 3.0 for details)
- Histologically confirmed, locally confined adenocarcinoma of the prostate;
- Clinical stages T1c - T2b (AJCC 6th Edition, see Appendix III);
- Zubrod Performance Scale 0-1;
- Patients must be ≥ 18 years of age;
- Combined Gleason score 7 if PSA < 10, combined Gleason score < 7 if PSA 10 - 20;
- PSA must be ≤ 20 ng/mL, before hormone therapy, if given (if Gleason score 2-6, then PSA must be ≥ 10 ng/mL);
- Prostate volume by TRUS ≤ 60 cc;
- No prior chemotherapy or pelvic radiation; no prior TURP, cryosurgery, TUNA, TUMT or radical surgery for carcinoma of the prostate;
- No previous hormonal therapy beginning < 2 months or > 6 months prior to registration;
- No distant metastases, no clinically or pathologically involved lymph nodes;
- No significant obstructive symptoms; AUA score must be ≤ 15 (alpha blockers allowed);
- No hip prosthesis;
- No major medical or psychiatric illness;
- Signed study-specific informed consent form prior to study entry.

Required Sample Size: 586

RTOG Institution # _____
RTOG 0232
Case # _____

ELIGIBILITY CHECKLIST (6/11/03, 2/15/05, 10/11/05)
(page 1 of 3)

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

_____(T1c-T2b) 2. What is the T stage? (AJCC 6th Edition, see Appendix III)

_____(N0) 3. What is the N stage? (2/15/05)

_____(0-1) 4. What is the Zubrod performance status?

_____(≤20) 5. What is the PSA level *(prehormones if given)*? (*If Gleason sum 7, then PSA must be < 10 ng/mL, conversely, if PSA is ≥ 10 (but ≤ 20), then Gleason sum must be < 7)*.

_____(N) 6. Has the patient had prior pelvic radiation? (2/15/05)

_____(N) 7. Has the patient had prior chemotherapy for prostate cancer? (2/15/05)

_____(Y/N) 8. Has the patient had any prior hormone therapy?
_____ (Y) If yes, did it begin within 2-6 months prior to study entry?

_____(Y/N) 9. Has the patient used a 5-alpha reductase inhibitor? (10/11/05)
_____(Y) If yes, has it been discontinued? (10/11/05)

_____(N) 10. Has the patient had prior radical surgery for prostate carcinoma? (10/11/05)

_____(N) 11. Is there evidence of distant metastases? (10/11/05)

_____(Y/N) 12. Has the patient had previous or concurrent cancer other than basal cell or squamous cell skin cancer or in situ at another site? (10/11/05)

_____If yes, has the patient been disease free for at least 5 years?

_____(N) 13. Are there any major medical or psychiatric illnesses that would prevent completion of treatment or interfere with follow-up? (10/11/05)

_____(N) 14. Has the patient had a prior TURP, cryosurgery, TUNA or TUMT? (10/11/05)

_____(N) 15. Is the PSA > 20? (10/11/05)

_____(N) 16. Is the Gleason sum > 7? (10/11/05)

_____(Y) 17. Has the patient had TRUS mapping done and is prostate volume ≤ 60 cc? (10/11/05)

_____(Y) 18. Has patient filled out AUA voiding questionnaire and is the score ≤ 15? (10/11/05)

_____(N) 19. Has the patient had a hip replacement? (10/11/05)

_____(Y) 20. Is the patient at least 18 years of age? (10/11/05)

RTOG Institution # _____
RTOG 0232 **ELIGIBILITY CHECKLIST (6/11/03, 2/15/05, 10/11/05, 2/16/06)**
Case # _____ *(page 2 of 3)*

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

_____ 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

_____ 13. Patient's Insurance Status

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

_____ 15. Is the patient going to receive 3D CRT or IMRT if randomized to receive external beam radiation therapy (Arm 1)? (10/11/05)

_____ 16. Tissue/Blood Used for Research in Current Study

_____ 17. Tissue/Blood Kept for Cancer Research

_____ 18. Tissue/Blood Kept for Medical Research

_____ 19. Allow contact for future research

_____ 20. Medicare data to be used for research in the current study? (2/16/06)
_____ Social Security number (2/16/06)

_____ 21. T Stage 1) T1c vs. 2) T2a - T2b (AJCC 6th Edition, see Appendix III)

_____ 22. Combined Gleason Score of Tumor 1) 2-6 vs. 2) 7

_____ 23. PSA 1) 0 - < 10 vs. 2) 10-20

_____ 24. Neoadjuvant hormone therapy 1) No vs. 2) Yes

_____ 25. Is the patient going to receive Isotope 1) I-125 or 2) Pd-103?

_____ 26. Treatment Start Date

_____ 27. Treatment Assignment

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 _____

1.0 INTRODUCTION

1.1 Background (1/11/08)

Approximately 60% to 70% of the men with newly diagnosed adenocarcinoma of the prostate present with organ-confined disease. Conventional treatment options that should be discussed with each patient in this category include radical prostatectomy, external beam radiation therapy, interstitial brachytherapy and watchful waiting, according to the NCI Consensus Conference in 1988.[1]

The use of brachytherapy as the sole modality of treatment for early-stage prostate cancer has gained popularity over the past decade due to the advent of the transrectal ultrasound-guided technique and the favorable reports of imaged-based brachytherapy with Isotopes Iodine-125 (I-125) and Palladium 103 (Pd-103). At the same time, dose escalation 3-dimensional conformal radiation therapy (3D CRT) has revealed promising results, especially for patients with early-stage disease.[2-4] The notion of stratifying patients into risk groups according to stage, Gleason score and PSA has become helpful for the purpose of comparing outcomes for various modalities of therapy.[5-14] The definition of "low risk" most often includes those patients with a Gleason sum of 6 or less, PSA of 10 or less and patients with stage T2a or less disease. "Intermediate risk" patients generally have up to Gleason 7 disease with a PSA up to 20 and palpable tumor to stage T2b. "High risk" patients generally either have a Gleason score of 8 or above, a PSA above 20 or advanced disease on digital exam beyond T2b. Zelefsky et al[4] reported five-year actuarial PSA relapse-free survival rate of 85% for low risk patients, 65% for intermediate risk and 35% for high risk patients, when treated with 3DCRT. When their analysis was limited to those of patients who received greater than 75.6 Gy, the four-year results reported were 95%, 79% and 60% for the low, intermediate and high risk groups, respectively. Similarly, the five-year PSA control outcomes reported by Blasko et al[6] for their Pd-103 monotherapy patients were 94%, 82% and 65% for low, intermediate and high risk categories. Given the excellent results with either single modality for the low risk patient, the challenge to improve on results clearly must be concentrated on those categorized in the intermediate and high risk groups. **(2/15/05)**

The role of brachytherapy as monotherapy for high grade disease is controversial in patients with Gleason score 7 to 10 disease which brings a high rate of relapse regardless of the treatment approach. In the series reported by Blasko et al[6], 91 patients presented with Gleason 7 or greater disease and PSA less than 10; these patients were treated with Pd-103 alone and achieved a five-year rate of PSA control of 80%. Wallner, et al.[15] used I-125 monotherapy for a similar group of 20 patients with Gleason score of 7 and PSA under 10 and found a control rate of 70%. In contrast, the Seattle group recently reviewed their long term combined radiation experience and found 90% and 80% biochemical control rates at 5 and 15 years, respectively, among patients with intermediate risk disease.[62]

To date, there is no evidence of superiority of one isotope over the other, and in fact, Cha et al.[16] recently compared their I-125 and Pd-103 experience using a matched-pair analysis and were unable to demonstrate any statistically significant difference in outcomes of all patients with Gleason scores between 2 and 8. Therefore, it appears reasonable, based on clinical observation, to use either isotope as monotherapy.

Some have argued that the combination of external beam radiotherapy with interstitial brachytherapy boost may allow for improved outcome in these categories relative to either single modality alone particularly for those intermediate risk patients at increased risk for extracapsular spread of disease [9,14] However, the addition of two modalities of radiation carries the potential risk of increased side effects and complications, including bowel and bladder toxicity, sexual difficulties, and an overall decrease in the patient's quality of life. In addition, the cost of such combination therapy is perhaps the highest for any form of treatment for prostate cancer, with published data suggesting Medicare patients incur average costs (including six months of follow-up) of more than $15,000 for prostate brachytherapy alone, over $19,000 for radical prostatectomy, but more than $24,000 for patients undergoing both brachytherapy and external beam therapy.[17] These differences are consistent with some individual institution-specific data that estimated significant differences in cost between prostatectomy and brachytherapy patients, although other investigators did not find significant differences in charges between the two procedures.[18-20] It is expected that reimbursement for such

combined therapy may become increasingly more difficult in the absence of scientific trials demonstrating a benefit for such aggressive therapy.

These studies illustrate, however, the importance of collecting cost data, not just for the peri-operative period, but also for an extended follow-up period. If indeed there is a difference in failure-free survival between the two study arms, such that patients undergoing combined radiation modalities have a hypothesized reduction of 33% in the yearly PSA failure rate as compared with those receiving brachytherapy alone, then the combined-modality arm may prove to be less costly with the inclusion of long-term follow-up cost data. PSA failures may result in higher utilization of medical care, including androgen suppression therapy, palliative treatments of metastatic disease, surgical procedures due to advancing local disease, or other procedures or medical interventions. Furthermore, disease recurrence may be associated with worsening symptoms, psychological implications, and overall decreased quality of life. Hence, even in the absence of a survival advantage, combined modality treatment may offer an improvement in quality-adjusted survival, or an advantage in overall costs. Since no such differences in costs have been linked with outcomes on an individual patient level, in the absence of scientific trials demonstrating a benefit for the more aggressive therapy, and in the absence of better understanding of the comparative costs and quality of life outcomes associated with such treatment, justification for the more aggressive combined modality therapy may not be seen as adequate from societal or payor perspectives.

As most patients with intermediate risk prostate cancers survive in the first 5-10 years after intervention, the morbidity associated with therapy for early stage prostate cancer is a pivotal component of patient outcome. Although traditional, physician-reported toxicity data are a useful component for evaluating treatment-related morbidity, it has been shown that patient-report data (collected via standardized questionnaires) are more sensitive than physician reports to the full severity and broad range of therapy effects on patient Health-Related Quality of Life (HRQOL), particularly among men with prostate cancer.[21] Attention to this paradigm, for example, recently led to evidence of superior HRQOL outcome after 3D-CRT compared to conventional external beam radiation for localized prostate cancer.[22] Two HRQOL instruments (EORTC-QLQC30-Prostate Module and Expanded Prostate Cancer Index Composite [EPIC]) have been validated for use in subjects undergoing brachytherapy with or without external radiation;[23,24] other instruments (UCLA-PCI and AUA-SI) have also been applied to evaluate HRQOL effects of brachytherapy, though these lack sensitivity to urinary irritative symptoms and hematochezia.[25,26] These studies showed that HRQOL domains impacted by prostate brachytherapy include urinary irritative, bowel, sexual, and (to a lesser extent) urinary incontinence.[21,27-30] When neoadjuvant hormonal therapy is used, a distinct domain representing vitality and hormonal functioning can be impacted also.[29] However, neither randomized or prospective studies have been conducted to determine whether combining prostate brachytherapy with external radiation leads to different HRQOL outcome than prostate brachytherapy alone. To address this question, this trial will compare the treatment arms for differences in HRQOL outcome (as measured by change over time in EPIC urinary-irritative, urinary-incontinence, bowel, and sexual domains).

The previous experience of the RTOG 98-05 included a Phase II trial in looking at the feasibility of I-125 interstitial brachytherapy as monotherapy for low risk patients in an effort to document both the feasibility with regard to standardization and quality assurance measures as well as toxicity. This was followed by RTOG P-0019, which evaluated patients with intermediate risk, clinically localized adenocarcinoma of the prostate and treated them with 45 Gy external beam radiotherapy followed two to six weeks later by permanent I-125 brachytherapy to a minimum peripheral dose of 108 Gy. The current trial is intended to evaluate the role of external beam radiotherapy with interstitial implant compared to interstitial implant alone for selected patients with intermediate risk prostatic carcinoma, including either combined Gleason 7 disease with a PSA under 10, or combined Gleason scores less than 7 with a PSA between 10-20.

2.0 OBJECTIVES (1/11/08)

2.1 Primary Objective

2.1.1 To determine whether combined external beam radiation (EBRT) and transperineal interstitial permanent brachytherapy will result in better freedom from progression (FFP) for 5 years compared to brachytherapy alone among selected patients with intermediate risk prostatic carcinoma.

2.2 Secondary Objectives

2.2.1 To compare EBRT in addition to transperineal interstitial brachytherapy versus interstitial brachytherapy alone as related to: (a) biochemicalfailure, (b) biochemical failure by the Phoenix definition , (c) disease-specific survival, (d) local progression, (e) distant metastases and (f) overall survival.

2.2.2 To evaluate differences in toxicity and quality of life between EBRT and transperineal interstitial brachytherapy arm and interstitial brachytherapy alone arm.

2.2.3 Feasibility of collecting Medicare data in large RTOG prostate trial for cost effectiveness and cost utility analysis of combined radiation therapy.

2.2.4 Prospectively collect diagnostic biopsy samples for future biomarker analyses.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility:

3.1.1 Histologically confirmed adenocarcinoma of the prostate, clinical stage T1c - T2b (AJCC 6th Edition, see Appendix III), N0, M0. Lymph node evaluation by either CT, MRI, or node dissection is required. (2/15/05)

3.1.2 Zubrod performance status 0-1.

3.1.3 Patient must be ≥ 18 years of age.

3.1.4 Patients with intermediate risk prostate cancer as determined by one of the following combinations:

Gleason < 7, PSA must be 10-20; Gleason 7, PSA must be < 10.

3.1.5 Prostate specific antigen (PSA) prior to study entry (and prior to any hormone treatment if given) must be ≤ 20 ng/ml.

3.1.6 Neoadjuvant hormonal therapy beginning 2-6 months prior to registration is acceptable. The use of 5-alpha reductase inhibitors (for example, finasteride) is allowed prior to registration but should be discontinued before registration. (10/11/05)

3.1.7 Prostate volumes by TRUS ≤ 60 cc.

3.1.8 AUA voiding symptom scores ≤ 15 (alpha blockers allowed); this is completed by the patient.

3.1.9 Patients must sign a study-specific informed consent form prior to study entry.

3.2 Conditions for Patient Ineligibility

3.2.1 Stage < T1c, T2c, T3 or T4 disease (AJCC 6th Edition, see Appendix III).

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, prior pelvic radiation, prior chemotherapy for prostate cancer, prior TURP, prior cryosurgery, TUNA, TUMT of the prostate. (2/15/05)

3.2.5 Previous hormonal therapy beginning < 2 months or > 6 months prior to registration. The use of hormones should not be a planned component of therapy.

3.2.6 Previous or concurrent cancers other than basal, in situ, or squamous cell skin cancers unless disease-free for ≥ 5 years.

3.2.7 Major medical or psychiatric illness, which in the investigator's opinion, would prevent completion of treatment and would interfere with follow-up.

3.2.8 Hip prosthesis.

4.0 PRE-TREATMENT EVALUATION

Protocol treatment must begin within four weeks after study entry.

4.1 History and physical (to include tumor measurements and DRE) and Zubrod performance status (Appendix II).

4.2 Histological evaluation of prostate biopsy with assignment of a Gleason score to the biopsy material.

4.3 Laboratory evaluations to include CBC, platelets, BUN, creatinine, free prostate specific antigen (PSA) if available, and PSA. PSA must be done:

- Within 60 days prior to study entry and prior to prostate biopsy *or*

- Within 60 days prior to study entry and at least 10 days after prostate biopsy *or*
- For patients receiving neoadjuvant hormone therapy, PSA must be done within 60 days prior to initiation of hormones.

Note: PSA obtained > 60 days prior to study entry and/or within 10 days following prostate biopsy must not be used for study entry PSA (for those patients not on hormones).

4.4 Transrectal ultrasound volume study of the prostate prior to the planned external beam radiation therapy. Patients will be placed in a dorsal lithotomy position with care taken to ensure that the patient's spine is centered on the table and that the elevation of the legs is symmetric and can reliably be reproduced during the brachytherapy procedure. Transrectal ultrasonography will be performed. Images should be obtained at 5 mm intervals, beginning at the base of the prostate, with contouring of the prostatic capsule at each axial image. A volumetric estimate based on a height-, width-, and length-derived formula obtained by the urologist at the time of biopsy may be used provided it is less than 50 cc and the investigator is confident in the accuracy of such measurement. (10/11/05)

4.5 Flexible cystoscopy, if advised by the urologist, may be performed to check for urethral strictures.

4.6 Lymph node evaluation must be performed by at least one of the following: CT or MRI of pelvis, or exploratory laparotomy or laparoscopy with lymph node biopsy (sampling). (2/15/05)

4.7 AUA Symptom Score completed by the patient (Appendix VI).

4.8 EPIC Questionnaire completed by the patient (Appendix X).

4.9 EQ5D Questionnaire completed by the patient (Appendix XI).

4.10 Utilization of Sexual Medications/Devices completed by the patient (Appendix XII) (10/11/05).

5.0 REGISTRATION PROCEDURES

5.1 Pre-Registration Requirements (10/11/05)

5.1.1 Brachytherapy (10/11/05)

Institutions must be pre-credentialed by the Radiological Physics Center (RPC) prior to registering any cases to this study. The credentialing materials may be found on the RPC website at http://rpc.mdanderson.org under the "credentialing" tab. (10/11/05)

5.1.1.1 If an institution was credentialed for either of the two previous RTOG prostate brachytherapy trials (RTOG 98-05, RTOG P-0019), they do not have to be re-credentialed for this trial if the radiation oncologist and physicist are the same as on the approved credentialing request, and the institution is using the same I-125 seed model and planning system as on the approved credentialing request. (Please note that RTOG 98-05 and RTOG P-0019 only permitted the use of I-125. Thus, if an institution wishes to use Pd-103 and has been previously credentialed for I-125, they must complete the RPC's physics credentialing for this source.) A change of physician will require submission of the Knowledge Assessment Form and Clinical Test Case. A change in physicist will require submission of the Knowledge Assessment Form, the Credentialing Questionnaire, and the Reference Cases. A change in either the treatment planning computer or brachytherapy source model will require resubmission of only the Reference Cases. (10/11/05)

5.1.2 3D-CRT and IMRT (10/11/05) (2/16/06)

Only institutions that have met the technology requirements and that have provided the baseline physics information that is described in 3D-CRT Quality Assurance Guidelines or the IMRT Quality Assurance Guidelines (see ATC website at http://atc.wustl.edu) may enter patients on this study. (10/11/05)

5.1.2.1 For those institutions wishing to use 3D-CRT techniques, the 3D Questionnaire (one per institution, see http://atc.wustl.edu) is to be sent to the Washington University Image-Guided Therapy Center (ITC) for review prior to entering any cases. Upon review and successful completion of "Dry-Run" or "Benchmark" QA test (See http://atc.wustl.edu), the ITC will notify both the registering institution and RTOG Headquarters that the institution is eligible to enter patients onto this study. Institutions that have previously enrolled patients on RTOG 94-06 may enroll patients on this study without further credentialing by the ITC. (10/11/05) (2/16/06)

5.1.2.2 Institutions or investigators anticipating the use of IMRT on this study must complete a new IMRT Facility Questionnaire. A copy of the IMRT Facility Questionnaire may be obtained only via the ITC website at http://itc.wustl.edu. The IMRT Facility Questionnaire requests information regarding the training and experience of the IMRT team, IMRT treatment planning and treatment equipment, and in-house QA procedures. All institutions must also successfully complete an IMRT "dry-run" or benchmark case with the ITC. In addition, an IMRT phantom

study or benchmark case with the RPC (see http://rpc.mdanderson.org) must be successfully completed if the institution has not previously met this credentialing requirement on another RTOG IMRT study, such as RTOG 0126, 0022, or 0225. (10/11/05) (2/16/06)

5.1.3 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 ITC web site at http://itc.wustl.edu.

5.2 Registration (10/11/05)

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://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp).
- The institution must complete the Password Authorization Form at www.rtog.org/members/webreg.html, 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 (www.rtog.org), going to "Data Center Login" 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 that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters at (215) 574-3191.

6.0 RADIATION THERAPY

6.1 External Beam Radiation Therapy (Arm 1 only; IMRT is allowed on this protocol) (10/11/05)

Protocol treatment must begin within four weeks after study entry. (2/15/05)

6.1.1 Non-IMRT external beam radiotherapy (10/11/05)

6.1.1.1 Physical Factors. Megavoltage equipment is required with photon energies ≥ 6 MV. The minimum source to axis distance is 100 cm. A minimum of four field arrangements (AP:PA:R:L) is required. Greater than four fields are permitted. 3DCRT is permitted, but not required. (10/11/05)

6.1.1.2 Target Volume. In order to evaluate the adequacy of the field margins, the submitted simulator films must contain contrast material in the bladder and/or urethra and the rectum. A retrograde urethrogram is highly recommended. If targeting is performed from a CT scan and the bladder, urethra and rectum are outlined on the CT scan and displayed on a digitally reconstructed radiograph (DRR), the use of contrast is not required. Patients will be treated to a CTV that includes the prostate and seminal vesicles. The PTV is equal to the prostate and seminal

vesicles with a minimum 1 cm margin except posteriorly where it may be less. The PTV must receive at least 95% of the prescribed dose. (2/15/05) (10/11/05)

6.1.1.3 Doses. The prostate and seminal vesicles will receive a dose of 45 Gy from the external beam portion of the treatment. Daily doses will be 1.8 Gy given 5 times per week. The prescribed dose will be defined at the ICRU reference point. The permitted dose variation will be ≤ 5%. A variation acceptable for the external beam treatment is defined as a dose variation between > 5% and ≤ 10%. A deviation unacceptable is a dose variation > 10%. (10/11/05)

6.1.1.4 Copies of simulation films of each field and initial port films, the monitor unit calculation form, isodose distribution, treatment prescription, and treatment chart will be sent to RTOG Headquarters only if requested. Beam verification (port) films must be obtained for each field at least every 2 weeks during treatment and when any adjustments are made. Port films of each field will be submitted to the RTOG Headquarters only if specifically requested. (10/11/05)

6.1.2 *IMRT External Beam Radiotherapy (10/11/05):*

6.1.2.1 Physical Factors. Megavoltage equipment is required with photon energies ≥ 6 MV. (10/11/05)

6.1.2.2 Target Volume. In order to evaluate the adequacy of the field margins, the submitted simulator films must contain contrast material in the bladder and/or urethra and the rectum. A retrograde urethrogram is highly recommended. If targeting is performed from a CT scan and the bladder, urethra and rectum are outlined on the CT scan and displayed on a digitally reconstructed radiograph (DRR), the use of contrast is not required. Patients will be treated to a target volume that includes the prostate and seminal vesicles. PTV is equal to the prostate and seminal vesicles with a minimum 0.5 to 1 cm margin. The PTV must receive at least 95% of the prescribed dose. (10/11/05)

6.1.2.3 Doses. The prostate and seminal vesicles will receive a dose of 45 Gy from the external beam portion of the treatment. Daily doses will be 1.8 Gy given 5 times per week. The prescribed dose will be defined at the ICRU reference point (defined in accordance with ICRU Report 62). The minimum dose to 98% of the PTV is 45 Gy; the minimum dose encompassing the CTV is 45 Gy; the maximum dose to the < 2% of the PTV is < 48.1 Gy (no variation), < 49.5 Gy (minor variation) or > 49.5 Gy (major variation). (10/11/05)

6.1.2.4 First day orthogonal isocenter verification films, or images, must be obtained. If modifications are made in field shaping or design, orthogonal isocenter verification films, or images, are required on the first day's treatment of that field. Thereafter, weekly verification films or images of orthogonal view are required. The intensity profiles of each beam must be independently verified and compared to the planned field intensity. (10/11/05)

6.1.2.5 Credentialing requirements and QA guidelines for institutions planning to participate in this study using IMRT can be found at the ATC website http://atc.wustl.edu. (10/11/05) (2/16/06)

6.1.3 *External Beam Radiation Toxicity.* All patients will be seen weekly by their radiation oncologist during external beam radiation therapy. Any observations regarding radiation reactions will be recorded. The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting beginning April 1, 2010. The CTCAE version 4.0 is located on the CTEP website at (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. (10/11/05) (3/29/10)

6.2 Brachytherapy

6.2.1 *Timing.* Brachytherapy will be performed 2-4 weeks following completion of external beam radiotherapy (Arm 1) or within 4 weeks of study entry (Arm 2).

6.2.2 *Treatment Volumes:*

6.2.2.1 Clinical Target Volume. The CTV is the pre-implant TRUS definition of the prostate.

6.2.2.2 Planning Target Volume. The PTV is an enlargement of the CTV. (2/15/05)

6.2.2.2.1 Laterally the PTV may be extended 2 to 3 mm on each axial slice of the TRUS.

6.2.2.2.2 Anteriorly the PTV may be extended 2 to 3 mm on each axial slice of the TRUS.

6.2.2.2.3 Posteriorly the CTV and the PTV should have the same border.

6.2.2.2.4 In the cranial and caudad directions, the CTV may be extended up to 5 mm.

6.2.2.3 Evaluation Target Volume. The ETV is the post implant CT definition of the prostate.

6.2.3 *Preplan.* The number of slices will be recorded. Slice spacing will be 5 mm. The planimetric volume of the prostate will be the CTV. Interoperative preplanning is allowed.

6.2.4 *Implant Procedure:*

6.2.4.1 Urethra. A method of visualizing the urethra will be used during the implant, either a Foley catheter or aerated gel.

6.2.4.2 Records. Seed locations, given as a template location and retraction, shall be recorded during the procedure. The location of anchoring devices should also be recorded. If a preplan was generated, this information may be annotated directly on the preplan.

6.2.4.3 Radiation Safety. Federal and state requirements shall be followed and appropriate records maintained.

6.2.5 *Seed Calibration and Handling.* Iodine-125 or Palladium-103 seeds may be used. The sources will be received and inventoried in accordance with state and federal regulations. At least 10% of the sources will be assayed in such a manner that direct traceability to either the National Institute of Standards and Technology (NIST) or an Accredited Dosimetry Calibration Lab (ADCL) is maintained. NIST 1999 standards will be used. Agreement of the average measured source strength shall agree with that indicated in the vendor's calibration certificate to within ± 5%. No measured source strengths should fall outside ± 10% of that indicated in the vendor's calibration certificate.[31]

6.2.5.1 Assay performed by a third party, such as a third party vendor, is allowed as long as the assay fulfills the requirements listed in Section 6.2.5. (2/15/05)

6.2.6 *Source Strength.* For Iodine-125, the allowable source strength for each seed is 0.277 U to .548 U (NIST 99 or later). For Palladium-103 sources, this is 1.29 U to 2.61 U (NIST 99 or later). (2/15/05)

6.2.7 *Brachytherapy Dosimetry.* The vendor's stated source strength shall be used in all dosimetry calculations. Calculations will be performed in accordance with NIST 1999 calibration standards, the point source formalism described in the report generated by AAPM Task Group43 and subsequent published AAPM Subcommittee Reports.[31,32,58-61] The AAPM's recommendations for Pd-103 dose specifications and prescription are being followed.

6.2.8 *Prescribed Dose.* The prescription doses for Iodine-125 are 145 Gy and 110 Gy for monotherapy and boost implants, respectively. For Palladium-103 this is 125 Gy and 100 Gy for monotherapy and boost implants. The prescription dose minimum peripheral dose (mPD) is intended to be delivered to the CTV and is the reference dose for the implant.

Procedure	Dose I-125	Dose Pd-103
Boost Therapy	110 Gy	100 Gy
Monotherapy	145 Gy	125 Gy

6.2.9 *Post Implant Dosimetric Analysis.* A CT scan will be performed 3 to 5 weeks following the implant. The patient will be scanned in a supine position. IV and/or bladder contrast may be used. Abutting slices of 3 mm or less will be acquired from 2 cm cephalad to the base of the gland to 2 cm caudad to the apex. All of the seeds used in the implant should be encompassed in the scan. The ETV shall be determined from this scan, as shall the location of the urethra and the rectum. These are the critical structures for this protocol. Due to the difficulty in CT visualization of the urethra, Foley catheterization is recommended. If catheterization is not performed, the urethra will not be contoured. The urethra and the rectum contours are to be drawn as the outer surface of the Foley catheter and rectal walls, respectively. The CT scan will be used to create a post-implant treatment plan (post plan). An AP or anterior oblique pelvic radiograph will be used to verify the number of sources and this will be recorded on the T5 form. A PA and lateral chest x-ray will be obtained to document any pulmonary source migration.

6.2.9.1 Planning System Calculation Requirements:

6.2.9.1.1 The planning system will be able to perform structure-based analysis from axial image sets. This shall include isodose display and generation of Dose-Volume Histograms (DVH).

6.2.9.1.2 The calculation grid should be set no larger than (2mm x 2mm x the axial slice width).

6.2.9.1.3 The planning system shall be capable of transmitting data via DICOM RT to the ITC electronically. Please see Appendix VII.

6.2.9.2 Reporting. Guidelines established by the American Brachytherapy Society[33] are to be followed. DVH-based analysis must be used in the post plan evaluation. The following values shall be reported. V_n is the percentage of the ETV that received at least n% of the prescription dose. D_m is the minimum dose received by m% of the ETV.

6.2.9.2.1 Coverage. V_{100}, V_{90}, V_{80}, D_{90}.

6.2.9.2.2 Uniformity. V_{150}.

6.2.9.2.3 Urethra. The maximum dose to the urethra and volume of urethra (in cm^3) that received more than 200% of the prescription dose [U_{200}(cc)].

6.2.9.2.4 Rectum. The outer rectal wall will be contoured behind every axial slice of the prostate. The maximum dose to the rectum and the volume of the rectum (in cm^3) that received more than 100% of the prescription dose [R_{100}(cc)].

6.2.10 *Post-Implant Confirmation.* Following implantation, cystoscopy may be performed to retrieve any seeds from the bladder or the urethral wall. An x-ray film will be taken post-implant to verify seed position.

6.2.11 *Post-Operative Care*. A Foley catheter may be left indwelling until the patient recovers fully from anesthesia. If the patient has significant symptoms of prostatism, the catheter may be left in place for several days as needed.

6.2.12 *Evaluation Criteria:*

6.2.12.1 Per protocol: D_{90} for the ETV is greater than 90% of the prescription dose but less than 130% of the prescription dose.

6.2.12.2 Variation acceptable: D_{90} for the ETV is greater than 80% of the prescription dose, but less than 90% of the prescription dose, or greater than 130% of the prescription dose.

6.2.12.3 Deviation unacceptable: D_{90} for the ETV is less than 80% of the prescription dose.

6.2.13 Dosimetric Data to be Submitted to the ITC:

6.2.13.1 Copies of pre-implant TRUS images with CTV and PTV annotated.

6.2.13.2 A copy of the implant record generated during the procedure.

6.2.13.3 A copy of the film taken after the procedure and a copy of the film or scout taken during the post implant CT.

6.2.13.4 A copy of the post implant CT scan, ETV and urethra and rectum delineation and dosimetry calculations (must be submitted electronically).

6.2.13.5 A copy of the post implant dosimetry report the (T5 Form, Appendix VIII) that contains the information required in paragraph 6.2.9 above.

6.3 Radiation Toxicity (3/29/10)

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:

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

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

6.3.1.3 Radiation dermatitis

6.3.2 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.

6.3.3 Acute toxicity monitoring: Beginning April 1, 2010, acute (≤ 180 days from RT start) side effects of radiation therapy will be documented using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE version 4.0 is located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

6.3.4 Late toxicity monitoring: All late (> 180 days from RT start) side effects will be evaluated and graded according to the RTOG/EORTC Late Radiation Morbidity Scoring Scheme (Appendix IV).

6.4 Radiation Adverse Event Reporting (1/11/08) (3/29/10)

6.4.1 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 Adverse Event Expedited Reporting System (AdEERS) application 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 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, 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.

Pharmaceutically supported studies will require additional reporting over and above that which is required by CTEP.

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

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 (3/29/10)

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.

The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting beginning April 1, 2010. The CTCAE version 4.0 is located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

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 without any leading zeros as the patient ID when reporting via AdEERS. In order to ensure consistent data capture, AEs and SAEs reported using AdEERS **must also be reported to RTOG on the appropriate case report form (see Section 12.1).** In addition, sites must submit CRFs in a timely manner after AdEERS submissions.

Certain SAEs as outlined below will require the use of the 24 Hour AdEERS 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 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 the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 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 (3/29/10)

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.

The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting beginning April 1, 2010. The CTCAE version 4.0 is identified and located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

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 AdEERS. SAEs must be reported 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 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 via AdEERS 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)

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

Not applicable to this study.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

9.1 Neoadjuvant Hormone Therapy

Neoadjuvant hormone therapy is permitted if initiated between 2-6 months prior to registration. The duration may not exceed 6 months. Hormone therapy is not allowed to begin at initiation of or during radiation treatment. It is important to document neoadjuvant hormone therapy until its completion. Extended use of hormone therapy could confound the effects related to the biochemical control and quality of life endpoints.

10.0 PATHOLOGY (4/3/08)

(FOR PATIENTS WHO HAVE CONSENTED TO PARTICIPATE IN THE TISSUE COMPONENT OF THE STUDY; SEE APPENDIX IB)

10.1 Central Review

10.1.1 The investigators at the treating institutions are **strongly encouraged** to recruit patient participation in the central review component of this trial. Slides/blocks from the pre-treatment diagnostic prostatic biopsy will be reviewed to confirm Gleason score and to record other histopathologic features, such as the extent of tumor in the biopsies, the number of biopsies positive, and mitotic index.

10.2 Collection of Tissue For Translational Research

10.2.1 The RTOG has been collecting diagnostic tissue from prostate cancer protocols using the original diagnostic material for several years. A number of histologic, cell kinetic/proliferation, and molecular markers are under investigation, with several showing promise for the stratification of patients in future trials. The results of these ongoing studies will lead to the investigation of promising similar or new biomarkers with the goals of 1) identifying factors predictive of outcome such that patients may be better stratified in future trials, and 2) developing novel treatment strategies which target the molecular abnormalities identified. A final decision on which markers will be studied awaits the results of completed RTOG prostate cancer trials that have reached maturity. The trial described here will not be ready for biomarker analysis for several years. The goal is to measure approximately ten biomarkers using the archived pathologic material.

10.3 RTOG Biospecimen Resource

10.3.1 *Rationale*

The purpose of the RTOG Biospecimen Resource is to acquire and maintain high quality specimens from RTOG trials, to provide uniform access of such tissues to investigators for correlative studies, and to preserve tissue from each block through careful block storage and processing. Correlative studies from these specimens are meant to integrate new research findings into future protocol development and to educate RTOG members.

10.3.2 *Central Pathology Review* (**strongly encouraged**) (2/15/05)

All consenting patients must have at least one H & E slide from each positive biopsy site submitted to the Biospecimen Resource in order for the case to be evaluable for central pathology review. (2/15/05) The following must be provided:

10.3.2.1 One H &E stained slide per positive biopsy site;

10.3.2.2 A Pathology report documenting that submitted blocks, core, or 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;

10.3.2.3 A Pathology Submission Form clearly stating that the tissue is being submitted for the central review; the form must include the RTOG protocol number and patient's case number.

10.3.3 *Tissue Banking for Biomarker Studies*

The investigators at the treating institutions are **strongly encouraged** to recruit patient participation in the translational research component of this trial. The following must be provided in order for the case to be evaluable for the Biospecimen Resource:

10.3.3.1 At least one paraffin-embedded tissue block of the tumor (containing the highest grade of tumor if multiple biopsy sites contain cancer), a 2 mm core of tumor from the block, obtained with a derm punch or similar device, or 15 unstained slides. Kits for punching blocks can be obtained free of charge from the Biospecimen Resource. Blocks/core/slides must be clearly labeled with the pathology identification number that agrees with the pathology report;

10.3.3.2 A Pathology Report documenting that submitted blocks, core, or slides contain tumor; the report must include the RTOG protocol number and patient's case number. The patient's name or other identifying information should be removed from the report;

10.3.3.3 A Pathology Submission Form clearly stating that tissue is being submitted for the RTOG Biospecimen Resource; the form must include the RTOG protocol number and patient's case number;

10.3.3.4 A copy of the patient's tissue consent form; the consent form must include the RTOG protocol number and the patient's case number. The patient's name and/or identifying information should be removed from the consent form.

10.3.4 Submit materials (for central review or tissue banking) to:

Mailing Address: For Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
1657 Scott Street, Room 223
San Francisco, CA 94143-1800

Courier Address (FedEx, DHL, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu

10.4 Reimbursement

10.4.1 RTOG will reimburse pathologists from submitting institutions $200 per case if a block or core of material is submitted and $100 per case if unstained slides are submitted. After confirmation from the Biospecimen Resource that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution.

10.5 Confidentiality (See RTOG Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/tissuebank/tissuefaq.html for further details)

10.5.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient's case number only. The Biospecimen Resource database includes only 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.

10.5.2 The specimens 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.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (10/11/05)

Parameters	Pre-treatment	Weekly During RT	Post-implant	Follow up[e] (Interval in months) 4	6	9	12	18	24
History, Physical Exam (DRE)	X	X[i]		X[i]	X	X	X	X	X
Zubrod Performance Status	X	X		X	X	X	X	X	X
Tumor Measurement	X			X	X	X	X	X	X
Prostate biopsy with Gleason score[f]	X								
CBC, platelets	X	X[d]							
BUN, creatinine	X								
PSA (pre-HT, if given)	X[a]				X		X	X	X
Free PSA (if available)	X[c]						X		X
TRUS	X								
Flexible Cystoscopy	X[c]								
Lymph node assessment	X[b]								
Post-Implant prostate CT[h]			X						
Post-Implant pelvic AP or anterior oblique X-ray[h]			X						
Post-Implant chest PA and lateral X-ray[h]			X						
AUA Symptom Index[g]	X			X			X		X
EPIC Questionnaire[g]	X			X			X		X
EQ5D Questionnaire[g]	X			X			X		X
Utilization of Sexual Medications/Devices[g]	X			X			X		X
Toxicity Evaluation		X		X	X	X	X	X	X

a. PSA must be done:
   - Within 60 days prior to study entry and prior to prostate biopsy *or*
   - Within 60 days prior to study entry and at least 10 days after prostate biopsy *or*
   - For patients receiving neoadjuvant hormone therapy, PSA must be done within 60 days prior to initiation of hormones.

   Note: PSA obtained > 60 days prior to study entry and/or within 10 days following prostate biopsy must not be used for study entry PSA (for those patients not on hormones).
b. Diagnostic pelvic CT scan or MRI and/or pelvic lymphadenectomy (2/15/05)
c. Optional
d. As indicated
e. Follow up 3-5 weeks post-implant, then every 4, 6, 9 and 12 months post treatment start for year 1; every 6 months for four years; then annually for the rest of the patient's life. (2/15/05)
f. At time of PSA failure
g. AUA is to be administered prior to registration. EPIC, Utilization of Sexual Medications/Devices, and EQ5D are to be administered at baseline (between study entry and treatment start). Then all four at 4, 12, and 24 months after treatment start (either implant or external beam), then annually thereafter for three years. (10/11/05)
h. Post-implant prostate CT, pelvic AP or anterior oblique x-ray, as well as chest PA and lateral x-ray to be performed 3-5 weeks post-implant. (10/11/05)
i. DRE is optional. (10/11/05)

11.2 Follow-up Schedule

11.2.1 Initial follow-up visit within 3-5 weeks of implant to coincide with post-implant CT.
11.2.2 After initial follow-up visit, follow-up will be done at 4, 6, 9 and 12 months post treatment start.
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.

11.2.6 HRQOL will be measured by administering EPIC, EQ5D, and AUA-SI at baseline and then at 4, 12, and 24 months after treatment start, then annually thereafter for three years. The Utilization of Sexual Medications/Devices will be administered to assess utilization of medications and devices for erectile dysfunction and effectiveness of such interventions, as reported by patients before and after definitive brachytherapy for prostate cancer; this tool also will be administered at baseline; at 4, 12, and 24 months after treatment start; then annually thereafter for three years. (10/11/05)

11.2.6.1 Method for patients to complete/record HRQOL survey responses: The HRQOL instruments will be self-administered by the patient at the beginning of each scheduled study clinic visit. The patient's self-reported quality of life will be assessed using the prostate cancer-specific EPIC, the EQ5D, and the AUA-SI. In addition, the patient-completed Utilization of Sexual Medications/Devices will be collected to provide a context for interpreting the sexual domain score of the EPIC questionnaire. The time needed for filling out the questionnaires is estimated at 25 to 30 minutes. The patient will be given the questionnaires directly PRIOR to being seen by the physician or nursing staff or having any tests/procedures done at the clinic visit. If the patient does not come in for a clinic visit, then questionnaires should be mailed to the patient at the time points indicated. There is a Spanish version of the EPIC questionnaire available; there are several official language versions of the EQ-5D available. (10/11/05)

11.2.6.2 Instructions for Clinical Research Associates (CRAs): The instructions given below (i through vii) are intended to serve as a guide for the administration of the HRQOL questionnaires. The HRQOL questionnaires will be self-administered by the patient.

i. Following the patient's check-in at clinic, the patient should be taken to a quiet area where he may complete the questionnaire without interruption. Adequate time should be provided to the patient so that the questionnaire can be completed at the beginning of the clinic visit.

ii. The patient will be given the questionnaire PRIOR to being seen by the physician or nursing staff or having any tests/procedures done at the clinic visit.

iii. The patient should be instructed to read the brief directions at the top of the page. After it has been confirmed that the patient understands the directions, he should be encouraged to complete every item in order without skipping any. Some patients may feel that a given question is not applicable to them and will therefore skip the item altogether. **Patients should be encouraged to circle the response that is most applicable**. If, for example, a patient is not bothered at all by a particular problem, the patient should circle "no problem", "not at all", "none of the time", rarely or never".

iv. The questionnaires must be completed by the patient alone, without coaching or suggestions as to the "correct" answer by health care personnel, relatives, or anyone else.

v. The study staff may provide clarification but should not rephrase questions, suggest answers, or discuss answers.

vi. The study staff will collect the questionnaires as soon as they have been completed, check to see that each question has been answered, and remind the patient to answer any questions that may have been missed. If the patient declines to answer some or any of the questions, the study staff should enter an explanatory comment on the questionnaires.

vii. The questionnaires should be completed in the clinic at the beginning of the visit. However, if the patient does not come in for a clinic visit, the questionnaires should be mailed to the patient at the time points indicated. **(These patients may not return for follow-up and then the data would be lost). NOTE:** Varying the environment in which the questionnaires are completed by allowing completion at other times than the time of the clinic visit

introduces unnecessary variables into the study. The information provided by the patient in the completed questionnaires is confidential and should not be discussed with, or shown to, anyone who is not a member of the study team.

11.3 Measurement of Effect/Response (1/11/08)

Prostate tumor dimensions in centimeters should be calculated from physical exam 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.

11.3.2 *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. If PSA failure occurs (as described in Section 11.3.5) within 24 months post-implant (due to possibility of "PSA bounce", see 11.3.5.3).

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 will be scored as digital examination failure. The time of failure will be backdated to the first occurrence of equivocal disease after a prior normal examination or to the end of radiation therapy treatment if a normal digital rectal examination was never achieved. Re-biopsy of the suspicious area must be done to document disease.

11.3.4 *Time to BiochemicalFailure:* Biochemical failure as defined below:

11.3.4.1 Failure is defined as having three consecutive rises of post-treatment PSA at the specified intervals or starting hormones after one or more elevations of post-treatment PSA but before three consecutive elevations are documented. If three consecutive PSA rises occur during the first 24 months followed by a subsequent non-hormonal induced PSA decrease, patients will not be considered PSA failures. Three consecutive rises with any of the three PSA values occurring more than 24 months after the implant procedure will constitute biochemical (PSA) failure. Starting hormones for any rise at any time will be considered failure. The failure day is the midpoint between the last non-rising PSA and first PSA rise. ASTRO consensus guidelines[34] of rising PSA will be used. 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. Re-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.

11.3.4.2 The sum of the rises in three consecutive rises of post-treatment PSA must exceed 1 ng/mL above the nadir.

11.3.4.3 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 re-biopsy at least 24 months post-treatment and/or clinical evidence of distant relapse (i.e., bone scan, CT scan, etc).

11.3.5 *Time to Biochemical Failure* by the Phoenix Definition

Failure is defined as having PSA ≥ 2 ng/ml over the nadir PSA after 24 months. 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. Re-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.

11.3.6 *Time to Local Progression:* The time to progression will be measured from the date of randomization 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 two years, and redevelopment of a palpable abnormality after complete disappearance of previous abnormalities. Needle biopsy is recommended.

11.3.6.2 *Histologic criteria* for local failure are presence of prostatic carcinoma upon biopsy and positive biopsy of the palpably normal prostate more than two years after the start of treatment.

11.3.7 *Time to Distant Failure*: The time to distant failure will be measured from the date of randomization to the date of documented metastatic disease **determined by radiographic criteria and/or tissue confirmation.**

11.3.8 *Overall Survival:* The survival time will be measured from the date of randomization to the date of death. All patients will be followed for survival. 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 randomization to the date of death due to prostate cancer. Causes of death may require review by the study chair or their 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.

11.4 Acute vs. Late Toxicity

11.4.1 *Acute toxicity monitoring*: Acute side effects ($\leq$ 180 days from RT start) will be documented using the using the NCI Common Toxicity Criteria version 2.0.

11.4.2 *Late toxicity monitoring*: All late (> 180 days from RT start) side effects will be evaluated and graded according to the RTOG/EORTC Late Radiation Morbidity Scoring Scheme (Appendix IV).

12.0 DATA COLLECTION (1/11/08)

RTOG, 1818 Market Street, Philadelphia, PA 19103, FAX# 215/928-0153 (2/15/05)

12.1 Summary of Data Submission (10/11/05) (4/3/08)

Item	Due
Demographic Form **(A5)** Initial Evaluation Form **(I1)** Pathology Report **(P1)** Slides/Blocks **(P2)** AUA Scoring Form **(PQ)** EPIC **(FA)** EQ5D **(QF)** Utilization of Sexual Medications/Devices **(SA)**	Within 2 weeks of study entry
External Beam Dosimetry Radiotherapy Form **(T1)***	Within 8 weeks post-implant to RTOG
Initial Followup Form **(FS)**	At 6 and 16 weeks after treatment start (EBRT Arm 1, implant Arm 2)
Followup Form **(F1)**	At 6, 9 and 12 months post treatment start (EBRT Arm 1, implant Arm 2); then q 6 months x 4 years, then annually. Also at progression/relapse and at death.
AUA Scoring Form **(PQ)** HRQOL (EPIC [**FA**], EQ5D [**QF**], Utilization of Sexual Medications/Devices [**SA**])	At 4, 12, and 24 months post treatment start, then annually for three years.
Autopsy Report **(D3)**	As applicable.

*** NOTE:** Copies of simulation and port films and Isodose Distribution for EBRT including IMRT (Arm 1 only) will be submitted to RTOG Headquarters ONLY if specifically requested. (10/11/05) (4/3/08)

12.2 Summary of RT QA Requirements (Image-Guided Therapy Center [ITC])

Submit to ITC via ATC website at http://atc.wustl.edu (10/11/05)

12.2.1 Brachytherapy (10/11/05)

Final Dosimetry Information (Digital Data): (Final dosimetry information will be based upon the post implant CT study)	Within 8 weeks post-implant
Post-Implant Form (Appendix VIII) **(T5)** CT Data Contours Dose Distributions	

12.2.2 (4/3/08)

Final Dosimetry Information: Within 1 week of RT end

- Copy of Radiotherapy Form **(T1)**
  COPY TO ITC and RTOG HQ
- Daily Treatment Record
  COPY TO ITC and RTOG HQ

12.2.3 *For Mail or Federal Express (10/11/05)*

Image-Guided Therapy Center (ITC)
4511 Forest Park Avenue, Suite 200
St. Louis, MO 63108
(314) 747-5414; FAX (314) 747-5423

12.2.4 *To send over Internet or using magnetic tape (10/11/05)*

Digital data submission may be accomplished using magnetic tape or the Internet. For network submission, the *ftp* account assigned to the submitting institution shall be used and e-mail 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.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints (1/11/08)

13.1.1 *Primary Endpoint*

Freedom from Progression (FFP): The event for FFP will be the first occurrence of the biochemical failure (see Section 11.3.4), clinical failure (local progression or distant metastases) or death due to any cause from the start of protocol treatment. Patients who are failure event free with less than 5 years of follow-up or who receive any secondary salvage therapy (e.g., salvage androgen deprivation, vaccine therapy, biologic/small molecule therapy, or chemotherapy) will be censored.

13.1.2 *Secondary Endpoints*

- Biochemical Failure (see Section 11.3.4)
- Biochemical failure by the Phoenix definition (see Section 11.3. 5)
- Disease-Specific Survival (see Section 11.3.9)
- Local Progression (see Section 11.3. 6)
- Distant Metastases (see Section 11.3.7)
- Overall Survival (see Section 11.3.8)
- Incidence of “acute” toxicities (based on CTC, v. 2.0.)
- Time to “late” 3+ toxicities (based on CTC, v. 2.0.)
- Early (4 months after therapy start) and late (2 years after therapy start) HRQOL change in 4 domains: HRQOL change is defined as HRQOL measured at baseline minus HRQOL measured at regular intervals in follow-up.
- Feasibility of collecting Medicare data in large RTOG prostate trial for cost effectiveness and cost utility analysis of combined radiation therapy.
- Prospectively collect diagnostic biopsy samples for future biomarker analyses

13.2 Sample Size (1/11/08)

13.2.1 *Stratification*: Patients will be stratified before randomization with respect to Stage (T1c vs. T2a-T2b), PSA (0 - <10 vs. 10-20), Gleason score (2-6 vs. 7), and neoadjuvant hormonal therapy (no vs. yes). The treatment allocation scheme described by Zelen[35] will be used because it balances patient factors other than institution. Patients will be randomized to external beam radiation (45 Gy dose)

and brachytherapy [Palladium-103 (100 Gy) or interstitial Iodine-125 (110 Gy)] vs. brachytherapy alone [Pd-103 (125 Gy) or I-125 (145 Gy)].

13.2.2 *Sample Size Derivation*:

The sample size calculation is based on the primary endpoint, freedom from progression (FFP) rate by 5 years. Based on the prior results from Blasko et al[6] we project that the rate of 5-year FFP of interstitial brachytherapy arm, p_1 is 80% and hypothesize a 10% improvement in patients treated in EBRT plus interstitial brachytherapy, i.e., p_2=90%. The sample size estimates are based on the ability to demonstrate that EBRT plus interstitial brachytherapy will improve a FFP rate at 5 years compared to interstitial brachytherapy alone by 10% with an α value of 0.025 (one-sided), statistical power of 90%. Two sample binomial testing is employed and five interim analyses with a final analysis are planned for early stopping for the efficacy and futility. Efficacy testing is based on Haybittle-Peto test[36,37], interim testing will be done at the significance level of 0.001, while a level of 0.02 will be used at the final analysis to preserve a 0.025 level. The futility testing is based on the Freidlin and Korn[38] method at a nominal significance level of 0.0001. Guarding against an ineligibility or lack-of-data rate of up to 10%, the final targeted accrual for this study will be 586 patients.

HRQOL change will also be a secondary objective of this study; however, sample size required for adequate power to detect clinically significant HRQOL differences is smaller than that required to detect differences in FFP

13.2.3 *Health Related Quality of Life (HRQOL) using EPIC* Patient self-assessment of symptoms will be performed using four primary EPIC scales: urinary-irritative, urinary-incontinence, bowel, and sexual. The endpoints for EPIC will be early (4 months after therapy start) and late (2 years after therapy start) HRQOL change in the four domains. The conditions for the HRQOL endpoints are as follows:

- A clinically significant difference in HRQOL change is defined as 0.5*standard deviation for each of 4 primary EPIC HRQOL endpoints (urinary-irritative, urinary-incontinence, bowel, and sexual);
- The observed differences from baseline for each of the four primary EPIC HRQOL scales are normally distributed;
- The two-sided level of significance is 0.05. To maintain this type I error and accommodate for four primary HRQOL comparisons (at four months and two years), the level of significance is adjusted by the Bonferroni approach and is reduced to 0.0125;
- Statistical power of at least 90%;

HRQOL will be collected on all cases participating in the trial. Therefore, there will be sufficient statistical power to detect a difference in HRQOL between the treatment arms. In addition, the standard error of measurement (SEM) will be used to classify these patients as having deteriorated from baseline.[39] The endpoint will be the two-year deterioration rate. Since there are four primary domains of EPIC, the type I error will also need to be adjusted. The Hommel method for adjusting the type I error will be utilized.[40] This method is dynamic while maintaining a pre-specified type I error. The two-sided level of significance is the same as stated above. Preliminary analysis of RTOG 98-05 showed a 29% rate of deterioration in the FACT prostate component domains. If the percentage of patients that deteriorate using the EPIC domains is the same as the FACT prostate component, then 29% of the patients will deteriorate using the EPIC scales on the brachytherapy alone arm. We want to be able to detect at an absolute difference of 14.5% or more (i.e., a relative change of 50% or more) in the 2-year deterioration rate between the brachytherapy and external beam radiation arm and brachytherapy alone arm. If there is correlation between the four EPIC domains, then the study will have at least 95% power to detect the difference between the treatment arms at the 0.05 (two-sided) level of significance. If there is moderate correlation between the scales, then the significance level will reduce to 0.025. If the four domains have low correlation, then the significance level will be 0.0167. If the domain results are completely independent, then the significance level will be reduced to 0.0125. There will be at least 95% power regardless of the correlation among the scales. As such, this study will have at least 95% statistical power to detect a difference in the two-year deterioration rate between the treatment arms.

13.2.4 *Health Related Quality of Life (QOL) Using EQ5D* The EQ 5D is a method for obtaining valuations of health-related quality of life (HRQOL) to be used as an adjustment to survival and in the cost-

utility analysis. It is a two-part questionnaire that takes approximately 5 minutes to complete.[41] The first part consists of 5-items covering 5 dimensions including: mobility, self care, usual activities, pain/discomfort, and anxiety/depression. Each dimension can be graded on 3 levels including: 1-no problems, 2-moderate problems and 3-extreme problems. Health states are defined by the combination of the leveled responses to the 5 dimensions, generating 243 (3^5) health states to which unconsciousness and death are added.[42] The second part is a visual analogue scale (VAS) valuing current health state, measured on a 20 cm 10 point-interval scale. Worst imaginable health state is scored as 0 at the bottom of the scale and best imaginable health state is scored as 100 at the top. Both the 5-item index score and the VAS score are transformed into a utility score between 0 "Worst health state" and 1 "Best health state". Either the index score or the VAS score can be used in the quality adjusted survival analysis, or enter the cost-utility equation, depending on the health state(s) of interest.[43]

Quality adjusted survival can be defined by the weighted sum of different time episodes added up to a total quality-adjusted survival time [**U=** sum of quality ($\mathbf{q_i}$) of health states **K** times the duration ($\mathbf{s_i}$) spent in each health state.[44]

$$\mathbf{U} = \sum_{\mathbf{i=1}}^{\mathbf{K}} \mathbf{q_i s_i}$$

13.2.5 *Cost Effectiveness/Cost Utility (Pilot)(1/11/08):* A pilot study is planned to collect cost data on patients who consent to participate. These data will be used to generate hypotheses regarding cost effectiveness and cost utility of the combined radiation treatment. The data will also be used for future studies and analyses. Patient identifiers (e.g., social security numbers and names) will be collected on all cases in which the patients have consented. These patient identifiers will be linked to Medicare claims data, detailing payments associated with the interventions on each arm of the trial, as well as with payments associated with longer-term outcomes of treatment, including recurrences and complications. This part of the costs analysis will only include patients whose care is reimbursed under the federal Medicare payment system, but will exclude those in Medicare HMOs as well as those under alternative federal coverage (including Medicaid, DOD, and the VA) as well as those covered by private payers or other payment systems.

These Medicare costs data will be extracted from the Health Care Financing Administration's Medicare Statistical System and National Claims History files, and will include claims data from both Medicare Part A and Part B. These data include Medicare claims for inpatient care in hospitals and skilled nursing facilities, home health services, hospice services, physician services, and outpatient services. The total amount Medicare deemed payable will be used as the measure of cost for this analysis. This total includes both the amount paid by Medicare as well as coinsurance deductible amounts due from the patient and others.

An adjunct study is being developed that will use a separate methodology for collecting patient-specific costs data, including detailed billing information from voluntarily participating institutions as well as patient-specific diaries, detailing medications, doctors' visits, hospitalizations, and medical interventions. This separate study may be used to test the generalizability of the Medicare data over the larger study population.

The Medicare cost data will enter the numerator and the quality-adjusted survival calculated as described in Section 13.2.4 will enter the denominator in the Quality Adjusted Life Year (QALY) model, producing a dollar per QALY ratio. The $/QALY is a function of the monetary cost per relative value of each health state and its duration. In this way, disparate end points are combined into an overall value to the patient as well as a common metric for comparison to any other health care intervention.

Cost-utility will be analyzed for planned publication at three time-points: (1) at time of study closure, looking at initial treatment costs and quality of life at one year post-therapy, (2) at five years follow-up; and (3) after all follow-up data are in. The time horizon for economic data collection will be seven-years of follow-up, with the same time points as the quality-of-life assessments.

Patient participation in this component will be limited to non-Canadian institutions. In the two previous brachytherapy trials, RTOG 98-05 and P-0019, 83% of the 101 cases and 79% of the 138 cases, respectively, came from non-Canadian institutions. Of the 84 cases registered from non-Canadian institutions in RTOG 98-05, 58% paid using Medicare, Medicare and Private Insurance, or Medicare and Medicaid. In RTOG P-0019, 32% used Medicare as their primary method of payment.

In this protocol, we project that 80% of the eligible cases will be randomized from non-Canadian institutions (N=426). Due to the recent changes in federal regulations regarding privacy and collection of patient identifiers (e.g., HIPAA), we expect 25% of these eligible cases will consent to providing their social security number and name for this pilot study (N=107). Table 3 below lists the number of eligible and analyzable cases for the cost effectiveness/cost utility component by the percentage paying by Medicare (%=25, 33, and 50).

Table 3. Number of Cases Eligible and Analyzable for Cost Effectiveness/Cost Utility Component by the Percentage Paying by Medicare

Percent Paying by Medicare	Number Eligible and Analyzable
25%	27
33%	36
50%	54

Thus, we expect between 27 and 54 cases to be eligible and analyzable for this component.

13.3 Patient Accrual (1/11/08)

Based on patient accrual in previous RTOG randomized prostate studies, there will be relatively few entries during the initial six months while institutions are obtaining IRB approval. In addition, due to the credentialing and data transfer requirements necessary for this protocol, this quiet period may be extended up to twelve months. Therefore, we do not expect to meet our targeted monthly accrual until the second year. Based on the projected accrual rate of 8 cases per month based on the past six months accrual, we project the total maximum study duration to be 7.7 years from now (January 9, 2008) with 2.7 years of accrual to accrue 254 to have 586 cases and at least 5 years of follow-up for all the patients.

The RTOG Data Monitoring Committee (DMC) will begin evaluating patient accrual semi-annually following the anticipated quiet period. If the average monthly accrual rate for the trial is less than 20% of the rate projected in the paragraph above (i.e., less than 2 patients per month), the study will close to further accrual. If the average monthly accrual rate is greater than 20% but less than 50% of projected (i.e., less than 4 patients per month), the trial will be placed on double-secret probation for six months. If the average monthly accrual rate at the end of the probationary period is less than 50% of projected, the study will close to future accrual. The participation of non-RTOG institutions through CTSU is expected to follow a similar pattern as seen in RTOG.

13.4 Analysis Plan (1/11/08)

All eligible patients who are randomized to the study will be included in the comparison of treatment arms (intent-to-treat analysis).

13.4.1 *Statistical Methods*: (1/11/08)

FFP failure event will be the first occurrence of the biochemical failure (see Section 11.3.4), clinical failure (local progression or distant metastases) or death due to any cause from the start of protocol treatment. Patients who are failure event free with less than 5 years of follow-up or who receive any secondary salvage therapy (e.g., salvage androgen deprivation, vaccine therapy, biologic/small molecule therapy, or chemotherapy) will be censored. The primary endpoint FFP rate by 5 years is defined as the proportion of patients with a FFP failure by 5 years

from the randomization among all eligible patients at baseline and will be estimated by the Kaplan-Meier method.[51] The Z-test statistic for the difference between the two rates with the standard errors estimated by Greenwood's method will be used with an overall significance level of 0.025. The following test statistics will be used for testing between the twp arms.

$$T = \frac{\hat{p}_1 - \hat{p}_2}{\sqrt{\hat{p}_1^2 \sum_{i=1}^{n_1} \frac{f_i}{r_i(r_i - f_i)} + \hat{p}_2^2 \sum_{i=1}^{n_2} \frac{f_j}{r_j(r_j - f_j)}}} \quad (1)$$

where, $\hat{p}_1$ and $\hat{p}_2$ are FFP rate of EBRT plus brachytherapy arm and brachytherapy only arm, respectively, estimated by Kaplan-Meier method, r_i is the number of patients who are at risk and f_i is the number of patients who have FFP events (i=1,2).

The following hypotheses are of interest to be tested, where, p_1 and p_2,are the rate of 5-year FFP of EBRT plus brachytherapy arm and brachytherapy only arm, respectively.

H_0: $p_1 \leq p_2$ vs. H_A: $p_1 > p_2$

If H_0 is rejected, then we conclude that EBRT plus brachytherapy arm is better than brachytherapy only arm. If H_0 is not rejected, then we conclude that EBRT plus brachytherapy arm is not better than brachytherapy only arm.

In addition, univariate and multivariate logistic regression[45] will be used to compare the treatment differences in the hypothesis. Odds ratios from univariate and multivariate logistic regression and the respective 95% confidence intervals will be computed. Stage (T1c vs. T2a-T2b), PSA (0 - <10 vs. 10-20), Gleason score (2-6 vs. 7), and neoadjuvant hormonal therapy (no vs. yes), age, and race (as appropriate) will be adjusted for in the Multivariate analysis.

For the HRQOL endpoint, change in each of 4 HRQOL domains (change from baseline to four months after therapy and from baseline to two years after therapy) will be compared between arms using the t-test because normal distribution of HRQOL scores is expected based on EPIC validation studies. EPIC HRQOL scores will be computed as described.[24] The EPIC HRQOL domains will also be analyzed using the clinically significant change at two years as defined by the SEM. The percentage of patients on each arm that have deteriorated according to the EPIC primary scales will be reported in this study. Any missing HRQOL data will be assumed to be missing completely at random (MCAR). Therefore, standard statistical methods will be used in all HRQOL analyses.

13.4.2 *Cost Effectiveness/Utility Analysis:* A (Medicare) perspective will be used in this analysis. Using the pilot data obtained (from consented patients), differences in charges between the two treatments will be assessed using multivariable ordinary least-squares regression. In addition, comparison of charges and outcomes will be reported as the ratio of dollars per life year saved. This ratio will be calculated as the difference in the costs between patients treated with brachytherapy and those treated with brachytherapy plus external beam radiotherapy divided by the difference in the probability of life years saved in these two groups. Cost-utility outcomes will be reported in U.S.$/Quality Adjusted Life Year using the EQ5D five item index score and the VAS score for current health. A 3% and 5% discount rate will be used for both costs and effects; sensitivity analysis will be undertaken at 1% and 7%. Sensitivity analysis will also be used to determine the relationship between variation in key cost variables and final results. We will assume all data are missing completely at random, or at a minimum, missing at random and use standard statistical methods for the cost effectiveness/cost utility analyses.

13.4.3 *Interim Analysis to Monitor the Study Progress*: Interim reports with statistical analyses will be prepared twice a year until the initial paper reporting the treatment results has been submitted. In general, the interim reports will contain information about the patient accrual rate with a projected completion date for the accrual phase; data quality; compliance rate of treatment delivery with the distributions of important prognostic baseline variables; and the frequencies

and severity of the toxicities by treatment arm. The interim reports will not contain the results from the treatment comparisons with respect to the primary endpoint, FFP, or secondary endpoints such as biochemical failure.

13.4.4 *Significance Testing for Early Termination and Reporting:*

13.4.4.1 Primary Endpoint: Freedom from Progression(1/11/08)

A group sequential test with five planned interim analyses and a final analysis will be performed. The interim analysis will be carried out when the cumulative accrual (patients whose follow-up is at least 5 years from the randomization date) are met. At each planned interim analysis, the p-value from the Z-test statistics, eq.1, for the difference between the two FFP rates assessing treatment efficacy or futility with respect to the primary endpoint will be compared to the nominal significance level. The significance level of 0.001, which is based on the Haybittle-Peto test[36,37], was chosen for efficacy testing. For the futility testing boundary, we will use a less aggressive boundary, Rule C (a level of 0.0001) in Freidlin and Korn[38]. The following hypotheses are tested.

$$H_0: p_1 \leq p_2 \quad \text{vs.} \quad H_A: p_1 > p_2$$

For efficacy testing, if H_0 is rejected, then we conclude that EBRT plus brachytherapy arm is better than brachytherapy only arm and report the results (stop accrual if applicable). For futility testing, the alternative hypotheses, H_A ($p_1 = p_2 + 0.1$) will be tested at 0.0001 level (the futility nominal significance level). If we stop the trial for futility, then we will conclude that the 5-year FFP of brachytherapy only arm will be better than EBRT plus brachytherapy arm and report the results. Otherwise, we will continue the trial.

Table 12: The Schedule for the Planned Analyses

Information Time	Estimated Analysis Time*	Cumulative Accrual in the Two Arms**
0.17	6.5	89
0.34	7.4	177
0.5	8.3	266
0.67	9.2	354
0.83	10.2	443
1.0	11.1	532

* Time to the interim analysis from the first patient entry without considering ineligibility or lack-of-data rate

**The number of eligible patients whose follow-up is at least 5 years from the randomization date

Based on the results of each interim analysis, the following action will be taken and the responsible statistician will recommend to the RTOG DMC that the randomization be discontinued, if applicable, and the study be considered for early publication. Before making such a recommendation, the accrual rate, treatment compliance, safety of the treatments, and the importance of the study are taken into consideration along with the p-value. The RTOG DMC will then make a recommendation about the trial to the RTOG Group Chair.

13.4.4.2 Time to Biochemical Failure-Related Endpoints (1/11/08)

Biochemical failure (Sections11.3.4 and 11.3.5) will be secondary endpoints of interest and will be reported after the primary endpoint result Blasko et al.[6] reported their five-year biochemical failure-free rate of 82% for palladium-103 monotherapy in intermediate risk patients. In light of the findings in Blasko et al.[6], power was calculated for different hazard ratios for the analysis of biochemical failure using the estimated sample size. The baseline biochemical (failure rate was 0.0389 per year and was assumed to be constant over time. It was also assumed that the frequency of deaths without a biochemical failure reported was 2% per year. This rate was used in Lakatos' method when calculating the number of biochemical failures and statistical power. Table 4 below lists the number of biochemical failures and power at the analysis time point for each hazard ratio (Δ=1.3, 1.4, 1.5, and 1.6). At the time of the biochemical failure analysis, there will be at least 80% power to detect a

hazard ratio greater than or equal to 1.5. The nominal significance level at this analysis is 0.025. The biochemical failure results will be reported following this analysis. Also, biochemical failure by the Phoenix definition (PSA ≥ 2 ng/ml over the nadir PSA)[46,47,48,49,50] will be analyzed in a similar fashion.

13.4.4.3 Time to Failure of Secondary Survival Endpoints (1/11/08)

The time to failure for secondary endpoints (disease-specific survival, local progression, distant metastases, and overall survival) will be measured from the date of randomization to the date of the event of interest. The events for secondary endpoints and time-to-events are defined in Sections 11.3. -11.3.9. The time-to-event distribution of overall survival will be estimated using the Kaplan-Meier method[51] and the log-rank test[49,50] will be used to test whether the overall survival rate in the EBRT and brachytherapy arm is higher than the brachytherapy alone arm at the significance level of 0.025. However, the treatment effect on other types of failure may impact the observable measures of disease-specific survival, local progression, and distant metastases and competing risks for each endpoint should be considered. We will use the cause-specific hazard rate[54,55] (the instantaneous rate of cause-specific mortality in the presence of competing failure types as a function of time) approach to consider the competing risk events. Freidlin and Korn[38] showed that the cause-specific hazard rate approach is better than other approaches, for example, the cumulative incidence method,[56] in most cases. The log-rank test on the times to the specific type of failure, which considers the presence of competing events, will be used to test whether the survival rates of these secondary endpoints the EBRT and brachytherapy arm is higher than the brachytherapy alone arm at a significance level of 0.025. In this approach, patients who experience other failure first are censored.

In addition, the Cox regression model[57] will be used to compare the treatment differences. Both unadjusted and adjusted hazard ratios and the respective 95% confidence interval will be computed. At least the treatment arm, to Stage (T1c vs. T2a-T2b), PSA (0 - <10 vs. 10-20), Gleason score (2-6 vs. 7), and neoadjuvant hormonal therapy (no vs. yes), age, and race (as appropriate) will be adjusted for in this analysis.

Table 4. Power of significance testing for early reporting of biochemical failure

Δ	Biochemical Failures	Power
1.30	194	49.5%
1.40	189	67.8%
1.50	184	81.1%
1.60	179	89.8%

13.4.4.4 Comparison of the Incidence of Acute Toxicity and Time to Late Grade 3+ Toxicity (1/11/08)

Acute toxicities are scored according to NCI Common Toxicity Criteria version 2.0. and will be defined as the worst severity of the adverse event occurring less than or equal to 180 days of RT start. Late toxicities are scored according to the RTOG/EORTC Late Radiation Morbidity Scoring Scheme (Appendix IV) and will be defined as the worst severity of the adverse event occurring more than 180 days of the RT start.

Both acute grade 2+ and 3+ toxicity will be examined separately. Univariate logistic regression[4] will be used to model the distribution of acute adverse events. Multivariate logistic regression will be used to model the distribution of acute adverse events, adjusting for covariates. Treatment arm, Stage (T1c vs. T2a-T2b), PSA (0 - <10 vs. 10-20), Gleason score (2-6 vs. 7), and neoadjuvant hormonal therapy (no vs. yes), and age (as appropriate) will be adjusted for in

the multivariate analysis. Both unadjusted and adjusted odds ratios and the respective 95% confidence interval will be computed and tested using a one-sided chi-square test with the significance level of 0.05.

The time to late grade 3+ adverse events will be measured from the RT start to the time of the worst late grade 3+ adverse event, respectively. If no such late adverse event is observed until the time of the analysis, the patient will be censored at the time of the analysis. The distribution of time to late grade 3+ adverse events will be estimated using the Kaplan-Meier method[51] and tested using a one-sided log-rank test[52,53] with the significance level of 0.025. A multivariate Cox regression model[57] will be used to compare the treatment differences of time to late adverse event. Both unadjusted and adjusted hazard ratios and the respective 95% confidence interval will be computed. Treatment arm, Stage (T1c vs. T2a-T2b), PSA (0 - <10 vs. 10-20), Gleason score (2-6 vs. 7), and neoadjuvant hormonal therapy (no vs. yes), age, and race (as appropriate) will be adjusted for in this analysis.

13.4.5 *Analysis For Reporting the Initial Treatment Results*: (1/11/08) The primary hypothesis of this study is whether the addition of external beam radiation to brachytherapy will improve the freedom from progression (FFP) by 5 years rate compared to brachytherapy alone. The final analysis will occur after each patient has been potentially followed for a minimum of five years for the primary endpoint, FFP unless the early stopping rule is satisfied. It will include tabulation of all cases entered and those excluded from the analyses with the reasons for such given; the distribution of the important prognostic baseline variables; and observed results with respect to the primary and secondary endpoints. All eligible patients randomized will be included in the comparison and will be grouped by assigned treatment in the analysis. Five interim analyses and one final analysis will be performed for efficacy and futility of the experimental treatment will be carried out as described in Section 13.4.4.1. The Z-test statistics for the difference between the two 5 years FFP rates with the standard errors estimated by Greenwood's method, eq. (1), will be used with an overall significance level of 0.025. The treatment comparison of biochemical related failures and secondary survival endpoints will be analyzed as described in Sections 13.4.4.2 and 13.4.4.3, respectively in Section 13. Also, where feasible, treatment comparisons with respect to the primary endpoint (freedom from progression) and secondary endpoints such as biochemical failure will be compared within each ethnic category.

13.5 Inclusion of Minorities (1/11/08)

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 prostate protocol data, we project that 80% of the men in the study are White, 15% are Black or African American, 3% are Hispanic, 0.5% are Asian, 0.3% are Pacific Islander, 0.2% are American Indian or Alaskan Native, and 1% are others and unknown. The following table lists the projected accrual for each racial group. Assuming no difference among races with respect to overall survival, the statistical power for detecting the hypothesized difference is 83% and 25% for white and black, respectively.

Obviously, with 80% and 15% of the available sample being white and African American, respectively, univariate comparisons by treatment will not yield sufficient power in most cases. The distribution of cases by race (African American vs. Non-African American) and treatment arm for the recently completed RTOG prostate trials 92-02 and 94-13 are shown in Table 5. There was no statistical evidence to support a difference in treatment outcome and race in either study The change in the relative risk of treatment contributed by the interaction is a factor close to one; i.e., the value equal to the e^{β}, where β is the parameter estimate for the interaction term. *[RTOG 94-13: e^{β} =1.06, p=0.77 (RT Field) and e^{β} =1.36, p=0.12 (HT Timing); RTOG 92-02: e^{β} =1.06, p=0.75*]. Thus, we do not expect to see any evidence of a treatment difference between brachytherapy alone and brachytherapy and EBRT in the African American population in the current study. We will, however, include the ethnicity variable in all regressions including the Cox model.

Table 5. Distribution of Race (African American vs. Non-African American) and Treatment Arm in RTOG Studies 94-13 and 92-02

			Race	
Study	Treatment Arms*	N	African American	Non-African American
RTOG 94-13				
Radiation Field	WP RT	641	153 (24%)	488 (76%)
	PO RT	638	176 (28%)	462 (72%)
Hormone Timing	NHT	635	159 (25%)	476 (75%)
	AHT	644	170 (26%)	474 (74%)
RTOG 92-02	STAD	761	92 (12%)	669 (88%)
	LTAD	753	105 (14%)	648 (86%)

- Treatment arms for: RTOG 94-13: WP RT = Whole Pelvis RT (Radiation Therapy)+Boost and TAS (Total Androgen Suppression); PO RT = Prostate Only RT and TAS; NHT= Neoadjuvant TAS and RT; and AHT = Adjuvant TAS and RT and RTOG 92-02: STAD = Short-term TAS (4 months) and RT; and LTAD = Long-term TAS (28 months) and RT.

Ethnic Category	**Sex/Gender**			
	Females	**Males**	**Unknown**	**Total**
Hispanic or Latino	N/A	18	0	18
Not Hispanic or Latino	N/A	568	0	568
Ethnic Category: Total of all subjects	N/A	586	0	586
Racial Category				
American Indian or Alaskan Native	N/A	1	0	1
Asian	N/A	3	0	3
Black or African American	N/A	100	0	100
Native Hawaiian or other Pacific Islander	N/A	1	0	1
White	N/A	481	0	481
Racial Category: Total of all subjects		586	0	586

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APPENDIX IA (12/16/03, 2/15/05, 10/11/05)
RTOG 0232

INFORMED CONSENT
FOR
A PHASE III STUDY COMPARING COMBINED EXTERNAL BEAM RADIATION AND TRANSPERINEAL INTERSTITIAL PERMANENT BRACHYTHERAPY WITH BRACHYTHERAPY ALONE FOR SELECTED PATIENTS WITH INTERMEDIATE RISK PROSTATIC CARCINOMA

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 compare the effects (good and bad) of two different radiation treatments in patients with prostate cancer. The effects of placing small radioactive pellets (hereinafter called seeds) inside your prostate (brachytherapy) after external radiation therapy will be compared to the effects of using brachytherapy alone in patients with prostate cancer.

This research is being done to see which treatment is better. This study will also look at your already biopsied prostate cancer tissue for information that may help to predict and treat prostate cancer in the future. In addition, the study will gather information about the effects of the treatment on your quality of life. A cost comparison between the two treatments, including long term costs thereafter, is also planned for participants under Medicare.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY (1/11/08)

About **586** people in North America will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

SCHEMA

S	**Stage** 1. T1c	**R**		**R**	**Arm 1**: 45 Gy EBRT Partial pelvis (1.8 Gy/fraction M-F for
T	2. T2a – T2b	**E**	**Isotope**	**A**	five weeks) followed 2-4 weeks later by Pd-103 (100 Gy) or I-125 (110
R	**Gleason Score** 1. ≤ 6	**C**	1. I-125	**N**	Gy)*
A	2. 7	**0**	2. Pd-103	**D**	or
T	**PSA** 1. 0 - < 10	**R**		**O**	
I	2. 10-20	**D**		**M**	**Arm 2** Pd-103 (125 Gy) or I-125 (145 Gy)*
F	**Neoadjuvant Hormonal**			**I**	
Y	**Therapy** 1. No 2. Yes			**Z**	
				E	

*PROTOCOL TREATMENT MUST BEGIN WITHIN FOUR WEEKS AFTER STUDY ENTRY.

You will be "randomized" into one of the study groups (arms) described below. Randomization means that you are put into a group by chance. It is like flipping a coin. Which group you are put in is done by a computer. Neither you nor the researcher will choose what group you will be in. You will have an equal chance of being placed in either group.

Treatment Arm 1: External Radiation Therapy and then Brachytherapy

External Radiation Therapy:

If you are randomized to receive this treatment, external radiation therapy to your prostate will be given once a day, five days a week, Monday to Friday, for five weeks. External radiation therapy treatments will be given on an outpatient basis at your institution.

Brachytherapy (Internal Radiation Therapy):

Two to four weeks after the completion of external radiation therapy, radioactive seeds will be implanted into your prostate. This procedure is done on an outpatient basis under anesthesia at your institution. Procedures that are done to deliver brachytherapy:

- **Local or general anesthesia will be given prior to and during the procedure.**

- **With the help of ultrasound, thin needles with radioactive pellets will be inserted through the skin between your anus and scrotum into your prostate.**
- **As each seed is placed in the correct position, the needle is pulled out leaving the seed in your prostate.**

The number of needles and seeds varies depending on the size and shape of your prostate.

Treatment Arm 2: Brachytherapy Alone

Brachytherapy (Internal Radiation Therapy):

This is the same as the Brachytherapy described under Arm 1 above, except that the radioactive seeds will deliver a somewhat higher dose of radiation.

Treatment Arms 1 and 2:

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

- A physical examination, including a digital rectal exam (DRE):
    - prior to beginning treatment,
    - weekly in Arm 1 during external radiation therapy *(NOTE: DRE is optional/at study doctor's discretion)*;
    - at 4, 6, 9 and 12 months for the first year following treatment, *(NOTE: at 4 months is DRE optional/at study doctor's discretion*);
    - every 6 months for the next four years;
    - and then annually for the rest of your life.

  The follow-up visits generally take 15 to 30 minutes (in addition to time for answering questionnaires described below).
- Blood tests prior to beginning treatment; weekly during radiation therapy if your doctor feels these tests are needed, and at each follow-up visit (except at the 4 and 9 month visits) as described above.
- An ultrasound examination of your prostate prior to brachytherapy. This is a brief, outpatient procedure in which an ultrasound probe is placed into your rectum to determine the precise size and shape of your prostate. This procedure determines where each needle and seed will be placed.
- Your doctor may want an examination of your bladder prior to treatment. This may include insertion of a small flexible tube through your penis into your bladder (cystoscopy).
- CT scan, MRI, or possible removal and biopsy of pelvic lymph glands, if indicated, to evaluate your cancer prior to treatment.
- If your disease worsens, your physician may request a needle biopsy of your prostate to see how your prostate has responded to treatment.
- A CT scan of your prostate, a pelvic x-ray, and two chest x-rays 3 to 5 weeks following radioactive seeds being implanted.

- You will be asked to complete four questionnaires about your sexual and urinary functioning and overall quality of life. These questionnaires should take about 25-30 minutes to complete. You will be asked to complete these forms prior to treatment, at 4 months, 12 months, and 24 months after treatment and once a year after that for three years.

HOW LONG WILL I BE IN THE STUDY?

If you receive Treatment 1, you will receive external radiation therapy once a day, five days per week for five weeks. Two to four weeks following radiation therapy, the radioactive seeds will be implanted into your prostate. Follow-up visits will continue for the rest of your life according to the above schedule.

If you receive Treatment 2, the radioactive seeds will be permanently implanted within 2 to 4 weeks from study enrollment. Follow-up visits will continue for the rest of your life according to the above schedule.

The researcher may decide to discontinue your treatment if it is in your medical best 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 of enough participants.

You can stop participating at any time. However, before you do this, we ask you to talk with 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. Other drugs will be given to make side effects less serious and uncomfortable, such as medication to reduce irritation of the bowel, rectum, or bladder. Trouble with erections also can be successfully treated with medication in many circumstances. Many side effects go away shortly after the radiation therapy is stopped, but in some cases side effects can be serious or long-lasting or permanent. Some side effects do not become apparent for months or years after all treatment has been delivered.

Risks Associated with Implant Therapy

Very Likely

- Infection that can be treated with antibiotics
- Soreness in the implant area
- Temporary fatigue
- Temporary nausea
- Temporary diarrhea
- Abdominal cramps
- Bladder irritation with some bleeding

- Inability to achieve an erection
- Urinary tract infection *(UTI)*

Less Likely, But Serious

- Injury to the bladder, urethra, bowel or other tissues in your pelvis or abdomen
- Rectal bleeding that requires medication or burning/cutting of tissue or surgery to correct
- Intestinal or urinary obstruction
- Inability to control urination
- Movement of a radioactive seed to the lungs
- Serious infection
- Rectal fistula (breakdown of tissue between the urinary tract and rectum)

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 nausea
- Temporary diarrhea
- Abdominal cramps
- Bladder irritation with a stinging sensation
- Frequency or urgency of urination
- Inability to control urination (incontinence)
- Rectal irritation with more frequent bowel movements
- Fatigue
- Urinary Tract Infection (UTI)
- Inability to achieve an erection

Less Likely, But Serious

- Injury to the bladder, urethra, bowel or other tissues in your pelvis or abdomen
- Intestinal or urinary obstruction
- Rarely, rectal bleeding that requires medication or burning/cutting of tissue or surgery to correct

Risks Associated with External Radiation Therapy AND Seed Implant Therapy:

- Worsening of bowel, bladder or sexual dysfunction problems
- An overall decrease in your quality of life

Reproductive Risks:

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. 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?

Other options that could be considered for your condition instead of this study may include the following: (1) external radiation therapy alone, whether standard, three dimensional conformal, or intensity modulated radiation therapy (IMRT); (2) internal radiation therapy (brachytherapy) like this study, or by temporary insertion of radioactive rods, called high dose rate therapy; (3) hormone therapy; (4) surgery to remove your prostate (radical prostatectomy); (5) watchful waiting with regularly scheduled monitoring with digital rectal exams (DRE) and PSA blood draws; or (6) no treatment except medications to make you feel better. With the latter choice, your tumor would continue to grow and your disease would likely eventually spread. The treatments (1) through (4) 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 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 groups such as the Food and Drug Administration *(FDA),* the National Cancer Institute *(NCI)* or its authorized representatives, the Cancer Trials Support Unit *(CTSU),* qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in this study.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. If you are randomized to receive Treatment 1, the combination of external radiation with implant may result in higher costs to you or your insurance

company than an implant alone. 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. Although no funds have been set aside to compensate you in the event of injury or illness related to your treatment or procedures, you do not waive any of your legal rights to compensation, if any, by signing this form.

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.

You may find a National Cancer Institute guide: "Clinical Trials and Insurance Coverage - a Resource Guide" helpful in this regard. You may ask your doctor for a copy, or it is available on the World Wide Web at http://www.nci.nih.gov/ClinicalTrials/insurance (and click on printable version).

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.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies 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

You may also call the Project Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only).

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 clinical trials information go to **http://cancer.gov/clinicaltrials**

for cancer information go to **http://cancer.gov/cancerinformation**

CancerFax: Includes NCI information about cancer treatment, screening, prevention, and supportive care. To obtain a contents list, dial 301-402-5874 or 800-624-2511 from a fax machine handset and follow the recorded instructions.

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. Upon request, I will also receive a copy of the protocol *(full study plan).*

_____	_____	_____
Patient's Name	Signature	Date

_____	_____	_____
Name of Person Obtaining Consent	Signature	Date

APPENDIX IB (2/15/05)
RTOG 0232

CONSENT FORM FOR USE OF TISSUE FOR RESEARCH

ABOUT USING TISSUE FOR RESEARCH

We would like to keep some of the tissue that remains from the biopsy you underwent in the diagnosis of your cancer 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.

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.

All possible methods will be used to ensure your privacy and confidentiality. Identifying information will be taken off anything associated with your tissue before it is given to a researcher. 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.

THINGS TO THINK ABOUT

The choice to let us keep the left over tissue for future research is up to you. **No matter what you decide to do, it will not affect your care or participation in the primary 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, and then any tissue that remains will no longer be used for research.

In the future, people who do research may need to know more about your health. While _____ (doctor/institution) may give researchers reports about your health, your doctor/institution will not give researchers 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. However, the research done with your tissue may help to develop new products in the future, or your tissue may be used to establish a cell line that could be patented and licensed. If this occurs, you will not be paid for this use.

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

There is a very small chance that information from your health records could be incorrectly released. All possible methods will be used to protect your privacy and ensure confidentiality. Unless you have given your specific permission, your _____ (doctor/institution) will not release your personal results or information to third parties such as employers or insurers.

In the case of injury or illness resulting from participating in this research, emergency medical treatment is available but will be provided at the usual charge. Although no funds have been set aside to compensate you in the event of injury or illness related to your participation in this research, you do not waive any of your legal rights to compensation, if any, by signing this form.

MAKING YOUR CHOICE

If you have any questions about the research involving your tissue or about this form, please talk to your doctor or nurse, or call the institution's research review board at _____ (IRB's phone number).

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". **No matter what you decide to do, it will not affect your care or participation in the primary study.**

1. My tissue may be used for the research in the current study.

Yes **No**

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

Yes **No**

3. 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**

4. Someone from _____ (doctor's office/institution) may contact me in the future to ask me to take part in more research.

Yes **No**

Participant statement:
I have read and received a copy of this consent form. I have been given an opportunity to discuss the information with my doctor/nurse, and all of my questions/concerns have been answered to

my satisfaction. My answers above and my signature below indicate my voluntary participation in this research.

Patient's Name	Signature	Date

Witness statement:
I have explained the information in this consent form to the patient and have answered any questions raised. I have witnessed the patient's signature.

Name of Person Obtaining Consent	Signature	Date

APPENDIX IC
RTOG 0232
CONSENT FORM FOR USE OF COST DATA FOR RESEARCH
(Limited to Participants Whose Health Care is Covered at Least in Part by Medicare)

ABOUT USING COST INFORMATION FOR RESEARCH

In comparing different treatments for prostate cancer, very little is known about long-term costs of different kinds of treatment. This study compares two different kinds of treatment that are different in their initial costs. However, the long-term costs of the two different treatments are not known. Obtaining this information would allow us to study both the cost and the benefits of the treatments involved in this study. This information would help patients; physicians and providers make more informed decisions about these therapies in the future.

We would like to obtain information about both the short-term and the long-term costs of treatment for your prostate cancer. To do this, we would like to use computerized information from the Medicare system to estimate the costs of your medical care. You are being asked to provide your name and Social Security Number so that we may link your treatment and outcomes to the cost data involved in both your treatment and follow-up care.

This information is private and confidential. We must have your permission to use a personal identifier to obtain your specific Medicare information. **The specific information about you that is collected will not be given to any other party, including your physician, the hospital, or any other third party. These reports will not be put in your health record.** The Medicare data will be aggregated with data from all patients participating in this portion of the study, and only reported in aggregate form. No personal identifying information will be made public.

This cost information will be used only for research.

THINGS TO THINK ABOUT

The choice to let us have access to your Medicare information is up to you. **No matter what you decide to do, it will not affect your care or participation in the primary study.**

If you decide now that your Medicare data may be used 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 information, and your information will be removed from the study database.

BENEFITS

The benefits of research using costs data include learning how to achieve the most effective treatments for cancer while avoiding added costs and decreased quality of life for patients. This information would help patients like you; physicians and providers make more informed decisions about these therapies in the future.

RISKS

There is a very small chance that information from your billing information could be incorrectly released. If you give your permission for us to use your Medicare information, that information will be furnished to the RTOG directly by Medicare, and will not be made available to any third party, including your physician, hospital, employer, or other insurer. All possible methods will be used to protect your privacy and ensure confidentiality.

MAKING YOUR CHOICE

If you have any questions about the research involving your cost data or about this form, please talk to your doctor or nurse, or call the institution's research review board at _____ (IRB's phone number).

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". **No matter what you decide to do, it will not affect your care** or participation in the primary study.

My Medicare data may be used for the research in the current study.

Yes **No**

Participant statement:
I have read and received a copy of this consent form. I have been given an opportunity to discuss the information with my doctor/nurse, and all of my questions/concerns have been answered to my satisfaction. My answers above and my signature below indicate my voluntary participation in this research.

_____ _____ _____
Patient's Name Signature Date

Witness statement:
I have explained the information in this consent form to the patient and have answered any questions raised. I have witnessed the patient's signature.

_____ _____ _____
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

RTOG/EORTC Late Radiation Morbidity Scoring Scheme *APPENDIX IV*

ORGAN TISSUE	0	*GRADE 1*	*GRADE 2*	*GRADE 3*	*GRADE 4*	5
SKIN	None	Slight atrophy; Pigmentation change; Some hair loss	Patch atrophy; Moderate telangiectasia; Total hair loss	Marked atrophy; Gross telangiectasia	Ulceration	**DEATH DIRECTLY RELATED TO RADIATION EFFECTS**
SUBCUTANEOUS TISSUE	None	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; Slight field contracture; <10% linear reduction	Severe induration and loss of subcutaneous tissue; Field contracture > 10% linear measurement	Necrosis	
MUCOUS MEMBRANE	None	Slight atrophy and dryness	Moderate atrophy and telangiectasia; Little mucous	Marked atrophy with complete dryness; Severe telangiectasia	Ulceration	
SALIVARY GLANDS	None	Slight dryness of mouth; Good response on stimulation	Moderate dryness of mouth; Poor response on stimulation	Complete dryness of mouth; No response on stimulation	Fibrosis	
SPINAL CORD	None	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurological findings at or below cord level treated	Mono, para quadriplegia	
BRAIN	None	Mild headache; Slight lethargy	Moderate headache; Great lethargy	Severe headaches; Severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or paralysis; Coma	
EYE	None	Asymptomatic cataract; Minor corneal ulceration or keratitis	Symptomatic cataract; Moderate corneal ulceration; Minor retinopathy or glaucoma	Severe keratitis; Severe retinopathy or detachment Severe glaucoma	Panopthalmitis/Blindness	
LARYNX	None	Hoarseness; Slight arytenoid edema	Moderate arytenoid edema; Chondritis	Severe edema; Severe chondritis	Necrosis	
LUNG	None	Asymptomatic or mild symptoms (dry cough); Slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough); Low grade fever; Patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis; Dense radiographic changes	Severe respiratory insufficiency/continuous O2/Assisted ventilation	
HEART	None	Asymptomatic or mild symptoms; Transient T wave inversion & ST Changes; Sinus tachycardia >110 (at rest)	Moderate angina on effort; Mild pericarditis; Normal heart size; Persistent abnormal T wave and ST changes ; Low ORS	Severe angina; Pericardial effusion; Constrictive pericarditis; Moderate heart failure; Cardiac enlargement; EKG abnormalities	Tamponade/Severe heart failure/Severe constrictive pericarditis	
ESOPHAGUS	None	Mild fibrosis; Slight difficulty in swallowing solids; No pain on swallowing	Unable to take solid food normally; Swallowing semi-solid food; Dilation may be indicated	Severe fibrosis; Able to swallow only liquids; May have pain on swallowing Dilation required	Necrosis/Perforation Fistula	
SMALL/LARGE INTESTINE	None	Mild diarrhea; Mild cramping; Bowel movement 5 times daily Slight rectal discharge or bleeding	Moderate diarrhea and colic; Bowel movement >5 times daily; Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis/Perforation Fistula	
LIVER	None	Mild lassitude; Nausea, dyspepsia; Slightly abnormal liver function	Moderate symptoms; Some abnormal liver; function tests; Serum albumin normal	Disabling hepatitic insufficiency; Liver function tests grossly abnormal; Low albumin; Edema or ascites	Necrosis/Hepatic coma or encephalopathy	
KIDNEY	None	Transient albuminuria; No hypertension; Mild impairment of renal function; Urea 25-35 mg%;Creatinine 1.5-2.0 mg%; Creatinine clearance > 75%	Persistent moderate albuminuria (2+); Mild hypertension; No related anemia; Moderate impairment of renal function; Urea > 36-60mg% Creatinine clearance (50-74%)	Severe albuminuria; Severe hypertension Persistent anemia (< 10%); Severe renal failure; Urea >60 mg% Creatinine >4.0 mg% Creatinine clearance < 50%	Malignant hypotension; Uremic coma/Urea > 100%	
BLADDER	None	Slight epithelial atrophy; Minor telangiectasia (microscopic hematuria)	Moderate frequency; Generalized telangiectasia; Intermittent macroscopic hematuria	Severe frequency & dysuria Severe generalized Telangiectasia (often with petechiae); Frequent hematuria; Reduction in bladder capacity (< 150 cc)	Necrosis/Contracted bladder (capacity < 100 cc); Severe hemorrhagic cystitis	
BONE	None	Asymptomatic; No growth retardation; Reduced bone Density	Moderate pain or tenderness; Growth retardation; Irregular bonesclerosis	Severe pain or tenderness; Complete arrest of bone growth; Dense bone sclerosis	Necrosis/Spontaneous fracture	
JOINT	None	Mild joint stiffness; Slight limitation of movement	Moderate stiffness; Intermittent or moderate joint pain; Moderate limitation of movement	Severe joint stiffness; Pain with severe limitation of movement	Necrosis/Complete fixation	

APPENDIX V

GLEASON CLASSIFICATION[1]

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.

APPENDIX VI **RTOG 0232**

ON-STUDY AUA SYMPTOM SCORE (PQ) **Case ____**

PATIENT NAME _____ **TOTAL SCORE** _____

INSTITUTION NAME _____

PLEASE FILL OUT THIS SHORT QUESTIONNAIRE TO HELP US FIND OUT MORE ABOUT ANY URINARY PROBLEMS YOU MIGHT HAVE. CIRCLE A NUMBER IN EACH COLUMN THAT BEST DESCRIBES YOUR SITUATION. YOU MUST ANSWER ALL QUESTIONS.

	Not at all	**Less than one time in five**	**Less than half the time**	**About half the time**	**More than Half the time**	**Almost always**
1.Over the past month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	**0**	**1**	**2**	**3**	**4**	**5**
2.Over the past month or so, how often have you had to urinate again, less than two hours after you finished urinating?	**0**	**1**	**2**	**3**	**4**	**5**
3.Over the past month or so, how often have you found you stopped and started again several times when you urinated?	**0**	**1**	**2**	**3**	**4**	**5**
4.How often do you find it difficult to postpone urination?	**0**	**1**	**2**	**3**	**4**	**5**
5.Over the past month or so, how often have you had a weak urinary stream?	**0**	**1**	**2**	**3**	**4**	**5**
6. Over the past month or so, how often have you had to push or strain to begin urination?	**0**	**1**	**2**	**3**	**4**	**5**
	Not at all	**Once every 8 hours**	**Once every 4 hours**	**Once every 3 hours**	**Once every 2 hours**	**At least once every hour**
7.Over the past month or so, how often did you most typically get up at night to urinate?	**0**	**1**	**2**	**3**	**4**	**5**

Total per column _____ _____ _____ _____ _____ _____

_____ _____

Patient Signature Date This Form was Completed

APPENDIX VII (2/15/05)

RTOG Permanent Prostate Implant Quality Assurance Guidelines

I. Purpose

To establish QA guidelines for the radiation oncologist, physicist, dosimetrists, and research associate. To participate in this protocol, the oncologist/physicist team must attest in writing to the fact that they have performed at least 10 such prostate implants prior to entering patients on this protocol.

II. Background

The following reports serve as background material for various aspects of this protocol:

1. ICRU Report 58, Dose and Volume Specification for Reporting Interstitial Therapy

2. Comprehensive QA for radiation oncology: Report of AAPM Radiation Therapy Committee Task Group 40 Medical Physics 21 (4), 1994, 581-618.

3. Dosimetry of interstitial brachytherapy sources: Recommendations of the AAPM Radiation Therapy Committee Task Group No. 43 Medical Physics 22 (2), 1995, 209 - 234.

4. Recommendations of the American Association of Physicists in Medicine on Pd interstitial source calibration and dosimetry: Implications for dose specifications and prescription: Medical Physics 27(4), 2000, 634-642.

III. Technology Requirements

Each institution that wishes to participate in the protocol must have the following capabilities:
a. A source calibration system, modeled after TG 40, with an NIST traceable calibration for I-125 and Pd-103.

b. A treatment planning system with the following characteristics:

1) A seed model whose results agree with the TG-43 data, as specified below. (See RPC web site at http://rpc.mdanderson.org)
2) The ability to calculate brachytherapy dose distributions which display contours, which can be either CT based or manually entered. The brachytherapy dose calculational grid must be 2 mm x 2 mm or smaller. Manual superposition of the dose distribution over the contour is permitted provided that this superposition is based upon the coordinates of the contour and the coordinates of the individual seed locations.
3) The ability to produce a dose-volume histogram, DVH. The manual creation of a DVH is permitted provided it is based upon the brachytherapy dose calculation grid which must be 2 mm x 2 mm or smaller.

c. Transrectal ultrasound for pre-implant images
d. CT images for post-implant analysis
e. DICOM RT for electronic data submission and compatible treatment planning software

IV. Credentialing

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

2. Institutions who have been previously credentialed to participate in RTOG 98-05/RTOG P-0019 are automatically eligible to participate in this protocol assuming that these institutions have the same radiation oncologist and physicist as were on their original credentialing request and that the institution is using the same I-125 seed model as was on their original credentialing request (Please note that RTOG 98-05 and RTOG P-0019 only permitted the use of I-125. Thus if an

institution wishes to use Pd-103 and has been previously credentialed for I-125, they must complete the RPC's physics credentialing for this source.) In the event that an institution has changed physicist or source model, the institution must resubmit to have the new physicist or new source credentialed with the RPC. In the event that the institution has changed radiation oncologist, then the institution must resubmit for clinical credentialing with the RPC. Additional information can be found at the RPC's web site, http://rpc.mdanderson.org.

In addition to the credentialing of the radiation oncologist, the physicist, and the source, institutions must also be credentialed through the RTOG Image-guided Therapy Center (ITC). The web site is http://itc.wustl.edu. This web site contains a section, which is entitled "Prostate Brachy Docs." The required information for credentialing can be obtained from this section. At this time, there are at least two commercial planning systems that have capabilities of a digital data exchange for prostate implants. Institutions must become credentialed using the digital approach and are encouraged to request this capability from their software vendor is currently available.

V. Patient Data Review Process

The data for all patients entered onto this protocol will be reviewed by the PI's and other selected reviewers. This review will comprise, in part, of:

1. An independent definition of the ETV and an independent recalculation of the dose and the DVH's.

RTOG Post-Implant Dosimetry Data Form (T5) **Case** _____

Patient_____/Physician:_____

Source: _____

Doses are based upon TG 43 Dosimetry

Date of Pre-Implant TRUS Study: _____

Number of slices on pre-implant TRUS _____

TRUS volumes

CTV _____ cm^3 PTV _____ cm^3

Date of Implant: _____

Basic Dosimetry Information

1. Average activity per seed as measured by institution:
   Source Strength: _____U Date:
2. Midpoint apparent activity stated by the vendor:
   Source Strength: _____U Date:
3. Number of Seeds Used:
4. Number of Needles Used:
5. Prescribed Dose: ___ Gy TG 43/NIST 99Dosimetry
6. Peripheral Dose: ___ Gy TG 43/NIST 99Dosimetry

Post Implant CT Analysis

Date of Implant _____

Date of Post-Implant CT: _____

No. of Seeds Counted on Post Implant A/P Radiograph _____

Prostate

Prostate is defined on _____ slices.

Post-Implant Volume (ETV) as determined from post-implant CT _____ cm^3

V_{100} _____ % V_{90} _____ % V_{80} _____ %

V_{150} _____ % D_{90} _____ Gy

Urethra: Maximum Dose _____ Gy U_{200} _____ cm^3

Rectum: Maximum Dose _____ Gy R_{100} _____ cm^3

Appendix IX

Scoring Instructions for the Expanded Prostate cancer Index Composite (EPIC)*

To request a copy of **EPIC** or related information, please contact any of the following investigators:

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*** A SAS macro for computing the EPIC scores is available at the EPIC web site: http://roadrunner.cancer.med.umich.edu/epic/**

Questions regarding the SAS macro should be addressed to:

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The **Expanded Prostate cancer Index Composite (EPIC)** was developed by researchers at University of Michigan and UCLA to measure health related quality of life among men with prostate cancer.[1] It represents an adaptation of the UCLA Prostate Cancer Index,[2] modified to enhance sensitivity to therapy effects by increasing the number of prostate-targeted items to 50 (compared to 20 in the original UCLA-PCI). EPIC has been validated in men with localized prostate cancer who underwent surgery, external beam radiation, or brachytherapy with or without the use of

hormonal adjuvants. EPIC is sensitive to specific HRQOL effects of these therapies and to HRQOL effects of cancer progression.[3]

EPIC assesses the disease-specific aspects of prostate cancer and its therapies and comprises four summary domains (Urinary, Bowel, Sexual and Hormonal). Factor analysis supports dividing the Urinary Domain Summary Score into two distinct *Incontinence* and *Irritative/Obstructive* subscales. In addition, each Domain Summary Score has measurable *Function Subscale* and *Bother Subscale* components. Response options for each EPIC item form a Likert scale, and multi-item scale scores are transformed linearly to a 0-100 scale (see following page: EPIC scoring), with higher scores representing better HRQOL. A summary of EPIC Summary Score and Subscale characteristics are tabulated (from Ref. 1):

HRQOL Domain	Number of items	Mean Score (sd)	Test-retest reliability	Internal consistency reliability
II. HRQOL Domain Summary Scores				
Urinary	12	80.2 (17.5)	0.88	0.88
Bowel	14	86.6 (15.7)	0.84	0.92
Sexual	13	33.1 (23.6)	0.91	0.93
Hormonal	11	86.6 (13.8)	0.80	0.82
III. Domain-Specific HRQOL Subscales				
Urinary Subscales				
Function	5	86.5 (16.7)	0.83	0.69
Bother	7	75.8 (20.4)	0.87	0.85
Incontinence*	4	83.2 (22.9)	0.87	0.89
Irritative/Obstructive*	7	79.7 (18.5)	0.85	0.81
Bowel Subscales				
Function	7	87.9 (13.6)	0.78	0.75
Bother	7	85.3 (18.8)	0.85	0.90
Sexual Subscales				
Function	9	29.5 (24.0)	0.90	0.92
Bother	4	41.1 (30.1)	0.78	0.84
Hormonal Subscales				
Function	5	84.0 (15.3)	0.79	0.51
Bother	6	88.7 (13.6)	0.73	0.73

*A single global urinary bother item, which does not distinguish bother related to incontinence from that related to urinary obstruction, is not included in the Urinary Incontinence or Urinary Irritative/Obstructive subscales; therefore, 11 urinary items comprise these 2 subscales whereas the Urinary Summary Domain includes 12 items.

EPIC can be used alone or combined with other instruments, including the AUA-SI, FACT-P, and Medical Outcomes Study SF-12 or SF-36. Inter-scale correlation between EPIC and these instruments has indicated that efficient (yet comprehensive) HRQOL assessment can be achieved by co-administering EPIC with SF-12.[4] Concurrent use of the AUA-SI can also provide useful complementary clinical information.[5] The following scoring instructions therefore assume that EPIC will be co-administered with SF-12 and the AUA-SI, with these 3 instruments combined according to the following format:

SF-12 General Health Function Survey (first 12 items):	Items 11-22
EPIC (subsequent 50 items excluding 7 AUA-SI items):	Items 23-34, 42-79
AUA Symptom Index (7 items embedded in EPIC Urinary Section):	Items 35-41

Scoring the EPIC

There are 2 steps involved in scoring EPIC:
Step 1. The response for each item is standardized to a 0 to 100 scale according to the table below.

Item Number	***Item Response Value***	Standardized Value
23,24,25,42,43,48,56,57,58,60,61, 62,63,64,69,70,71,72	1	0
	2	25
	3	50
	4	75
	5	100
26.59	1	0
	2	33
	3	67
	4	100
27	0	100
	1	67
	2	33
	3	0
28,29,30,31,32,33,49,50,51,52,53, 54,65,66,67,74,75,76,77,78,79	0	100
	1	75
	2	50
	3	25
	4	0
34,44,45,46,55,68	1	100
	2	75
	3	50
	4	25
	5	0
47	1	100
	2	50
	3	0
73	1	0
	2	50
	3	100
	4	50
	5	0

Step 2. **Using the item groupings listed below for each HRQOL Domain Summary Score or Subscale score, average the standardized values (see Step 1, above) for all items within a group to create the summary or subscale score. (If ≥20% of the items that comprise a domain summary score or subscale score are missing a response, the corresponding domain summary or subscale score can not be calculated).**

To calculate the following HRQOL do Summary Score or Subscale Score:	***Determine the average of the Standardized Values (see Step 1 above) for the following items:***	***Number of non-missing items n to compute score (otherwise, se score to missing)***
HRQOL Domain Summary Scor		
Urinary Summary	23-34	10
Bowel Summary	42-55	12
Sexual Summary	56-68	11
Hormonal Summary	69-79	9
Domain-specific HRQOL Subsca		
Urinary Subscales:		
Function	23-27	4
Bother	28-34	6
Incontinence	23,26-28	4
Irritative/Obstructive	24,25,29-33	6
Bowel Subscales:		
Function	42-48	6
Bother	49-55	6
Sexual Subscales:		
Function	56-64	8

Bother	65-68	4
Hormonal Subscales:		
Function	69-73	4
Bother	74-79	5

Please note:

- Item numbers are indicated along the right border of the questionnaire (question numbers on left of questionnaire pages are not used for scoring because some questions contain multiple items).
- The **AUA Symptom Index** (AUA-SI) is included to provide a clinical context for EPIC urinary measures. [5] However, the seven AUA-SI items are not included in the calculation of any EPIC domain scores. For ease of reference, scoring instructions for the AUA-SI are provided in the Appendix below.
- The **Medical Outcomes Study SF-12** is a validated measure of General Health Function developed by RAND.[4] It is intended to be used here to derive 2 summary scores (physical and mental component summaries) relevant to general HRQOL status, which provide a context for EPIC score results. The SF-12 items themselves are not included in the calculation of any EPIC domain scores. For ease of reference, scoring instructions for the SF-12 are provided in the Appendix below.
- Optional satisfaction and socio-demographic/medical history items (Items 80-117) from the original UCLA-PCI can be administered with EPIC. These items are not included in any EPIC domain score calculations.

REFERENCES

(1) Wei JT, Dunn R, Litwin M, Sandler H, Sanda MG. Development and Validation of the Expanded Prostate Cancer Index Composite (EPIC) for Comprehensive Assessment of Health-Related Quality of Life in Men with Prostate Cancer. Urology 2000; In press.

(2) Litwin MS, Hays RD, Fink A, Ganz PA, Leake B, Brook RH. The UCLA Prostate Cancer Index: development, reliability, and validity of a health-related quality of life measure. Medical Care 1998; 36(7):1002-1012.

(3) Sanda MG, Dunn RL, Sandler HM, McLaughlin PW, Montie JE, and Wei JT. Comparison of HRQOL after brachytherapy, radical prostatectomy, or external beam radiation for localized prostate cancer. ASCO Proceedings 2000; 19:327a.

(4) Ware JE, Keller SD, Kosinski M. SF- 12: How to Score the SF-12 Physical and Mental Health Summary Scales. Second ed. Boston: The Health Institute, New England Medical Center, 1995.

(5) Barry MJ, Fowler FJ, Jr., O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. Journal of Urology 1992; 148(5):1549-57; discussion 1564.

APPENDIX: Scoring the AUA-SI and SF-12

Scoring the AUA Symptom Index:

The sum of the raw values for items 35-41 provides the total AUA symptom score.[5]

Scoring the Medical Outcomes Study SF-12:

There are 3 steps involved in calculating the SF-12 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores.

Step 1. Check for missing or out-of-range values for items 11-22 (SF-12 portion of combined survey). If any missing or out-of-range values are found for those items, the PCS and MCS scores can not be calculated.

Step 2. Convert each item response into both physical and mental standardized values according to the table on the following page.

Step 3. Sum the physical standardized values from step 2 across all 12 items and add 56.57706 to create the SF-12 PCS score. Sum the mental standardized values in similar fashion and add 60.75781 to create the SF-12 MCS score.

Converting SF-12 Item Responses to Physical and Mental Standardized Values:

Item Number	Item Response V	Physical Standarc Value	Mental Standardizec
11 (General Health)	1	0	0
	2	-1.31872	-0.06064
	3	-3.02396	0.03482
	4	-5.56461	-0.16891
	5	-8.37399	-1.71175
12 (Moderate Activities)	1	-7.23216	3.93115
	2	-3.45555	1.86840
	3	0	0
13 (Climbing Several Flights of Stairs)	1	-6.24397	2.68282
	2	-2.73557	1.43103
	3	0	0
14 (Accomplish less than you would like	1	-4.61617	1.44060
	2	0	0
15 (Limited in the kind of activities)	1	-5.51747	1.66968
	2	0	0
16 (Accomplish less than you would like	1	3.04365	-6.82672
	2	0	0
17 (Didn't do activities as carefully as usu	1	2.32091	-5.69921
	2	0	0
18 (Pain interferes with normal work)	1	0	0
	2	-3.80130	0.90384
	3	-6.50522	1.49384
	4	-8.38063	1.76691
	5	-11.25544	1.48619
19 (Felt calm and peaceful)	1	0	0
	2	0.66514	-1.94949
	3	1.36689	-4.09842
	4	2.37241	-6.31121
	5	2.90426	-7.92717
	6	3.46638	-10.19085
20 (Have a lot of energy)	1	0	0
	2	-0.42251	-0.92057
	3	-1.14387	-1.65178
	4	-1.61850	-3.29805
	5	-2.02168	-4.88962
	6	-2.44706	-6.02409
21 (Felt downhearted and blue)	1	4.61446	-16.15395
	2	3.41593	-10.77911
	3	2.34247	-8.09914

	4	1.28044	-4.59055
	5	0.41188	-1.95934
	6	0	0
22 (Health interferes w/social activities	1	-0.33682	-6.29724
	2	-0.94342	-8.26066
	3	-0.18043	-5.63286
	4	0.11038	-3.13896
	5	0	0

APPENDIX X

EPIC

The Expanded Prostate Cancer Index Composite

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

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

Today's Date (please enter date when survey completed): Month_____Day_____Year_____

Name (optional): _____

Date of Birth (optional): Month_____Day_____Year_____

URINARY FUNCTION

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

1. Over the **past 4 weeks**, how often have you leaked urine?

   More than once a day..... 1
   About once a day..... 2
   More than once a week..... 3 (Circle one number) 23/
   About once a week..... 4
   Rarely or never..... 5

2. Over the **past 4 weeks**, how often have you urinated blood?

   More than once a day..... 1
   About once a day..... 2
   More than once a week..... 3 (Circle one number) 24/
   About once a week..... 4
   Rarely or never..... 5

3. Over the **past 4 weeks**, how often have you had pain or burning with urination?

   More than once a day..... 1
   About once a day..... 2
   More than once a week..... 3 (Circle one number) 25/
   About once a week..... 4
   Rarely or never..... 5

4. Which of the following best describes your urinary control **during the last 4 weeks**?

   No urinary control whatsoever..... 1
   Frequent dribbling..... 2 (Circle one number) 26/
   Occasional dribbling..... 3
   Total control..... 4

5. How many pads or adult diapers per day did you usually use to control leakage **during the last 4 weeks**?

None	0		
1 pad per day.....	1		
2 pads per day.....	2	(Circle one number)	
3 or more pads per day.....	3		27/

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

(Circle one number on each line)

		No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a.	Dripping or leaking urine ….....	0	1	2	3	4	28/
b.	Pain or burning on urination.....	0	1	2	3	4	29/
c.	Bleeding with urination.....	0	1	2	3	4	30/
d.	Weak urine stream or incomplete emptying……..	0	1	2	3	4	31/
e.	Waking up to urinate……..	0	1	2	3	4	32/
f.	Need to urinate frequently during the day ……..	0	1	2	3	4	33/

7. Overall, how big a problem has your urinary function been for you **during the last 4 weeks**?

No problem.....	1		
Very small problem.....	2		
Small problem.....	3	(Circle one number)	34/
Moderate problem.....	4		
Big problem.....	5		

BOWEL HABITS

The next section is about your bowel habits and abdominal pain.
Please consider **ONLY THE LAST 4 WEEKS**.

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

More than once a day.....	1		
About once a day.....	2		
More than once a week.....	3	(Circle one number)	42/
About once a week.....	4		
Rarely or never.....	5		

9. How often have you had uncontrolled leakage of stool or feces?

More than once a day.....	1		
About once a day.....	2		
More than once a week.....	3	(Circle one number)	43/
About once a week.....	4		
Rarely or never.....	5		

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

Never.....	1		
Rarely.....	2		
About half the time.....	3	(Circle one number)	44/
Usually.....	4		
Always.....	5		

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

Never.....	1		
Rarely.....	2		
About half the time.....	3	(Circle one number)	45/
Usually.....	4		
Always.....	5		

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

Never..... 1
Rarely..... 2
About half the time..... 3 (Circle one number) 46/
Usually..... 4
Always..... 5

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

Two or less..... 1
Three to four..... 2 (Circle one number) 47/
Five or more..... 3

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

More than once a day..... 1
About once a day..... 2
More than once a week..... 3 (Circle one number) 48/
About once a week..... 4
Rarely or never..... 5

15. How big a problem, if any, has each of the following been for you? (Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a. Urgency to have a bowel movement	0	1	2	3	4	49/
b. Increased frequency of bowel movements.....	0	1	2	3	4	50/
c. Watery bowel movements.....	0	1	2	3	4	51/
d. Losing control of your stools.....	0	1	2	3	4	52/
e. Bloody stools	0	1	2	3	4	53/
f. Abdominal/ Pelvic/Rectal pain...	0	1	2	3	4	54/

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

No problem..... 1
Very small problem..... 2
Small problem..... 3 (Circle one number) 55/
Moderate problem..... 4

Big problem..... 5

SEXUAL FUNCTION

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

17. How would you rate each of the following during the last 4 weeks? (Circle one number on each line)

	Very Poor to None	Poor	Fair	Good	Very Good	
a. Your level of sexual desire?.....	1	2	3	4	5	56/
b. Your ability to have an erection?.....	1	2	3	4	5	57/
c. Your ability to reach orgasm (climax)?.....	1	2	3	4	5	58/

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

None at all..... 1
Not firm enough for any sexual activity..... 2
Firm enough for masturbation and foreplay only..... 3 (Circle one number) 59/
Firm enough for intercourse..... 4

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

I NEVER had an erection when I wanted one..... 1
I had an erection LESS THAN HALF the time I wanted one..... 2
I had an erection ABOUT HALF the time I wanted one ..... 3 (Circle one number) 60/
I had an erection MORE THAN HALF the time I wanted one..... 4
I had an erection WHENEVER I wanted one..... 5

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

Never …..... 1
Less than once a week..... 2
About once a week..... 3 (Circle one number) 61/
Several times a week..... 4
Daily……..... 5

21. **During the last 4 weeks**, how often did you have <u>any</u> sexual activity?

Not at all.....	1		
Less than once a week.....	2		
About once a week.....	3	(Circle one number)	62/
Several times a week.....	4		
Daily…….....	5		

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

Not at all.....	1		
Less than once a week.....	2		
About once a week.....	3	(Circle one number)	63/
Several times a week.....	4		
Daily…….....	5		

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

Very poor.....	1		
Poor.....	2		
Fair.....	3	(Circle one number)	64/
Good.....	4		
Very good.....	5		

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

	No <u>Problem</u>	Very Small <u>Problem</u>	Small <u>Problem</u>	Moderate <u>Problem</u>	Big <u>Problem</u>	
a. Your level of sexual desire.....	0	1	2	3	4	65/
b. Your ability to have an erection.	0	1	2	3	4	66/
c. Your ability to reach an orgasm.	0	1	2	3	4	67/

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

No problem.....	1		
Very small problem.....	2		
Small problem.....	3	(Circle one number)	68/
Moderate problem.....	4		
Big problem.....	5		

HORMONAL FUNCTION

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

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

More than once a day.....	1		
About once a day.....	2		
More than once a week.....	3	(Circle one number)	69/
About once a week.....	4		
Rarely or never.....	5		

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

More than once a day.....	1		
About once a day.....	2		
More than once a week.....	3	(Circle one number)	70/
About once a week.....	4		
Rarely or never.....	5		

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

More than once a day.....	1		
About once a day.....	2		
More than once a week.....	3	(Circle one number)	71/
About once a week.....	4		
Rarely or never.....	5		

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

More than once a day..... 1
About once a day..... 2
More than once a week..... 3 (Circle one number) 72/
About once a week..... 4
Rarely or never..... 5

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

Gained 10 pounds or more……..1
Gained less than 10 pounds …..…….2
No change in weight……. …..…….3 (Circle one number) 73/
Lost less than 10 pounds …..…….4
Lost 10 pounds or more…….……5

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

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a. Hot flashes…….....	0	1	2	3	4	74/
b. Breast tenderness/enlargement..	0	1	2	3	4	75/
c. Loss of Body Hair...….....	0	1	2	3	4	76/
d. Feeling depressed...….....	0	1	2	3	4	77/
e. Lack of energy.....….....	0	1	2	3	4	78/
f. Change in body weight	0	1	2	3	4	79/

Overall Satisfaction

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

Extremely dissatisfied..... 1
Dissatisfied..... 2
Uncertain..... 3 (Circle one number) 80/
Satisfied..... 4
Extremely satisfied..... 5

THANK YOU VERY MUCH!!

APPENDIX XI
EQ 5D

By placing a tick in one box in each group, please indicate which statement best describes your health today.

Mobility

I have no problems in walking about ☐
I have some problems in walking about ☐
I am confined to bed ☐

Self-Care

I have no problems with self-care ☐
I have some problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

Usual Activities

I have no problems with performing my usual activities ☐
I have some problems with performing my usual activities ☐
I am unable to perform my usual activities ☐

Pain/Discomfort

I have no pain or discomfort ☐
I have moderate pain or discomfort ☐
I have extreme pain or discomfort ☐

Anxiety/Depression

I am not anxious or depressed ☐
I am moderately anxious or depressed ☐
I am extremely anxious or depressed ☐

The EQ5D Group. EQ5D- a new facility for the measurement of health-related quality of life. Health Policy 1990;(16)3:199-208.

APPENDIX XI
EQ 5D

The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a one-digit number expressing the level selected for that dimension. The digits for five dimensions can be combined in a five-digit number describing the respondent's health state. It should be noted that the numerals 1-3 have no arithmetic properties and should not be used as a cardinal score.

Although self-explanatory instructions are provided within the text, the following guidelines may be helpful.

A respondent may sometimes find that the number of levels is too limited. For example, for the mobility question, a respondent in a wheelchair is not 'confined to bed', but he/she may find 'some problems in walking about' appears to under-estimate their level of difficulty. If an administrator is present he/she should stress the instruction: please indicate which statements *best* describe your own health state today'. It is the respondent's personal evaluation that is required and on no account should a prompt be given.

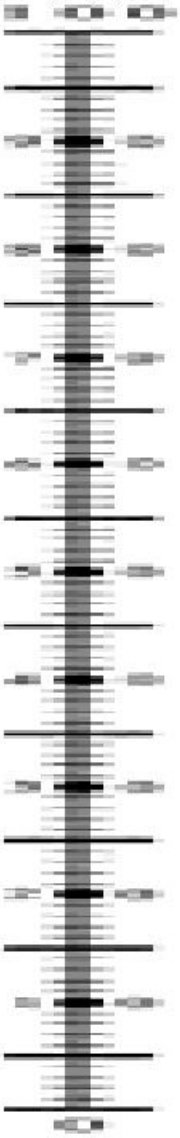
The EQ VAS generates a self-rating of health-related quality of life. It should be used with the 5-digit health state classification to build a composite picture of the respondent's health status. The respondent rates his/her health state by drawing a line from the box marked "Your health state today" to the appropriate point on the EQ VAS.

Sometimes, respondents tend to rate their health state by placing a mark on the thermometer instead of drawing a line. There is no reason why this could not be interpreted as a valid response. If the line does not cross the thermometer, the value horizontally opposite where the line stops should be taken and not where it would be if hypothetically extended. It is important to ensure that the respondent is not prompted in any way by the administrator and that it is the respondent's own rating of health-related quality of life that is being recorded.

Note: This is an example only. The actual reproducible visual analogue scale is being sent to us by the EuroQol Group.

Best Imaginable Health State

100



0

Worst Imaginable Health State

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked by 100 and the worst state you can imagine is marked by 0.

We would like you to indicate in this scale how good or bad is your own health today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your current health is.

Your own health state today _____

APPENDIX XII (10/11/05)
Utilization of Sexual Medications/Devices

This questionnaire is designed to assess the use of erectile aids among patients treated for prostate cancer. To help us get the most accurate measurement, please answer all questions honestly and completely. You may refuse to answer any questions for any reason. All information contained within this survey will remain strictly confidential. Thank you for participating and for helping us improve the quality of care for prostate cancer patients.

Today's Date (please enter data when survey completed): Month____ Day_____ Year_____

Please indicate your response to each question by clearly marking an "X" through the box corresponding to your answer : X ☐

The following questions relate to any treatments you may have received to assist with your erections.

1. Do you have a penile prosthesis?

Yes (1) ☐ → (Skip Questions 2-4) No (2) ☐

2. Have you used any medications or devices to aid or improve erections?

Yes (1) ☐ No (2) ☐ → (Skip Question 3, answer Question 4)

3. For each of the following medicines or devices, please indicate (by marking an x in each row)
Whether or not you have tried it or currently use it to improve your erections:

	Have NOT tried it	Tried it, but was NOT HELPFUL	It HELPED, but I am NOT using it NOW	It HELPED, and I use it SOMETIMES	It HELPED, and I use it ALWAYS
a. Viagra or other pill (name pill if not Viagra): _____	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
b. Muse (intra-urethral alprostadil suppository)	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
c. Penile injection therapy (Such as caverject)	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
d. Vacuum erection device (Such as erect-aid)	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
e. Other (name medication/device if not listed) _____	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

(Utilization of Sexual Medications/Devices, courtesy of M Sanda, D Miller, and J Wei)

4. How would you describe the usual quality of your erections WITHOUT THE ASSISTANCE of medicines or devices DURING THE LAST 4 WEEKS? (Please select only one)

1 ☐ None at all

2 ☐ Not firm enough for any sexual activity

3 ☐ Firm enough for masturbation and foreplay only

4 ☐ Firm enough for intercourse

(Utilization of Sexual Medications/Devices, courtesy of M Sanda, D Miller, and J Wei)

APPENDIX XIII (2/15/05, 10/11/05, 1/24/07)(4/3/08)

CTSU LOGISTICS

ADDRESS AND CONTACT INFORMATION FOR RTOG-0232

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the RTOG unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone - 1-888-823-5923 Fax – 215-569-0206	CTSU Patient Registration Voice Mail – 1-888-462-3009 Fax – 1-888-691-8039 Hours: 9:00 AM – 5:00 PM Eastern Time, Monday – Friday (excluding holidays) [For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301-704-2376. Please use the 1-888-462-3009 number for ALL other CTSU patient enrollments.]	RTOG Headquarters 1818 Market Street, Suite 1600 Philadelphia, PA 19103 Please do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
For patient eligibility questions: Contact the RTOG Research Associate for Protocol, Data Management section at 215-574-3214. **For treatment-related questions:** Correspond by e-mail (preferred) or by phone with the study chair designated on the protocol cover page.		
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Public Web site is located at: www.ctsu.org **The CTSU Registered Member Web site** is located at: http://members.ctsu.org		

CANCER TRIALS SUPPORT UNIT (CTSU) PARTICIPATION PROCEDURES

REGISTRATION/RANDOMIZATION

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member Web site or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site at http://members.ctsu.org

APPENDIX XIII (Continued)

All forms and documents associated with this study can be downloaded from the RTOG-0232 Web page on the CTSU registered member Web site (http://members.ctsu.org). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS.

Requirements for RTOG-0232 site registration:

- **All patients MUST be treated with either 3DCRT or IMRT on this trial and all institutions must be pre-credentialed.** Credentialing requirements for 3DCRT and IMRT Treatment Approach are outlined in Section 5.1 of the protocol and on the Advanced Technology Consortium (ATC) web site at http://atc.wustl.edu. Submission of digital data to the Image-Guided Therapy Center (ITC) requires advanced request for an FTP account with the ITC (itc@castor.wustl.edu). The ITC will notify the registering institution when that institution is eligible to enter patients on study. The status of the credentialing review will be reflected on the RSS Site Registration Status screen http://members.ctsu.org/rss/

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet
- CTSU RT Facilities Inventory Form

  Note: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Radiological Physics Center (RPC) monitoring program. For sites enrolling through the CTSU an RT Facilities Inventory From must be on file with CTSU. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility.

Pre-study requirements for patient enrollment on RTOG-0232

- Patient must meet all inclusion criteria, and no exclusion criteria should apply.
- Patient has signed and dated all applicable consents and authorization forms.
- All baseline laboratory tests and prestudy evaluations performed within the time period specified in the protocol.

CTSU Procedures for Patient Enrollment

1. Contact the CTSU Patient Registration Office by calling 1-888-462-3009. Leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, e.g. within one hour, call the registrar cell phone at 1-301-704-2376.

2. Complete the following forms:

- CTSU Patient Enrollment Transmittal Form
- RTOG-0232 Eligibility Checklist

3. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 5:00 p.m., Mon-Fri, Eastern Time (excluding holidays); however, please be aware that RTOG registration hours end at 4:30 pm Eastern Time. The CTSU registrar will check the investigator and site information to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and follow-up with the site to resolve any discrepancies.

4. Once investigator eligibility is confirmed and enrollment documents are reviewed for compliance, the CTSU registrar will contact the RTOG within the confines of RTOG's registration hours to obtain assignment of a treatment arm and assignment of a unique patient ID (to be used on all future forms and correspondence). The CTSU registrar will confirm registration by fax.

Study treatment must begin within 4 weeks of patient registration.

APPENDIX XIII (Continued)

DATA SUBMISSION AND RECONCILIATION

1. All case report forms (CRFs) and transmittals associated with this study must be downloaded from the RTOG-0232 web page located on the CTSU registered member Web site (http://members.ctsu.org). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.

2. Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and transmittals to RTOG Headquarters unless an alternate location is specified in the protocol. Do not send study data to the CTSU. See the Special Materials or Substudies section below for submission of dosimetry data.

3. The RTOG Headquarters will send query notices and delinquency reports to the site for reconciliation. Please send query responses and delinquent data to the RTOG and do not copy CTSU Data Operations. Each clinical site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and the RTOG.

4. Please affix the RTOG study/case label to all source documentation and redact the patient's name.

SPECIAL MATERIALS OR SUBSTUDIES

Radiation Therapy (section 6.0)
Dosimetry data for 3DCRT and IMRT must be submitted to the Image-Guided Therapy Center (ITC), either by digital transmission using the ITC-assigned FTP account or tape submission (contact ITC for acceptable tape types and format). Hard copy materials accompanying digital data should also be sent directly to the ITC. See section 12.2 for a complete inventory of dosimetry items to be submitted.

Tissue/Specimen Submission– strongly encouraged (section 10.0)

1. With patient's consent, tumor tissue will be collected for central review. A pathology report and RTOG Specimen Transmittal Form must accompany specimens in order for the case to be considered evaluable by the RTOG Biospecimen Resource.

2. With patient's consent, tumor tissue will be banked for biomarkers research. Submit specimens, pathology report, RTOG Specimen Transmittal Form, and a copy of the patient's tissue consent form to the RTOG Biospecimen Resource.

3. See protocol section 10.0 for detailed instructions on collection, preparation, and shipment of samples. All reports must include the protocol number and patient's case number (or RTOG label attached). Surgical pathology numbers and information must not be removed from the report; however, the patient's name and/or other identifying information should be redacted. Do not send specimens, forms, reports, or transmittals to the CTSU.

4. CTSU clinical sites qualify for specimen reimbursement in the amounts stated in section 10.4 of the protocol. Payments will be made in accordance with RTOG's pathology payment cycle and forwarded to the enrolling sites by the Cooperative Group credited with the accrual.

SERIOUS ADVERSE EVENT (SAE) REPORTING

1. CTSU sites must comply with the expectations of their local Institutional Review Board (IRB) regarding documentation and submission of adverse events. Local IRBs must be informed of all reportable serious adverse reactions.

2. CTSU sites will assess and report adverse events according to the guidelines and timelines specified in the protocol. You may navigate to the CTEP Adverse Event Expedited Report System (AdEERS) from either the Adverse Events tab of the CTSU member homepage (http://members.ctsu.org) or by selecting Adverse Event Reporting Forms from the document center drop down list on the RTOG-0232 web page.

3. Do not send adverse event reports to the CTSU.

4. Secondary AML/MDS/ALL reporting: Report occurrence of secondary AML, MDS, or ALL via the NCI/CTEP AML-MDS Report Form in lieu of AdEERS. Submit the completed form and supporting documentation as outlined in the protocol.

DRUG PROCUREMENT
Not applicable to this study.

REGULATORY AND MONITORING

Study Audit

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/ Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol. (e.g., NSABP members may only request credit for protocols pertaining to breast or colorectal cancers). Registrations to protocols for other disease sites may still take place through CTSU without receiving credit for your NSABP activities. Per capita reimbursement will be issued directly from CTSU.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up are available for download from the CTSU Operations Manual located on the CTSU Member Web site.

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU website.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US sites.

Clinical Data Update System (CDUS) Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. The sponsoring Group fulfills this reporting obligation by electronically transmitting to CTEP the CDUS data collected from the study