A PHASE II STUDY OF EXTERNAL BEAM RADIATION THERAPY COMBINED WITH PERMANENT SOURCE BRACHYTHERAPY FOR INTERMEDIATE RISK CLINICALLY LOCALIZED ADENOCARCINOMA OF THE PROSTATE

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RADIATION THERAPY ONCOLOGY GROUP  
RTOG P-0019  

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SCHEMA  

<table>
<thead>
<tr>
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<th>PSA</th>
<th>E</th>
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<td>2.</td>
<td>&gt; 10 to ≤ 20</td>
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<td>G</td>
<td>external beam radiation therapy to the prostate, followed (within 2-6 weeks) by permanent I-125 brachytherapy 108 Gy (TG 43)</td>
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<tr>
<td>O</td>
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<tr>
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R T Stage  

1. T1c  
2. T2a-b  

E  

Eligibility: (See Section 3.0 for details)  
- Institution must be precredentialed (Section 5.1)  
- Histologically-confirmed, adenocarcinoma of the prostate  
- One of the following combination of factors  
  - Clinical stage T1c-T2b, Gleason score 2-6 and PSA > 10 but ≤ 20  
  - Clinical stage T1c-T2b, Gleason score 7 and PSA ≤ 20  
- Prostate biopsy tumor grading by the Gleason Score classification  
- Zubrod Performance Status 0-1  
- Combined Gleason score ≤ 7  
- Prostate volume by TRUS ≤ 60 cc  
- No prior chemotherapy or pelvic radiation  
- No distant metastases  
- No prior TURP  
- No clinically or pathologically involved lymph nodes  
- No significant obstructive symptoms; AUA score must be ≤ 18  
- No radical surgery for carcinoma of the prostate  
- No previous hormonal therapy beginning > 6 months prior to registration  
- No hip prosthesis  
- No major medical or psychiatric illness  
- Signed study-specific consent form prior to registration  

Required Sample Size: 110
1. Is there histologically confirmed, locally confined adenocarcinoma of the prostate?
2. What is the T stage?
3. What is the N stage?
4. If N0, was surgical sampling done?
5. What is the performance status?
6. What is the PSA level (prehormones if given)? (If Gleason score 2-6 then PSA must be >10 ng/mL)
7. Has the patient had prior pelvic radiation or chemotherapy?
8. Has the patient had any prior hormone therapy?
   If yes, did it begin within 6 months prior to study entry?
9. Has the patient had prior radical surgery for prostate carcinoma?
10. Is there evidence of distant metastases?
11. Has the patient had previous or concurrent cancer other than basal cell or squamous cell skin cancer?
   If yes, has the patient been disease free for at least 5 years?
12. Are there any major medical or psychiatric illnesses that would prevent completion of treatment or interfere with follow-up?
13. Has the patient had a prior TURP?
14. Is the combined Gleason score ≤ 7?
15. Has the patient had TRUS mapping done and is prostate volume ≤ 60 cc?
16. Has patient filled out AUA voiding questionnaire and is the score ≤ 18?
17. Has the patient had a hip replacement?
18. How many patients have you registered to this study?

(cont’d on next page)
The following questions will be asked at Study Registration:

1. Name of institutional person registering this case?
2. Has the Eligibility Checklist (above) been completed? (Y)
3. Is the patient eligible for this study? (Y)
4. Date the study-specific Consent Form was signed? (must be prior to study entry)
5. Patient’s Name
6. Verifying Physician
7. Patient’s ID Number
8. Date of Birth
9. Race
10. Social Security Number
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. Treatment Start Date
16. AUA Symptom Score ($\leq 18$)
17. Combined Gleason Score of Tumor ($\leq 7$)
18. Size of Gland by TRUS (cc) ($\leq 60$)
19. PSA ($\leq 20$) (prehormones if given)
20. T Stage ($T1c, T2a, T2b$)
21. Treatment Assignment

Completed by ___________________________________________ Date ________________
1.0 INTRODUCTION

1.1 Background

Adenocarcinoma of the prostate will affect over 180,400 U.S. males in 2000 and approximately 31,900 males will die of the disease.\(^1\) The majority of men will be diagnosed with clinically organ-confined disease (AJCC T1-2).\(^1\) In men with T1-2 prostate cancer treatment options include expectant management, radical prostatectomy and definitive radiation therapy. A NCI Consensus Conference in 1988 concluded that no treatment approach was superior and recommended that patients be fully informed of their options. Proponents of each technique continue to aver that their approach is superior in the absence of scientific evidence.

Definitive radiotherapy may take several forms, although the majority of North American men receiving radiation therapy for T1-2 prostate cancer will be treated with a 6-8 week course of external beam radiation therapy.\(^2\) Retrospective data from several institutions suggests that improved results may be possible by increasing the total radiation dose to the prostate gland.\(^3,4\) Dose-escalation strategies have included the use of proton beams, three-dimensional conformal radiation therapy (3D-CRT) and brachytherapy following external beam radiation therapy.\(^3,4,5,6,7\) To date a single phase III trial of dose-escalation has been reported.\(^8\) This trial included men with locally advanced disease. Other randomized trials examining dose escalation in men with T1-2 tumors using proton beams and 3D-CRT are ongoing or planned.

The use of brachytherapy or implantation of radioactive sources into the prostate for adenocarcinoma was first reported in 1911 by Pasteau.\(^9\) Over the intervening eighty years some investigators have favored the use of brachytherapy, as it potentially could deliver a very high dose to the tumor and limit the doses to the surrounding normal tissue (i.e., bowel and bladder). In the late 1960s and 1970s retropubic Iodine125 implantation alone was popularized by the group at Memorial Sloan-Kettering.\(^10\) This technique utilized free-hand placement of sources and dosimetric results were often suboptimal. Although initial reports were optimistic, the long-term results were felt to be inferior to that which could be achieved with external beam radiation therapy.\(^10\) At roughly the same time, investigators at Baylor were combining brachytherapy (Au 198 as the source) with external beam radiation therapy.\(^11\) Long term follow-up in patients with T1-2 tumors treated in this fashion demonstrates similar disease-specific survival to that seen with external beam radiation therapy alone.\(^12\)

The development of transrectal ultrasound (TRUS) of the prostate with the ability to map the prostate in several planes, as well as the associated development of transperineal implantation of the prostate, has resurrected the technique of permanent implantation. With these techniques, the prostate can be implanted in a more dosimetrically reliable, less invasive way. Excellent results with brachytherapy alone have been reported in men with favorable disease.\(^13\) The RTOG has completed a phase II trial (RTOG 98-05) to determine if these excellent results using brachytherapy alone can be duplicated in a multi-institutional setting. Reports of men treated with a combination of external beam radiation therapy and permanent source brachytherapy also appear excellent.\(^5,6,13\)

Combining external beam radiation therapy with brachytherapy offers several potential advantages compared to the use of either treatment alone: 1) greater intraprostatic dose than can be achieved with either modality alone 2) ability to deliver doses to the periprostatic region that cannot be achieved with brachytherapy alone 3) ability to “fill-in” low dose regions that may result from inaccurate source placement. At the same time this combination therapy may increase the risk of normal tissue injury compared to either modality alone. For a true improvement in the therapeutic ratio, increased tumor control probability should not be overshadowed by an increase in normal tissue complications. This phase II trial will estimate the rate of gastrointestinal and genitourinary morbidity following a combination of external beam radiation therapy and permanent source interstitial brachytherapy with Iodine-125. Biochemical relapse-free survival will also be analyzed.

2.0 OBJECTIVES

2.1 The primary goal of this study is to estimate the rate of acute and late Grade 3-5 genitourinary and gastrointestinal toxicity following treatment with external beam radiation therapy and permanent source brachytherapy.

2.2 Secondary goals of this study include an estimation of:
   a) Freedom from PSA failure
   b) Overall survival
c) Disease-specific survival  
d) Clinical relapse, local and/or distant

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility:

3.1.1 Histologically confirmed, adenocarcinoma of the prostate, clinical stage T1c-T2b, NX, N0, M0 (Appendix III).

3.1.1.1 Nodes evaluated negative by imaging methods will be classified as NX. Only nodes evaluated negative by surgical sampling will be classified as N0.

3.1.2 Zubrod status 0-1 (Appendix II).

3.1.3 Prostate tumor biopsy grading by Gleason score classification is mandatory prior to registration (Appendix VI).

3.1.4 No prior pelvic radiation or chemotherapy for any reason; induction hormonal therapy beginning ≤ 6 months prior to registration is acceptable.

3.1.5 Prostate volumes by TRUS ≤ 60 cc prior to registration.

3.1.6 AUA voiding symptoms score ≤ 18 (Appendix VII).

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

3.1.8 One of the following combination of factors: Clinical stage T1c-2b, Gleason score 2-6 and PSA > 10 but ≤ 20; or clinical stage T1c-T2b, Gleason score 7 and PSA ≤ 20.

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

3.2 Conditions for Patient Ineligibility

3.2.1 Stage T3 or T4 disease.

3.2.2 Lymph node involvement (NI).

3.2.3 Evidence of distant metastases (MI).

3.2.4 Radical surgery for carcinoma of the prostate.

3.2.5 Previous hormonal therapy beginning > 6 months prior to registration.

3.2.6 Previous or concurrent cancers other than basal 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 Prior TURP

3.2.9 Hip prosthesis.

4.0 PRE-TREATMENT EVALUATION

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

4.2 Transrectal ultrasound volume study of 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. Transrectal ultrasonography will be performed. The probe will be advanced until the base of the gland is visualized. This will be designated the zero plane. Serial images of the prostate at 0.5cm increments will be obtained and the prostatic capsule outlined on each. On each image the grid position is evaluated to meet the following criteria: the grid must bisect the prostate into equal right and left halves, the first row of the template is positioned 1-2mm inside the prostatic capsule at the mid-gland, and the bottom row of the grid is outside the rectal wall at all levels. The serial prostate images will be mounted and delivered to the radiation physicist for dosimetry calculations.

4.3 Flexible cystoscopy, if advised by the urologist, may be performed to check for urethral strictures, bladder pathology, or a large median prostate lobe.

4.4 Tumors must be graded. Gleason score must be provided.

4.5 Prostate specific antigen (PSA) prior to study entry (prehormone therapy if given).

4.6 CT or MRI of pelvis.

4.7 Lymph node evaluation can be performed by at least one of the following: CT or MRI of pelvis, or exploratory laparotomy or laparoscopy with lymph node biopsy (sampling).

4.8 AUA Symptom Score.
5.0 REGISTRATION PROCEDURES

5.1 Institutions must be precredentialed by the Radiation Physics Center (RPC) prior to registering any cases to this study. Prior approval for RTOG 98-05 is acceptable. Credentialing information is available in Appendix VIII, on the RTOG web page (www.rtog.org), or by calling the RPC (713-792-3226). A maximum of 12 patients from each institution may be registered.

5.2 Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated Checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/RTOG audit.

6.0 RADIATION THERAPY

6.1 External Beam Radiation Therapy

6.1.1 Physical Factors
Megavoltage equipment is required with effective photon energies of ≥ 6 MV. Minimum source to axis distance is 100 cm. The minimum source to skin distance is 80 cm. Four-field arrangement (AP:PA:R:L) is required.

6.1.2 Target Volumes
The clinical target volume for the external beam treatment is the prostate and seminal vesicles. Shaped cerrobend blocks (or equivalent) are encouraged to limit the dose to nearby normal structures. The CTV to block margin should be 1.5-2.0 cm to allow for organ motion and setup uncertainty. In order to evaluate the adequacy of field margins, it is essential that simulator films or planning CT scans used for defining the treatment volume to be submitted to the RTOG Headquarters for review. Retrograde urethrogram is highly recommended. Representative portal films must be submitted to RTOG Headquarters for review.

6.1.3 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 five times per week for a total dose of 45 Gy. The prescribed dose will be defined on the central axis at the intersection of the four beams. The permitted dose variation will be ± 5%

6.1.4 External Beam Radiation Toxicity
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 side effects: skin reactions, small bowel or rectal irritation (cramping, diarrhea, urgency, hematochezia), bladder irritation (urinary frequency, urinary hesitancy, hematuria, incontinence) and impotence.

6.2 Brachytherapy
Brachytherapy will be performed 2-6 weeks following completion of external beam radiation therapy. The target volume definitions are, for the most part, based upon the ICRU Report 58, Dose and Volume Specification for Reporting Intersitial Therapy.

Volumes:
- Clinical Target Volume, CTV
  Pre-implant TRUS definition of the prostate
- Planning Target Volume, PTV
  An enlargement of the CTV as follows:
  1. Expand the TRUS definition of the prostate by 2 to 3 mm in the lateral dimension for each TRUS axial image. Thus, the lateral dimension of the prostate will increase by approximately 5 mm.
  2. Expand the TRUS definition of the prostate by 2 to 3 mm in the anterior dimension for each TRUS axial image.
  3. Maintain the same posterior border of the prostate as defined by TRUS.
  4. Project the expanded most cephalad axial definition to a plane 5 mm cephalad to the cephalad most TRUS plane.
  5. Project the expanded most caudad axial definition to a plane 5 mm caudad to the caudad most TRUS plane.

The PTV is approximately 10 mm longer in the caudad-cephalad dimension than the CTV.
- Evaluation Target Volume, ETV
  The ETV is defined as the post-implant CT definition of the prostate (the ETV concept is not found in the ICRU report).
6.3 Pre-plan

Prior to external beam radiation therapy the patient will undergo a transrectal ultrasound study. The volume of the prostate will be determined and used as the CTV. See Section 4.2.

6.4 Seed Calibration and Handling

6.4.1 I-125 seeds, which are eligible to be used in this study, must meet the AAPM criteria, which was published in Medical Physics 25 (12), December 1998 pp. 2269-2270, namely:

- have a calibration of their activity which is directly traceable to the NIST.
- have their dosimetric characteristics published in two separate articles in peer reviewed journals.

A list of manufacturers of I-125 seeds which meet these criteria will maintained by the Radiological Physics Center in cooperation with the RTOG Medical Physics Committee.

6.4.2 Any I-125 source with a NIST traceable standard may be used. The sources will be received and inventoried according to each institution’s policy and procedures in a manner consistent with federal or state regulations. A random sampling of at least 10% of the I-125 seeds shall be calibrated in a manner such that there is direct traceability to either the NIST or an AAPM ADCL as described by AAPM Report TG 40, paragraph V. A. 2. The measured activity will be compared against the vendor’s statement of activity. If I-125 seeds in sterile absorbable material are used, then one seed from every 5 packets will be removed and calibrated.

The expected activity for I-125 seeds for this protocol is 0.30-0.51 U per seed (0.25-0.40 mCi per seed).

6.5 Brachytherapy Dosimetry

The dosimetry of the I-125 seeds is based upon the dosimetric information that is contained in AAPM Report TG 43 for I-125 seeds.

6.5.1 Prescribed Dose

The prescribed dose is the dose that the oncologist intends to deliver and is the dose entered into the treatment record. For the purposes of this protocol, the prescribed brachytherapy dose to the PTV is 108 Gy (according to NIST 1999 specifications).

6.5.2 Minimum Target Dose

ICRU 58 defines the minimum target dose as the minimum dose at the periphery of the CTV. For the purposes of this protocol, the minimum target dose will be defined as the minimum dose to the ETV. This can be determined by an evaluation of the dose distribution in each CT image containing the prostate.

6.5.3 High Dose Volume

For the purposes of this protocol, the high dose volume is defined as the volume enclosed by 200% of the prescribed dose. The maximum dimensions of the high dose volume in all axial planes shall be reported on the appropriate data form.

6.5.4 Low Dose Volume

ICRU 58 defines the low dose volume as the volume within the clinical target volume, encompassed by an isodose corresponding to 90% of the prescribed dose, which for this protocol is 97 Gy (TG 43 Dosimetry). For the purposes of this protocol, the low dose volume will be defined in terms of the evaluation target volume, the ETV. The maximum dimensions of the low dose volume in any plane that contains the ETV should be reported on the appropriate form.

6.5.5 Dose Volume Histograms

The size of the grid and the voxels used in these calculations shall be stated.

1. A DVH for the ETV shall be calculated in 10 Gy increments and presented in tabular form.
2. A DVH for the rectum, as defined in the region of the prostate such that the high dose volume of the implant is included, shall be calculated in 10 Gy increments and presented in tabular form.
3. A DVH for the bladder, as defined in the region of the prostate such that the high dose volume of the implant is included, shall be calculated in 10 Gy increments and presented in tabular form.

6.6 Post-Implant Confirmation

Following implantation, cystoscopy may be performed to retrieve seeds that have been extruded into the bladder or lodged in the urethral wall. Cytoscopy is not required. Fluoroscopy or anterior radiograph and ultrasound are used to confirm uniform seed distribution. Extra seeds are implanted into any identified “cold spots.”

6.7 Post-Operative Care

A Foley catheter may be inserted at the end of the case and left indwelling until the patient recovers fully from spinal or general anesthesia. If the patient has significant symptoms of prostatism, the catheter may be left indwelling for several days as needed.

6.8 Post-Operative Evaluation
6.8.1 The post-implant CT shall be taken between 3 to 5 weeks after the implant. The patient shall be positioned in a supine position. Contrast will not be used. Axial 5 mm thick slices or less shall be acquired from at least 20 mm cephalad to the base of the prostate to at least 20 mm caudad to the apex of the prostate. The images will be filmed such that there are four CT images on one 14 inch x 17 inch film.

As defined above, the post-implant CT definition of the prostate is the evaluation target volume (ETV).

As a minimum, dose distributions shall be calculated on each image on which the ETV is defined. The post-implant dosimetry data form shall be completed. This form requires the determination of the minimum dose of the ETV for each axial image on which the ETV is defined, the dimensions of the high dose area on each axial image on which the ETV is defined, the dimensions of the low dose area on each axial image on which the ETV is defined, and tabular DVH’s for the prostate and high dose regions of the rectum and bladder in 10 Gy increments.

6.8.2 The Evaluation Criteria are as Follows

Per Protocol: greater than or equal to 80% of the ETV receives at least 90% of the prescription dose.

Variation, Acceptable: greater than or equal to 50% of the ETV receives at least 90% of the prescription dose.

Deviation, Unacceptable: greater than or equal to 50% of the ETV receives less than 90% of the prescription dose.

6.8.3 The Dosimetric Related Data to be Submitted for Each Patient Includes

6.8.3.1 Copies of pre-implant TRUS images

6.8.3.2 Drawing of the PTV which also displays the CTV (the TRUS images), and includes the projection of the PTV 5 mm in the cephalad and caudad directions.

6.8.3.3 A pre-implant form that describes the actual prostate seed loading pattern. The pre-implant form will be attached to the above material.

6.8.3.4 Film copies of the post-implant CT in a format which displays four images on a 14 x 17 inch film. Films must be provided of the entire prostate and any other axial level which contains seeds. Two separate sets of films shall be provided. The first set should not contain any annotations. The second set should be annotated to display the definition of the prostate, rectum, and bladder.

6.8.3.5 A post-implant form that describes the volumes, the dose description, and the dose volume histograms as defined above. The post-implant form will be attached to the above material.

6.9 Toxicity Report

6.9.1 This study will utilize the Common Toxicity Criteria (CTC) version 2.0 for toxicity and Adverse Event Reporting. A copy of the CTC version 2.0 can be downloaded from the CTEP Home page (http://ctep.info.nih.gov). All appropriate treatment areas should have access to a copy of the CTC.

7.0 DRUG THERAPY

Not applicable to this study.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

Not applicable to this study.

10.0 PATHOLOGY

Not applicable to this study.
11.0 PATIENT ASSESSMENTS

11.1 Study Parameters

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a. As indicated.
b. 3 to 5 weeks post implant. See Sections 6.8.1.
c. Following implantation. See Section 6.6.
d. At two years post implant and/or at PSA failure. See Section 11.3.2.
e. At 3, 6, 9 and 12 months; then at 18, 24, 36, 48, and 60 months.

11.2 Follow-up Schedule

11.2.1 Initial follow-up visit within one month (i.e., 4 weeks) of implant, i.e., 3-5 weeks for pelvic CT.

11.2.2 After initial follow-up visit, follow-up will be done at 3, 6, 9, and 12 months post implant.

11.2.3 Every six months for two years.

11.2.4 Annually, after third year for the remainder of the patient’s life.

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

11.3 Measurement of Effect/Response

Prostate tumor dimensions in centimeters and PSA values must be recorded on the data collection forms for the initial and follow-up evaluations of the patient. After study entry, disease evaluations will be made and recorded using the following criteria:

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 not to represent tumor.
2) If clinical evidence of residual tumor is present but has regressed from a previous examination (initial registration).
3) PSA 2.1 - 4 ng/mL. Rebiopsy is required, before starting hormone therapy, in any patient with PSA failure but with negative bone scan and CT scans. If the biopsy is negative, then they will be scored as NED.

11.3.3 Progressive Disease (PD): Progressive disease will be declared if one or more of the following criteria are met: 1) clinical evidence in the prostate gland of disease progression or recurrence, 2) clinical or radiographic evidence of tumor recurrence within the pelvic lymphatics or soft tissue beneath the bifurcation of the common iliac arteries, 3) clinical or radiographic evidence of hematogenous (osseous, hepatic, etc.) and/or extrapelvic lymphatic of soft tissue relapse.

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

11.3.5 Time to Complete Response (CR): Time in months from accession to documentation of no evidence of disease (NED).

11.3.6 Time to PSA Failure: PSA failure is defined according to the ASTRO consensus meeting. The PSA nadir will be defined as the lowest PSA value reached immediately before a biochemical failure (PSA relapse). Biochemical failure is defined as a consistent and significant rise in the PSA level. When the serum PSA rises on three consecutive occasions from the nadir value, biochemical failure has occurred and the date of failure is midway between the last non-rising PSA and the first rise in PSA.
11.3.7 **Time to Local Progression**: The time to progression will be measured from the date of study entry to the date of documented local progression as determined by clinical exam.

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

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

11.3.10 **Disease Specific Survival (DSS)**: The following will be considered as endpoints in assessing disease specific survival, i.e., events:
- Death certified as due to prostatic cancer.
- Death from other causes with active malignancy *(clinical or biochemical progression)*.
- Death due to complications of treatment, irrespective of the status of malignancy.
- Death from other causes with previously documented relapse *(either clinical or biochemical)* but inactive at the time of death will not be considered in disease-specific survival, but will be analyzed separately.

11.4 **Toxicity**

Toxicity will be measured according to the NCI Common Toxicity Criteria *(CTC)* at designated follow-up visits. The CTC Version 2.0 will be used for acute treatment toxicity *(up to 9 months following the start of external RT)*: the RTOG Late Radiation Morbidity Scoring Scheme *(Appendix IV)* will be used to score toxicities persisting or appearing beyond that period.

Patients who have a Foley catheter inserted within one week after the implant should not be scored as grade 4; however, the event, including date of insertion, must be recorded.

12.0 **DATA COLLECTION**

*(RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX#215/928-0153)*

12.1 **Summary of Data Submission**

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form <em>(A5)</em></td>
<td>Within 2 weeks of study entry</td>
</tr>
<tr>
<td>Initial Evaluation Form <em>(I1)</em></td>
<td></td>
</tr>
<tr>
<td>Pathology Report <em>(P1)</em></td>
<td></td>
</tr>
<tr>
<td>AUA Scoring Form <em>(PQ)</em></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>External Beam Dosimetry</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy Form <em>(T1)</em></td>
<td>Within 2 weeks post implant</td>
</tr>
<tr>
<td>External Beam Films <em>(Sim &amp; port)</em> <em>(TP)</em></td>
<td></td>
</tr>
<tr>
<td>Calculate Form <em>(TL)</em></td>
<td></td>
</tr>
<tr>
<td>Daily Treatment Record &amp; External Beam Isodose Distribution <em>(TM)</em></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Brachytherapy Information:</strong></th>
<th></th>
</tr>
</thead>
</table>
| a) Preliminary brachytherapy dosimetry will be based upon the transrectal ultrasound volume study of the prostate performed prior to external beam radiation therapy. The purpose of this dosimetry will be to approximate the number and location of seeds to be used for this implant with the goal of delivering the prescribed dose of 108 Gy *(TG 43 dosimetry)* for I-125 to the PTV. The radiation oncologist and the physicist will review this dosimetry prior to ordering of the radioactive seeds at the institution.
| Pre Implant Form *(Appendix IX)* *(T2)* | Within 8 weeks post implant |
| Pre Implant Films *(TRUS Images)* Calculations |          |
| b) Final brachytherapy dosimetry information will be based upon the post implant CT study. |          |
13.0 STATISTICAL CONSIDERATIONS

13.1 Overview
The primary goal of this study is to estimate the rate of acute and late grade 3-5 genitourinary and gastrointestinal toxicity following treatment with external beam radiation therapy and brachytherapy. Acute toxicity will be defined as toxicity occurring within nine months from the start of radiotherapy treatment and late toxicity will be defined as toxicity occurring more than nine months from the start of radiotherapy.

13.2 Endpoints

13.2.1 Primary Endpoint
Late severe GU and GI toxicity is defined as grade 3-5 GU and GI toxicity more than nine months from the start of the protocol treatment. It is graded based on RTOG/EORTC late radiation morbidity scoring system.

13.2.2 Secondary Endpoints
- Acute severe GU and GI toxicity is defined as grade 3-5 toxicity within nine months from the start of protocol treatment. It is graded based on CTC 2.0.
- Biochemical failure
- Overall survival
- Clinical progression including local, regional and distant relapse

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

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

13.5 Analysis Plan
13.5.1 Interim Reports
Interim reports will be prepared every six months until the RTOG meeting after the last patient has been entered to the study. In general, the interim reports will contain information about patient accrual rate with projected completion dates of the trial, status of QA review and compliance rate of treatment per protocol, the frequencies and severity of toxicity.
13.5.2 *The Analysis of Severe Late GU/GI Toxicity*
This analysis will be carried out when each patient has had at least 18 months of follow-up. The time to the occurrence of severe late GU/GI toxicity is defined as the time interval from the tenth month after start of protocol treatment to the date of onset of grade 3-5 GU/GI toxicity. If no such toxicity is observed till the time of the analysis, the patient will be censored at the time of the analysis. The hazard rate will be estimated by life table approach with time span of 18 months. Then the one-sided Z-test will be performed to test the significance of the difference between the logarithm of the observed hazard rate and the logarithm of the hypothesized hazard rate of 0.012/month with the variance equal to the reciprocal of the number of cases with late toxicity observed. Because of the lead time of 9 months for the acute period, the 18-month late toxicity will be estimated by the 9-month toxicity rate using the cumulative incidence approach\textsuperscript{14} to the defined time to severe late GU/GI toxicity.

13.5.3 *Estimation of Secondary Endpoints Related to the Efficacy*
Cumulative incidence approach\textsuperscript{14} will be used to estimate the failure rate for biochemical, local-regional and distant failures. Kaplan-Meier method\textsuperscript{15} will used to estimate the overall survival rate.

13.6 *Inclusion of Minorities*
In conformance with the National Institute of Health Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, we have also considered the possible interaction between race and treatments. Based on the on-going RTOG 94-08, we project that 24% of men in the study are non-white. Thus, 65 whites and 20 non-whites are expected to enter into the study. If the same analysis is performed within each racial group, The statistical power to distinguish late GU/GI toxicity between 10% and 20% at 18 month is 68% and 36%, respectively.
REFERENCES


APPENDIX I
RTOG P-0019

SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE
A Phase II Study of External Beam Radiation Therapy Combined with Permanent Source Brachytherapy for Intermediate Risk Clinically Localized Adenocarcinoma of the Prostate

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. You are being asked to take part in this study because you have prostate cancer.

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.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to find out what effects (good and bad) the use of a permanently implanted radiation source (brachytherapy) after external radiation therapy has on you and your prostate cancer.

This research is being done because although the use of brachytherapy for prostate cancer is not new, using brachytherapy after external beam radiation therapy is a more recent combination.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 110 men will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

• All patients will receive:

  **External Radiation Therapy:**
  External radiation therapy to the prostate will be given once a day, five days a week for up to five weeks. External radiation therapy treatments will be given on an outpatient basis at your institution.
Brachytherapy (Internal Radiation Therapy):
Two to six 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:

- Anesthesia will be given prior to and during procedure.
- With the help of ultrasound, thin needles with radioactive seeds will be inserted through the skin between the anus and scrotum into the prostate.
- When the seed is in the correct position the needle is pulled out leaving the radioactive seed in the prostate.

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

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

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

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Exam</td>
<td>Prior to study entry and at follow-up exams</td>
</tr>
<tr>
<td>Tumor Measurements</td>
<td></td>
</tr>
<tr>
<td>PSA Blood Test</td>
<td></td>
</tr>
<tr>
<td>Sexual Status Assessment</td>
<td></td>
</tr>
<tr>
<td>Pelvic CT or MRI Scan</td>
<td>Prior to study entry</td>
</tr>
<tr>
<td>Prostate Biopsy</td>
<td>Prior to study entry</td>
</tr>
<tr>
<td>Cystoscopy (bladder exam)</td>
<td>As medically indicated</td>
</tr>
</tbody>
</table>

- Procedures being done because you are in this study;

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRUS (Transrectal ultrasound)</td>
<td>Prior to study entry</td>
</tr>
<tr>
<td>Pelvic CT or MRI Scan</td>
<td>Two to five weeks after implant</td>
</tr>
<tr>
<td>Prostate Biopsy</td>
<td>Two years after implant</td>
</tr>
<tr>
<td>Cystoscopy (bladder exam)</td>
<td>After implant, if your doctor feels it’s necessary.</td>
</tr>
</tbody>
</table>

- Follow up visits with your physician will be scheduled for one month after your implant, then every three months for one year, then every six months for two more years, and then annually for the rest of your life.

HOW LONG WILL I BE IN THE STUDY?

You will receive external radiation therapy once a day, five days per week for five weeks. Two to six weeks following radiation therapy you will undergo a procedure to permanently implant radioactive seeds into your prostate. 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 participation.

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

WHAT ARE THE RISKS OF THE STUDY?

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

**Risks Associated with External Radiation Therapy**

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

**Less Likely, But Serious**
- Injury to the bladder, urethra, bowel or other tissues in the pelvis or abdomen
- Rectal bleeding, intestinal or urinary obstruction, and impotence

**Risks Associated with Implant Therapy**

**Very Likely**
- Infection that can be treated with antibiotics
- Soreness in the implant area
- Temporary fatigue, nausea or diarrhea
- Abdominal cramps
- Bladder irritation with some bleeding
- Impotence
- Urinary tract infection (UTI)

**Less Likely, But Serious**
- Injury to the bladder, urethra, bowel or other tissues in the pelvis or abdomen
- Rectal bleeding, intestinal or urinary obstruction, and incontinence
- Movement of a radioactive seed to the lungs
- Serious infection

**Risks Associated with Anesthesia**

**Less Likely**
- Nausea, vomiting
Headache
Sore throat

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

Reproductive Risks:
Very small amounts of radiation from the implants can reach other people. You should follow special precautions prescribed by your doctor if you are sexually active or are in close contact with small children and/or pregnant women. Ask your doctor about counseling and information about preventing pregnancy.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with prostate cancer in the future.

WHAT OTHER OPTIONS ARE THERE?
You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: (1) external radiation therapy only; (2) implant alone; (3) chemotherapy; (4) surgery; (5) hormones, 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 spread. These treatments could be given either alone or in combination with each other.

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

Your doctor can tell you more about your condition and the possible benefits of the different available treatments. Please talk to your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?
Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). Your personal information may be disclosed if required by law.
Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (FDA), the National Cancer Institute (NCI), qualified representatives of applicable drug or device 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. Please ask about any expected added costs or insurance problems.

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

You or your insurance company will be charged for continuing medical care and/or hospitalization.

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

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

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

A Data Safety and Monitoring Board, an independent group of experts, may 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:

(ORPR suggests that this person not be the investigator or anyone else directly involved with the research)

Name __________________________  Telephone Number __________________________

WHERE CAN I GET MORE INFORMATION?

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


SIGNATURE

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

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

Patient Signature (or legal Representative) __________________________  Date ________________
## APPENDIX II

### KARNOFSKY PERFORMANCE SCALE

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

### ZUBROD PERFORMANCE SCALE

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all predisease activities without restriction <em>(Karnofsky 90-100).</em></td>
</tr>
<tr>
<td>1</td>
<td>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 <em>(Karnofsky 70-80).</em></td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours <em>(Karnofsky 50-60).</em></td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair 50% or more of waking hours <em>(Karnofsky 30-40).</em></td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair <em>(Karnofsky 10-20).</em></td>
</tr>
</tbody>
</table>
DEFINITION OF TNM

**Primary Tumor, Clinical (T)**

| T0 | No evidence of primary tumor |
| T1 | Clinically inapparent tumor not 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 within the prostate* |
| T2a | Tumor involves one lobe |
| T2b | 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 the 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 not classified as T3, but as T2.

**Regional Lymph Nodes (N)**

| N0 | No regional lymph node metastasis |
| N1 | Metastasis in regional lymph node or nodes |

**Primary Tumor, Pathologic (pT)**

| pT2*** | Organ confined |
| pT2a | Unilateral |
| pT2b | Bilateral |
| pT3 | Extraprostatic extension |
| pT3a | Extraprostatic extension |
| pT3b | Seminal vesicle invasion |
| pT4 | Invasion of bladder, rectum |

***Note: There is no pathologic T1 classification

**Distant Metastasis**** (M)**

| MX | Presence of distant metastasis cannot be assessed |
| M0 | No distant metastasis |
APPENDIX III (continued)

AJCC STAGING SYSTEM
PROSTATE, 5th Edition

M1 Distant metastasis
    M1a Non regional lymph node(s)
    M1b Bone(s)
    M1c Other site(s)

****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)
G2 Moderately differentiated (moderate anaplasia)
G3-4 Poorly undifferentiated or undifferentiated (marked anaplasia)

Stage Grouping

Stage I
T1a N0 M0 G1

Stage II
T1a N0 M0 G2, G3-4
T1b N0 M0 Any G
T1c N0 M0 Any G
T1 N0 N0 Any G
T2 N0 M0 Any G

Stage III
T3 N0 M0 Any G

Stage IV
T4 N0 M0 Any G
    Any T N1, M0 Any G
    Any T Any N M1 Any G
APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates. **When a protocol toxicity requires more intense, special handling, study-specific reporting procedures supersede the General Guidelines.**

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/574-3214) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.
   a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.

2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone.

3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).

4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.

5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

   A copy of all correspondence submitted to NCI, or to another Cooperative Group (in the case of RTOG-coordinated intergroup studies) must also be submitted to RTOG Headquarters when applicable.

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.

7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.

8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (grade 5) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

2. All life-threatening (grade 4) toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

An adverse reaction is a toxicity or an undesirable effect usually of severe nature. Specifically, this may include major organ toxicities of the liver, kidneys, cardiovascular system, central nervous system, skin, bone marrow, or anaphylaxis. These undesirable effects may be further classified as "known" or "unknown" toxicities.

*Known* toxicities are those which have been previously identified as having resulted from administration of the agent. They may be identified in the literature, the protocol, the consent form or noted in the drug insert.

*Unknown* toxicities are those thought to have resulted from the agent but have not previously been identified as a known side effect.

**Commercial and Non-Investigational Agents**

i. Any fatal (*grade 5*) or life threatening (*grade 4*) adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters' Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. *Known* grade 4 hematologic toxicities need not be reported by telephone.

ii. Unknown adverse reactions (≥ *grade 2*) resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters' Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.

iii. All neurotoxicities (≥ *grade 3*) from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.

iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

Reactions definitely thought not to be treatment related should not be reported, however, a report should be made of applicable effects if there is a reasonable suspicion that the effect is due to protocol treatment.

**Investigational Agents**

Prompt reporting of adverse reactions in patients treated with investigational agents is mandatory. Adverse reactions from NCI sponsored drugs are reported to:

Investigational Drug Branch (*IDB*)  
P. O. Box 30012  
Bethesda, MD 20824  
Telephone number available 24 hours  
(*301*) 230-2330 FAX # 301-230-0159

i. **Phase I Studies Utilizing Investigational Agents**

- All deaths during therapy with the agent.  
  
  Report by phone within 24 hours to IDB and RTOG Headquarters.  
  **A written report to follow within 10 working days.**
- All deaths within 30 days of termination of the agent.

- All life threatening (grade 4) events which may be due to agent.

- First occurrence of any toxicity (regardless of grade).

As above

Report by phone within 24 hours to IDB

drug monitor and RTOG Headquarters.

**A written report may be required.

ii. Phase II, III Studies Utilizing Investigational Agents

- All fatal (grade 5) and life threatening (grade 4) known adverse reactions due to investigational agent.

- All fatal (grade 5) and life threatening (grade 4) unknown adverse reactions resulting from or suspected to be related to investigational agent.

- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent.

Report by phone to RTOG Headquarters and the Study Chairman within 24 hours

**A written report must be sent to RTOG within working days with a copy to IDB.

(Grade 4 myelosuppression not reported to IDB)

Report by phone to RTOG Headquarters, the Study Chairman and IDB within 24 hours.

**A written report to follow within 10 working days.

**Report in writing to RTOG Headquarters and IDB within 10 working days.

** See attached (if applicable to this study) NCI Adverse Drug Reaction Reporting Form
## APPENDIX VI

### GLEASON CLASSIFICATION

Histologic patterns of adenocarcinoma of the prostate

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

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

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

(Primary = 2, Secondary = 1, Gleason = 3)
(Primary = 2, Secondary = 2, Gleason = 4)

## ON-STUDY AUA SYMPTOM SCORE (PQ)

Case ______

<table>
<thead>
<tr>
<th>PATIENT NAME</th>
<th>TOTAL SCORE</th>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>INSTITUTION NAME</th>
<th></th>
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</thead>
<tbody>
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</tbody>
</table>

**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.**

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

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Patient Signature _____________________________ Date This Form was Completed ____________

24
APPENDIX VIII

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

This protocol is the precursor to other phase II protocols and to eventually a phase III protocol. One goal of this protocol is to collect data to define actual practice at multiple institutions. Thus, no institution will be allowed to enter more than 12 patients. 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


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.

b. A treatment planning system with the following characteristics:
   1) An I-125 seed model whose results agree with the TG-43 data, as specified below.
   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 3 mm x 3 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 3 mm x 3 mm or smaller.

c. Transrectal ultrasound for pre-implant images
d. CT images for post-implant analysis

IV. Credentialing

Institutions who have been previously credentialed to participate in RTOG 98-05 are automatically eligible to participate in this protocol. Two options are available for institutions which have not been previously credentialed:

Option One is the analog option, which was previously used. This credentialing is performed by the Radiological Physics center.

Option two is a digital option through the RTOG 3D QA Center. The web site is http://rtog3dqa.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. There is at least one commercial planning system which has capabilities of a digital data exchange for prostate implants. Institutions are encouraged to either become credentialed using the digital approach or to request this capability from their software vendor.

Both the analog and the digital process involve a physics/dosimetry review and a clinical review. For the clinical review, a non-protocol permanent prostate patient shall be planned and the dosimetry calculated as if the patient were to be treated according to the protocol. The pre-implant form, the post-implant form, and the supporting dosimetry documentation shall be
provided for review. The purpose of this review is to ensure that the institution understands the requirements of the protocol and has the appropriate capabilities to meet these requirements.

V. Patient Data Review Process

The data for all patients entered onto this protocol will be reviewed by the PI's. Section 6.8.3 describes the data to be submitted for each patient. This review will compromise, in part, of:

1. A review of the pre-implant plan and films

2. An independent definition of the ETV and an independent recalculation of the dose and the DVH's.
### Prostate Seed Loading Pattern

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Implant Type</th>
<th>Target MPD</th>
<th>Seed Activity</th>
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<tr>
<td>I-125</td>
<td>Permanent</td>
<td>108 Gy</td>
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<table>
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<th>Needle Number</th>
<th>Retraction cm</th>
<th>Hole Location</th>
<th>Seed Number</th>
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<table>
<thead>
<tr>
<th>Template Coordinates Used for Implant</th>
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<tbody>
<tr>
<td>Right</td>
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<tr>
<td>5.0</td>
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<tr>
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<td>1.0</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Retraction Planes</th>
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<tbody>
<tr>
<td>Plane 1</td>
</tr>
<tr>
<td>0.0 cm</td>
</tr>
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<td>Δ</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of Needles</th>
<th>Seeds Per Needle</th>
</tr>
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<tbody>
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<table>
<thead>
<tr>
<th>Total Needles</th>
<th>Total Seeds</th>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Seed Activity</th>
<th>Extra Seeds</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>

| Total Number of Seeds to Order: |
RTOG Post-Implant Dosimetry Data Form (T5)

Patient: _____________________________ /Physician: _____________________________

Source: I-125, model 6711
Doses are based upon TG 43 Dosimetry

Date of Pre-Implant TRUS Study: _____________________________
Date of Implant: _____________________________
Date of Post-Implant CT: _____________________________

Basic Dosimetry Information
1. Average activity per seed as measured by institution:
   Activity: _______ mCi  Date: _____________________________

2. Midpoint apparent activity stated by the vendor:
   Activity: _______ mCi  Date: _____________________________

3. Number of Seeds Used: _____________________________
4. Number of Needles Used: _____________________________
5. Prescribed Dose: 145 Gy  TG 43 Dosimetry
6. Peripheral Dose: __________ Gy  TG 43 Dosimetry

Post Implant CT Analysis

Date of Implant: _____________________________
Date of Post Implant CT study: _____________________________

1. Prostate is defined on ___ slices.
2. Seeds are defined on ___ slices.

Analysis of each CT Image

28
<table>
<thead>
<tr>
<th>Slice</th>
<th>Min Dose to Prostate (ETV) Gy (TG 43 Dosimetry)</th>
<th>Dimensions of: High Dose Area cm x cm</th>
<th>Low Dose Area cm x cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Base</td>
<td>________________</td>
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</table>
### Dose Volume Histogram Analysis

Doses are based on TG 43 Dosimetry

<table>
<thead>
<tr>
<th>Dose/ Gy</th>
<th>Volume/% Prostate</th>
<th>Volume/% Rectum</th>
<th>Volume/% Bladder</th>
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<tbody>
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<td>Dose/Gy</td>
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