

RADIATION THERAPY ONCOLOGY GROUP

RTOG 96-01

A PHASE III TRIAL OF RADIATION THERAPY WITH OR WITHOUT CASODEX IN PATIENTS WITH PSA ELEVATION FOLLOWING RADICAL PROSTATECTOMY FOR pT3N0 CARCINOMA OF THE PROSTATE

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CTSU (R9601)

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RADIATION THERAPY ONCOLOGY GROUP

RTOG 96-01

A PHASE III TRIAL OF RADIATION THERAPY WITH OR WITHOUT CASODEX IN PATIENTS WITH PSA ELEVATION FOLLOWING RADICAL PROSTATECTOMY FOR pT₃N₀ CARCINOMA OF THE PROSTATE

SCHEMA

<p>S</p> <p>T</p> <p>R</p> <p>A</p> <p>T</p> <p>I</p> <p>F</p> <p>Y</p>	<p><u>Neoadjuvant Hormone Therapy</u></p> <p>1. No 2. Yes</p> <p><u>Positive Surgical (inked) Margins</u></p> <p>1. No 2. Yes</p> <p><u>PSA Nadir after Surgery <0.5 ng/ml</u></p> <p>1. No 2. Yes</p> <p><u>Entry PSA level</u></p> <p>1. 0.2 to 1.5 ng/ml 2. 1.6 to 4.0 ng/ml</p>	<p>R</p> <p>A</p> <p>N</p> <p>D</p> <p>O</p> <p>M</p> <p>I</p> <p>Z</p> <p>E</p>	<p>Radiation Therapy^a plus Casodex 150 mg^b vs. Radiation Therapy^a plus placebo^b daily</p>
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a. Radiation Therapy: 64.8 Gy in 36 fx (1.8 Gy in 5 daily sessions per week) to the original prostate volume, the tumor resection bed and the proximal membranous urethra.

b. Casodex or Placebo: Patients will receive either one (150 mg) tablet of Casodex or placebo in a double-blinded fashion p.o. daily for two years beginning immediately upon, or just prior to, the initiation of irradiation.

Recommended treatment at relapse: Maximal androgen blockage. (See Section 9.0)

Eligibility: (See Section 3.0 for details)

- Pathologic stage T3 N0 with radical prostatectomy, or pT2 pN0 with a positive inked resection margin or positive prostate fossa/anastomosis biopsy.
- Entry PSA ≥ 0.2 ng/ml to ≤ 4.0 ng/ml.
- No distant metastases.
- Karnofsky performance status ≥ 80.
- No prior chemotherapy, prior hormones, (except for neoadjuvant hormone therapy) or radiation for prostate cancer.
- Treatment on both arms must begin within 4 weeks after randomization.
- Hgb ≥ 10, WBC ≥ 4,000, platelets, ≥100,000, SGOT (or SGPT) ≤ 2.5 x institutional upper normal limit, serum creatinine ≤ 2 x institutional upper normal limit.
- PSA levels prior to surgery until study entry must be available.
- Life expectancy > 10 years
- Signed study-specific informed consent

Required Sample Size: 810

9/8/98
10/26/99
9/5/00

Institution # _____

RTOG 96-01

ELIGIBILITY CHECK (9/5/00)

Case # _____

(page 1 of 2)

- _____(Y) 1. Has the patient undergone a radical prostatectomy and pelvic lymphadenectomy at least 12 weeks prior to randomization?
- _____(pT2, pT3) 2. What is the pathologic T classification?
_____(Y/N) If pT2 N0, was there a positive inked resection margin?
_____(Y) If no, did the patient have a prostatic/anastomosis fossa biopsy at time of rising PSA?
- _____(N0) 3. What is the pathologic nodal classification?
- _____(0.2 to 4) 4. What is the patient's entry PSA level (*within 6 weeks prior to randomization*)?
- _____(Y) 5. Does the patient meet all scan and laboratory requirements specified in Sections 3.1.3, 3.1.7 and 3.1.8 of the protocol?
- _____(≥ 80) 6. What is the patient's Karnofsky Performance Status?
- _____(Y/NA) 7. Is the patient NED of any prior cancers for 5 or more years (*prior or concurrent basal or squamous cell skin cancer is eligible*)?
- _____(N) 8. Did the patient receive any hormonal therapy after the prostatectomy?
- _____(N) 9. Has the patient received any previous radiation therapy or biologics for prostate cancer?
- _____(N) 10. Has the patient received any previous chemotherapy for any reason?
- _____(Y) 11. Will treatment start within the next 4 weeks?
- _____(Y) 12. Does the patient have a life expectancy of at least 10 years?
- _____(Y) 13. Has the patient been evaluated by both a Radiation Oncologist and Urologist and judged suitable for protocol?

The following questions will be asked at Randomization:

- _____ 1. Institutional person randomizing this patient?
- _____(Y) 2. Has the Eligibility Checklist (*above*) been completed?
- _____(Y) 3. Is the patient eligible for this study?
- _____ 4. Date the study-specific Consent Form was signed? (*must be prior to study entry*)
- _____ 5. Patient's Name
- _____ 6. Verifying Physician

(continued on next page)

Institution # _____

RTOG 96-01

ELIGIBILITY CHECK (9/5/00)

Case # _____

(page 2 of 2)

_____ 7. Patient ID#

_____ 8. Birthdate

_____ 9. Race

_____ 10. Social Security Number

_____ 11. Patient's country of residence

_____ 12. Zip Code *(9 digit if available)*

_____ 13. Method of Payment

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

_____ 15. Treatment Start Date

_____ 16. Neoadjuvant hormones *(no vs. yes)*

_____ 17. Positive surgical margins *(no vs. yes)*

_____ 18. PSA nadir after surgery < 0.5 ng/ml? *(no vs. yes)*

_____ 19. Specify PSA level at study entry? *(0.2 to ≤ 4.0 ng/ml)*

_____ Treatment Assignment

Completed by _____

Date _____

1.0 INTRODUCTION

1.1 Background

Radical prostatectomy is an effective treatment for prostate cancer when the tumor is found pathologically to be confined to the gland. However, when on pathologic examination tumors are found to extend through the prostatic capsule and/or to have a positive surgical (*inked*) margin, these patients are likely to develop recurrent disease.^{1,2,35} The median time to develop clinical recurrence with positive surgical margins is approximately seven years. Serum prostatic specific antigen (*PSA*) has been evaluated in many centers as an early predictor of clinical recurrence following primary therapy. A rising PSA following radical prostatectomy occurs earlier than clinical disease recurrence.^{2,3} The frequency of PSA progression following radical prostatectomy for margin positive patients at 3-4 years after surgery is 50-70% which is similar to the long term failure suggesting that PSA progression is an important predictor of surgical treatment failure. Local clinical recurrence following radical prostatectomy is a poor prognostic finding with a low long term disease free salvage rate following either radiation or hormonal therapy.^{1,4} Treatment of clinically recognized metastatic prostate cancer by hormonal therapy results in a median survival of less than 3 years.⁵ There are data suggesting that early or adjuvant treatment of patients at high risk for PSA progression (*those with pathologic T3 disease and/or positive surgical margins*) can significantly lower the rate of PSA progression and possibly the clinical course.^{6,7} However, at many institutions, adjuvant radiation therapy is not given to those patients at substantial risk of local failure based on their pathologic staging, following radical prostatectomy. Instead, treatment by either radiation or hormonal therapy is reserved if PSA progression subsequently occurs. The justification is that a blanket policy of adjuvant radiation for all pathologic stage T3 patients would needlessly risk irradiating men who may either have no disease or occult metastatic disease, neither of whom would stand to benefit. In addition, the use of stringent disease recurrence of criteria (*by PSA progression*) now allows the early detection of relapse. This has allowed for more rapid detection than previously of surgical treatment failure and thus has encouraged this wait and watch policy.

A substantial proportion of patients (*at least 80%*) with PSA progression and a negative metastatic workup will respond to local external beam radiation therapy.⁸ However, while 50% or more of men will respond completely with PSA returning to undetectable levels, the durability of this response is uncertain. A number of reports suggested that only one quarter to one third of these men will remain free of a second biochemical progression at five years after irradiation.⁹⁻¹¹ When patients with node positive disease are excluded, the actuarial three year freedom from second PSA progression is higher at 48%.⁷⁻⁹ Further exclusion of those patients with histologic evidence of seminal vesical invasion, who may be at greater risk for having had distant dissemination, takes the figure still higher to 56%. A recent article from Washington University reported an even higher figure of 68% for a 3 year freedom from a second PSA progression in men given external beam radiation for an isolated PSA failure.¹² However, there is no long term follow-up for these reports attempting "early" external beam irradiation to attempt to cure surgical failures detected by PSA progression. This is because clinical "serial PSA testing" after prostatectomy has only been available for six years. Nevertheless, with even this moderate follow-up, there is significant PSA relapse indicating that "early" radiation therapy in an attempt to salvage these patients is not always curative.

Prior phase III RTOG trials have studied the potential benefit of adjuvant hormonal monotherapy (*RTOG 85-31 and RTOG 92-02*) and the benefit of maximum androgen blockade as neoadjuvant hormonal therapy (*RTOG 86-10*). The early results of these trials combining radiation and hormonal therapy compared to radiation therapy alone are encouraging.^{13,14} In addition, although the benefit of early hormonal therapy in metastatic prostate cancer remains unclear, there is increasing evidence that this may afford a survival benefit.¹⁵

While many controversies still exist in virtually all areas of the treatment of prostate cancer, several conclusions can be made: 1) a significant portion of patients who have radical prostatectomy with pathologic stage T3 disease will fail; 2) PSA elevation (*either as persistence following radical surgery or as progression*) is an early predictor of treatment failure; and 3) hormonal therapy only at the time of clinically documented metastases does not prevent death from prostate cancer and the survival interval is inversely related to the extent of the disease treated. Above recent data suggests that: 1) radiation therapy is locally effective in controlling locally recurrent disease following radical prostatectomy and 2) there may be advantages to combining early hormonal therapy with radiation therapy in other settings of localized prostate cancer not confined to the organ. In an early adjuvant setting the optimal method of hormonal

therapy has not been defined. Casodex (*Astra Zeneca Pharmaceuticals*), or bicalutamide, is a new nonsteroidal antiandrogen with a long half-life compatible with once-daily dosing. Casodex is well tolerated and has good response rates in phase II trials.^{16,17} Like other anti-androgens, it is less likely to impair libido and potency than are LHRH agonists or orchiectomy.

Bicalutamide has been studied extensively in terms of endocrinology, anti-tumor activity, toxicity and oncogenicity in several animal species. Full details of this work can be found in the Investigational Drug Brochure (*IDB*). RTOG Headquarters will provide copies of the IDB upon request.

This study will evaluate radiation therapy with or without Casodex in patients following radical prostatectomy who have PSA persistence or progression as their only evidence of failure. This study, as have other RTOG trials previously, will evaluate the effect of radiation vs. radiation plus systemic adjuvant hormonal therapy of limited duration (*2 years*) on overall survival and freedom from tumor-related deaths in patients with moderately advanced prostate cancer.

2.0 OBJECTIVES

- 2.1 To compare overall survival outcome of radiation therapy plus Casodex to radiation therapy plus placebo by a randomized trial for patients who, following radical prostatectomy demonstrating pathologic T3 disease and pathologic N0 disease status, have an elevated PSA (*either as persistence or as a relapse*) and have no evidence of metastatic disease.
- 2.2 To compare the treatment with respect to time to second PSA-based progression, time to distant failure, and disease-specific survival.
- 2.3 To compare the treatment with respect to time to third PSA failure (*or PSA progression on hormonal therapy for second PSA failure*) as a potential predictor for impending cancer death.²⁴
- 2.4 To allow for subsequent analysis of emerging molecular pathologic predictors of outcome with the prospective collection of the paraffin blocks from the radical prostatectomy specimen.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility (9/8/98, 10/26/99, 9/5/00)

- 3.1.1 The patient on entry will have no clinical evidence of disease by physical exam or by imaging studies. A positive ProstaScint scan alone without a confirmatory biopsy must not be used to exclude a patient. Eligible patients will be those who have undergone a radical prostatectomy (*either retropublic or perineal*) and pelvic lymphadenectomy (*either open or laparoscopic*) for carcinoma of the prostate, pathologic stage T3N0, or pT2 pN0 with positive inked resection margin, at least 12 weeks prior to study entry.
 - 3.1.1.1 Pathological T2 patients without positive margins, who are also pathologic N0 with prostatic fossa/anastomosis biopsy at the time of rising PSA documenting recurrent cancer, are eligible.
- 3.1.2 At entry, the PSA must be between ≥ 0.2 and ≤ 4.0 ng/ml.
- 3.1.3 A post-prostatectomy radioisotopic bone scan which was done within 16 weeks prior to entry must reveal no evidence of metastatic disease.
- 3.1.4 Patient must be evaluated by both the radiation oncologist and the urologist prior to entry and judged to be a suitable candidate for radiation and hormonal therapy.
- 3.1.5 Patient must have Karnofsky performance status ≥ 80 .
- 3.1.6 Patients must have a life expectancy in excess of 10 years.
- 3.1.7 Patients must have, within 6 weeks prior to entry, a Hgb of ≥ 10 gm, a WBC of ≥ 4000 cells/ml³, a platelet count of $\geq 100,000$ cells/ml³, a serum bilirubin \leq the institutional upper limit of normal, a serum SGOT (*or SGPT*) of ≤ 2.5 times the institutional upper limit of normal, and a serum creatinine of ≤ 2.0 times the institutional upper limit of normal.
- 3.1.8 A post-prostatectomy pelvic CT, within 16 weeks prior to randomization, must reveal no evidence of metastatic disease.
- 3.1.9 Patients must sign a study-specific informed consent form.
- 3.1.10 Patients with prior invasive cancers are eligible if disease free for at least 5 years; prior or concurrent basal or squamous cell skin cancer is eligible.

3.2 Conditions for Patient Ineligibility (9/8/98, 10/26/99)

- 3.2.1 Pathologic stage T2 (*without positive inked resection margin*) or less except as stated in Section 3.1.1.1.
- 3.2.2 Pathologic lymph node stage of pN1 or greater.
- 3.2.3 An entry serum PSA of > 4.0 ng/ml.
- 3.2.4 Patients with persistent urinary extravasation after prostatectomy.
- 3.2.5 Patients who have been previously treated with any hormonal therapy after prostatectomy.

- 3.2.6 Patients who have previously been treated with radiation therapy or biologic therapy for prostate cancer.
- 3.2.7 Karnofsky performance status < 80.
- 3.2.8 Treatment start > 4 weeks after randomization.
- 3.2.9 Prior chemotherapy for any reason.

4.0 PRE-TREATMENT EVALUATION (9/8/98, 10/26/99, 9/5/00)

- 4.1 History, physical examination (*to include digital evaluation for tumor of the prostatic fossa*) and Karnofsky Performance status. Documentation must include comorbidity and concurrent medications. Worksheets are provided in the Data Set.
- 4.2 Assessment of potency status prior to entry.
- 4.3 Histopathologic evaluation: Margin positive patients are those whose microscopic tumor extends to the ink margin and/or tissues submitted subsequent to the resection of suspicious tissues in the resection bed that contain microscopic tumor. Gleason scores must be provided.
- 4.4 Mandatory laboratory studies: CBC (*including differential and platelet count*), SGOT (*or SGPT*), bilirubin, creatinine, serum testosterone levels and a PSA mandatory in all patients. PSA must be obtained prior to surgery (*and prior to neoadjuvant hormone therapy, if given*), between 2 and 20 weeks post-surgery and at entry (*within 6 weeks prior to randomization*).
- 4.4.1 Acceptable Commercial PSA Assays
 - Hybritech
 - Abbott
 - Bayer (*Immuno-1 system*)
 - Tosoh Medics (*Tosoh AIA-Pack*)
 - DPC (*Immulite PSA*)
 - Roche Diagnostic (*Elecsys 2010 and Elecsys 1010*)
- 4.5 Radiographic studies: A pretreatment bone scan is mandatory. This can be within 16 weeks prior to entry.
- 4.6 The pre-entry pelvic CT scan is mandatory.

5.0 REGISTRATION PROCEDURES (9/5/00)

5.1 RTOG Institutions

- 5.1.1 **All institutional documentation listed in Appendix VIII must be on file at RTOG.**
- 5.1.2 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.

5.2 CTSU Investigators

- 5.2.1 CTSU Address and Contact Information
Patient Registration and Adverse Event Reporting:
 Phone – 1-888-462-3009
 Fax – 1-888-691-8039

All other questions (including forms-specific questions) should be communicated by phone or e-mail to: CTSU General Information line – 1-888-823-5923 or ctsucontact@westat.com. All calls will be triaged to the appropriate CTSU representative.

The CTSU website is located at: www.ctsu.org

To mail forms or data:
 CTSU Data Processing Manager
 CTSU Data Center
 WB 408
 1441 W. Montgomery Avenue
 Rockville, MD 20850-2062

- 5.2.2 Registration / Randomization, CTSU Investigators:

Prior to the recruitment of a patient for this study, investigators and their institutions must be registered members of the CTSU. Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol before they can enroll patients. **Patients can be registered only after pre-treatment evaluation (Section 4.0 of protocol) is completed, all pertinent documents listed in Appendix VIII are approved and on file at CTSU, and eligibility criteria are met.**

CTSU Procedures for Patient Enrollment: Contact the CTSU Patient Registration Office by calling 1-888-462-3009 to alert the CTSU Patient Registrar that an enrollment is forthcoming. To enroll the patient, the investigator should complete the following forms:

- CTSU Enrollment Coversheet
- CTSU version of RTOG-96-01 Eligibility Checklist

These forms should be faxed to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 8:00 am and 4:30 pm Eastern time. The CTSU registrar will check the investigator and site information provided to insure that all regulatory requirements have been met. The registrar will also check the forms for completeness and follow-up with the site to resolve any discrepancies. Once investigator and patient eligibility are confirmed, the CTSU will contact RTOG to register the patient. As this is a double-blinded study, a number code will be assigned at time of randomization. See Drug Distribution section of protocol for details. The CTSU will then contact the enrolling site and convey the patient ID number to be used on all future forms and correspondence. This will be confirmed by a RTOG-generated confirmation of registration (*RTOG A0 Form*) e-mail to the enrolling site, followed by the mailing of a data submission calendar and case-specific labels with the patient ID number.

6.0 RADIATION THERAPY

6.1 Physical Factors (9/8/98)

Megavoltage equipment is required with effective photon energies ≥ 10 MeV. Equipment with photon energies of 6 to up to 10 MeV is permitted unless the patient is large, i.e., the anterior/posterior separation is > 24 cm. Minimum source-to-axis distance is 100 cm. The treatment technique (*field arrangement*) will be by a 4 field (*anterior, posterior, right and left lateral*) coplanar technique with blocks designed for all fields to protect adequately uninvolved structures using at least 5 half-value layers of attenuating material. Focused block techniques should be used to minimize the penumbra around the photon field. The use of wedges and filters is encouraged to create a maximally homogeneous dose at depth.¹⁸

6.2 Treatment Volumes

6.2.1 Calculation of the Clinical Target Volumes (CTV) will primarily be based upon: (1) the histopathologic information of the prostate size and the tumor extent to specific inked boundaries of the surgical resection and (2) the imaging information available at the time of simulation which requires (a) 60cc of Cystocon dye introduced into an empty bladder followed by a retrograde urethrogram demonstrating the apex or beak of dye at the GU diaphragm and (b) barium contrast in the distal rectum with the location of the external end of the anal canal marked. Additional information which may be of secondary assistance are the preoperative TRUS and pelvic tomographic studies (*if available*), and the present TRUS and pelvic CT information. The CTV calculation will be based on the estimated location of the preoperative prostate tumor volume plus sites of microscopic tumor extension. The superior margin for the CTV will be, in patients judged to have a normal-size prostate prior to surgery (*i.e. then a prostatic urethral length of 4.0 cm*), 5.5 cm superior to the beak of the urethrogram. This is the sum of 4.0 cm (*the urethral length*) plus 1.0 cm (*the usual but not consistent distance between the beak and the inferior extent of the prostatic urethra*) plus 0.5 cm (*for possible superior extension of the capsule of the median lobe above the proximal prostatic urethra*). The anterior border of the CTV will be 3 cm posterior to the anterior tip of the symphysis. The posterior extent of the CTV will be at the anterior rectal wall. The original volume of seminal vesicles will not be considered target if they were not microscopically involved with tumor. If there was microscopic involvement of the seminal vesicles then the distal 1 1/2 cm of the seminal vesicles will be considered target.

6.2.2 Planning Target Volume Calculation The planning target volume (PTV) will add .5 cm circumferentially for day to day variation in set up and will add an additional 1.0 cm posteriorly and 0.5 cm superiorly for CTV motion associated with variability in rectal and bladder filling. The patients will be treated with an empty bladder.

6.2.3 Field Borders will add 1.5 cm outside the PTV. The individually shaped anterior, posterior, right and left lateral fields will have the following light-field borders when the patient is judged to have had a

normal sized prostate (*prostatic urethral length of 4.0 cm*) prior to surgery and have had no microscopic involvement of the seminal vesicals (*see Figures 1 and 2*).

Inferiorly a border that is 2.0 cm inferior to the apex or the beak of the contrast held under pressure in the penile urethra.

Superiorly 2.5 cm beyond the calculation of the original superior extent of the lateral lobes of the prostate (*or further superior if microscopic seminal vesical disease was identified*). This field should be, as a minimum 9.5 cm in the longitudinal (*cranial to caudal*) axis.

Posteriorly 2.5 cm posterior to the most anterior portion of the anterior rectal wall. Anteriorly 1.0 cm posterior to the anterior tip of the symphysis laterally.

Laterally the field should cover as a minimum the lateral margins of the obturator foramenae.

6.2.4 Films

Simulation films of each treatment field as well as portal films of each treatment field must be submitted to RTOG Headquarters for review.

6.3 Radiation Doses

Daily tumor doses will be 1.8 Gy given once a day five sessions a week. The prescribed doses are defined at the isocenter using a SAD technique. The prescribed dose to the isocenter will be 64.8 Gy given in 36 fractions of 1.8 Gy. The minimal dose to the CTV shall not be less than 95% of the prescribed dose; the maximum, not more than 105% of the prescribed dose.

6.4 Critical Normal Structures

6.4.1 The inferior portion of the bladder will receive the same dose as the clinical target volume.

6.4.2 Doses to the whole rectum should not exceed 55 Gy. Portions of the anterior wall will, by necessity, receive the same dose as the clinical target volume.

6.4.3 Doses to the femoral heads should not exceed 50 Gy.

6.5 Radiation Toxicity

6.5.1 All patients will be seen weekly by their radiation oncologist during radiation therapy. Any observations regarding radiation reactions will be recorded (*See Appendix IV for grading*) and should include attention toward the following potential side effects:

6.5.1.1 Small bowel or rectal irritation manifesting as abdominal cramping, diarrhea, rectal urgency or hemochezia.

6.5.1.2 Bladder complications including urinary frequency, dysuria, hematuria, urinary tract infection, and incontinence.

6.5.1.3 Impotence in previously potent patients.

6.5.1.4 Reaction within 90 days of treatment start will be scored using the RTOG Acute Radiation Morbidity Scoring Criteria. For reactions beyond 90 days, refer to the Late Radiation Morbidity Scoring Scheme.

6.6 Compliance Criteria

6.6.1 Field Borders

- Per protocol: 1 cm. beyond borders stated in the protocol
- Variation, acceptable: > 1 to 2 cm beyond borders as stated in protocol
- Deviation, unacceptable: > 2 cm beyond borders as stated in protocol

6.6.2 Dose

- Per protocol: ≤ 5% of protocol specified dose
- Variation, acceptable: > 5 to 10% of protocol specified dose
- Deviation, unacceptable: > 10% of protocol specified dose

6.6.3 Minimum and Maximum Allowances

- Per protocol: 95% isodose coverage
- Variation, acceptable: < 95 to 90% isodose coverage
- Deviation, unacceptable: < 90% isodose coverage
- Per protocol maximum 105%
- Variation, acceptable: > 105 to 110%
- Deviation, unacceptable: > 110%

6.6.4 Fractionation

- Will be directed by dose score

6.6.5 Elapsed Days

- Per protocol: 1 to 7 break days
- Variation, acceptable: 8 to 14 days
- Deviation, unacceptable: > 14 days

7.0 DRUG THERAPY

7.1 Casodex (IND# 54,972)

7.1.1 Drug Administration

Double-blinded, randomized therapy is to be administered in tablet form as a once-daily oral dose. Subjects will receive either one Casodex 150 mg tablet or one look-alike placebo tablet daily for two years beginning immediately upon, or just prior to, the initiation of irradiation.

Patients will be instructed to take their one tablet once daily (*e.g., in the morning*) and to record it on their pill diary. They must return the remaining tablets, pill bottle and pill diary at each visit to assess drug compliance and ensure drug accountability. The bottles of Casodex and placebo will be equipped with two-part label whose tear-off portion must be affixed to the patient's drug accountability forms each time a new bottle is dispensed.

7.1.2 Description

Casodex (*bicalutamide*) is a new, nonsteroidal antiandrogen which has no androgenic or progestational properties. The chemical name is Propanamide, N-[4-cyano-3(trifluoromethyl)phenyl]- 3- [(4-fluorophenyl)sulphonyl]- 2- hydroxy- 2- methyl, (+,-). Casodex is a racemic mixture with the antiandrogen activity residing exclusively in the (-) or (*R*) enantiomer. Casodex 50 mg has the status of an approved new drug, 150 mg is experimental. Casodex has a long half-life compatible with once-daily dosing. Casodex is well tolerated and has good response rates in phase II trials (*Kennealey and Furr, 1991, Tyrrell 1994*). As a single agent, Casodex at the dose of 50 mg was inferior to castration with regards to survival (*Bales and Chodak 1996*). Dose ranging studies with PSA decrease at 3 months as surrogate end point lead to the evaluation of the 150 mg dose as single agent therapy versus castration in trials enrolling 1453 patients. In patients with metastatic disease (*M1*), Casodex 150 mg monotherapy was inferior to castration in terms of time to progression and survival. In patients with a lower tumor burden, *i.e.*, with non-metastatic (*M0*), locally advanced (*T3/T4*) prostate cancer, Casodex 150 mg monotherapy showed no difference to castration in terms of survival, although these data are immature with only 15% of patients having died. (*Tyrell et al. ASCO 1996 abstr 411*). A quality of life analysis showed a significant difference in sexual interest in favor of Casodex 150 mg over castration. In trials where Casodex is evaluated as adjuvant therapy, 150 mg monotherapy is compared to placebo in patients with early stage, *i.e.*, non-metastatic, prostate cancer.

7.1.3 Formulation, Packaging, and Storage

Casodex will be supplied as white tablets containing 150 mg of micronized drug (*F11156*). Subjects randomized to placebo will receive matched placebo tablets (*F11192*). Casodex and placebo will be provided in bottles of 100 tablets. Supplies will be dispensed at the 3-month visits.

All packages of Casodex and placebo should be stored securely in a dry place at room temperature between 68°-77°F.

7.1.4 Supply and Distribution (9/8/98, 9/5/00)

7.1.4.1 Casodex and placebo for this trial will be provided by Astra Zeneca. The distribution of the drug and the placebo will be by RTOG through McKesson BioServices (*MBS*). See Appendix IX.

7.1.4.2 Each institution must submit a Pharmacy Registration Form (*Appendix X*) to RTOG Headquarters.

7.1.4.3 Casodex/placebo will be shipped by second day delivery for each patient randomization.

7.1.4.4 Bottles will be numbered with the patient-specific double-blinded number assigned at randomization. A prescription with the drug identification number, the RTOG case number, and the amount of drug to be taken during the interval between visits will be written by the investigator for each patient. A new prescription must be provided for each new supply of study drug. Additional supplies will be requested directly from MBS. Requests should be made 4 to 6 weeks in advance to ensure prompt delivery. MBS will include a reorder form with the initial shipment.

7.1.4.5 Each bottle will include the protocol number, drug assignment number, packaging lot number, storage requirements and all necessary information required by Federal Regulations. Dose administration information will also be provided on the labeling.

7.1.4.6 Two part labels will be computer generated for this double-blinded study. One part of the label will be attached to the container; the other part will be tear-off portion bearing the patient number and treatment information. This tear-off label will be removed at the time of dispensing and attached to the prescription slip.

7.1.4.7 All tablets returned by the patient will be counted and that number will be subtracted from the number dispensed. The difference will determine the number of pills taken by the patient and will be recorded in the patient record and will be reported on the followup case report forms. Protocol compliance will be measured by pill count and pill diaries.

7.1.4.8 Drug Distribution, CTSU Investigators:

Casodex and placebo for this trial will be provided by Astra Zeneca. The distribution of the drug and the placebo will be by RTOG through McKesson BioServices (MBS). Casodex/placebo will be shipped by second day delivery for each patient randomization.

Each institution must submit a Pharmacy Registration Form (*Appendix X*) and the additional paperwork outlined in Appendix VIII to the CTSU before they can enroll a patient on this study. Study drugs are to be prescribed only by the CTSU investigator(s) listed on the FDA form 1572. The investigator must maintain accurate records accounting for the receipt and disposition of both Casodex and placebo. All unused product will be returned to MBS. See Section 7.1 and Appendix IX and X of the protocol for complete details regarding drug supply, administration, and accountability.

7.1.5 Drug Accountability

The study drugs are to be prescribed only by the RTOG investigator(s) listed on the FDA form 1572. The investigator must maintain accurate records accounting for the receipt and disposition of both Casodex and placebo. All unused product will be returned to MBS.

7.1.6 Dose Modification Schedule

Casodex or placebo should be discontinued in instances of chemical liver toxicity. SGOT (*or SGPT*) and bilirubin will be measured pretreatment, at 3 weeks after the start of radiation, at the completion of radiation, then every 3 months at followup. If the bilirubin rises > 1.5 x the institutional upper limit of normal or if the SGOT (*or SGPT*) rises > 2.5 x the institutional upper limit of normal the Casodex or placebo may be stopped at the investigator's discretion. Casodex/placebo can be restarted when the bilirubin and SGOT are within normal range.

7.1.7 Toxicity

In animal experiments, birth defects (*abnormal genitalia, hypospadias*) were found in male offspring from female animals dosed with Casodex during pregnancy. Although offspring from male animals dosed with Casodex did not show any birth defects, patients enrolled in this trial are advised to neither cause pregnancy nor to donate sperm while receiving trial therapy or during the first 3 months after cessation of therapy. The use of barrier contraceptives is therefore advised.

The most frequent adverse events reported among subjects receiving bicalutamide therapy are the pharmacological effects of breast tenderness, breast swelling, and hot flashes.

Adverse events not directly related to the pharmacological properties of bicalutamide were infrequent. Nonpharmacological adverse events, reported in the trial using bicalutamide 50 mg as monotherapy include asthenia, pelvic pain, peripheral edema, pruritus, rash, constipation, impotence, dyspnea, nausea, and pain (*Kaisary 1994; data on file*). There has been no observed change in cardiac parameters during long-term administration of bicalutamide 50 mg daily (*data on file*).

When bicalutamide 50 mg was given in combination with an LHRH analogue, the LHRH analogue adverse event profile predominated with a high incidence of hot flashes (49%) and relatively low incidences of gynecomastia (4.7%) and breast pain (3.2%), the associated pharmacological effects of bicalutamide monotherapy (*Schellhammer et al. 1995*).

Extensive experience with the monotherapy dose of 150 mg has been generated. As of August 1994, over 1200 subjects with advanced prostate cancer have received 150 mg bicalutamide monotherapy. More than 200 subjects received bicalutamide for periods of 18 to 24 months. The total subject exposure to bicalutamide 150 mg monotherapy is in excess of 1000 subject years. In the comparative monotherapy prostate cancer trials at a dose of 150 mg, 5.2% of subjects were withdrawn from therapy because of adverse events; only 2.9% of subjects were withdrawn because of adverse events that were considered to be treatment related by the investigator. The principal adverse events seen with bicalutamide at a dose of 150 mg include gynecomastia, breast pain, and hot flashes, though these rarely led to withdrawal from therapy in both treatment groups. Approximately 2% of the subjects had constipation, diarrhea, or nausea that was considered to be bicalutamide related versus approximately 1% for subjects treated with castration. These events very rarely led to withdrawal (< 0.5%). The most frequently reported adverse events in subjects taking bicalutamide 150 mg from the two comparative trials (*up to September 1993*) are presented below.

Number of subjects (%) with adverse events occurring with an incidence of 5% or more, regardless of causality, during bicalutamide 150 mg monotherapy

Adverse event	Bicalutamide 150 mg (n = 851)	Castration (n = 341)
Breast pain	268 (32.0)	3 (0.7)
Gynecomastia	220 (26.0)	8 (1.9)
Hot flashes	78 (9.2)	165 (39.0)
Asthenia	63 (7.4)	13 (3.1)
Pain	60 (7.1)	30 (7.1)
Constipation	58 (6.8)	26 (6.2)
Worsening of pre-existing condition	55 (6.5)	30 (7.1)
Back pain	53 (6.2)	28 (6.6)

NB: Individual subjects may have more than one adverse event.

Bicalutamide 150 mg has been associated with changes in liver function, though these are infrequent (< 2%). Many of these changes improved or resolved despite continuation of bicalutamide therapy. A small number of cases of jaundice have been seen for which bicalutamide-induced hepatotoxicity cannot be excluded. One subject treated with 150 mg bicalutamide died of prostate cancer, however, the investigator considered chronic renal failure and jaundice (*of unknown etiology*) to be contributing factors to the subject's death. The clinical trials comprising the proposed clinical trial program will ensure that subjects with serious abnormal liver function (*ie, > 2.5 x upper limit of normal [ULN]*) will not be entered, and liver function tests will be carried out on all randomized subjects, while receiving therapy.

7.1.8 Drug Termination

Once patient has permanently discontinued protocol drug therapy for any reason, the institution must notify MBS to stop future shipments. All unused product will be returned to MBS.

7.2 RTOG Adverse Event Reporting (fax #215/928-0153)

7.2.1 The following guidelines for reporting adverse drug reactions (*ADRs*) apply to any research protocol which uses commercial anticancer agents. The following *ADRs* experienced by patients accrued to these protocols and attributed to the agent(s) should be reported to RTOG within 10 working days:

7.2.1.1 Any *ADR* which is both serious (*life threatening, fatal*) and unexpected.

7.2.1.2 Any increased incidence of a known *ADR* which has been reported in the package insert or the literature.

7.2.1.3 Any death on study if clearly related to the commercial agent(s).

7.2.1.4 Acute myeloid leukemia (*AML*). The report must include the time from original diagnosis to development of *AML*, characterization such as FAB subtype, cytogenetics, etc. and protocol identification.

7.2.2 The *ADR* report should be documented on Form FDA 3500 (*Appendix V*) and mailed to the address on the form, to RTOG Headquarters and to:

Investigational Drug Branch
P.O. Box 30012
Bethesda, MD 20824
Telephone (301) 230-2330
available 24 hours
fax 301-230-0159

7.2.3 Additional Reporting Requirements Specific to this Study

- All grade ≥ 4 Adverse Events will be reported to RTOG Headquarters by telephone within 24 hours of the institution being informed of the event. An adverse event is any noxious, pathologic, or unintended change from patient's baseline status that is an anatomic, physiologic, or metabolic function as indicated by physical signs, symptoms, and/or laboratory changes (*excluding therapeutic failure*) and includes, but is not limited to, all adverse events causing disability or requiring hospitalization.

- All other adverse events not meeting the above criteria for phone reporting must be reported on Data Forms and submitted to RTOG Headquarters.
- Any death, regardless of cause, while the patient is receiving protocol treatment or occurring within 30 days of completion of treatment must be reported to RTOG Headquarters by telephone (215/574-3214) within 24 hours of the institution's being informed of this.

7.3 CTSU Investigators Adverse Event (AE) Reporting: (9/5/00)

This study will utilize the CTC version 2.x for toxicity and Adverse Event (AE) reporting. A hyperlink to the CTEP home page that contains CTC information is available on the CTSU website. CTSU investigators are responsible for reporting adverse events according to the RTOG guidelines, including notification of their local IRB. All reporting should be conducted within the timeframes specified in the protocol and completed forms and reports should be faxed to the CTSU Data Center. The CTSU will review the documents to ensure that all necessary information is included and will forward these to RTOG. RTOG will then distribute the documents internally and to the appropriate regulatory agencies.

For those AE's requiring **24-hour phone notification**, the CTSU investigator is responsible for reporting the event within 24 hours to the following persons/agencies:

- CTSU Data Center at 1-888-462-3009
- NCI Investigational Drug Branch at 301-230-2330 (*if NCI 24-hour notification is indicated in AE section of protocol*)
- RTOG Primary Study Chairman (*see cover page of protocol*)

7.4 Code Breaks

The actual treatment assignment would be available only if an emergency situation arises that in the opinion of the investigator or patient's attending physician, requires the knowledge of the code. The investigator must contact McKesson BioServices at (800) 861-1627 to make this request. The date and reason(s) for breaking the code must be submitted to RTOG by the investigator within 48 hours. See Section 9.2.

8.0 SURGERY

- 8.1** There is no planned surgery for any non progressing patients.
- 8.2** Unplanned surgery for bladder neck stricture: Because these patients are at a 5% to 20% risk of developing a bladder neck stricture following radical prostatectomy, this possibility should be continually monitored by clinicians if their patients develop progressive urinary frequency during radiation therapy. This can be well corrected by minimally invasive procedures with a minimal, if any, radiation treatment break, although it would be better to anticipate this problem, if possible, and to correct prior to starting protocol therapy.
- 8.3** As is outlined in the treatment algorithm in Section 9.1 for patients developing a PSA progression, prostate bed/vesical-urethral anastomotic re-biopsy may be indicated. This will be done using conventional TRUS-guided biopsy procedures.
- 8.4** For PSA progression in some special categories (*see Section 9.0*), castration by orchiectomy (*or by LHRH analog*) will be recommended.

9.0 OTHER TREATMENT

9.1 At the Time of Subsequent PSA Progression

If the patient is found to have subsequent PSA progression (*a PSA increase of greater than 0.5 ng/ml at 6 or more months after entry; see Section 11.3*), the patient will be evaluated by bone scan. If metastases are demonstrated, the patient will be recommended to have maximum androgen blockade. Maximum androgen blockade will be the combination therapy of castration (*either orchiectomy or LHRH analogs*) plus anti-androgen (*either Casodex 50 mg t.i.d., or Eulexin 250 mg t.i.d.*) is recommended. If no metastases are found on bone scan the patient will be observed. If another PSA increase of 0.5 or greater is subsequently detected, the patient will first undergo an abdominal and pelvic CT scan. If there is evidence of metastatic disease in the lymph nodes, he will be recommended to have maximum androgen blockade. If there are no metastases found on CT scan, he will undergo a TRUS-guided rebiopsy of his anastomosis. If the biopsy documents histologic tumor persistence, the patient will be recommended to have maximum androgen blockade. If neither of these evaluations detect disease, the patient will be observed. If during observation

the patient subsequently develops a PSA of greater than 4.0, ng/ml, then he will be recommended to undergo maximum androgen blockade. If in the above algorithm the patient is recommended to have maximum androgen blockade, and the progression has occurred while the patient is on study medication, the following steps are suggested to prevent a patient, who may have an altered androgen receptor, from being at increased risk if he is maintained on antiandrogen therapy. The patient should stop the study medication and have his PSA assessed 6 weeks later. If the PSA decreases, no therapy need be instituted until there is another PSA rise. At that point orchectomy or an LHRH antagonist is recommended. If the PSA remains stable or increases, maximum androgen blockade should be employed.

The above is an algorithm for evaluation of a patient with PSA progression. The therapeutic interventions are suggested for the participating clinicians but the use of maximal androgen blockade as described is not binding. The individual practitioners have the ultimate choice of therapy for their patient should PSA progression or clinical relapse without PSA progression develop.

9.2 Unblinding

- 9.2.1** If it is the investigator's opinion that a relevant medical decision is totally dependent upon knowledge of the randomized therapy, for example, in case of a serious or life-threatening adverse event that is considered to be associated with the use of the trial drug, the blind can be broken. The investigator must contact McKesson BioServices at (800) 861-1627 to make this request. It is anticipated that this will happen only in rare instances. The date and reason(s) for breaking the code must be submitted to RTOG within 48 hours. See Section 7.4.
- 9.2.2** Completion of the 2-year treatment period, progression of disease, or adverse events less severe than described above are not reasons for breaking the blind. It is considered that in this population of subjects the necessity to break the code in the above way will be a rare event, since the subsequent choice of therapy following progression can be made without knowledge of the randomized therapy.
- 9.2.3** Subjects and investigators will be unaware of the actual randomized assignment.

10.0 PATHOLOGY (9/5/00)

- 10.1** Central pathology review will be done on the original radical prostatectomy specimen and on any TRUS-guided rebiopsy materials. Previous central pathology reviews have demonstrated a 34% discrepancy in histologic grading with the institutional pathologists.
- 10.2** A representative hematoxylin and eosin (H&E) stained slide and a representative tissue block of tumor from the prostatectomy specimen, the pathology report and a Pathology Submission Form will be submitted to the RTOG Tissue Bank:

**LDS Hospital
Dept. of Pathology
E.M. Laboratory
8th Ave & C Street
Salt Lake City, UT 84143
(801) 408-5626
FAX (801) 408-5020
Ldafurne@ihc.com**

- 10.2.1** To encourage compliance, your Pathology Department could be reimbursed for obtaining blocks or cutting slides.
- 10.2.2** 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*).
- 10.2.3** H & E stained slide(s) and block (s) will be retained for the special studies outlined below.
- 10.2.4** If a block will not be released, submission of 10-15 unstained sections and mounted on sialinized (*or other "sticky slides"*) may be substituted.
- 10.3** All tumor will be graded according to Gleason (*see Appendix VI*).
- 10.4** DNA content and proliferation rate may be assessed in selected cases by image analysis (*Feulgen staining*) and immunocytochemistry (*MIB-1 antibody*).
- 10.5** The tumor in the radical prostatectomy specimen of patients randomized to receive Casodex will be evaluated for expression of the bcl-2 proto-oncogene by immunohistochemistry. Over expression of bcl-2 has been found to correlate with hormone resistance.^{19,20} In this study, the potential value of bcl-2 as a predictor of hormone resistance will be studied.
- 10.6** Post-treatment biopsies will be assessed for the presence of tumor.
- 10.6.1** All positive biopsies will be histologically graded according to Gleason and the degree of therapy effect in the tumor cells will be graded according to Dhom and Degro.²¹

10.6.2 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.^{22,23}

10.7 CTSU Investigators:

All pathology materials and associated forms and reports are to be submitted directly to the RTOG Tissue Bank at LDS Hospital within two weeks of randomization. Refer to Sections 10.1 and 10.2 above for further details on collection and submission.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (9/5/00)

Parameter	Pretreatment	At end of XRT	Follow-up (per Sec. 12.1)
History and Physical ^d	X	X	X
Karnofsky Status	X	X	X
PSA	X	X	X
SGOT (or SGPT), Bilirubin	X	X ^a	X ^a
Serum Testosterone	X		
CBC	X	X	X
Sexual function status	X	X	X
Bladder function status	X	X	X
Bone scan	X		X ^b
Pelvic CT scan	X		X ^b
Creatinine	X		
TRUS-guided biopsy			X ^c

- a. Three weeks after beginning XRT, at the completion of XRT, then every 3 months during followup (Section 7.1.6).
- b. As clinically indicated, and at 30 months after study entry.
- c. See Section 9.1.
- d. Must include comorbidity information and concurrent medications. Worksheets are included with the Data Forms Set.

11.2 Follow up Schedule

11.2.1 Patients should be evaluated one month following completion of the radiation therapy. The patients will thereafter be seen every 3 months for two years. The investigator or designee will see the patient prior to prescribing new drug supplies in order to evaluate the patient side effects, compliance and continuation of drug. Then, until month 60 the patients will be seen at 6 month intervals. Then, after month 60 the patients will be seen at 12 month intervals for the remainder of the patient's life.

11.2.2 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. A bone scan should be done 30 months after entry (6 months after termination of adjuvant treatment) as a new baseline.

11.2.3 The patient will be asked whether he is able to achieve an erection and if he is able to have sexual relations. This assessment and that of bladder function must be done prior to the start of radiation therapy and at the end of treatment and at each follow up visit.

11.3 Measurement of Response and Freedom from Progression (10/26/99)

11.3.1 The patient on entry will have no clinical evidence of disease by physical exam or by imaging studies. A positive ProstaScint scan alone without a confirmatory biopsy must not be used to exclude a patient. The evaluation of response to treatment then will only be a biochemical one based on his serial PSA levels which should be measured by the same assay and preferably at the same lab.

11.3.2 A complete response or full biochemical remission will be defined as reaching a PSA nadir of less than detectable by institutional assay, or less than 0.3 ng/ml for those laboratories specifying PSAs below that level.

11.3.3 Time to PSA Progression

PSA progression will be defined as an increase in PSA of 0.5 or more above a nadir reached at any time following treatment or an increase in PSA of 0.5 or more in patients compared to entry PSA in patients who have no decrease in PSA following treatment. This is synonymous with the time to second PSA

failure. However, time to second PSA failure will not be evaluated between treatment groups before all evaluated patients have been followed at least 30 months after entry.

11.3.4 **Time to Local Progression**

Time to local progression will be measured from the date of randomization to the date of documented local progression as determined by clinical exam.

11.3.5 **Time to Distant Failure**

The time to distant failure will be measured from the date of randomization to the date of documented metastatic disease.

11.3.6 **Time to Clinical Progression**

11.3.6.1 The time to clinical progression will be measured from the date of randomization to the date of documented local progression or distant failure.

11.3.6.2 Any of the following will be sufficient evidence for clinical progression of disease:

- a) evidence of objective progression, eg, by bone scan, computer tomography (*CT*) scan, magnetic resonance imaging (*MRI*), biopsy, etc.
- b) local or symptomatic progression:
 - the development of a palpable mass in the prostatic fossa that on biopsy is positive for prostate cancer.
 - ureteric obstruction either by primary tumor or pelvic nodal disease.
 - lymphedema of lower extremities due to pelvic nodal involvement.
 - recurrent vesical obstruction, bleeding or pain due to growth of primary tumor (*not due to radiation therapy*).

NB: if these symptoms are reported, assessments as in Item (*a*) should be made to seek confirmation of objective progression

11.3.6.3 **Time to Second PSA Progression**

This will be measured from the date of randomization to the date of a rise in the PSA of 0.5 ng/ml or more above the nadir PSA reached after Arm 1 or Arm 2 treatment , or in patients whose PSA nadir is in the undetectable range, the date of developing a PSA of 0.5 ng/ml or greater.

Changes in serum PSA alone are not considered evidence of objective progression. Subject with rises in PSA may be treated according to the algorithm in Section 9.1 or at the discretion of the investigator. When additional treatment is considered, combination therapy of castration (*either orchiectomy or LHRH analogues*) plus antiandrogen (*either bicalutamide 50 mg [after approval] or flutamide 250 mg tid*) is recommended. Subjects will be followed up until the first date of clinical progression is documented and subsequently will be monitored for survival.

11.3.7 **Time to Third PSA Progression**

This will be measured from the date of randomization to the date of a rise in PSA of 0.5 ng/ml or more above the nadir PSA reached for patients placed on maximum androgen blockade following PSA progression as indicated in Section 11.3.3 and as outlined in Section 9.0.

11.3.8 **Survival**

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

11.3.9 **Disease Specific Survival**

The following will be considered as endpoints in assessing disease specific survival (*DSS*) , i.e., events:

- Death certified as due to prostatic cancer.
- Death from other causes with active prostate cancer (*clinical or biochemical progression while on androgen suppression therapy*).
- Death due to complications of treatment, irrespective of the status of malignancy.
- Death from other causes with previously documented relapse (*either clinical or biochemical*) but inactive at the time of death, will not be considered in disease-specific survival but will be analyzed separately.

12.0 DATA COLLECTION

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

12.1 Data Submission Summary

<u>Item</u>	<u>Date Due</u>
Demographic Form (A5)	Within 2 weeks of randomization
On Study Form (I1)	
Diagnostic Pathology Report (P1)	
Pathology Slides/Blocks (P2)	
Surgical Operative Report (S2)	
Surgical Pathology Report (S5)	
<u>Preliminary Dosimetry Information:</u>	Within 1 week of start of RT
RT Prescription (<i>Protocol Treatment Form</i>) (T2)	
Films (<i>simulation and portal</i>) (T3)	
Calculations (T4)	
Radiotherapy Form (T1)	Within 1 week of RT end
<u>Final Dosimetry Information:</u>	
Daily Treatment Record (T5)	
Isodose Distribution (T6)	
Boost Films (<i>simulation and portal</i>) (T8)	
Drug Flowsheet (M1)	As needed (<i>see F1, Q7</i>)
Follow-up Form (F1)	At one month after completion of radiotherapy, then every 3 mos during years 1 and 2 , every 6 mos during years 3-5, then annually. Also at progression/relapse and at death.
Pill Diary (DP)	With each F1 as long as patient is on drug.
Autopsy Report (D3)	As applicable

12.2 Data Submission, CTSU Investigators (9/5/00)

Data Forms: All data forms for this study are available for download from the CTSU website. CTSU investigators should use the protocol-specific RTOG forms and adhere to the RTOG schedule for data submission. A CTSU Data Transmittal Form should accompany all forms and reports submitted to the CTSU.

Patient registration forms should be faxed to the CTSU. Pathology materials, forms and reports should be sent directly to the RTOG Tissue Bank at LDS Hospital (*see Section 10.0 of protocol*). Dosimetry forms, with the exception of the Radiotherapy Form (T1), should be sent to the RTOG Dosimetry Department. All other forms must be mailed directly to the CTSU. The CTSU will forward all information to the RTOG.

Mail forms or data to:

**CTSU Data Processing Manager
CTSU Data Center
WB 408
1441 W. Montgomery Avenue
Rockville, MD 20850-2062**

12.3 Radiation Therapy Documentation Submission, CTSU Investigators (9/5/00)

Radiation therapy data (*preliminary dosimetry information and final dosimetry information*) are to be submitted directly to the Dosimetry Department, RTOG, at the address listed in Section 12.0 of the protocol. Please note that there are two separate intervals for submission: preliminary data (T2, T3, T4)

within 1 week of start of RT and final data (*T5, T6, T8*) within 1 week of completion of RT. See Section 12.1 of the protocol for a complete inventory of dosimetry items to be submitted. No dosimetry items should be sent to the CTSU other than the Radiotherapy Form (*TI*). Any dosimetry questions should be directed to the Dosimetry Department at RTOG headquarters (*215*) 574-3219.

13.0 STATISTICAL CONSIDERATIONS

13.1 Endpoints

- 13.1.1 Overall Survival (*Failure: death from any cause*)
- 13.1.2 Disease-Specific Survival (*Failure defined in Section 11.3.9*)
- 13.1.3 Time to second PSA failure (*Defined in Section 11.3.3*)
- 13.1.4 Time to Third PSA failure (*Defined in Section 11.3.7*)
- 13.1.5 PSA Complete Response (*Defined in Section 11.3.2*)
- 13.1.6 Time to Distant Failure (*Failure: first appearance of distant metastasis*)
- 13.1.7 Toxicity

13.2 Overview

The trial is designed to test the addition of Casodex to radiation therapy alone. Patients will be randomized 1:1 between adjuvant Casodex for 2 years or placebo for 2 years. The primary endpoint to test for efficacy is overall survival. In addition, disease specific survival and time to third PSA failure will be used as secondary endpoints for efficacy evaluation. In addition, time to second PSA progression or to clinical relapse without PSA progression will be evaluated. It is this event that will trigger, in both Arms, the recommendation to begin maximal androgen blockade.

13.3 Sample Size

For planning purposes, the median survival for the radiation therapy alone arm is assumed to be 11.0 years and the survivals for both arms are assumed to be exponentially distributed. It is projected that the addition of Casodex will reduce the yearly death rate by at least 28.5% from .063 to .045. Patients will enter the study uniformly over three years with four additional years follow up. For significance level of .05, statistical power of .80, and a two-sided test, a total of 1110 patients will be required.²⁵ Guarding against an ineligibility/unevaluability (*no data*) rate up to 10%, **a total of 1220 patients will be entered.**

13.4 Inclusion of Women and Minorities

In conformance with the National Institute of Health (*NIH*) 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. Analysis of three prior RTOG studies failed to show a significant difference.²⁶ Based upon prior RTOG studies, the protocol population is projected to 12% black and 88% white/other. If 88% of patients recruited in this study are white/other, the statistical power to detect a reduction in yearly death rate of 28.5%, 33%, and 50% are respectively .67, .81, and .99. If 12% of patients recruited in this study are black, the statistical power to detect a reduction in yearly death rate of 28.5%, 33%, and 50% are respectively .14, .18, and .38. Rate of minority accrual are estimated below:

Planned Gender and Minority Inclusion:

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown	Total
Female							
Male	1	6	180	40	961	12	1200
Total	1	6	180	40	961	12	1200

13.5 Accrual for the Study

It is anticipated that this study will be done as an Intergroup Study with a projected accrual rate of approximately 400 patients per year. If the average yearly accrual falls below 200 cases after 18 months, the feasibility of continuing it will be discussed at the RTOG Data Monitoring Committee (*DMC*).

13.6 Randomization (10/26/99, 9/5/00)

The treatment allocation scheme described by Zelen will be used because it balances patient factors other than institution.²⁷ The stratifying variables are:

1. Neoadjuvant hormone therapy (*Yes vs. No*);
2. Positive surgical (*inked*) margins (*Yes vs. No*);
3. PSA nadir after surgery of less than 0.5 ng/ml (*Yes vs. No*);
4. Entry PSA level (*0.2 to 1.5 ng/ml vs. 1.6 to 4.0 ng/ml*)

13.7 Analyses plan

13.7.1 Methods for Estimation and Testing

Gelman et al. and Gaynor et al.²⁹ pointed out in their respective papers that the Kaplan Meier methods tend to overestimate the cause specific survival, time to third PSA failure, and time to distant metastases. So the cumulative incidence approach will be used to estimate them as a function of time because this approach specifically accounts for competing risks such as dying without a recurrence from the prostate cancer.³⁰ Their distributions between the two arms will be compared a method especially developed for the task by Gray.³¹ Overall survival will be estimated by the usual Kaplan-Meier method³² and the survivals between the two arms will be compared with log rank test.³³

13.7.2 Interim Analyses to Monitor the Study Progress

Interim reports with statistical analyses will be prepared twice a year until the initial paper reporting the treatment results has been submitted. In general, the interim reports will contain information about the patient accrual rate with a projected completion date for the accrual phase, data quality, compliance rate of treatment delivery with the distributions of important prognostic baseline variables and the frequencies and severity of the toxicities by treatment arm. The interim reports will not contain the results from the treatment comparisons with respect to the efficacy endpoints, such as overall survival. These endpoints will be reported in a blinded fashion only to the RTOG DMC until all the required patients have been entered on-study and completed their assigned protocol treatment. It is anticipated that Astra Zeneca will request RTOG to make available to them information on the results of time to clinical progression in all patients at the time of the first interim analysis of efficacy. Astra Zeneca proposes to only use this data as part of a meta-analysis with other Astra Zeneca trials and that these results will be kept confidential (*known only to themselves, the FDA and the DMC of the RTOG*). The DMC of the RTOG have recommended going ahead with the trial, although they have not now agreed to Astra Zeneca's request for a release of data in the future. However, they have invited a subsequent request from Astra Zeneca for release of data when the recruitment of patients is completed and with the understanding there would be no public release of the data and that the DMC would consider the request at that time.

13.7.3 Significance Testing for Early Termination (9/8/98)

Three interim significance testings of treatment difference are planned. The first two interim analyses will be performed for the first RTOG semi-annual meeting after 50% and 100% of the target sample size has been accrued. The third one will be performed for the first RTOG semi-annual meeting two years after the last patient has been randomized. The results will be reported to RTOG DMC with the treatment blinded.

The significance level for each interim analysis will be calculated using the O'Brien-Fleming alpha spending function. The maximum number of deaths required for the study is 289. Under the alternative hypothesis given in Section 13.3, the projected numbers of deaths at the time of these three interim analyses are 23, 86 and 191, respectively. Thus, the corresponding nominal significance levels are < .0001, .0001, and .0126. It must be noted that the nominal significance level will be recalculated at time of interim analysis based on the observed number of deaths. If the difference is significant at level specified, the study statistician will recommend to the RTOG DMC that the randomization be discontinued (*if applicable*) and the study be immediately written up for publication.

13.7.4 Analysis for Reporting the Initial Treatment Results (9/8/98)

This major analysis will occur after each patient has been potentially followed for a minimum of four years unless the study is stopped earlier. It will include tabulation of all cases entered, and those excluded from the analyses with the reasons, the distribution of the important prognostic baseline variables, and observed results with respect to the endpoints mentioned in Section 13.1. The primary hypothesis for the study is whether the control and the experimental arms have different effects on overall survival. All eligible patients randomized will be included in the comparison. All eligible patients randomized will be grouped by assigned treatment arm in the analysis. The significance level of 0.046 will be used in this analysis to preserve an overall significance level of .05 for the study. The primary hypothesis of treatment benefit will be tested using the Cox proportional hazard model with the four stratification factors included as fixed covariates.³⁴ Additional analyses of treatment effect will

include modifying factors such as age, race, and other patient characteristics. These analyses will also use the Cox proportional hazard model. The treatment comparison on disease specific survival, time to third PSA failure, and time to distant metastases will be analyzed in a similar fashion. The treatment comparison on the patterns of treatment failures and of 3+ grade toxicity will use the z-statistic for testing binomial proportions.

In conformance with the National Institute of Health (*NIH*) Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, the treatment comparisons will be done for overall survival within each race.

13.8 Sample Size (9/5/00)

From March 1998 to November 1999, the study accrued at a slower pace than expected with only 125 cases entered to the study. With the goal of 1220 cases unlikely to be reached within originally projected three years (*i.e., more than 1000 cases in the next 18 months*), it is necessary for us to make some adjustment to the study design without compromising the study objectives.

The original design called for a two-sided test with a significance level of 0.05. However, a recent European study suggested the Casodex was as effective as castration for M0 prostate cancer patients in survival.^{36,37} Therefore, the primary question of this study is whether the addition of Casodex improves survival. This can be answered by a one-sided hypothesis test using a significance level of 0.05. Without changing other assumptions in the hypothesized hazard ratio and median survival for the control arm, a total of 230 deaths are required in order to have a statistical power of 80%.

As of 11/30/99, the overall average accrual was 6.7 cases per month. However, since the last protocol amendment (*10/18/99*), the average accrual has been increased to 13.5 cases per month. At this rate, we expect to accrue 160 cases per year in the years to come. To meet the above assumptions, a total of 725 evaluable patients are required to be entered within six years (*i.e., to accrue for another 4.5 years*) and will be followed for additional four years. Considering 10% ineligible or loss-of-data cases, **a total of 810 men are required.**

13.9 Significance Testing for Early Termination (9/5/00)

Three interim significance tests of treatment difference are planned. They will be carried out when 46, 110 and 174 deaths are observed. Thus, the corresponding nominal significance levels are .0001, .005, .023, respectively. The first and second interim analyses are projected to be carried out for the first RTOG meeting after 60% and 100% of total accrual has been reached. The third interim analysis is projected to be carried out for the first RTOG meeting two years after the closure of the study accrual.

13.10 Analysis for Reporting the Initial Treatment Results (9/5/00)

The one-sided significance level of 0.042 will be used in the analysis of testing the primary hypothesis.

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* added 9/5/00

APPENDIX I

RTOG 96-01

A PHASE III TRIAL OF RADIATION THERAPY WITH OR WITHOUT CASODEX IN PATIENTS WITH PSA ELEVATION FOLLOWING RADICAL PROSTATECTOMY FOR pT₃N₀ CARCINOMA 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 have an opportunity to decide whether or not to undergo the procedure after knowing the risks, benefits, and alternatives involved. This disclosure 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 early evidence of persistent prostate cancer, because of the detectable PSA blood study, following my radical surgery. My doctors judge that the prostate cancer cells persist near the site of my surgery. Radiation therapy to this area is now indicated as an appropriate treatment. It is not known whether the addition of a medication called Casodex will better control my tumor. My doctor feels that my participation in this study may be helpful in developing better treatment for this disease but that there are no guarantees for me specifically. This study involves the evaluation of the drug Casodex used during and after my radiation therapy. The purpose of this study is to determine whether Casodex may improve tumor control when used with radiation therapy.

DESCRIPTION OF PROCEDURES

This study involves at random (*by chance*) assignment to one of two treatment arms. It is not clear at the present time which of the two treatments is better. For this reason the therapy which is to be offered to me will be based upon a method of selection called randomization. Randomization means that my physician will call a statistical office which will assign me one of the two regimens by computer. The chance of my receiving one of the two therapies is approximately equal. I will be assigned to one of two treatments:

- I will receive external beam radiation treatment as an outpatient for 5 days a week for approximately 6 1/2 weeks. I will also take one tablet of Casodex every day for two years beginning at the start of radiation treatment.
- OR**
- I will receive external beam radiation treatment as an outpatient for 5 days a week for approximately 6 1/2 weeks. I will also take one tablet of inactive agent (*placebo*) every day for two years beginning at the start of radiation treatment.

Neither I nor my physicians will know whether the tablets I am taking contain the drug Casodex. In case of a medical emergency, the code can be broken so my doctor can know which tablets I have been taking. Casodex is an approved agent which will be supplied by the manufacturer (*Astra Zeneca Pharmaceuticals*) for this study. Astra Zeneca will also supply the tablets containing the inactive agent. Both Casodex and the inactive agent will be provided free of charge.

RISKS AND DISCOMFORTS (9/8/98)

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.

Radiation Therapy may cause reddening or tanning of the skin, hair loss in the treatment area, temporary fatigue, nausea, diarrhea, abdominal cramps, bladder irritation, and in some patients permanent impotence. There is also a small probability of injury to the bladder, urethra, bowel and other tissues in the pelvis or abdomen.

Casodex: The principal discomforts reported among patients taking Casodex are breast tenderness, breast swelling, and hot flashes. Approximately 2% of patients had constipation, diarrhea, or nausea. The most frequently reported discomforts have been fatigue, back pain, and fluid retention. Casodex has been associated with changes in liver function, though these are

infrequent, less than 2%, impotence or loss of libido, and rarely with jaundice (*yellowing of skin*). Many of these changes improved or went away despite continuation of Casodex therapy.

In animal experiments birth defects (*abnormal external sex organs*), were found in male offspring from female animals dosed with Casodex during pregnancy. Although offspring from male animals dosed with Casodex did not show any birth defects, patients enrolled in this trial are advised to neither cause pregnancy nor to donate sperm both while receiving trial therapy and during the first 3 months after stopping the medication. The use of barrier contraceptives is therefore advised.

If study medication (*Casodex or placebo*) results in any harm to my body in certain circumstances compensation for medical expenses not otherwise covered may be available from Astra Zeneca. These circumstances include that 1) Casodex was prescribed and taken as described by the protocol, 2) all requirements of the consent form have been complied with, 3) the injury was not deliberately caused, 4) the study physician is immediately notified of the harm and 5) that his or her advice for medical care has been followed.

Except for such compensation of medical expenses, I fully understand that no other compensation is or will be available for payment of my lost wages or other damages or losses resulting from any injury incurred as a result of my participation in the study.

My physician will be checking me closely to see if any of these side effects are occurring. Routine blood tests will be done to monitor the effects of treatment. Side effects of Casodex usually disappear after the treatment is stopped. 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.

CONTACT PERSONS

In the event that injury occurs as a result of this research, treatment will be available. I understand, however, I will not be provided with reimbursement 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 addition, I may contact _____ at _____ for information regarding patients' rights in research studies.

BENEFITS

It is not possible to predict whether or not any personal benefit will result from the treatment program. I understand that the information which is obtained from this study may be used scientifically and 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 I understand this is not guaranteed.

I have been told that should my disease become worse, should side effects become very severe, should new scientific developments occur that indicate the treatment is not in my best interest, or should my physician feel that this treatment is no longer in my best interest, the treatment would be stopped. Further treatment would be discussed.

ALTERNATIVES

Alternatives which could be considered in my case include radiation or hormones either alone or together or treatments to make me feel better, but not necessarily cure me or make my disease less. An additional alternative is no further therapy, which would probably result in continued growth of my tumor. I understand that my doctor can provide detailed information about my disease and the benefits of the various treatments available. I have been told that 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. In addition, I understand that I am free to ask my physician any questions concerning this study.

My physician will explain any procedures related solely to research. 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 understand that 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. In the event of a research-related injury, I understand my participation has been voluntary.

CONFIDENTIALITY (9/5/00)

I understand that records of my progress while on the study will be kept in a confidential form at this institution and also 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 the conduct of this study may have access to medical records which contain my identity. However, no information by which I can be identified will be released or published. If you are participating in this study through the Clinical Trial Support Unit (*CTSU*), a record of your progress will also be kept by the CTSU. 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 of 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 not 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 within 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

APPENDIX V

ADVERSE REACTION 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 special handling, study-specific reporting procedures supercede 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. In the absence of the Group Chairman, the report should be made to the Headquarters Data Management Staff (215/574-3214). 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.
2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone .
3. A written report 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.
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 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 (<i>grade 4</i>) | As above |

events which may be due to agent.

- 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 CLASSIFICATION

Histologic patterns of adenocarcinoma of the prostate

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

The Gleason Classification is a system of histologic grading based on over-all pattern of tumor growth at relatively low-magnification (40 to 100x). Five patterns of growth are recognized and numbered in order of increasing malignancy. Because of histologic variation in the tumor, 2 patterns are recorded for each case, a primary or predominant pattern and a secondary or lesser pattern.

The Gleason Score is the sum of the primary and secondary pattern. If only 1 pattern is present, the primary and secondary pattern receive the same designation.

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

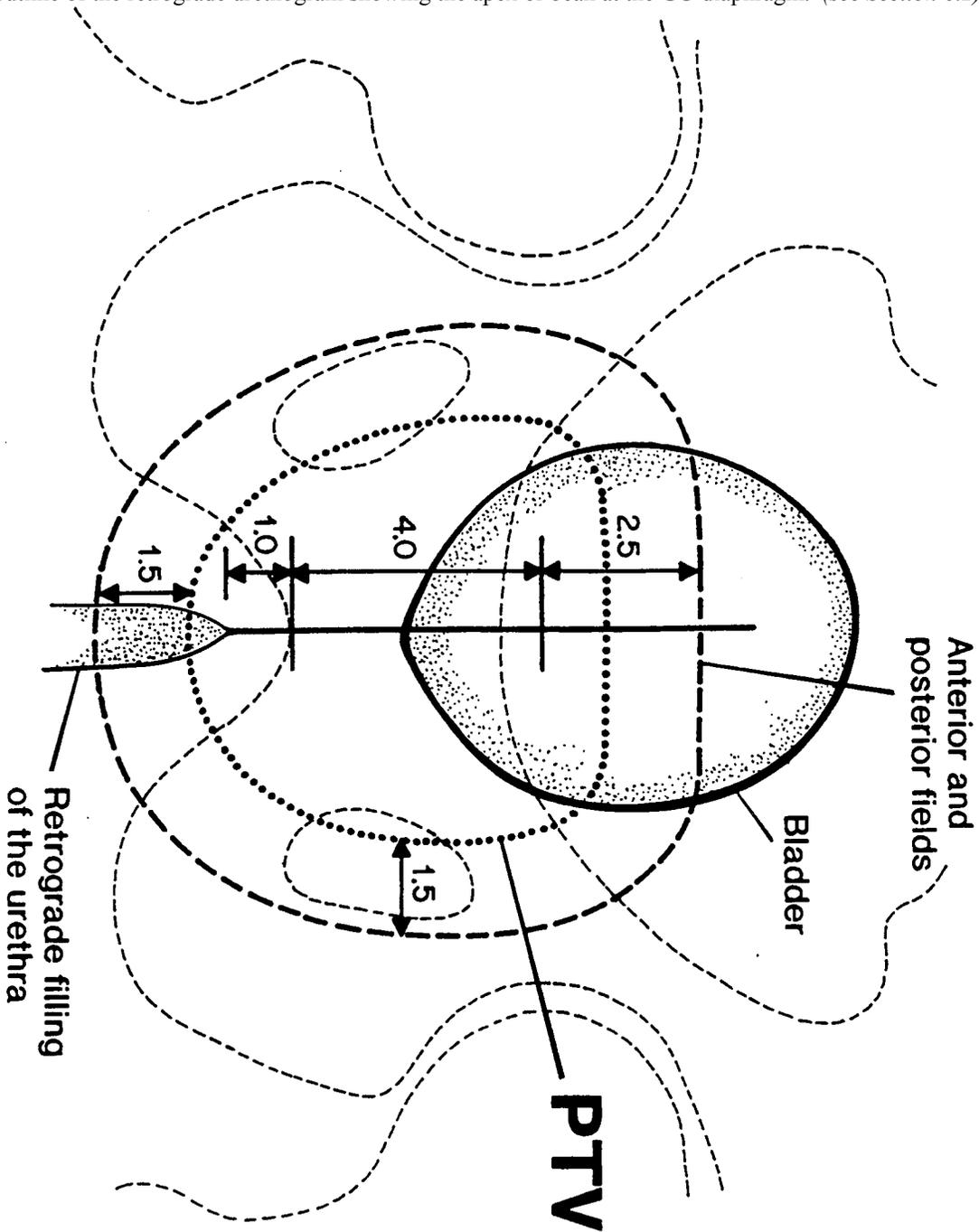
(Primary = 2, Secondary = 2, Gleason = 4)

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

Figure 1

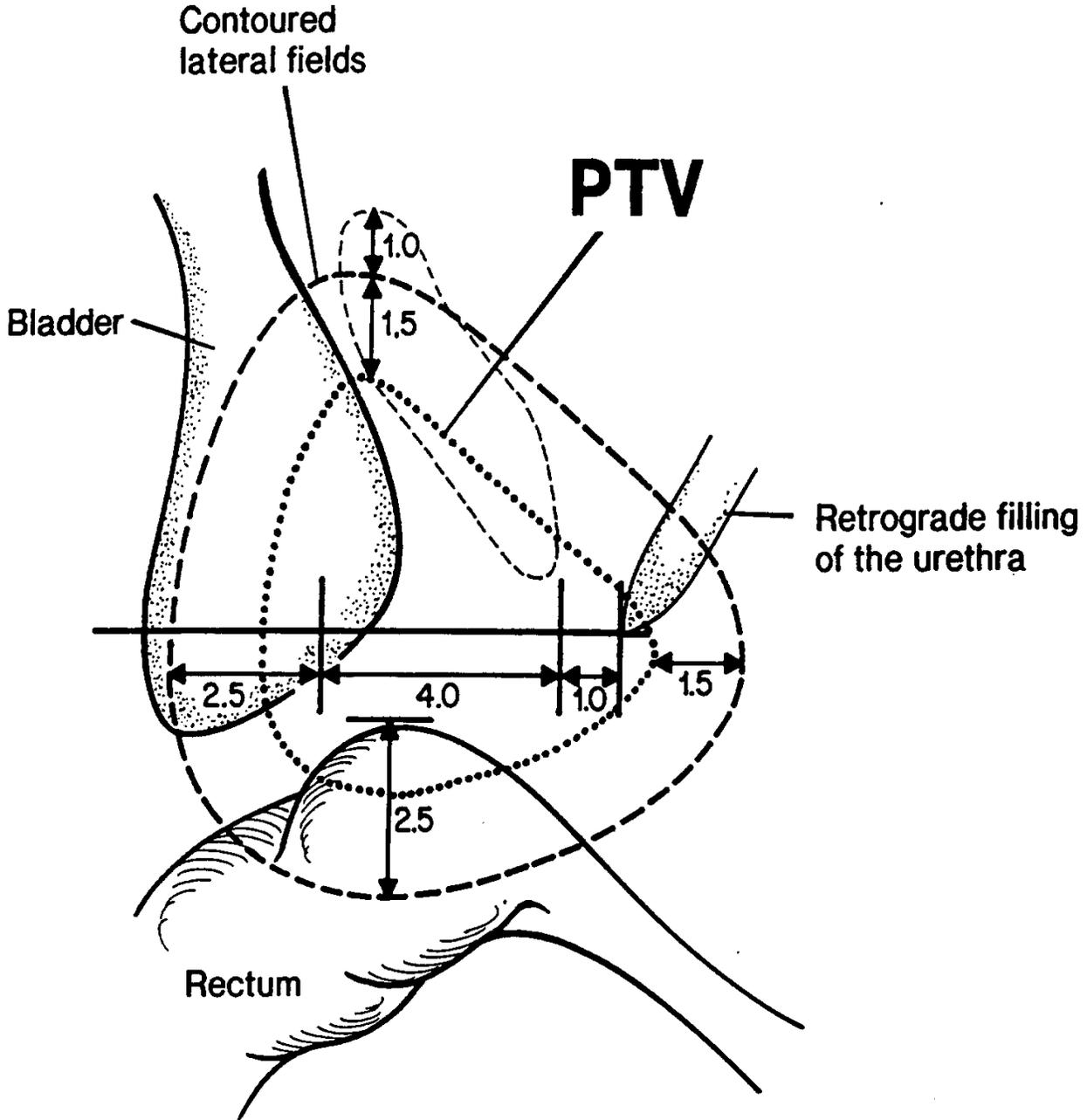
The anterior and posterior fields for a patient with an average size prostate (4.0 cm in urethral length) prior to prostatectomy with no documented microscopic involvement of the seminal vesicals. This line diagram shows the bladder outlined as well as the outline of the retrograde urethrogram showing the apex or beak at the GU diaphragm. (see Section 6.2).



APPENDIX VII

Figure 2

A line diagram of the right and left lateral fields for a patient with an average sized prostate (4.0 cm urethral length) and without microscopic involvement of the seminal vesicals. The line diagram shows outline of the bladder, the rectum and the dye in the penile urethra under pressure showing an apex or beak at the GU diaphragm. (see Section 6.2).



APPENDIX VIII (9/5/00)

Investigator Responsibilities for RTOG 96-01

The following is a list of items that should be maintained in an "Investigators File" at your site for this study. Your institution may be site audited as part of this study and in order to comply with FDA regulations these items must be available at the time of the site audit. This list was compiled from the Federal Regulations (21 CFR) as well as accepted standards on conducting clinical trials (*The Code of Good Clinical Practices [GCP]*).

Documents	Federal Regulation	Good Clinical Practice	To RTOG	Comments
Investigation Drug Brochure		X		Available from RTOG Headquarters.
FDA Form 1572	X		X	A study-specific 1572 must be submitted to RTOG and must include all subinvestigators involved in the study. Your copy must be available on site.
Protocol	X			If a signature page is provided, sign and date.
IRB Approvals	X		X	Full IRB approval is required of the protocol, of all versions of the informed consent form, and of all study amendments.
Proof of IRB Submission	X	X		There must be proof of submission to IRB of all IND safety reports if different from study amendments.
IRB Membership List & Assurance #	X		X	The assurance number is issued by OPRR.
Curriculum Vitae (CV)	X		X	For Principal Investigator as well as all subinvestigators listed on the FDA 1572.
Laboratory Certification	X	X	X	Name and address of facility must be provided on FDA 1572. Acceptable certifications are CAP (<i>College of American Pathologists</i>) and/or state licensures.
Laboratory Norms.		X		Should be on file as a ref. to assess out of range values.
Medical License		X		For the Investigator and all subinvestigators listed for this study.
Pharmacy Registration Form			X	See Appendix X.
Drug Shipment/Account/Records	X			May be kept and maintained by pharmacy. Tracks drug flow to and from the site as well as administration to pts.
Correspondence		X		All communiques between the site, RTOG, IRB and FDA.

NOTE: ALL CORRECTIONS SHOULD BE MADE PER THE FDA PRESCRIBED METHOD OF PLACING ONE LINE THROUGH THE OLD ENTRY, WRITE THE CORRECTION NEXT TO THE OLD ENTRY, INITIAL AND DATE.

- 1) Items listed in the RTOG column must be on file at RTOG Headquarters prior to randomization of your first patient to this study. **CTSU Investigators will submit all required paperwork to the CTSU office.**
- 2) You may be site visited with very little prior notice.
- 3) You will be asked to comply with certain FDA requirements, as outlined above.
- 4) Completion of pretreatment evaluations as outlined in Section 4.0 of the protocol will be used in determining evaluability for case reimbursement purposes (*RTOG members*).
- 5) Patients are to be assessed for treatment toxicity on a regular basis (*patient reporting acceptable*). Documentation of the assessments is mandatory.
- 6) Timely data submission and serious adverse event reporting as specified by the protocol is critical.
- 7) Case reimbursement (*RTOG*) will be evaluated at two points: following completion of treatment and after completion of the three month followup assessment (*or death, whichever comes first*). The maximum reimbursement will be based on timely submission of data, completion of study parameters, and compliance with adverse event reporting requirements.

APPENDIX IX (9/8/98, 5/2/03)

**Drug Handling Procedures for
RTOG 96-01**

1. **This is a double-blinded study.** Only RTOG who will provide the code to McKesson BioServices (*MBS*), distributor of Casodex and the placebo, and MBS will know which treatment is assigned.
2. All bottles of drug will be precoded and labelled by MBS with a unique patient-specific number to ensure double-blinded distribution. Active drug and placebo will be supplied in identical 150 mg tablet form and can be stored at room temperature in a dry location
3. Only the RTOG-registered pharmacy (*Appendix X*) will dispense the study drug and maintain the logs.
4. The pharmacist will receive a patient-specific supply of drugs from MBS after each patient randomization.
5. Prescriptions must include the patient's name, RTOG case number and the drug identification code assigned at randomization. The pharmacist will dispense the bottle(s) bearing the identical code and attach the tear-off strips to the prescription slip.
6. The RTOG-registered pharmacist must maintain inventory records on the Drug Accountability Record (*NIH-986*). Records will be reviewed as part of the NCI-mandated Quality Control audit program and may be requested periodically to assess compliance.
7. Study drug will be dispensed only to patients entered on this trial and unused (*undispensed*) supplies must be returned to MBS upon completion of the study, when supply is outdated, when patient discontinues protocol drug, or if requested by MBS. Returns should be made via "return-receipt". Patients who do not finish taking their prescribed medication will be instructed to return all tablets to their physician who will count the tablets before returning to the pharmacy where it will be recorded on the log, then returned to MBS. All returns must include the following: institution name, address, and RTOG number, RTOG protocol and case numbers, product lot number, and quantity enclosed.
8. Institutions will notify MBS (*see Item 9*) when patients have permanently discontinued protocol agent.
9. Questions about drug distribution and handling, requests for additional drug, and returns should be directed to:

**Jun Lee, R.Ph.
McKesson BioServices
Pharmaceutical Services Division
14665 Rothgeb Drive
Rockville, MD 20850
telephone (301) 315-8460
FAX (301) 738-2478**

10. Refer to Section 7.0 of the protocol for additional drug information.

APPENDIX X (9/5/00)

PHARMACY REGISTRATION

RTOG 96-01

CASODEX/PLACEBO

Double-blinded packs will be sent only to institutions who have identified a single individual to whom they will be shipped. This form, and the documentation listed in Appendix VIII, must be completed and returned to RTOG Headquarters prior to registering any patient on study. **CTSU Investigators will submit all paperwork to the CTSU office.** Allow adequate processing time (7-10 days) before calling to randomize your first patient.

SHIP TO:

Pharmacist: _____

Address: (No P.O. Box. Avoid general receiving addressees)

Telephone: _____

Fax#: _____

RTOG Institution#: _____

Institution Name: _____

Affiliation (circle one): **RTOG** **CTSU**

IRB Approval Date: _____

Investigator (PI) Signature _____ Date: _____

Investigator Name (Print) _____

Investigator NCI # _____

Send Completed Form to:

*RTOG Headquarters
1101 Market Street
Philadelphia, PA 19107*

ATTN: ELAINE PAKURIS

RTOG Headquarters Approval _____ Date: _____