

RADIATION THERAPY ONCOLOGY GROUP

RTOG 98-05

PHASE II TRIAL OF TRANSRECTAL ULTRASOUND GUIDED PERMANENT RADIOACTIVE IMPLANTATION OF THE PROSTATE FOR DEFINITIVE MANAGEMENT OF LOCALIZED ADENOCARCINOMA OF THE PROSTATE

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RADIATION THERAPY ONCOLOGY GROUP

RTOG 98-05

**Phase II Trial of Transrectal Ultrasound Guided Permanent
Radioactive Implantation of the Prostate for Definitive
Management of Localized Adenocarcinoma of the Prostate**

SCHEMA

S	<u>PSA</u>	R
	1. ≤ 4	
T	2. > 4 to ≤ 10	E
		Patients will receive I-125
R	<u>Grade</u>	G Permanent implantation of the prostate,
	1. Well (<i>Gleason Scores 2-4</i>)	145 Gy (<i>TG 43</i>)
A	2. Moderate (<i>Gleason Scores 5-6</i>)	I
T		S
	<u>T Stage</u>	T
I	1. T1b, T1c	
F	2. T2a	E
Y		R

Eligibility: (*See Section 3.0 for details*)

- Institution must be precredentialed (*Section 5.1*)
- Histologically confirmed, locally confined adenocarcinoma of the prostate
- Clinical stages T1b - T2a
- No clinically or pathologically involved lymph nodes
- No distant metastases
- Karnofsky Performance Status ≥ 70
- No prior chemotherapy, pelvic radiation or any hormonal therapy, including Proscar
- PSA is mandatory, must be ≤ 10 ng/mL
- No prior TURP
- Prostate volume by TRUS ≤ 45 cc
- No significant obstructive symptoms; AUA score must be ≤ 18
- No hip prosthesis
- Combined Gleason score ≤ 6
- Signed study-specific consent form prior to registration

**A maximum of six patients
per institution will be registered**

Required Sample Size: 95

Institution # _____

- _____ (Y) 1. Is there histologically confirmed, locally confined adenocarcinoma of the prostate?
- _____ (T1b-T2a) 2. What is the T stage?
- _____ (N0-Nx) 3. What is the N stage?
- _____ (Y) 4. If N0, was surgical sampling done?
- _____ (≥ 70) 5. What is the KPS?
- _____ (≤ 10 ng/mL) 6. What is the PSA level?
- _____ (N) 7. Has the patient had prior pelvic radiation or chemotherapy?
- _____ (N) 8. Has the patient had any prior hormone therapy?
- _____ (N) 9. Has the patient had prior radical surgery for prostate carcinoma?
- _____ (N) 10. Is there evidence of distant metastases?
- _____ (Y/N) 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?
- _____ (N) 12. Are there any major medical or psychiatric illnesses that would prevent completion of treatment or interfere with follow-up?
- _____ (N) 13. Has the patient had a prior TURP?
- _____ (Y) 14. Is the combined Gleason score ≤ 6 ?
- _____ (Y) 15. Has the patient had TRUS mapping done and is prostate volume ≤ 45 cc?
- _____ (Y) 16. Was the serum testosterone and PSA done within 30 days prior to registration?
- _____ (Y) 17. Has patient filled out AUA voiding questionnaire and is the score ≤ 18 ?
- _____ (N) 18. Has the patient had a hip replacement?
- _____ (≤ 6) 19. How many patients have you registered to this study?

(continued on next page)

The following questions will be asked at Registration:

- _____(Y) 1. Has the eligibility checklist (*above*) been completed?
_____(Y) 2. Is the patient eligible?
_____ 3. Date the study-specific Consent Form was signed? (*must be prior to study entry*)

_____	Patient's Name
_____	Verifying Physician
_____	Patient ID Number
_____	Referring Institution Number (<i>if different</i>)
_____	AUA Symptom Score (≤ 18)
_____	Combined Gleason Score of Tumor (≤ 6)
_____	Size of Gland by TRUS (<i>cc</i>) (≤ 45)
_____	PSA (≤ 10)
_____	Grade of Tumor Differentiation (<i>well or moderately</i>)
_____	T Stage (<i>T1, T1c, T2a</i>)
_____	Birthdate
_____	Race
_____	Social Security Number
_____	Zip Code
_____	Method of Payment
_____	Will any component of the patient's case be given at a VA or military facility?
_____	Implant Date

Completed by: _____ Date: _____

1.0 INTRODUCTION

1.1 Background

Adenocarcinoma of the prostate will affect over 184,500 U.S. males this year and approximately 39,200 males will die of the disease.¹ Prostate specific antigen (*PSA*) is a very useful tumor marker in early detection of this malignancy.² It also is a very reliable marker for control after definitive therapy with either

surgery or irradiation.^{3,4} Unfortunately, the results with regards to permanent control or cure of localized prostate cancer after either definitive external beam irradiation or radical prostatectomy are not nearly as good as investigators once thought because post-treatment PSA levels have demonstrated recurrence or persistent disease at a much higher level than was previously understood.^{5,6}

The use of brachytherapy or implantation of radioactive sources into the prostate for adenocarcinoma was first reported in 1911 by Pasteau.⁷ He utilized radium as his brachytherapy source. This fell into disfavor as, over the next several years, many surgical developments occurred, as well as the understanding of the hormonal dependence of prostatic carcinoma. Subsequently, megavoltage external beam radiation therapy began to be used in the management of localized prostatic carcinoma in North America after it was first developed in 1956.⁸ Yet, some investigators still 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*). Iodine¹²⁵ as a permanent implantation source was utilized extensively at Memorial Sloan-Kettering where they implanted patients at laparotomy with a free hand technique, the results of which initially looked favorable but subsequently were found to be less favorable in regards to local control.⁹ The main problem was that "ideal" geometry or an ideal implant with well-spaced radioactive seeds was very hard to achieve. Therefore, isodose "hot" and "cold" spots occurred. Presumably it was in the relative cold or underdosed areas that the prostate cancer was never controlled. Other investigators that used a similar technique also had these results and this type of implantation fell out of favor.^{10,11}

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 perineal implantation of the prostate, has resurrected the concept of permanent implantation. With these techniques, the prostate can be implanted in a more dosimetrically reliable, as well as less invasive way. A large series on this type of implantation comes from Blasko, et al.^{12,13,14} In this series, 197 patients have been treated with this technique for localized disease (*i.e.*, *T stages T1a-T2c*) with 137 of their patients being T2a. At five years, the freedom from PSA relapse is 93%.¹⁴ These are very good results, whether one looks at external beam as a comparison or the best surgical results.^{5,6} The Seattle technique is an outpatient, one-time treatment whose cost and morbidity appear to be low.^{12,13} As a result, we are looking at trying to utilize their technique with the hope of attaining similar results which may be better than those achieved historically with external beam irradiation and seem to be at least as good as the best series reported for radical prostatectomy in a similar cohort of patients. The benefit over surgery would potentially be in the area of complications, although further data needs to be collected to determine this.

1.2 Quality of Life

Increasingly the health care community has recognized the importance of using quality of life measurements as an essential component of a treatment modality's efficacy. The need for this type of evaluation in the treatment of prostate cancer is clearly evidenced by the variation in treatment options provided to men with clinically localized disease. To date there are very few prospective quality of life studies in men treated with radical prostatectomy or external beam radiation therapy.^{18,19} In men treated with interstitial brachytherapy, there are no prospective QOL studies that have been published. An important component of this phase II study will be to make use of a validated quality of life tool to prospectively estimate the quality of life in men treated with interstitial brachytherapy.

The instruments chosen for measuring quality of life in this study have been prospectively examined and validated. The FACT-P has been developed as a disease-specific instrument to measure quality of life in men with prostate cancer. The FACT-P is made up of a general measure (*FACT-G*) plus a 12-item prostate cancer subscale (*PCS*). The *FACT-G* is a 34-item generic QOL measurement including four *domains* (*physical well being, social/family well being, emotional well being and functional well being*) plus a brief assessment of the relationship with the doctor. The *FACT-G* has well-established validity and reliability, a sixth-grade reading level and has been administered to thousands of patients. The *FACT-P* questionnaire is generally completed in 10-12 minutes.²⁰

The prostate cancer specific subscale has been validated recently in 79 men with early stage prostate cancer.²¹ The internal consistency of the *FACT-G* and the *PCS* was good to excellent. Cronbach's alpha for the *FACT-G* measure ranged from 0.85 to 0.87; Cronbach's alpha for the *PCS* ranged from 0.65 to 0.69 and the Cronbach's alpha for the entire *FACT-P* ranged from 0.87 to 0.89. The mean scores (Standard Deviations) were *FACT-G* 92.2-96.0 (10.3-12.0); *PCS* 37.8-37.9 (5.5-6.7); *FACT-P* 129.9-133.9 (14.3-15.7). Concurrent validity was confirmed by the ability to discriminate patients by disease-stage, performance status and baseline prostate-specific antigen (*PSA*) level. The *PCS* appeared to be sensitive to

meaningful clinical change (*change in performance status and PSA level*). The RTOG uses Version 2 of FACT-G and Version 3 of Fact-P.

The Sexual Adjustment Questionnaire (SAQ) is a 16-item patient self-assessment form modified from an original version developed by Metcalfe and Waterhouse. The RTOG has recently reported a preliminary validation analysis of the SAQ.²² The RTOG version of the SAQ retained 5 subscales including desire, activity, arousal, orgasm and satisfaction. A total of 456 men completed the questionnaire prior to radiotherapy. A confirmatory factor analysis (FA) using LISREL with oblique rotation yielded a five-factor solution. On the basis of content, factors were labeled as follows: 1. Dysfunction (5 items, 0-25 range), 2. Satisfaction (2 items, 0-10 range), 3. Desire (6 items, 0-30 range), 4. Activity (2 items, 0-10 range), 5. Fatigue (1 item, 0-5 range) with a total score range of 0-80. Cronbach's alpha for the new subscales ranged from 0.59 to 0.80 with an overall alpha of 0.79. The mean scores (*Standard Deviations*) were: SAQ 52.1 (12.9); dysfunction 16.6 (5.6); satisfaction 7.4 (2.4); desire 19.4 (4.8); activity 4.5 (2.3); and fatigue 3.8 (0.9). Younger patients had better adjustment, desire, activity and less dysfunction than did older patients.

2.0 OBJECTIVES

- 2.1 The aim of this study is to evaluate the effectiveness of TRUS permanent implantation of the prostate for organ confined adenocarcinoma of the prostate compared to historical data of prostatectomy or external beam therapy within cooperative group setting. Other goals of this study are to collect appropriate data from multiple institutions upon which to establish QA standards for future protocols and to test dosimetric evaluation approaches and standard definitions.
- 2.2 Endpoints of the study will be:
- Freedom from PSA failure
 - Overall survival
 - Disease-specific survival
 - Clinical relapse, local and/or distant
 - GU and GI morbidity
 - Quality of life of men receiving interstitial brachytherapy

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility:

- 3.1.1 Histologically confirmed, locally confined adenocarcinoma of the prostate, clinical stage T1b, 1c, 2a, NX, N0 (*see Section 4.7.1*).
- 3.1.2 Karnofsky status ≥ 70 .
- 3.1.3 PSA is mandatory and must be ≤ 10 ng/ml.
- 3.1.4 No prior pelvic radiation, chemotherapy, or any hormonal therapy, including Proscar.
- 3.1.5 Prostate volume by TRUS ≤ 45 cc at least one week, but no more than 4 weeks, prior to implant.
- 3.1.6 AUA voiding symptom score ≤ 18 .
- 3.1.7 Mandatory lab studies: Prostate specific antigen (PSA) and serum testosterone within 30 days prior to registration.
- 3.1.8 Combined Gleason Score ≤ 6 .
- 3.1.9 Patients must sign a study-specific consent form prior to registration.

3.2 Conditions for Patient Ineligibility

- 3.2.1 Stage T1a or \geq T2b disease.
- 3.2.2 Lymph node involvement (NI).
- 3.2.3 Evidence of distant metastases (M1).
- 3.2.4 Radical surgery for carcinoma of the prostate.
- 3.2.5 Previous or concurrent cancers other than basal or squamous cell skin cancers unless disease free for ≥ 5 years.
- 3.2.6 Major medical or psychiatric illness which, in the investigator's opinion, would prevent completion of treatment and would interfere with follow up.
- 3.2.7 Prior TURP.
- 3.2.8 Hip prosthesis.

4.0 PRE-TREATMENT EVALUATION

- 4.1 History and physical (*to include tumor measurements*) and KPS.

- 4.2** Transrectal ultrasound volume study of prostate at least one week, but no more than four weeks, prior to the planned implant.
The volume study will be attained with the patient on the same type cystoscopy/x-ray table that will be used for the permanent seed implantation. 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 and stepping apparatus will be stabilized to the floor or to the table and the probe inserted into the rectum and the volume in the "step-off" balloon adjusted so that the bottom row of the perineal puncture template grid markers lines up 1 to 2 mm inside the posterior prostatic capsule. 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 0.5 cm 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 1-2 mm inside the prostatic capsule at the mid-gland, and the bottom row of the grid is outside the rectal wall at all levels. The total volume of the gland is calculated automatically and displayed on the monitor. As the probe is moved to the prostatic apex the volume of water in the "step-off" balloon is adjusted to keep the posterior row of the puncture template 1 mm. inside the posterior prostatic capsule. After serial imaging of the prostate the pubic arch study is performed by moving the probe caudally until the pubic arch shadowing is visualized. The prostate is then traced from the image with the widest dimensions and superimposed over the pubic arch image and the grids lined up. The intersection of the pubic arch and the prostate cross-section is then determined and the amount of the gland area that will be blocked by the pubic arch estimated. 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, can 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*) and serum testosterone within 30 days prior to registration.
- 4.6** CT 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*).
- 4.7.1** Nodes evaluated negative by imaging methods will be classified as NX. Only nodes evaluated negative by surgical sampling will be classified as N0.
- 4.8** AUA Symptom Score (*Appendix VII*).
- 4.9** Quality of Life Questionnaires must be completed prior to the implant.

5.0 REGISTRATION PROCEDURES

- 5.1** Institutions **must** be precredentialed by the Radiation Physics Center (*RPC*) prior to registering any cases to this study. Credentialing information is available in Appendix VIII, on the RTOG web page (www.rtog.org), or by calling the RPC (713/792-3226).
- 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 am to 5:00 pm ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The following information must be provided:
- Institution Name & Number
 - Patient's Name & ID Number
 - Verifying Physician's Name
 - Eligibility Criteria Information
 - Stratification Information
 - Demographic Data
 - Treatment Start Date

6.0 RADIATION THERAPY

6.1 Implant Volumes

The target volume definitions are, for the most part, based upon the *ICRU Report 58, Dose and Volume Specification for Reporting Interstitial 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*).

Central plane

Mid-axial plane of the prostate

6.2 Pre-plan

At least one week prior to the implant, the patient will undergo a transrectal ultrasound study. The volume of the prostate will be determined and used as the CTV.

6.3 Seed Calibration and Handling

Only I-125, model 6711, seeds will be used. The seeds will be received and inventoried according to each institution's policy and procedures in a manner consistent with federal or state regulations. A random sampling of at least 10% of the seeds shall be calibrated in such a manner such that there is direct traceability to either the NIST or an AAPM ADCL for the I-125 seeds, 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 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 0.508U per seed (*0.4 mCi per seed*).

6.4 Dosimetry

The dosimetry of the I-125 seeds is based upon the new dosimetric information that is contained in AAPM Report TG 43 for I-125 seeds. Appendix IX contains information on the dose model and the credentialing process.

6.4.1 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 dose to the PTV is 145 Gy (*TG-43 dosimetry*).

6.4.2 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.

6.4.3 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.

6.4.4 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 130 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.

6.4.5 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.

6.5 Post-Implant Confirmation

Following implantation, cystoscopy will be performed to retrieve seeds that have been extruded into the bladder or lodged in the urethral wall. Fluoroscopy or anterior radiograph and ultrasound are used to confirm uniform seed distribution. Extra seeds are implanted into any identified "cold spots."

6.6 Post-Operative Care

A Foley catheter maybe 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. The patients will complete a 4 day course of ciprofloxacin 500 mg q 12 hours.

6.7 Post-Operative Evaluation

6.7.1 The post-implant CT shall be taken between 3 to 5 weeks after the implant. This time period represents approximately two half-lives of swelling reduction, i.e. the swelling caused by the procedure will be significantly reduced. 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.

6.7.2 *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.

6.7.3 *The Dosimetric Related Data to be Submitted for Each Patient Includes:*

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

6.8 Toxicity Report

6.8.1 This study will utilize the Common Toxicity Criteria (CTC) version 2.X for toxicity and Adverse Event Reporting. A copy of the CTC version 2.X 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 version 2.X.

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

10.1 Central pathology review of the diagnostic and of the 2-year biopsies are planned for this study. Central reviews of previous prostate studies have demonstrated a 34% discrepancy in histological grading.

10.2 Hematoxylin and eosin(*H & E*) stained slides and a representative tissue block of all pathologic material, the pathology report, and a pathology submission form will be submitted to:

**LDS Hospital
Department of Pathology
E.M. Laboratory
8th Avenue & C Street
Salt Lake City, UT 84143
(801) 321-1929
FAX (801) 321-5020**

10.2.1 H& E stained slides will be retained until completion of the analysis of the study. Slides will be returned if specifically requested at that time.

10.2.2 Blocks will be retained for the special studies outlined below. Slides prepared from the blocks will also be retained.

10.2.3 If blocks will not be released, submission of 10 unstained sections mounted on sialinized (*or other "sticky slides"*) may be substituted.

10.3 All pretreatment biopsies will be assessed for the presence of tumor and graded according to Gleason.

10.4 DNA content and proliferation rate will be assessed in all cases by image analysis (*Feulgen staining*) and immunocytochemistry (*MIB-1 antibody*).

10.5 Post-treatment biopsies will be assessed for the presence of persistent tumor.

10.5.1 All positive biopsies will be histologically graded according Gleason and the degree of therapy effect in the tumor cells will be graded according to Dhom and Degro.

10.5.2 In cases where there is difficulty in diagnosis, immunohistochemical staining for high molecular weight cytokeratin will be performed to aid in the distinction of atypical benign glands from carcinoma.

10.6 RTOG will reimburse pathologists from submitting institutions \$100. per case if proper materials are submitted (*reimbursement is handled through an invoice submitted to RTOG Administration, ATT: Path Reimbursement*).

10.7 Patient consent form should give the Pathology Department authority and responsibility to comply with this request (*pathology blocks belong to the patient from whom tissue has been removed*).

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters

<u>Parameter</u>	<u>On Study</u>	<u>Follow-up</u>
History & Physical	X	X
Tumor Measurement	X	X
KPS	X	X
Sexual Status	X	X
TRUS	X	
Lymph node assessment	X	Xa
PSA	X	X
Serum testosterone	X	
Prostate Biopsy	X	Xd
Quality of Life	X	Xe
AUA Symptom Score	X	Xe
CT Pelvis	X	Xb
Cystoscopy		Xc

a. As indicated.

- b. 3 to 5 weeks post implant. See Section 6.7.1.
- c. Following implantation. See Section 6.5.
- 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.
- 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.
- 11.2.6** The patient will be asked whether he is able to achieve and maintain an erection capable of vaginal intercourse. This assessment must be done prior to the implant procedure and at each follow-up visit.

11.3 Measurement of Effect/Response

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) 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** 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 rectal 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. Rebiopsy of the suspicious area must be done to document disease.
- 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 as defined below:
 - 11.3.6.1** A rise in PSA on at least two consecutive occasions above the nadir. In patients who have been declared a PSA relapse, every effort should be made to withhold further Rx until clinical relapse is evident. When this is impossible, the site of failure should be ascertained before instituting further Rx. This will necessitate a bone scan, CT, and prostate rebiopsy.
 - 11.3.6.2** The rises in PSA must exceed 1 ng/mL above the nadir.
- 11.3.7** Time to Local Progression: The time to progression will be measured from the date of accession 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 accession to the date of documented metastatic disease.
- 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 at designated follow-up visits. **Patients who have a Foley catheter inserted within one week after the implant should not be scored as grade 4; however the event must be recorded.**

12.0 DATA COLLECTION

12.1 Summary of Data Submission

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

<u>Item</u>	<u>Due</u>
Demographic Form (A5)	Within 2 weeks of study entry
Initial Evaluation Form (I1)	
Pathology Report (P1)	
Pathology Slides/Blocks (P2)	
Quality of Life Assessments (SA, FA)	
AUA Scoring Form (PQ)	
Radiotherapy Form (T1)	Within 3 weeks post implant
<u>PreImplant Dosimetry Information:</u>	Within 8 weeks post implant
Preliminary dosimetry will be based upon the transrectal ultrasound volume study of the prostate performed at least 1 week prior to implant.	
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 145 Gy (<i>TG 43 dosimetry</i>) 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.	
<ul style="list-style-type: none"> • Pre Implant Form (<i>Appendix IX</i>) (T2) • Pre Implant Films (<i>TRUS Images</i>) • Calculations 	
<u>Final Dosimetry Information:</u>	
<i>(final dosimetry information will be based upon the post implant CT study).</i>	
<ul style="list-style-type: none"> • Post Implant Form (<i>Appendix X</i>) (T5) • Isodose Distribution (T6) • Post Implant Films/CT Study (T0) 	
Initial Followup Form (FS)	At 1, 3, and 6 months after the implant
Followup Form (F1)	At 9 and 12 months post implant; then q 6 months x 2 years, then annually. Also at progression/relapse and at death.
Quality of Life Assessments (SB, QF)	At 3, 6, 9 and 12 months; then at 18, 24,
AUA Scoring Form (PQ)	36, 48, and 60 months.
Pathology Report (P1)	At 2 years or for PSA failure

13.0 STATISTICAL CONSIDERATIONS**13.1 Overview**

13.1.1 The main objective of this study is to evaluate the effectiveness of TRUS permanent implantation of the prostate in a multi-center setting. Thus the primary hypothesis of this phase II trial is whether hospitals nationwide can achieve results as good as in a single institution reported by Blasko.¹⁴ Thus, the study is designed in such a way that the treatment failure rate at three years since implantation is not 10% worse than that reported in Blasko series with 95% confidence if the hypothesis is true.

13.1.2 Because this study is a pilot for future phase III studies, other measures are considered for the planning purposes. The data from post-implant evaluation will be analyzed to establish Quality Assurance (QA) standards based on clinical relevance. An interim analysis at two years after the closure of the study is planned to evaluate the effectiveness of the implantation. If a positive result is found, the planning for a future phase III study will be warranted.

13.2 Endpoints**13.2.1 Primary Endpoints**

Treatment failure is defined as either PSA failure (see Section 11.3.6) or positive rebiopsy post implantation.

13.2.2 Secondary Endpoint

- Overall survival
- Disease specific survival
- Time to local progression
- Time to distant failure
- Toxicity

13.2.3 Tertiary Endpoint

To evaluate the main hypothesis (Section 13.1.1), the following definition for chemical (PSA) failure, according to Blasko's report will be utilized to build up the sample size. This chemical (PSA) failure is defined as the occurrence of any of three events:

- 1) Two consecutive increasing values of PSA
- 2) First post-implant PSA value greater than 4.0 ng/ml in patients with pre-implant PSA value greater than 4.0 ng/ml.
- 3) PSA values greater than the pre-implant value in patients with a normal (< 4.0ng/ml) pre-implant PSA value.

13.2.4 Quality of Life Consideration**13.3 Sample Size Determination****13.3.1 Outcome Statistics from Early Studies****Table 1: Freedom from chemical (PSA) failure in early studies**

Study	Strata	Freedom from chemical (PSA) failure at year			Estimated yearly hazard
		2	3	5	
Blasko ¹⁴ (implant)	PSA 0-4.0	100%	98%	98%	.0054
	4.1--10	95%	95%	90%	.0213
John Hopkins ⁶ (prostatectomy)	GS 2-6			89%	.0239
	7-10			56%	.1157
	PSA 0-4.0			92%	.0167
	4.1--10			83%	.0373

13.3.2 Patient Population and Hypothesis

Blasko’s series has indicated that patients with higher pre-treatment PSA values tended to have a higher failure rate (Table 1). Based on the current accrual in RTOG 94-08, for patients with pre-treatment PSA of less than or equal to 10 there are 21.6% less than or equal to 4. For the study design, we assume there are 25% of patients with PSA values within the range of 0 to 4.

RTOG studies also showed that there was discordance between Gleason scores reported by institutions and those centrally reviewed. Patients with Gleason scores of 7-10 have had a poor prognosis and may not be suitable to I-125 permanent implant. However, because it is unrealistic to have Gleason scores centrally reviewed before patients are registered, we will take this into account while calculating the targeted failure rate. Based on RTOG 77-06, for patients with both institutional Gleason scores of 2-6, 8.3% turned out to be 7-10 by the central review. For the study design, we assume about 8% of study population are in fact belong to Gleason score group of 7-10.

Table 2: Hypothesized Failure Rates for the Study

Subgroup		Projected % in Population	Freedom from chemical (PSA) Failure at year 3	Estimated Yearly Hazard	Combined Freedom from Failure rate at Year 3
GS: 2-6	PSA 0 – 4	92%*25%	98%	.0054	94.9%
	4 – 10	92%*75%	94%	.0213	
GS: 7-10		8%	71%	.1157	

Table 2 lists the hypothesized failure (*hazard*) rates for the study broken down by subgroups assuming constant hazard. Because there is no series published for patients with Gleason 7-10 treated with I-125 permanent implant, we assume that these patients would have the similar outcome to the prostatectomy series. Using a linear combination of the hazard rate, the targeted freedom from chemical (PSA) failure rate at 3 years (2 years) for the study population is 92.7% (95%).

13.3.3 Sample Size

The sample size of the study is determined in such a way that we have 95% confidence that the observed freedom from chemical (PSA) failure rate at three years post implantation is no worse than 82.7% if the proposed I-125 permanent implant in multi-center setting can achieve a similar outcome to the single institution experience given by Blasko (*three-year freedom from chemical [(PSA)] failure rate of 92.7%*). As alluded to in the overview, an interim analysis at two years after the last patient has been entered will be performed. Based on Bonferroni multiple testing approach, the confidence interval at each stage of the analysis is adjusted to 97.5% level so that the overall level of the confidence is at least 95%.

Following the asymptotic property of the observed hazard and Rubinstein’s work¹⁷, the confidence interval calls for 4.7 chemical (PSA) failures at the end of the study. Considering an annual 2% loss to follow-up or death from non-prostate cancer, 64 patients who are treated per protocol or with acceptable variation are required to be uniformly accrued within six months and then be followed up for additional three years. Because we have no prior knowledge of the clinical outcome for a patient whose treatment compliance is scored as an unacceptable deviation, the sample size is expanded to safeguard against a possible 25% unacceptable deviation cases. Thus, 85 evaluable cases are required. Accounting for 10% unevaluable cases, **the total sample size of the study is 95 patients.**

If the projected 8% misclassification rate in Gleason score holds in the study population, we will expect to accrue 59 evaluable cases (*compliance score of per protocol or acceptable variation*) with Gleason scores of 2-6 confirmed by the central review. With such a sample size, the low bound of the confidence interval for the 3-year freedom of chemical (PSA) failure rate is 85.4% if the hypothesized rate of 94.9% is true.

13.4 Accrual and Study Duration

With a good track record of accession for low risk prostate cancer patients in RTOG, an accrual rate of 16 cases/month is expected. However, because each institution has to go through IRB and QA credentialing processes before they put cases on the study, it is expected that it will take approximately a year to complete the study.

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 toxicities.

- 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 toxicities.

13.5.2 Interim Efficacy Analysis at Year 2 after Closure

For the purpose of planning future trials, an interim analysis at year two after the closure will be performed to evaluate the efficacy of I-125 permanent implant in a multi-center setting. With 64 evaluable patients cases (*compliance score of per protocol or acceptable variation*), the lower bound of 95% confidence interval for freedom from chemical (PSA) failure at two-year post implant is 88% if the true rate is 95%. Thus if the observed freedom from chemical (PSA) failure rate at two years post implant estimated by the Kaplan-Meier method¹⁶ is greater than the lower bound, we will conclude the outcome of treatment delivered by multi-centers is compatible to that of the single institution experience reported by Blasko. If the estimate is between 88% and 82.7% (*the lower bound for year three*), we are unable to make conclusions at this point. Lastly, if the estimate is below 82.7%, we will conclude that the study fails to repeat the Seattle experience.

A subset of patients with centrally reviewed Gleason scores of 2-6 will be analyzed. The estimate of freedom from chemical (PSA) failure and treatment failure will be calculated using the cumulative incidence method.

13.5.3 Analysis and Reporting of Initial Treatment Results

The major analysis will be undertaken at three years after the last patient has been entered to the study. The estimate of freedom from chemical (PSA) failure rate for the whole population will be calculated using by the Kaplan-Meier method. The estimate based on a subset of patients whose compliance score of per protocol or acceptable variation will be compared to the lower bound of the 95% confidence interval given in Section 13.3.3. However, if in fact there is a discrepancy in percentage of patients with Gleason scores 7-10 from what we projected, the lower bound shall be recalculated based on the characteristic of the accrued population. It is the time we have to reexamine the estimated freedom from chemical (PSA) failure rate at year three post implant. If the estimate is greater than the lower bound, the study will conclude the treatment delivered in multi-centered setting is compatible to the Seattle experience. Otherwise, it is unlikely that the outcome of the treatment reported by Blasko can be repeated in a multi-center setting.

Estimates for treatment failure and other secondary endpoints will be done using the Kaplan-Meier method¹⁶ and the cumulative incidence method¹⁵ whenever they are appropriate. A subset analysis for patients with centrally reviewed Gleason scores of 2-6 will be performed in similar fashion. The maximum toxicity until the last follow-up will be reported according to RTOG toxicity grading system. An exploratory analysis will be performed to study the statistical relationship between QA standards for compliance and clinical outcomes.

13.6 Gender and Minority Compliance

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 this study will be non-white. Thus, 72 whites and 23 non-whites are expected to enter into the study. If the same analysis is performed within each racial group, the lower bounds of the 95% confidence interval of 3-year PSA control rate for white and non-white are 81.2% and 62.3%, respectively.

13.7 Quality of Life

Quality of life will be measured using FACT-P and SAQ. When the sample size is 95, a two-sided 95.0% confidence interval for a single mean for FACT will extend 2.413 from the observed mean, assuming that

the standard deviation for FACT is known to be 12.000 and the confidence interval is based on the large sample z statistic.

REFERENCES

1. Cancer Statistics 1998. CA: A Cancer Journal for Clinicians, American Cancer Society, 1998.
2. Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS, and Redwine E. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. NEJM 317:909-916, 1987.
3. Zagars GK, Sherman NE, Babaian RJ. Prostate-specific antigen and external beam radiation therapy in prostate cancer. Cancer 67:412-420, 1991.
4. Lange PH, Ercole CJ, Lightner DJ, et al. The value of serum prostate-specific antigen determinations before and after radical prostatectomy. J Urol 141:873-879, 1989.
5. Zagars GK, and von Eschenbach AC. Prostate-specific antigen: An important marker for prostate cancer treated by external beam radiation. Cancer 72:538, 1993.
6. Partin AW, Poend CR, Clemmes JQ, and Walsh PC. Serum PSA with anatomic radical prostatectomy. The Johns Hopkins experience after 10 years. Urol Clin N America 20:713-725, 1993.
7. Pasteau O. Traitment du cancer de la prostate par le Radium. Rev Mal Nutr 363-7, 1911.
8. Bagshaw MA, Kaplan HS, and Sagerman RH. Linear accelerator supervoltage radiotherapy: Carcinoma of the prostate. Radiology 85:121-129, 1965.
9. Fuks Z, Leibel SA, Wallner KE, Begg CB, Fair WR, Anderson LL, et al. The effect of local control on metastatic carcinoma of the prostate: Long term results in patients treated with I-125. Int J Radiat Oncol Biol Phys 21:537-547, 1991.
10. Kuban DA, El-Mahdi AM, Schellhammer PF: I-125 interstitial implantation for prostate cancer. What have we learned 10 years later? Cancer 63:2415-2420, 1989.
11. Koprowski CD, Berkenstock KG, Borofski AM, Ziegler JC, Lightfoot DA, Brady LW: External beam irradiation versus 125 iodine implant in the definitive treatment of prostate carcinoma. IJROBP 21:955-960, 1991
12. Blasko JC, Grimm PD, Ragde H: Brachytherapy and organ preservation in the management of carcinoma of the prostate. Seminars in Rad Onc 3:240-249, 1993.
13. Blasko JC, Ragde H, Grimm PD: Transperineal vs. guided implantation of the prostate: Morbidity and complications. Scand J Urol Nephrol 137 (Suppl):113-118, 1991.
14. Blasko JC, Walker K, Grimm PD, Ragde H: Prostate specific antigen based disease control following ultrasound guided ¹²⁵Iodine implantation for stage T₁/T₂ prostatic carcinoma. J Urol 154:1096-1099, 1995.
15. Gray RJ: A Class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat. 16:1141-1154, 1988.
16. Kaplan EL and Meier P: Nonparameteric estimation form incomplete observations. J. Amer. Statist. Assoc. 53:457-481, 1958.
17. Rubinstein, LV, Gail, MH, and Santner, TJ Planning the duration of a comparative clinical trial with loss to follow-up and period of continued observation. J. Chron. Dis. 34: 469-479, 1981.
18. Litwin MS, Hays RD, Fink A, Ganz PA, Leake B, Leach GE, Brook RH. Quality of life outcomes in men treated for localized prostate cancer. JAMA 1995; 273:129-135.

19. Shrader-Bogen CL, Kjellberg JL, McPherson CP, Murray CL. Quality of life and treatment outcomes: Prostate cancer patients' perspectives after prostatectomy or radiation therapy. *Cancer* 1997; 79:1977-1986.
20. Cella DF, Tulsky DS, Gray G, et al. The functional assessment of cancer therapy scale: Development and validation of the general measure. *J Clin Oncol* 1993; 11:570-579.
21. Esper P, Mo F, Chodak G, Sinner M, Cella D, Pienta K. Measuring quality of life in men with prostate cancer using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) Instrument. *Urology* 1997; 50:920-928.
22. Bruner DW, Scott CB, McGowan D, Lawton C, Hanks G, Prestidge B, Gaspar L, Gore E, Asbell S. Validation of the sexual adjustment questionnaire (SAQ) in prostate cancer patients enrolled on Radiation Therapy Oncology Group (RTOG) studies 90-20 and 94-08. Accepted for presentation at 1998 ASTRO.

APPENDIX I

RTOG 98-05

Phase II Trial of Transrectal Ultrasound Guided Permanent Radioactive Implantation of the Prostate for Definitive Management of Localized Adenocarcinoma of the Prostate

Sample Patient Consent Form

RESEARCH STUDY

I have the right to know about the procedures that are used in my participation in clinical research so I can decide whether to undergo the procedure after knowing the risks, benefits, and alternatives involved. This is an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

PURPOSE OF THE STUDY

It has been explained to me that I have prostate cancer. My doctor feels that a prostate implant may be an appropriate treatment option. This study uses permanent radioactive seeds implanted in the prostate through needles inserted through the area between the anus and the scrotum. The procedure is done under anesthesia so it is almost painless. The purpose of this study is to determine whether a prostate implant is as good as the usual treatments for this disease which are surgery or external radiation treatments. The other objective of the study is to analyze the risk of complications of this procedure as compared to surgery or radiation treatments.

DESCRIPTION OF PROCEDURES

Before I undergo the implant procedure a physical examination will be done by my physician. I will have an ultrasound study of the prostate (*a special scan of my prostate*) obtained by inserting a probe into my rectum so that my physicians can plan my treatment. I may also have a flexible cystoscopy (*insertion of a flexible tube which allows my doctors to see into my bladder*) and lymph node evaluation, which can be performed by a CT or MRI scan of my pelvis, lymph node biopsy or exploratory laparoscopy (*an abdominal operation using a special type of instrument called a laparoscope, which allows my doctors to see my abdominal contents*) with lymph node biopsy.

I will also need to have tests for prostate specific antigen (*PSA*) and serum testosterone. These tests will require that about 2 tablespoons of blood be taken from a vein in my arm. After all of these tests have been completed, I will be scheduled for my implant.

Implants are normally done in the hospital as an outpatient procedure taking about one hour. The anesthesiologist will give me anesthesia so the procedure will not be painful. Thin needles with radioactive seeds will be placed through the skin between the anus and scrotum into the prostate with the help of ultrasound. When each needle is in its correct position in the prostate, each needle is slowly pulled out leaving the seeds in the prostate. The number of needles and seeds varies from patient to patient depending on the size of the prostate that will absorb the radioactivity from the seeds. I can probably leave the hospital the same day and resume my normal activities within several days. The seeds will remain in my prostate and cannot be passed to another person through sexual activity.

After my implant, my doctor will see me at the following time intervals: within one month after my implant, then every 3 months for the first year, then every 6 months for two years. After the third year, I will be seen by my doctor every year. When I see my doctor for these follow-up visits, he/she will perform a physical examination including a rectal exam, evaluate my sexual status, and take a PSA blood test (*which requires that about 1 teaspoon of blood be drawn from my arm*). If my condition requires, I will have a bone scan, ultrasound, or CT of my pelvis. A prostate biopsy will be done if there evidence of tumor growth in my prostate on rectal exam, or if my PSA goes up and my bone and CT show no evidence of disease. I will be asked to complete questionnaires to evaluate my quality of life before and after treatment. They will take 5-10 minutes each to complete.

RISKS AND DISCOMFORTS

Cancer treatments often have side effects. The treatment used in this program may cause all, some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.

Implant: The possibility exists for infection but this should be controlled with antibiotics should infection occur. There will be soreness in the implant area. The implant itself has the possible side effects of temporary fatigue, diarrhea, abdominal cramps, bladder irritation with some bleeding, incontinence and, in some patients, inability to have an erection. There is also a chance of permanent injury to the bladder, urethra, bowel, and other tissues in the pelvis. The side effects related to the bladder, urethra, and bowel may take some months to years to occur. Another small risk is the movement of a radioactive seed to the lungs. Very small amounts of radiation can reach other people. I should follow the special precautions from my doctor if I'm around small children and pregnant women.

Transrectal ultrasound: Other than discomfort, there really is not a great risk from the transrectal ultrasound.

CT scan with contrast: An allergic reaction due to the contrast dye could occur but, otherwise, this doesn't carry any serious risk.

Anesthesia: There is the possibility of blood pressure problems, heart rhythm problems, breathing changes, drug reactions, nausea, vomiting, headache, sore throat, heart attack, stroke, or death.

Other: There may be some unknown or unanticipated discomforts or risks in addition to those specified above, as this irradiation technique, although not new, is somewhat different from techniques with permanent implantation in the past. Every precaution will be taken to assure my safety to minimize any discomfort that I may experience.

My physician will be checking me closely to see if any of these side effects are occurring. In the meantime, my doctor may prescribe medication to keep these side effects under control. I understand that the use of medication to help control side effects could result in added costs. This institution is not financially responsible for treatments of side effects caused by the study treatment.

There may be laboratory testing and procedures required by this study for research purposes. These additional tests may increase my medical bills although the impact will be dependent on my insurance company.

CONTACT PERSONS

If injury occurs as a result of this research, treatment will be available. However, I will not be reimbursed for medical care other than what my insurance carrier may provide nor will I receive other compensation. For more information concerning the research and research-related risks or injuries, I can notify Dr. _____ the investigator in charge at _____. In addition, I may contact _____ at _____ for information regarding patients' rights in research studies.

BENEFITS

Because the seeds are placed directly into the area of the cancer, the seeds can deliver 2-3 times more concentrated radiation to the prostate than external radiation therapy can. The external radiation treatments must use a lower dose so as not to injure surrounding healthy tissue. The information obtained from this study will be used scientifically. It may possibly be helpful to others. The possible benefits of this treatment program are greater shrinkage and control of my tumor and prolongation of my life but this is not guaranteed.

Should my disease become worse, should side effects become very severe, or should developments occur that indicate the treatment is not in my best interest, further treatment would be discussed.

ALTERNATIVES

Alternatives that could be considered in my case include surgery or external radiation therapy with or without hormones. An additional alternative is watchful waiting with careful followup of PSA and rectal exams to detect any progression of the cancer. This would probably result in continued growth of my tumor. My doctor can provide detailed information about my disease and the benefits of the various treatments available. I should feel free to discuss my disease and my prognosis with the doctor. The physician involved in my care will be available to answer any questions I have concerning this program. I am free to ask my physician any questions concerning this program that I wish in the future.

My physician will explain procedures related to this protocol. Some of these procedures may result in added costs but may be covered by insurance. My doctor will discuss these with me.

VOLUNTARY PARTICIPATION

Participation in this study is voluntary. No compensation for participation will be given. I am free to withdraw my consent to participate in this treatment program at any time without prejudice to my subsequent care. Refusal to participate will involve no penalty, or loss of benefits. I am free to seek care from a physician of my choice at any time. If I do not take part in or withdraw from the study, I will continue to receive care.

CONFIDENTIALITY

I understand that records of my 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*). The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (*FDA*), the National Cancer Institute (*NCI*), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in this study may have access to medical records that contain my identity. However, no information by which I can be identified will be released or published. Histopathologic material, including tissue and/or slides, may be sent to a central office for review and research investigation associated with this protocol.

I have read all the above, asked questions, received answers concerning areas I did not understand, and willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

Patient Signature (*or Legal Representative*)

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 no imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

APPENDIX III

AJCC STAGING SYSTEM PROSTATE, 1997

DEFINITION OF TNM

Primary Tumor, Clinical (T)

TX	Primary tumor cannot be assessed
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 (<i>e.g., because of elevated PSA</i>)
T2	Tumor confined with prostate*
T2a	Tumor involves one lobe
T2b	Tumor involves both lobes
T3	Tumor extends through prostate capsule**
T3a	Extracapsular extension (<i>unilateral or bilateral</i>)
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)

NX	Regional lymph nodes cannot be assessed
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
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 (<i>slight anaplasia</i>)
G2	Moderately differentiated (<i>moderate anaplasia</i>)
G3-4	Poorly undifferentiated or undifferentiated (<i>marked anaplasia</i>)

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	D
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	E
MUCOUS MEMBRANE	None	Slight atrophy and dryness	Moderate atrophy and telangiectasia; Little mucous	Marked atrophy with complete dryness; Severe telangiectasia	Ulceration	H
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	D
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	R
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	C
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	Y
LARYNX	None	Hoarseness; Slight arytenoid edema	Moderate arytenoid edema; Chondritis	Severe edema; Severe chondritis	Necrosis	R
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	E
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	T
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	D
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	T
LIVER	None	Mild lassitude; Nausea, dyspepsia; Slightly abnormal liver function	Moderate symptoms; Some abnormal liver; function tests; Serum albumin normal	Disabling hepatic insufficiency; Liver function tests grossly abnormal; Low albumin; Edema or ascites	Necrosis/Hepatic coma or encephalopathy	E
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%	E
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	S
BONE	None	Asymptomatic; No growth retardation; Reduced bone Density	Moderate pain or tenderness; Growth retardation; Irregular bone sclerosis	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

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 (\geq *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 (\geq *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. | As above |

- All life threatening (*grade 4*) events which may be due to agent. As above
 - First occurrence of any toxicity (*regardless of grade*). 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. 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*)
 - All fatal (*grade 5*) and life threatening (*grade 4*) unknown adverse reactions resulting from or suspected to be related to investigational agent. Report **by phone** to RTOG Headquarters, the Study Chairman and IDB within **24 hours**.
**A written report to follow within 10 working days.
 - All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent. **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 CLASSIFICATION¹

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
<u>or</u> 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
<u>or</u> 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 VII

RTOG 98-05

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

	Not at all	Once every 8 hours	Once every 4 hours	Once every 3 hours	Once every 2 hours	At least once every hour
6. 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 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 six 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
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.

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

The credentialing process would be a two step process, a physics/dosimetry review and a clinical review. The credentialing process will be conducted by the Radiologic Physics Center.

The Clinical Review

A non-protocol permanent prostate implant patient shall be planned and 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 insure 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 6.7 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.

RTOG Prostate Pre-Implant Form (T2)

Patient: _____	Physician: _____
Date: _____	
Volume _____	

Prostate Seed Loading Pattern			
Isotope	Implant Type	Target MPD	Seed Activity
I-125	Permanent	145 Gy	

Needle Number	Retraction cm	Hole Location	Seed Number
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
27			
28			
Total Seeds			
Seed Activity			

Template Coordinates Used for Implant													
<== Right							Left ==>						
5.0	•	•	•	•	•	•	•	•	•	•	•	•	•
4.5	•	•	•	•	•	•	•	•	•	•	•	•	•
4.0	•	•	•	•	•	•	•	•	•	•	•	•	•
3.5	•	•	•	•	•	•	•	•	•	•	•	•	•
3.0	•	•	•	•	•	•	•	•	•	•	•	•	•
2.5	•	•	•	•	•	•	•	•	•	•	•	•	•
2.0	•	•	•	•	•	•	•	•	•	•	•	•	•
1.5	•	•	•	•	•	•	•	•	•	•	•	•	•
1.0	•	•	•	•	•	•	•	•	•	•	•	•	•
	A	a	B	b	C	c	D	d	E	e	F	f	G

Retraction Planes				
Plane 1	Plane 2	Plane 3	Plane 4	Plane 5
0.0 cm	0.5 cm	1.0 cm	1.5 cm	2.0 cm
	Δ		X	☆

Number of Needles	Seeds Per Needle
Total Needles	Total Seeds
Seed Activity	Extra Seeds
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

Slice	Min Dose to Prostate (ETV) Gy (TG 43 Dosimetry)	Dimensions of: High Dose Area cm x cm	Low Dose Area cm x cm
1 Base	_____	_____	_____
2	_____	_____	_____
3	_____	_____	_____
4	_____	_____	_____
5	_____	_____	_____
6	_____	_____	_____
7	_____	_____	_____
8	_____	_____	_____
9	_____	_____	_____
10	_____	_____	_____
11	_____	_____	_____
12	_____	_____	_____

Dose Volume Histogram Analysis

Doses are based on TG 43 Dosimetry

Dose/ Gy	Volume/% Prostate	Volume/% Rectum	Volume/% Bladder
10	_____	_____	_____
20	_____	_____	_____
30	_____	_____	_____
40	_____	_____	_____
50	_____	_____	_____
60	_____	_____	_____
70	_____	_____	_____
80	_____	_____	_____
90	_____	_____	_____
100	_____	_____	_____
110	_____	_____	_____
120	_____	_____	_____
130	_____	_____	_____
140	_____	_____	_____
150	_____	_____	_____
160	_____	_____	_____
170	_____	_____	_____
180	_____	_____	_____
190	_____	_____	_____
200	_____	_____	_____
210	_____	_____	_____
220	_____	_____	_____
230	_____	_____	_____
240	_____	_____	_____
250	_____	_____	_____

Dose/Gy	Volume/% Prostate	Volume/% Rectum	Volume/% Bladder
260	_____	_____	_____
270	_____	_____	_____
280	_____	_____	_____
290	_____	_____	_____
300	_____	_____	_____
310	_____	_____	_____
320	_____	_____	_____
330	_____	_____	_____
340	_____	_____	_____
350	_____	_____	_____
360	_____	_____	_____
370	_____	_____	_____
380	_____	_____	_____
390	_____	_____	_____
400	_____	_____	_____