

RADIATION THERAPY ONCOLOGY GROUP

RTOG 99-10

A PHASE III TRIAL TO EVALUATE THE DURATION OF NEOADJUVANT TOTAL ANDROGEN SUPPRESSION (TAS) AND RADIATION THERAPY (RT) IN INTERMEDIATE-RISK PROSTATE CANCER

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CTSU (R9910)

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SCHEMA (6/7/04)

	PSA		R
S	1. ≤ 10		A
	2. $> 10-20$		Arm 1
T	3. > 20 to ≤ 100	N	TAS (<i>LHRH agonist and Casodex or Eulexin</i>) x 8 weeks followed by
R	Gleason Score	D	RT ^a with concurrent TAS (<i>LHRH agonist and Casodex or Eulexin</i>).
	1. 2-4		
A	2. 5-6		O
	3. 7-10		Arm 2
T	Tumor stage	M	TAS (<i>LHRH agonist and Casodex or Eulexin</i>) x 28 weeks followed
	1. T1b-2	I	by RT ^a with concurrent TAS (<i>LHRH agonist and Casodex or</i>
I	2. T3-4	Z	<i>Eulexin</i>).
F	Prior Hormones		
	1. No		E
Y	2. Yes		

^aRT: (See Section 6.0 for details)

- prostate and any extraprostatic tumor extension + 1.0-1.5 cm margin will receive 70.2 Gy (1.8 Gy/day x 39 fractions, five days/week)

or

- regional nodes, prostate and seminal vesicles + 1.0-1.5 cm margin will receive 46.8 Gy (1.8 Gy/day x 26 fractions, five days/week), followed by a 23.4 Gy (1.8 Gy/day x 13 fractions, five days/week) boost to the prostate and any extraprostatic tumor extension + 1.0-1.5 cm margin.

Eligibility: (See Section 3.0 for details)[1/15/02,6/7/04]

- Histologically confirmed prostate adenocarcinoma within 180 days of randomization
- Zubrod performance score 0-1
- Prostatic biopsy tumor grading by the Gleason Score classification
- One of the following combinations of factors:
 - Clinical stage T1b-4, Gleason score 2-6, and prostate-specific antigen >10 but ≤ 100
 - Clinical stage T1b-4, Gleason score 7, and prostate-specific antigen <20
 - Clinical stage T1b-1c, Gleason score 8-10, and prostate-specific antigen <20
- Clinically negative lymph nodes (N0) as established by imaging (*pelvic \pm abdominal CT, MRI, or LAG*), or histologically negative by nodal sampling or dissection
- No distant metastases (M0)
- ALT must be within 2 x upper normal limits
- Life expectancy ≥ 10 years
- No previous or concurrent invasive cancers, other than localized basal cell or squamous cell skin carcinoma, unless continually disease free for at least 5 years
- No prior pelvic RT, prostate brachytherapy, bilateral orchiectomy, or chemotherapy for prostate cancer
- Prior LHRH agonists are allowed only if started no more than 30 days before the date of randomization, and only if Casodex or Eulexin was (*or will be*) started within (*before or after*) 14 days of the LHRH agonist injection date. Any finasteride therapy must be discontinued
- No radical surgery or cryosurgery for prostate cancer
- Treatment must begin within 6 weeks after randomization
- Signed study-specific informed consent form prior to randomization

Required Sample Size: 1540

6/6/01

RTOG Institution # _____

RTOG 99-10

ELIGIBILITY CHECKLIST (6/6/01, 1/15/02, 6/07/04)

Case # _____

(page 1 of 3)

- _____(Y) 1. Is there histologically confirmed prostate adenocarcinoma within the past 180 days?
- _____(2-10) 2. What is the combined Gleason Score classification (*primary + secondary*)?
- _____(≤ 100) 3. What is the (*FDA-approved assay method*) PSA level?
- _____(T1b-4) 4. What is the T stage?
- _____(N) 5. Is there evidence of nodal metastases?
- _____(N) 6. Is there evidence of distant metastases?
- _____(Y) 7. Is there the following combination of factors?
 - Clinical stage T1b-4, Gleason Score classification 2-6, and PSA > 10 but ≤ 100, or
 - Clinical stage T1b-4, Gleason Score classification 7, and PSA < 20, or
 - Clinical stage T1b-1c, Gleason Score classification 8-10, and PSA < 20.
- _____(0-1) 8. What is the Zubrod Performance Status?
- _____(N) 9. Has the patient had prior pelvic radiation, prostate brachytherapy, bilateral orchiectomy, or chemotherapy for prostate cancer?
- _____(N) 10. Has the patient had prior radical surgery or cryosurgery for prostate carcinoma?
- _____(Y) 11. Is life expectancy ≥ 10 years?
- _____(N) 12. Has the patient had previous or concurrent invasive cancer within the past 5 years other than localized basal cell or squamous cell skin carcinoma?
- _____(Y) 13. Will protocol treatment begin within the next 6 weeks?
- _____(N) 14. Are there any major medical or psychiatric illnesses, which would prevent completion of treatment and/or interfere with follow-up?
- _____(N) 15. Is the patient participating in another research study that involves prostate cancer treatment?
- _____(N) 16. Did the patient receive any of the following androgen suppression therapy?
 - LHRH agonist started > 30 days ago, or
 - Casodex or Eulexin started > 14 days before or after the day the first LHRH agonist injection was given
- _____(N) 17. Is the ALT value more than 2 x upper limit of normal?

(cont'd on next page)

RTOG Institution # _____

RTOG 99-10

ELIGIBILITY CHECKLIST (6/6/01, 1/15/02,6/7/04)

Case # _____

(page 2 of 3)

The following questions will be asked at Study Registration:

- _____ 1. Name of institutional person registering this case?
- _____ (Y) 2. Has the Eligibility Checklist (*above*) been completed?
- _____ (Y) 3. Is the patient eligible for this study?
- _____ 4. Date the study-specific Consent Form was signed? (*must be prior to study entry*)
- _____ 5. Patient's Name
- _____ 6. Verifying Physician
- _____ 7. Patient's ID Number
- _____ 8. Date of Birth
- _____ 9. Race
- _____ 10. Social Security Number
- _____ 11. Gender (male)
- _____ 12. Patient's Country of Residence
- _____ 13. Zip Code
- _____ 14. Patient's Insurance Status
- _____ 15. Will any component of the patient's care be given at a military or VA facility?
- _____ 16. Stratification for PSA (≤ 10 or $> 10-20$ or $> 20-100$)
- _____ 17. Stratification for Combined Gleason Score ($2-4$ or $5-6$ or $7-10$)
- _____ 18. Stratification for Tumor Stage ($T1b-2$ or $T3-4$)
- _____ 19. Hormones Started (*Yes or No*)?
- _____ If yes, date of study entry (*LHRH agonist must have started ≤ 30 days before randomization and Casodex or Eulexin must have (or will be) started ≤ 14 days from the date of LHRH agonist injection.*)
- _____ If no, date of planned start of hormones (*Must start < 6 weeks after randomization.*)

(cont'd on next page)

RTOG Institution # _____

RTOG 99-10

ELIGIBILITY CHECKLIST (6/6/01)

Case # _____

(page 3 of 3)

_____ 20. What is the PSA value?

_____ 21. What is the combined Gleason Score?

_____ 22. What is the tumor stage?

_____ 23. Randomization Date

_____ 24. Treatment Assignment

Completed by _____

Date _____

1.0 INTRODUCTION

1.1 Conventional Treatment Approaches

For most patients with clinical stage II prostate cancer,¹ external beam radiation therapy (RT) as sole treatment is considered an appropriate management option.²⁻⁴ Although conventional dose RT may result in intermediate-to-long term clinical disease control,⁵ post-RT prostatic biopsy⁶ and serum prostate-specific antigen (PSA) determinations⁷ suggest that locally persistent tumor may exist in a substantial proportion of patients. Residual disease may serve as a source of tumor de-differentiation⁸ and systemic dissemination.⁹ Conformal dose-escalation RT may be one means of improving local tumor control,¹⁰⁻¹² whereas an alternative method would rely on conventional RT dose levels (*e.g.*, 70.2 Gy) with addition of a modality that enhances tumor cell killing. Although total androgen suppression (TAS) may exert such an effect, precise indications for its use and the optimal manner of combining the two modalities have not been established. At present, the Radiation Therapy Oncology Group (RTOG) is seeking to determine whether conventional duration (*i.e.*, 8 week) cytoreductive TAS improves radiotherapeutic outcome for patients with clinical stage II prostate cancer at low-to-intermediate relapse risk (RTOG study 94-08).

Compared with conventional dose RT alone, the addition of cytoreductive¹³ or long-term adjuvant androgen suppression^{14, 15} is associated with improved outcome in patients with clinical stage III disease,¹ and RT with TAS is a suitable approach for this condition.²⁻⁴ However, the optimal sequence and duration of androgen suppression in the cytoreductive and adjuvant settings has not been resolved. At present, ongoing clinical trials were designed to evaluate: (1) the role of conventional duration cytoreductive TAS vs. short-term (*i.e.*, 16 week) adjuvant TAS (RTOG 94-13), (2) the benefit of long-term (≥ 24 month) adjuvant androgen suppression added to conventional duration cytoreductive TAS (RTOG study 92-02), and (3) the preferred duration of adjuvant androgen suppression (6 months vs. 36 months) used in conjunction with conventional dose RT (EORTC 22961).

1.2 Androgen Suppression Therapy

Necrosis and apoptotic (*i.e.*, programmed) cell death are the principle mechanisms through which cell loss is thought to occur. For malignant prostatic epithelial cells, the clinical manifestation of apoptosis is the androgen-dependent state. In this setting, androgen deprivation produces tumor regression by inhibiting DNA synthesis and cell proliferation¹⁶ and by triggering apoptosis of normal and neoplastic cells independent of cell cycle considerations.¹⁷ The effects of androgen suppression on the primary prostatic tumor may be assessed through histologic examination of prostatectomy specimens. Several reports demonstrated that TAS administered for two to three months before surgery decreased prostatic volume,¹⁸⁻²⁵ and increased the likelihood of obtaining organ-confined disease²²⁻²⁷ and tumor-free margins.^{22, 23, 25-27} Although the optimal duration of TAS required to obtain maximal tumor cytoreduction has not been defined,²⁸ recent research efforts suggested a longer duration may be beneficial.²⁹

Gleave *et al.* demonstrated that androgen suppression resulted in a precipitous fall in serum PSA levels within the first month, but further decline was observed with the passage of time.²⁹ After three months, 34% of patients achieved a PSA nadir, whereas 84% had reached a nadir after eight months of androgen suppression. These investigators postulated that the initial PSA response resulted from down-regulation of PSA synthesis and induction of apoptosis, and that further PSA decline resulted from continued tumor volume reduction. Immunohistochemical stains for proliferation markers (*i.e.*, PCNA, Ki-67) suggested androgen-independent tumor progression did not occur during an eight-month time frame. Thus, it appears a duration of neoadjuvant TAS that extends beyond a traditional two-month period¹³ may result in greater tumor volume reduction (*i.e.*, cytoreduction), more favorable dose-volume response characteristics,³⁰⁻³² and an enhanced therapeutic ratio.

1.3 Radiation-Androgen Deprivation Interactions

The combination of RT and androgen suppression may improve prospects for the complete eradication of localized prostate cancer through two possible mechanisms: (1) androgen suppression-induced apoptosis of androgen-dependent tumor cells results in cytoreduction, reduced tumor volume, and an improved tumor control probability at a fixed RT dose level, and (2) enhanced tumor cell kill effects occur due to radiation-induced DNA damage, which may lead to induction of alternative pathways for apoptosis. Evidence for improved tumor control through what is apparently a cytoreductive mechanism is present in surgical series³³ and through *in vitro* and *in vivo* experiments performed in animal models.^{34, 35} For example, Zietman *et al.* demonstrated that the tumoricidal dose to control 50% (TCD₅₀) of transplanted Shionogi tumors was substantially less after maximal androgen deprivation-induced cytoreduction than after RT with or without adjuvant androgen deprivation.³⁵ Furthermore, Joon *et al.* demonstrated a supraadditive apoptotic response in the R3327-G tumor model that depended on the interval from androgen deprivation to the administration of RT.³⁶

Controlled clinical studies demonstrated improved local tumor control when androgen suppression was added to RT.¹³⁻¹⁵ Although long-term androgen suppression administered concurrently with or after RT was associated with enhanced local tumor control,^{14, 15} it was uncertain whether this was due to disease eradication or delayed tumor outgrowth. In contrast, the limited duration of neoadjuvant TAS used in RTOG study 86-10 strongly suggested that local tumor ablation and (*perhaps secondarily*) metastatic disease control⁹ was more likely with the combined approach.¹³ These results, in particular, combined with pre-clinical studies³⁵ and surgical findings,²⁹ illustrate the potential therapeutic benefit that may result from a more extended duration of TAS administered in a neoadjuvant setting. Indeed, the First International Conference on Neoadjuvant Hormonal Therapy of Prostate Cancer concluded that the optimal duration of neoadjuvant androgen suppression was not well defined and that further study was “urgently” needed.²⁸

1.4 Patient Selection

Pretherapy clinical tumor stage, tumor grade (*e.g. Gleason Score classification*), and serum PSA level are independently associated with the risk of disease relapse following external beam RT.^{37, 38} These factors may be combined to improve upon the accuracy of anatomically-based systems¹ for estimating therapeutic outcome in patients with clinical stage II-III prostate cancer.^{12, 38-43} Because patients with clinically localized disease have a highly variable risk of disease relapse,^{37, 38, 40, 42, 43} a method to focus research strategies along the lines that befit the risk of relapse is desirable.⁴⁴ Recently, the Prostate Cancer Progress Review Group, established by the National Cancer Institute to sharpen the focus of its site-specific research programs, confirmed the importance of this view. The Group concluded that “selection of an appropriate homogeneous patient population is essential for success of a given clinical trial.”⁴⁵

At present, the optimal means of combining clinical tumor stage, tumor grade (*e.g. Gleason Score classification*), and serum PSA level to identify “low”, “intermediate”, and “high” risk groups has not been firmly established. Nonetheless, several investigators provided insight into patient groupings based on the association of these pretherapy factors with post-RT biochemical failure.^{12, 38-43} In particular, Pisansky *et al.* developed and validated a predictive model to estimate the risk of clinical or biochemical failure after external beam RT for the patient with newly diagnosed, non-metastatic prostate cancer,³⁷ and used this methodology to group patients according to relapse risk.⁴¹ Other investigators applied this model to separate validation data sets, and found it was a useful methodology.^{40, 46} In addition, D’Amico *et al.*,⁴² Shipley *et al.*,⁴³ and Zagars *et al.*³⁸ provided insight into the characteristics of patients who may be considered at “intermediate” risk of biochemical failure, as displayed in the following tabular format, where the values beneath the “Gleason” column represent appropriate PSA value ranges:

<u>Author</u>	<u>Stage T1-2</u>		<u>Stage T3-4</u>	
	<u>Gleason 2-6</u>	<u>Gleason 7-10</u>	<u>Gleason 2-6</u>	<u>Gleason 7-10</u>
D’Amico ⁴²	10.1-20	<20	-	-
Pisansky ⁴¹	13-56	5-21	5-23	2-8
Shipley ⁴³	> 10	< 20	-	-
Zagars ³⁸	4.1-20	≤ 20	≤ 20	< 10

In addition, the definition of an “intermediate” risk group may be derived through a process of elimination. That is, patients with “low” or “high” relapse risks may be removed from consideration for purpose of the present investigation. Patients at “low” risk for biochemical failure after external beam RT are those with clinical stage T1-2 disease, biopsy Gleason Score classification 2-6, and serum PSA level ≤10.^{12, 38, 39, 41-43} Such patients are the subject of an alternative direction of investigation by the RTOG, and may be considered appropriate candidates for the study of transperineal interstitial permanent prostate brachytherapy (*RTOG study 98-05*) as a sole treatment approach. Furthermore, patients considered at “high” risk may have a serum PSA ≥20 and Gleason Score classification ≥7 (*any clinical tumor stage*), or may have a clinical tumor stage ≥T2 and Gleason Score classification ≥8 (*any PSA*) tumor. These patients are at particularly high risk for distant disease relapse, and may be considered for the evaluation of systemic therapies (*RTOG study 99-02*).

1.5 Rationale for the Control Arm

Although results from controlled clinical trials are not available for patients with “non-bulky” intermediate-risk prostate cancer, external beam RT with (*or without*) TAS is considered an appropriate treatment strategy in contemporary clinical practice.^{3, 4} At present, the role of 8-week duration neoadjuvant TAS in patients with low-to-intermediate risk, organ-confined disease is under investigation by the RTOG (*RTOG study 94-08*). Consequently, a clearly defined “standard” treatment for the current study is open to debate. Nonetheless, patients treated with neoadjuvant TAS and RT in RTOG 94-08 are not likely to fare worse

than those managed with RT alone. If that trial's central hypothesis is correct, neoadjuvant TAS will be advantageous, and the combination may be considered standard therapy. Therefore, external beam RT with 8-week duration neoadjuvant TAS will be considered the "standard" therapy for patients with clinical stage II disease in the present investigation. For patients with clinical stage III disease, the results of RTOG 86-10¹³ are sufficiently robust to include 8-week duration TAS as "standard" therapy.

2.0 OBJECTIVES

- 2.1** The primary endpoint is to compare the efficacy of moderate-duration (*28-week*) neoadjuvant total androgen suppression and RT with short-duration (*8-week*) neoadjuvant total androgen suppression and RT as related to disease-specific survival.
- 2.2** The secondary endpoints are to compare moderate-duration (*28-week*) neoadjuvant total androgen suppression and RT with short-duration (*8-week*) neoadjuvant total androgen suppression and RT as related to: (a) overall survival, (b) disease-free survival, (c) clinical patterns of tumor recurrence (*time to local tumor progression or distant failure*), (d) time to first biochemical failure, (e) time to second biochemical failure while on salvage androgen deprivation therapy (*i.e., hormone-refractory state*), and (f) treatment-induced morbidity.
- 2.3** To establish a clinical trial outcome data set that may be used to correlate with the findings of future basic science studies.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility (6/6/01)

- 3.1.1** Adenocarcinoma of prostatic origin histologically-confirmed within 180 days of the randomization date.
- 3.1.2** Zubrod Performance Status 0-1 (*Appendix II*).
- 3.1.3** Prostatic biopsy tumor grading by the Gleason Score classification (*Appendix VI*) is mandatory prior to randomization.
- 3.1.4** Patients at intermediate risk for disease relapse as determined by any of the following combinations of factors (**NOTE: tumor found in one or both lobes on biopsy, but not palpable, will not alter T stage**):
- Clinical stage T1b-4, Gleason score 2-6, and prostate-specific antigen >10 but ≤ 100.
 - Clinical stage T1b-4, Gleason score 7, and prostate-specific antigen < 20.
 - Clinical stage T1b-1c, Gleason score 8-10, and prostate-specific antigen <20.
- 3.1.5** Clinically negative (*N0*) lymph nodes (*LN*) as established by imaging (*pelvic ± abdominal CT, MRI or LAG*), or negative *LN* by nodal sampling or dissection (*laparoscopy or laparotomy*). Patients with radiologic (*e.g., CT, MRI or LAG*) or radioimmunoscintigraphy (*i.e., ProstaScint™*) findings suggestive of regional nodal involvement are eligible if cytologic (*e.g., needle aspiration*) or histologic (*e.g., surgical sampling*) evaluation shows no evidence of a neoplastic process (*i.e., prostatic or non-prostatic malignancy*). Patients with equivocal radiologic findings (*maximum nodal size ≤ 1.5 cm*) are eligible.
- 3.1.6** No distant (*M0*) metastases. Patients with radionuclide imaging (*e.g., bone scintigraphy, ProstaScint™*) findings suggestive, but not diagnostic of metastatic disease are eligible if radiologic (*e.g., standard or tomographic radiography, or CT/MRI*) imaging does not confirm metastatic disease.
- 3.1.7** Pretherapy serum (*total*) prostate-specific antigen value performed with a Federal Drug Administration approved assay method, *e.g.* Abbott, Hybritech, etc.
- 3.1.8** Treatment must begin within 6 weeks after randomization.
- 3.1.9** ALT must be within 2 x upper normal limit.
- 3.1.10** Patients must sign a study-specific informed consent form (*Appendix I*) prior to randomization.

3.2 Patient Ineligibility (6/6/01, 1/15/02, 6/7/04)

- 3.2.1** Patients at high risk for disease relapse as determined by either:
- Prostate-specific antigen ≥ 20 and Gleason score ≥ 7 (*any T stage*).
 - Clinical stage ≥ T2 and Gleason score ≥ 8 (*any prostate-specific antigen*).
- 3.2.2** Patients at low risk for disease relapse as determined by:
- Clinical stage ≤ T2, Gleason score ≤ 6, and prostate-specific antigen ≤ 10.
- 3.2.3** Clinical stage Tx, T0, or T1a.
- 3.2.4** Histologic or radiologic evidence of tumor involvement of regional lymph nodes (*NI*) or the presence of metastatic disease (*MI*).
- 3.2.5** Pretherapy serum prostate-specific antigen level > 100.
- 3.2.6** Co-morbid medical illness which in the opinion of the investigator is expected to result in a life expectancy of <10 years.
- 3.2.7** Any of the following prior therapies:

- Pelvic external beam radiation therapy.
 - Radionuclide prostate brachytherapy.
 - Prostatectomy or prostatic cryosurgery.
 - Prior bilateral orchiectomy.
 - Prior androgen suppression therapy; however, patients begun on LHRH agonist therapy remain eligible if (1) LHRH agonists were started no more than 30 days before randomization, and (2) Casodex or Eulexin was (*or will be*) started no more than 14 days **before or after** the date that the LHRH agonist injection was given. Any finasteride therapy administered for prostatic hypertrophy must be discontinued.
 - Chemotherapy for prostatic carcinoma.
- 3.2.8** Previous or concomitant invasive cancer, other than localized basal cell or squamous cell skin carcinoma (*AJCC Stage 0-II*), unless continually disease free for at least 5 years.
- 3.2.9** Major medical or psychiatric illness which, in the opinion of the investigator, would prevent completion of treatment or would interfere with follow-up.
- 3.2.10** The patient's participation in another medical research study that involves prostate cancer treatment.

4.0 PRETREATMENT EVALUATION (6/6/01)

- 4.1** History, physical examination (*including prostate tumor measurements*), and Zubrod Performance Status (*Appendix II*).
- 4.2** Histologic evaluation of the diagnostic biopsy specimen by the Gleason Score classification (*Appendix VI*).
- 4.3** The following laboratory studies will be obtained within 28 days prior to randomization: complete blood cell count (*hemoglobin, white blood cells, platelets*), serum ALT, alkaline phosphatase, total bilirubin, and creatinine.
- 4.4** A whole body radionuclide bone scan and serum prostate-specific antigen will be performed within 90 days prior to randomization. A prostate-specific antigen value must be available within this time frame but before the start of any hormonal therapy (*exclusive of finasteride*).
- 4.5** The pelvic lymph nodes will be assessed by one of the following methods within 90 days prior to randomization: pelvic ± abdominal computed tomography, pelvic ± abdominal (*external body coil*) magnetic resonance imaging, lymphangiogram, or pelvic lymph node dissection or sampling (*via laparoscopy or laparotomy*).

5.0 REGISTRATION PROCEDURES

5.1 RTOG Institutions (8/25/00)

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 (8/25/00)

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 ctscontact@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 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 are approved and on file with the 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 Cover sheet
- CTSU version of RTOG-99-10 Eligibility Checklist

These forms should be faxed to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 8:00 a.m. and 4:30 p.m. Eastern time. The CTSU registrar will verify that the investigator is CTSU-credentialed and that all regulatory requirements have been met. The registrar will also check the enrollment forms for completeness and follow-up with the site to resolve any discrepancies.

Once investigator and patient eligibility are confirmed, the CTSU will contact the RTOG to obtain a randomization assignment and assignment of a unique patient ID. The CTSU will then contact the enrolling site and convey the patient ID number (*to be used on all future forms and correspondence*) and the patient's treatment assignment. 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 NOTE-IMRT IS NOT ALLOWED ON THIS STUDY (6/7/04)

6.1 Treatment Arms (1/15/02)

Radiation therapy (*RT*) will be delivered identically to patients in both Arm 1 and Arm 2.

6.1.1 Arm 1

For patients assigned to Arm 1, RT will begin 8 weeks after the date of the first LHRH agonist injection.

6.1.2 Arm 2

For patients assigned to Arm 2, RT will begin 28 weeks after the date of the first LHRH agonist injection.

6.2 Physical Factors

Conventional or CT simulation on equipment that reproduces the geometry of the treatment machine and provides diagnostic (*or CT-based digitally reconstructed*) radiographs is required. Bladder contrast material should be used,⁴⁷ and a retrograde urethrogram may be performed as a treatment planning aid.⁴⁸ A catheter may be placed into the rectum and approximately 10-15 cc. of contrast material may be introduced. After conventional simulation, a treatment planning CT scan referenced to the simulation fields will be done in a manner that reproduces the simulation (*including bladder and rectal contrast*) and treatment conditions (*e.g., patient immobilization, and bladder distention*).

6.2.1 Field Arrangement

A multiple (≥ 4), preferably isocentric, stationary field arrangement will be used.

6.2.2 Field Design

Customized blocking material with $\leq 5\%$ primary beam transmission (≥ 4.3 HVL) or a multileaf collimation system will be used to comply with field margin and normal tissue dose requirements. Blocking will be necessary to shield portions of the urinary bladder and the posterior segment of the rectum on lateral and/or oblique treatment fields.

6.2.3 Treatment Equipment

Treatment will be administered on an isocentrically mounted megavoltage unit with photon energy ≥ 6 MV (≥ 10 MV is preferred). The minimum source-to-axis (*SAD*) distance will be 100 cm.

6.3 Target Volumes

6.3.1 Regional Lymphatic Irradiation (6/6/01)

6.3.1.1 For patients in whom the regional lymph nodes were assessed with radiologic methods (*e.g., CT and/or MRI*), the clinical tumor (*T*) stage (*Appendix III*), prostatic biopsy Gleason Score (*GS*) classification, and serum PSA level will be used to define a subset of patients with a risk of regional lymph node involvement that reaches or exceeds 15%.^{49, 50} These (*protocol eligible*) patients have the following pretherapy combination of factors:

Lymph Node Risk \geq 15%		
PSA = 4.1-10.0 and	PSA = 10.1-20.0 and	PSA >20 and
GS 7 and T3-4	GS 6 and T3-4 or GS 7 and T2a-T4 or GS 8-10 and T1b-1c	GS 6 and T2a-T4

In all other patients in whom the regional lymph nodes were assessed with radiologic methods (e.g., CT and/or MRI), and whose PSA, clinical tumor (T) stage, and Gleason Score combination are not included in the above table, prostatic irradiation only will be administered as defined in Section 6.3.2.

6.3.1.2 For patients in whom the regional lymph nodes were assessed with pelvic lymph node dissection or sampling (via laparoscopy or laparotomy) and were node-negative (N0), prostatic irradiation only will be administered as defined in Section 6.3.2.

6.3.1.3 The regional lymphatic target volume will include the external and internal iliac lymph node-bearing areas, and is optimally defined with the planning CT scan.⁵¹ In lieu of CT-based target definition of the nodal volume, the following landmarks may be used to determine the field borders: (1) superiorly - S1-S2 interspace; (2) inferiorly - 2.0 cm below the most inferior aspect of the prostate; (3) laterally - 2.0 cm lateral to the pelvic brim (arcuate line); (4) anteriorly - anterior symphysis pubis; and, (5) posteriorly - S3-4 interspace. Although care must be taken to adequately cover the internal and external iliac lymph nodes below the SI joints and to include the posterior extension of the seminal vesicles, complex blocking to shield portions of the small intestine and rectum is recommended.

6.3.1.4 The regional lymph node irradiation fields will also include the primary tumor target volume (as defined in Section 6.3.2.1) and seminal vesicles plus 1.0-1.5 cm margin as determined by treatment planning CT scan.

6.3.2 Prostatic Irradiation (6/7/04)

6.3.2.1 The primary tumor target volume will be defined with CT-based treatment planning. The gross tumor volume (GTV) will consist of the prostate gland and any clinically or radiologically evident extraprostatic tumor extensions (e.g., seminal vesicle invasion). The planning target volume (PTV) will conform to the GTV plus 1.0-1.5 cm margin to account for subclinical extraprostatic tumor extension and variations in treatment set up and internal organ motion (see Section 6.8 for potential modifications based on normal tissue considerations). Field and block margins will be placed to account for the field edge effect of dose build-up, such that the PTV receives the specified dose within the compliance criteria (Section 6.10).

6.4 Doses

6.4.1 Dose Specification

The prescribed doses will be defined in accordance with the ICRU Report #50 reference point(s) which typically are located on the central axis at the projected center of the target volume(s) or at the intersection of the beam axes. All patients will require transverse plane isodose plans at the center of both the regional lymphatic irradiation (when treated; see Section 6.3.1.1) and the prostatic target volumes.

6.4.2 Regional Lymphatic Irradiation

The total cumulative target dose will be 46.8 Gy delivered in 26 fractions at a daily dose fraction of 1.8 Gy. All fields will be treated at each once daily session, 5 days per week, over an approximate 5-week duration.

6.4.3 Prostatic Irradiation

The PTV (see Section 6.3.2.1) will receive a total cumulative target dose of 70.2 Gy delivered in 39 fractions at a daily dose fraction of 1.8 Gy. For patients treated with regional lymphatic irradiation (46.8 Gy), the prostatic “boost” treatments (i.e., the PTV as described in Section 6.3.2.1) will begin immediately upon completion of regional lymphatic irradiation, and an additional 23.4 Gy will be administered in 13 fractions at a daily fraction rate of 1.8 Gy. All fields will be treated at each once daily session, 5 days per week, over a cumulative (prostatic \pm nodal) approximate 8-week duration.

6.4.4 Dose Modification

With judicious use of ancillary treatment (see Section 9.1) and/or treatment interruption (see Section 6.5.1), RT dose reduction will rarely be necessary. However, if RT-related toxicity is severe enough that

administration of full dose is considered contraindicated by the responsible Radiation Oncologist, the study chair (*Thomas M. Pisansky, M.D. 507/284-4655; pisansky.thomas@mayo.edu*) should be contacted. The reason(s) for the dose reduction must be documented in the radiation therapy treatment record.

6.5 Treatment Parameters

Specific instructions will be given to assure patients are treated with full bladder in order to potentially displace small bowel and a greater amount of bladder out of the treatment volume.

6.5.1 Treatment Interruption

Use of a treatment interruption(s) will be permitted only when RT-related toxicity is not reduced to an acceptable level with use of ancillary treatment (*see Section 9.1*), or when acute grade ≥ 3 toxicity occurs. See Section 6.9.1.4. The reason(s) for the interruption must be documented in the radiation therapy treatment record. The duration of treatment interruption should be minimized, but RT should not resume until toxicity is grade < 3 .

6.6 Beam Verification (Port) Films

Beam verification films of each treatment field will be obtained until satisfactory. Thereafter, beam verification films will be obtained each 5-10 treatments and at the time of any field modification.

6.7 Dosimetry

Isodose distributions, not corrected for any tissue inhomogeneity, in a transverse plane containing central axis of each treatment volume (*i.e., prostatic \pm regional lymphatic*), will be obtained and will represent the summation of all treatment fields with wedges and blocking. The margins of the GTV (*see Section 6.3.2.1*) and the rectum at the relevant contour level will be indicated as internal structures on this/these contour(s). The maximum allowable dose inhomogeneity will be +5% (*measured as an isodose area > 2 cm² rather than as "hotspots"*) and -5% of the dose at the specification point(s).

6.8 Critical Normal Structures

6.8.1 The bladder may receive the same dose as the regional lymphatics (*when included in the target volume*). By necessity, the bladder base will receive the prostatic target dose. However, bladder distention will be performed to minimize the volume of irradiated bladder. Doses to the entire bladder will not exceed 60 Gy.

6.8.2 Doses to the full rectal circumference will not exceed 55 Gy. Portions of the anterior rectal wall will, by necessity, receive the same dose as the prostatic target volume.

6.9 Radiation Toxicity

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

6.9.1.1 Skin reactions.

6.9.1.2 Small bowel or rectal irritation manifesting as abdominal cramping, diarrhea, rectal urgency or hematochezia.

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

6.9.1.4 Reactions within 90 days of the treatment start date will be scored with the revised NCI Common Toxicity Criteria, Version 2.0. For reactions appearing or persisting beyond 90 days, refer to the RTOG/EORTC Late Radiation Morbidity Scoring Scheme (*Appendix IV*).

6.10 Compliance Criteria

Assessment	Per Protocol	Variation, Acceptable	Deviation, Unacceptable
Field Borders	up to 1 cm. beyond borders as stated in protocol	> 1 to 2 cm beyond borders as stated in protocol	> 2 cm beyond borders as stated in protocol
Total Dose	$< 5\%$ of protocol specified dose	> 5 to 10% of protocol specified dose	$> 10\%$ of protocol specified dose
Fractionation	Within 0.05 Gy of specified 1.8 Gy daily fraction size	> 0.05 Gy to 0.10 Gy of 1.8 Gy	> 0.10 Gy of 1.8 Gy
Elapsed Days During Radiotherapy	1 to 7 break days	8 to 14 days	> 14 days

7.0 DRUG THERAPY

7.1 Treatment Plan (6/6/01, 1/15/02) (6/7/04)

All patients will receive total androgen suppression (*LHRH agonist and Casodex or Eulexin*) (*TAS*) before and during radiation therapy (*RT*). For patients who began LHRH agonists \leq 30 days before randomization, the time to beginning RT will be determined from the date the LHRH agonist was first started. As previously stated (*Section 3.2.7*), patients treated with prior androgen suppression therapy are eligible for this study only if the LHRH agonist was started within 30 days of the randomization date and the Casodex or Eulexin was (*or will be*) started within (*before or after*) 14 days of the first LHRH agonist injection.

7.1.1 Arm 1 (1/15/02)

For patients assigned to Arm 1, TAS will be administered for 8 weeks prior to the initiation of RT, and will be given throughout RT. The LHRH agonist will be given for a total duration of 16 weeks (*8 weeks before and 8 weeks during RT*). Casodex (*see Section 7.5*) or Eulexin (*see Section 7.4*) will begin within (*before or after*) 14 days of the date the first LHRH agonist injection is administered, and will be terminated on the last day of RT or on day 112 (*16 weeks*), whichever occurs first. During RT interruptions, TAS will be continued.

7.1.1.1 Commercially available LHRH agonists will be prescribed by physician preference and administered per package instructions.

7.1.1.2 Casodex
Casodex is administered orally at a dose of one 50 mg tablet per day.

7.1.1.3 Eulexin
Eulexin is administered orally at a dose of two 125 mg capsules three times a day for a total daily dose of 750 mg (*six capsules*).

7.1.2 Arm 2 (1/15/02)

For patients assigned to Arm 2, TAS will be administered for 28 weeks prior to the initiation of RT, and will be given throughout RT. The LHRH agonist will be given for a total duration of 36 weeks (*28 weeks before and 8 weeks during RT*). Casodex (*see Section 7.5*) or Eulexin (*see Section 7.4*) will begin within (*before or after*) 14 days of the date that the first LHRH agonist injection is administered, and will be terminated on the last day of RT or on day 252 (*36 weeks*), whichever occurs first. During RT interruptions, TAS will be continued.

7.1.2.1 Commercially available LHRH agonists will be prescribed by physician preference and administered per package instructions.

7.1.2.2 Casodex
Casodex is administered orally at a dose of one 50 mg tablet per day.

7.1.2.3 Eulexin
Eulexin is administered orally at a dose of two 125 mg capsules three times a day for a total daily dose of 750 mg (*six capsules*).

7.2 LHRH agonists (such as leuprolide, goserelin, buserelin, triptorelin)

7.2.1 Description
LHRH agonists are long acting analogs of the native LHRH peptide and are effective at reducing serum testosterone.

7.2.2 Supply
LHRH agonists are commercially available. Currently 4 have been approved by the FDA in the US and are considered similarly effective at reducing serum testosterone.

7.2.3 Storage
LHRH agonists should be stored as directed by the commercial supplier.

7.2.4 Administration
LHRH agonists are administered with a variety of techniques, including subcutaneous insertion of a solid plug in the anterior abdominal wall (Zoladex), intramuscular injection (Lupron), subcutaneous injection (Eligard), or insertion of a long-acting cylinder that slowly releases the agent (Viadur). The manufacturer's instructions should be followed.

7.2.5 Toxicity
Class related toxicity is generally a manifestation of the mechanism of action and due to low testosterone levels. In the majority of patients, testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. The most common side effect of LHRH agonists is vasomotor hot flashes; edema, gynecomastia, bone pain, thrombosis, and GI disturbances have occurred.

Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in patients with urinary obstruction or hematuria which, if aggravated, may lead to worsening of urinary symptoms.

7.3 Eulexin (Flutamide)

7.3.1 Description

Eulexin (*flutamide*) is a substituted anilide. It is a fine, light, yellow powder, insoluble in water but soluble in common organic solvents such as aromatic or halogenated hydrocarbons. Its concentration in plasma can be determined by gas chromatography. Eulexin is a non-steroid anti-androgen that is metabolized into a hydroxylated derivative, which effectively competes with hydrotestosterone for androgen receptor sites.

7.3.2 Supply

Eulexin is commercially available as a 125 mg capsule.

7.3.3 Storage

Eulexin should be stored at temperatures ranging from 20°-30°C (36°-86°F) and should be protected from excessive moisture.

7.3.4 Administration

The drug is administered orally at a dose of two 125 mg capsules three times a day for a total daily dose of 750 mg (*six capsules*). Administration of the drug will be suspended only if there is an apparent or suspected reaction to the drug.

7.3.5 Toxicity

The reported side effects of treatment include diarrhea and anemia. A high percentage of patients treated with flutamide alone developed gynecomastia within 2-8 months. There have been post-marketing reports of hospitalization, and, rarely, death due to liver failure in patients taking flutamide. Evidence of hepatic injury included elevated serum transaminase levels, jaundice, hepatic encephalopathy, and death related to acute hepatic failure. The hepatic injury was reversible after prompt discontinuation of therapy in some patients. Approximately half of the reported cases occurred within the initial 3 months of treatment with flutamide.

7.3.6 Dose Modification Schedule (6/6/01)

If gastrointestinal disturbances (*cramps, diarrhea*) occur prior to initiation of radiotherapy, flutamide will be withheld until the side effects subside and then reintroduced at a dose of 250 mg/day increasing the dose (*at 3 day intervals*) to 500 mg/day then to 750 mg/day as tolerated.

If gastrointestinal disturbances occur after administration of radiotherapy, it might be difficult to identify their cause. However, if severity of diarrhea exceeds the level commonly observed during pelvic irradiation, the toxicity will be ascribed to flutamide and the drug will be permanently discontinued.

ALT will be measured pretreatment, then monthly during oral antiandrogen therapy. If ALT increases > 2 x upper institutional limit of normal, flutamide must be discontinued.

7.4 Casodex (Bicalutamide)

7.4.1 Description

Casodex (*bicalutamide*) is a 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. 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*).

7.4.2 Supply

Casodex is commercially available as a 50 mg tablet.

7.4.3 Storage

Casodex should be stored in a dry place at room temperature between 68°-77° F.

7.4.4 Administration

Casodex is administered orally at a dose of one 50 mg tablet per day. Administration will be suspended (*see Section 7.5.6*) only if there is an apparent or suspected reaction to the drug.

7.4.5 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 protocol therapy or during the first 3 months after cessation of therapy. The use of barrier contraceptives is advised.

The most frequent adverse events reported among subjects receiving Casodex therapy are breast tenderness, breast swelling, and hot flashes. Adverse events not directly related to the pharmacological properties of Casodex were infrequent.

Nonpharmacological adverse events, reported in the trial using Casodex 50 mg as monotherapy, include asthenia, pelvic pain, peripheral edema, pruritus, rash, constipation, impotence, dyspnea, nausea, and pain (*Kaisary 1994*). There has been no observed change in cardiac parameters during long-term administration of Casodex 50 mg daily.

When Casodex 50 mg was given in combination with an LHRH analogue, the LHRH analogue adverse event profile predominated with a high incidence of hot flashes (53%) and relatively low incidences of gynecomastia (4.7%) and breast pain (3.2%).

7.4.6 Dose Modification Schedule

Casodex should be discontinued in instances of chemical liver toxicity. ALT will be measured pretreatment and then monthly during antiandrogen therapy. If the ALT rises > 2 x the institutional upper limit of normal, Casodex must be discontinued.

7.5 Toxicity Reporting (6/7/04)

7.5.1 The revised NCI Common Toxicity Criteria Version 2.0 (3/98) will be used to score acute drug therapy and radiation (≤ 90 days) toxicity. The following guidelines for reporting adverse drug reactions (ADRs) apply to any research protocol that uses commercial anticancer agents. The following ADRs experienced by patients accrued to these protocols and attributed to the commercial agent(s) should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days. This study will be monitored by the Clinical Data Update System (CDUS) version 1.X. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. The following ADR's attributed to commercial agent(s) should be:

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

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

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

7.5.2 The ADR report should be documented on Form FDA 3500 and mailed to all the following addresses:

FDA	Investigational Drug Branch	RTOG Headquarters
MedWatch	P.O. Box 30012	1101 Market St. 14 th floor
Rockville, MD 20852	Bethesda, MD 20824	Philadelphia, PA 19107
Fax 800-332-0178	301-230-2330 (24 hrs.)	215-717-2762 (24 hrs.)
FDA only via internet: www.fda.gov/medwatch	Fax 301-230-0159	Fax 215-717-0990

7.6 CTSU Investigators - Adverse Event (AE) Reporting (8/25/00)

This study will utilize the CTC version 2.0 (3/98) 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.

8.0 SURGERY

8.1 Prostate Rebiopsy (6/7/04)

- 8.1.1** A prostatic biopsy is strongly recommended for patients with a persistent (typically at least 30 months after radiation therapy) and suspicious post-treatment residual prostatic abnormality, growth of a palpable prostatic abnormality, or two or more PSA values \geq the nadir PSA value (the lowest PSA after radiation therapy) + 2 ng/ml. Although the ASTRO definition of biochemical progression⁵² will not be used per se as a recommendation for prostatic biopsy, it will be reported should it occur.
- 8.1.2** A prostatic biopsy is strongly recommended for patients with evidence of nodal and/or distant failure to assist in accurately determining the “true” local control rate. In the absence of a biopsy, such patients will be considered local failures if their exam is abnormal. If their exam is normal or if they are on long-term androgen suppression therapy, they will be censored at the last point in time they were considered locally controlled and considered “inevaluable” for further assessment of local control.

9.0 OTHER THERAPY

9.1 Ancillary Treatment

Acute radiation therapy induced side effects may be managed at the discretion of the radiation oncologist. Measures such as a low residue diet, antiemetic or antidiarrheal medications, steroid-containing topical preparations, topical bladder analgesic (e.g., *phenazopyridine HCl*) or anti-spasmodic (e.g., *α -adrenergic blockers*) agents may be administered in accordance with manufacturer recommendations.

9.2 TAS-Induced Hot Flashes

Total androgen suppression therapy may cause bothersome symptoms of vasomotor instability (i.e., *hot flashes*). These symptoms may be managed at physician discretion with Megace (*megestrol acetate*),⁵³ 20 mg orally twice daily (*titrated as necessary*), or with Effexor (*venlafaxine hydrochloride*),⁵⁴ 12.5 mg orally twice daily (*titrated as necessary*).

10.0 PATHOLOGY (6/7/04)

- 10.1** Central pathology reviews of the diagnostic and any post-treatment prostatic biopsies are planned.
- 10.2** Hematoxylin and eosin (*H & E*) stained slides and a representative tissue block of all pathologic material, the pathology report, and a Pathology Submission Form will be submitted to the RTOG Tissue Bank:

LDS Hospital
Department of Pathology
E.M. Laboratory
8th Avenue & C Street
Salt Lake City, UT 84143
(801) 408-5626
FAX (801) 408-5020
e-mail: ldhflinn@ihc.com

The collection, storage, and distribution of tissue specimens will conform to guidelines developed by the Intergroup Specimen Banking Committee. Because of the long-term nature of this clinical research effort, emerging (*and perhaps yet unknown*) technologies may have the greatest relevance to the clinical data resources when this becomes available. Thus, the tissue resource will not be released for investigation until such time as deemed appropriate for its association with the clinical endpoints this study aims to assess.

- 10.2.1** Hematoxylin & eosin (*H & E*) stained slides will be retained until completion of the analysis of the study. Slides will be returned if specifically requested at that time.
- 10.2.2** One paraffin block of tumor or, if the block cannot be released, 10 unstained slide sections (*maximum thickness of 5 microns each*) mounted on sialinized (*or other “sticky”*) slides will be submitted. The block/slides must be clearly labeled with the same pathology identification number as on the institutional pathology report.
- 10.2.3** A Pathology Submission Form must be included and must clearly identify the enclosed materials as being for the RTOG Tissue Bank.
- 10.3** All pretreatment biopsies will be assessed for the presence of tumor and graded according to the Gleason Score classification (*Appendix VI*).
- 10.4** Post therapy biopsies will be assessed for the presence of residual tumor.

- 10.4.1** All positive biopsies will be histologically graded according to the Gleason Score classification, and the degree of therapy effect in the tumor cells will be graded according to Rakozy et al.⁶²
- 10.4.2** In cases where there is difficulty in diagnosis, immunohistochemical staining for cytokeratin and/or high molecular weight cytokeratin will be performed to aid in the distinction of atypical benign glands from carcinoma.
- 10.5** RTOG will reimburse pathologists from submitting institutions \$100 per case if proper materials are submitted (*reimbursement is handled through an invoice submitted to RTOG Administration, ATT: Path Reimbursement*).
- 10.6** Patient consent form should give the Pathology Department authority and responsibility to comply with submission of these materials (*pathology blocks belong to the patient from whom tissue has been removed*).
- 10.7** **CTSU Investigators (8/25/00, 6/6/01, 1/15/02)**
All pathology materials and associated forms and reports are to be submitted directly to the RTOG Tissue Bank within two weeks of randomization. Refer to Section 10.0 of the protocol (*above*) for further details on collection and submission. Please submit a copy of the Pathology Submission Form(s) and Pathology Report(s) to the CTSU Data Center.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (8/25/00, 6/6/01) (6/7/04)

Parameters	Pre-Random.^d	Prior to radiotherapy	Weekly during radiotherapy	At completion of radiotherapy	Follow-up^j	At disease progression
H&P, including Tumor Measurement	X	X ^g		X	X	X
Zubrod Perform.	X	X ^g	X	X	X	X
Hgb, WBC, Plt	X		X ¹		X ¹	X ¹
Chemistry ^a	X	X ^h	X ^h		X ¹	X ¹
PSA	X ^e	X ^g		X	X	X
Bone Scan ^b	X ^c	X ¹			X ¹	X
Pelvic lymph node assessment ^c	X ^c	X ¹			X ¹	X
Toxicity Assessment		X ^g	X	X	X	X
Prostate Biopsy	X ^{e,i}				X ^{f,i}	X ^{f,k}

- Serum ALT, Alk Phos, Total Bilirubin, Creatinine.
- Diagnostic imaging studies (*e.g., standard radiography, tomography, magnetic resonance imaging*) may be necessary to evaluate suspicious areas noted on bone scan.
- May be performed with pelvic \pm abdominal computed tomography or (*external body coil*) magnetic resonance imaging, lymphangiography, or pelvic lymph node dissection or sampling (*via laparoscopy or laparotomy*).
- Within 28 days prior to randomization, unless otherwise specified.
- Performed within 90 days (*PSA, bone scan, node assessment*) or 180 days (*prostate biopsy*) before randomization. The PSA must also be done before the start of any hormonal therapy (*exclusive of finasteride*).
- Must include Gleason Score classification.
- Within one week before start of RT (*Arm 1 patients*) or every two months and within one week before the start of RT (*Arm 2 patients*).
- ALT and total bilirubin every month during androgen suppression therapy; alk phos and creatinine may be omitted.
- At physician discretion as clinically indicated.
- Every 3 months for 1 year, then every 6 months for years 2-5, then annually.
- A prostatic biopsy is strongly recommended in patients with a consistent and “significant” rise in the serum PSA level (*see Section 8.1.1*), a persistent and suspicious post-treatment residual prostatic abnormality (*see Section 8.1.1*), or growth of a prostatic abnormality (*see Section 11.3.2.6*). A prostate biopsy is recommended for patients with nodal or distant failure (*see Section 8.1.2*).

11.2 Follow-up Schedule

11.2.1 Every 3 months for 1 year.

11.2.2 Every 6 months for years 2 through 5, then annually for the remainder of the patient’s life.

11.2.3 A bone scan will be performed in the patient with bone pain that cannot be attributed to intercurrent illness (e.g., trauma). Diagnostic imaging studies (e.g., standard radiography, tomography, or magnetic resonance imaging) may be necessary to confirm the diagnosis of metastatic disease.

11.3 Measurement of Effect

11.3.1 PSA levels and prostate tumor dimensions expressed in centimeters (cm) must be recorded on the diagrams on the data collection forms for initial and follow-up evaluations of the patient. All PSA levels done during a follow-up interval will be recorded on the data forms.

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

11.3.2.1 PSA Complete Response (PSA-CR): A PSA-CR will be declared if the PSA becomes undetectable (< 0.3 ng/ml) by the day of discontinuation of total androgen suppression therapy.

11.3.2.2 Clinical Complete Response (CR): complete resolution of all palpable prostate abnormalities. *Note*: patients with non-palpable lesions will not be considered in this category.

11.3.2.3 Equivocal Disease (ER): prostate changes are abnormal due to treatment and not representative of tumor.

11.3.2.4 Partial Response (PR): $> 50\%$ reduction in the sum of the products of the largest clinically palpable perpendicular dimensions of the prostate tumor that is present for at least one month. *Note*: patients with non-palpable lesions will not be considered in this category.

11.3.2.5 Stable Disease (SD): $\leq 50\%$ reduction in the sum of the products of the largest clinically palpable perpendicular dimensions of the prostate tumor. *Note*: patients with non-palpable lesions will be considered to have SD, unless there is evidence of disease progression.

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

- Local tumor progression: clinical evidence of disease progression or recurrence measured by a $\geq 25\%$ increase in the product of the two largest perpendicular dimensions of the prostate tumor, and/or development (i.e., not present at initial diagnosis) of one or more of the following: extension of the prostate tumor into periprostatic tissue or seminal vesicle (T3); tumor fixation or invasion of adjacent structures other than the seminal vesicles (T4); ureteric obstruction at the level of the ureterovesical junction; urethral obstruction that requires prostatic resection (and resected tissue demonstrates prostatic adenocarcinoma) or urinary diversion; or hematuria due to prostate cancer progression.
- Regional nodal recurrence: clinical and/or radiologic evidence of tumor recurrence within the pelvic lymphatic or soft tissues below the bifurcation of the common iliac arteries, or development of ureteric obstruction at a site other than the ureterovesical junction. Confirmation by biopsy is recommended.
- Distant relapse: clinical and/or radiologic evidence of hematogenous (e.g., osseous, hepatic, etc.) and/or extrapelvic lymphatic or soft tissue tumor relapse. Confirmation by biopsy is recommended for non-osseous sites of relapse.

11.4 Other Response Parameters (6/7/04)

11.4.1 Freedom from Biochemical (PSA) Failure: The “PSA nadir” will be defined as the lowest PSA value reached immediately before a biochemical failure, from the time of the first required follow-up visit (3 months after completing radiation therapy). Biochemical failure is defined as a consistent and significant rise in the serum PSA level. The ASTRO definition of rising PSA will be used.⁵² Thus, when the serum PSA rises on three consecutive occasions from the nadir value, biochemical failure has occurred and the date of failure is midway between the last non-rising PSA and the first rise in PSA.

11.4.2 Time to Local Progression: The time to progression will be measured from the date of randomization to the date of local tumor recurrence (see Section 11.3.2.6). Patients with a normal prostate examination and no evidence of biochemical failure will be considered locally controlled. Patients with a residual prostate abnormality (typically at least 30 months after radiation therapy), growth of a prostatic abnormality, or a consistent and “significant” rise in the serum PSA level (see Section 8.1.1) should undergo prostate biopsy. If the prostate examination is normal or if the patient is on long-term “salvage” androgen suppression therapy, they will be censored at the last time point they were considered locally controlled and considered “inevaluable” for further assessment of local control.

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

11.4.4 Disease-Free Survival: The disease-free survival duration will be measured from the date of randomization to the date of disease progression or the date of death from any cause. This endpoint will

include all measures of disease status (*examination, imaging studies, biopsy results, and PSA determinations*).

11.4.5 Disease-Specific Survival: Disease-specific survival duration will be measured from the date of randomization to the date of death due to prostate cancer. Causes of death may require review by the study chair or their designee. Death due to prostate cancer will be defined as:

11.4.5.1 Primary cause of death certified as due to prostate cancer.

11.4.5.2 Death in association with any of the following conditions:

- Further clinical tumor progression occurring after initiation of “salvage” anti-tumor (*e.g., androgen suppression*) therapy.
- A rise (*that exceeds 1.0 ng/ml*) in the serum PSA level on at least two consecutive occasions that occurs during or after “salvage” androgen suppression therapy.
- Disease progression in the absence of any anti-tumor therapy.

11.4.5.3 Death from a complication of therapy, irrespective of disease status.

11.4.6 Overall Survival: Survival duration will be measured from the date of randomization to the date of death from any cause. A post-mortem examination will be performed whenever possible and a copy of the final post-mortem report will be sent to RTOG Headquarters.

12.0 DATA COLLECTION (6/7/04)

(*RTOG, American College of Radiology 1101 Market Street, Suite 1400, Philadelphia, PA 19107,)*

12.1 Summary of Data Submission

<u>Item</u>	<u>Due</u>
Demographic Form (A5) Initial Evaluation Form (I1) Pathology Report (P1) Pathology Blocks/Slides (P2)	Within 2 weeks of study entry.
Post Induction Form (F0) (*M1 data will be incorporated into the F0 form.)	At 9 weeks (<i>Arm 1</i>); at 9, 17, 25, and 29 weeks (<i>Arm 2</i>)
<u>Preliminary Dosimetry Information:</u> RT Prescription (<i>Protocol Treatment Form</i>) (T2) Films (<i>simulation and portal</i>) (T3) Calculations (T4)	Within 1 week of start of RT.
Initial Follow-up Form (FS) Submit an additional FS Form to report toxicity presenting ≤90 days from the start of RT. (*M1 data will be incorporated in the FS form.)	Arm 1: Within 1 week of RT end (<i>17 weeks</i>) Arm 2: Within 1 week of RT end (<i>37 weeks</i>)
<u>Final Dosimetry Information:</u> Radiotherapy Form (T1) Daily Treatment Record (T5) Isodose Distribution (T6) Boost Films (<i>simulation and portal</i>) (T8)	Within 1 week of RT end.
Follow-up Form (F1)	Arm 1: Week 29, then every 3 months x 3 (<i>1st year post-RT</i>), then every 6 months x 4 years, then annually. Also at disease progression/relapse and at death. Arm 2: Week 49, then every 3 months x 3 (<i>1st year post-RT</i>), then every 6 months x 4 years, then annually. Also at disease progression/relapse and at death.
Pathology Report (P1), rebiopsy Pathology Blocks/Slides (P2), rebiopsy	As applicable.

12.2 CTSU Investigators (8/25/00, 1/15/02)**12.2.1 Data Submission**

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 Data Center (1-888-691-8039) according to instructions in the CTSU registration procedures section of the protocol.
- Pathology materials and accompanying forms and reports should be sent directly to the RTOG LDS Hospital in accordance with the pathology section of the protocol. A copy of the RTOG Pathology Submission Form(s) and Pathology Report(s) also should be sent to the CTSU Data Center for tracking purposes.
- RT forms, with the exception of the Radiotherapy Form (T1), should be sent to the RTOG Dosimetry Department. Form T1 should be sent to the CTSU Data Center. A copy of the Dosimetry Transmittal Form also should be sent to the CTSU for tracking purposes.

All other forms must be mailed directly to the CTSU at the address below. The CTSU will forward all information to the RTOG.

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

12.2.2 Radiation Therapy Documentation Submission (1/15/02)

Dosimetry materials and data (*preliminary dosimetry information and final dosimetry information*) are to be submitted directly to the Dosimetry Department, RTOG, at the address listed in Section 12.1 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 12.0 of the protocol for a complete inventory of dosimetry items to be submitted. Radiotherapy Form (T1) is considered a case report form and should be sent to the CTSU Data Center for forwarding to RTOG. A copy of the Dosimetry Transmittal Form also should be sent to the CTSU for tracking purposes. Any dosimetry questions should be directed to the Dosimetry Department at RTOG headquarters (215) 574-3219.

13.0 STATISTICAL CONSIDERATIONS**13.1 Study Endpoints(6/7/04)****13.1.1 Primary Endpoint**

- Disease-specific survival

13.1.2 Secondary Endpoints

- Overall Survival
- Disease-free survival
- Clinical patterns of tumor recurrence (*i.e., local regional progression, distant metastasis*)
- Time to first biochemical failure (the ASTRO consensus failure definition for patients treated with only radiation therapy will be used⁵². However, other failure definitions for patients receiving hormones in addition to radiation, which are validated and published during the conduct of this trial may also be employed. If one definition becomes the consensus definition of biochemical failure for this type of combined treatment regimen, it will also be used.)
- Time to second biochemical failure while on salvage androgen suppression (*i.e., hormone-refractory state*)
- Treatment-induced morbidity

13.2 Sample Size**13.2.1 Stratification**

The treatment allocation scheme described by Zelen will be used at randomization. The stratifying variables are serum PSA (≤ 10 , $> 10 - 20$, > 20), tumor stage (*T1b-2*, *T3-4*), Gleason Score (*2 - 4*, *5 - 6*, *7 - 10*), and prior hormones (*no*, *yes*).

13.2.2 Overview

The primary hypothesis of this trial is that the extended duration of total androgen suppression (*TAS*) prior to radiation therapy (*Arm 2*) will reduce the mortality rate due to prostate cancer. Disease-specific survival was selected (*instead of overall survival*) as the primary endpoint of the sample size derivation and analysis plan because a high proportion of deaths may be due to causes other than prostate cancer. A 33% reduction in the average annual hazard for prostate cancer death is considered of clinical importance. According to a similar population of patients entered in RTOG 86-10 with median follow-up of 6 years, approximately 45% of all deaths were certified due to prostate cancer. Because patients eligible for the present study are apt to have lower pre-treatment PSA levels than patients entered in RTOG 86-10, the proportion of prostate cancer-related deaths may be less. If we assume 40% of all deaths will be due to prostate cancer in the present study, a 33% reduction in the hazard of prostate cancer death corresponds to a 13% reduction in all cause mortality given the treatment has no impact in the risk of dying from non-prostate cancer-related causes. Because there may be inconsistency in death certification among clinicians, the study chair or their designate will review the cause of death in all deceased patients.

13.2.3 Sample Size Derivation

Assuming proportional hazards for disease-specific survival, **1540 cases are required to be uniformly entered over 4 years** to reject the null hypothesis with 90% power and a significance level of 0.05 (*0.025 for one-sided test*). The “initial” analysis will occur approximately 6 years after the closure of the study, when 270 prostate cancer-related deaths have been observed on both arms. The sample size accounts for three interim analyses and 10% ineligible or lack-of-data cases. The projected numbers of prostate deaths are 160 and 110 for Arm 1 and Arm 2, respectively.

Based on a similar population treated with 4-month duration neoadjuvant *TAS*, the 8-year disease-specific survival for the control arm (*Arm 1*) was estimated to be 79%. With 770 cases in each arm, a two-sided logrank test with significance level of 0.05 will have 90% power to detect a 33% reduction in the hazard for prostate cancer-related death by Arm 2 compared with the control arm. Similarly, with such a sample size, there will be a 90% power to detect a 22% reduction in the hazard of all cause deaths in Arm 2 compared to the control arm.

13.3 Analysis Plan

13.3.1 Statistical Methods

Disease-specific, overall, and disease-free survivals will be calculated by the Kaplan-Meier method.⁵⁵ The treatment effect with respect to all endpoints will be done with the logrank test statistics.^{56, 57} All eligible and evaluable patients will be included in the intent-to-treat analysis. The cumulative incidence method⁵⁸ will be used to estimate the 5-year rates of biochemical failure and the clinical patterns of tumor recurrence.

13.3.2 Interim Reports

Interim reports are prepared every six months until the closure of the study. In general, the interim reports will include:

- The patient accrual rate including the rates in each stratum;
- Protocol compliance and quality of submitted data;
- The frequencies and severity of toxicity.

13.3.3 Interim Treatment Analysis for Early Stopping

Three such interim treatment comparisons shall be performed when we observe 50, 130, and 200 prostate cancer-related deaths. The first interim analysis is projected to take place when 100% total accrual is reached. The second interim analysis is projected to take place at the third year after the closure (*2 years of follow-up*). The third interim analysis is projected to take place at the fifth year after the closure (*4 years of follow-up*). For each of these interim analyses, toxicity, treatment delivery and efficacy statistics will be reported to RTOG Data Monitoring Committee (*DMC*). The boundary for early stopping (*or the nominal significance level for the test*) will be computed based on the observed number of deaths according to the O’Brian-Fleming alpha spending function approach.^{59, 60} If the difference is highly significant, i.e., p value less than the nominal level, the responsible statistician will recommend to Data Monitoring Committee that the study be written up for publication. In addition, the conditional power for the hypothesized treatment difference given observed events will also be calculated and presented to the DMC. The low conditional power will provide a basis for the possible early stopping or publication for the lack of efficacy.

13.3.4 Initial Analysis for Reporting Treatment Effects

This analysis will be done after the end of the follow-up period or 270 prostate cancer-related deaths are observed unless the criteria for early stopping are met. It will compare the two treatment arms with respect to the endpoints stated in Section 13.1.

13.4 Inclusion of Minorities

In conformance with the National Institute of Health Revitalization Act of 1993 with regard to inclusion of women and racial/ethnic minorities in clinical research, we also considered the possible interaction between race and treatments. Based on accrual statistics from RTOG 94-13 and 94-08, we projected that 73% of men in the study are white, 23% are black (*not of Hispanic origin*), 3% are Hispanic, 0.4% are Asian or Pacific Islander, 0.2% are American Indian or Alaskan Native, and 0.5% are others and unknown. The following table lists the projected accrual for each racial group. Assuming no difference among races with respect to survival, the statistical power for detecting the hypothesized difference is 80% and 35% for white and black, respectively. With an estimated 54 deaths in the African American population, we are able to detect a 50% hazard reduction by Arm 2 for this subset with statistical power of 80%.

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
Male	3	6	354	46	1123	8	1540

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APPENDIX I (6/7/04)

RTOG 99-10

A PHASE III TRIAL TO EVALUATE THE DURATION OF NEOADJUVANT TOTAL ANDROGEN SUPPRESSION (TAS) AND RADIATION THERAPY (RT) IN INTERMEDIATE-RISK PROSTATE CANCER

SAMPLE CONSENT FOR RESEARCH STUDY

THERE IS A RESEARCH STUDY ABOUT YOUR CONDITION AND ITS TREATMENT. THIS CONSENT FORM WILL TELL YOU ABOUT THIS STUDY AND HOW THE TREATMENT MAY OR MAY NOT HELP YOU.

IT IS IMPORTANT THAT YOU READ AND UNDERSTAND THIS FORM, THE STUDY AND THE TREATMENT BEFORE YOU DECIDE TO BE PART OF THIS STUDY. IF YOU HAVE ANY QUESTIONS ABOUT THIS STUDY, THE TREATMENT OR HOW IT WILL AFFECT YOU, PLEASE ASK YOUR DOCTOR.

RESEARCH STUDY

You have the right to know about the procedures used in this research study and the risks, benefits and alternatives to the treatment in this study. You should know and understand the treatment proposed in this study, how it will be given, how the treatment may help you, how the treatment may harm you, and the choices available to you. This form will tell you about the study, the benefits, the risks and the alternatives so you can decide whether to be a part of this research study.

PURPOSE OF THIS STUDY (6/7/04)

This study uses hormones (*LHRH agonists and Eulexin or Casodex*) given before and during radiation therapy. Half of the patients will receive the hormones for eight (8) weeks before starting radiation therapy. The other half will receive the hormones for 28 weeks before starting radiation therapy. The purpose of the study is to determine whether one of these two schedules is better for prostate cancer. This study will also try to find out more about the side effects of the two different schedules.

DESCRIPTION OF PROCEDURES (6/7/04)

The treatment you will be given will be one of two treatment methods. You will be assigned to one or the other treatment method by chance (*at random*). Although both treatments may be good, it is not known right now which of the two methods of treatment is better. The treatment you get will be assigned by a computerized selection process. Your doctor will call a statistical office where a computer will assign you to one of the two treatment methods. Your chance of receiving one of the two treatments is approximately equal. You will be assigned to one of the following:

Treatment 1: Beginning eight weeks (2 months) before starting your radiation treatments, you will receive injections of hormone therapy and daily Eulexin or Casodex pills. If you are given Eulexin, you will take six (6) pills by mouth every day for eight (8) weeks. If you are given Casodex, you will take one (1) pill by mouth every day for eight (8) weeks. After the eight (8) weeks are up, you will have radiation to your prostate once a day, five (5) days a week, for approximately eight (8) weeks. The hormones will continue on the same schedule during radiation as before the radiation started. Once radiation is completed, you will stop taking the Eulexin or Casodex capsules and no further injections of hormone therapy will be given. The total treatment time will take approximately four months.

Treatment 2: Beginning 28 weeks (7 months) before starting your radiation treatments, you will receive injections of hormone therapy and daily Eulexin or Casodex pills. If you are given Eulexin, you will take six (6) pills by mouth every day for twenty-eight (28) weeks. If you are given Casodex, you will take one (1) pill by mouth every day for twenty-eight (28) weeks. After the twenty-eight (28) weeks are up, you will have radiation to your prostate once a day, five (5) days a week, for approximately eight (8) weeks. The hormones will continue on the same schedule during radiation as before the radiation started. Once radiation is completed, you will stop taking the Eulexin or Casodex capsules and no further injections of hormone therapy will be given. The total treatment time will take approximately nine months.

Also, at the time of your diagnosis by biopsy, all or some of your tumor was removed. As is usually done, this tissue went to the hospital's pathology department for routine testing and diagnosis. After that process was complete, the remaining tumor

samples were stored in the pathology department. You are being asked for permission to use the remainder of the tumor samples for additional tests. Since this tissue was removed at the time of surgery or biopsy, your permission to use this tissue will not lead to any additional procedures or expense. This tissue may be sent to a central office for review and research investigation associated with this protocol.

RISKS AND DISCOMFORTS (6/7/04)

Cancer treatments, whether given in a research study or in the ordinary practice of medicine, may often hurt or harm you (*side effects*). The treatment used in this study 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 tiredness, 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.

LHRH agonists (hormone therapy) can cause hot flashes, sweats, dizziness, breast swelling/tenderness and impotence while taking the drug. Less frequently reported side effects include unusual taste in the mouth, diarrhea, increased skin redness, hives, bone pain, and increased thirst and urination. If you are given leuprolide, in the first few weeks of treatment, leuprolide may cause increased difficulty in urination. If you are given goserelin, an allergic reaction of generalized rash and difficulty breathing has been reported while taking this drug. In animal studies, there is an increased incidence of non-cancerous tumors of the pituitary gland, pancreas, ovary and adrenal gland with large doses of goserelin. However, there is no evidence to date that this has been associated with cancerous or non-cancerous tumors in humans.

Eulexin (Flutamide) and Casodex (Bicalutamide) can cause impotence, loss of libido, breast tenderness, anemia, breast swelling, and hot flashes. The most frequently reported discomforts have been fatigue, back pain, and fluid retention. Approximately 2% of patients had constipation, diarrhea, or nausea or changes in liver function, though these are infrequent. Your liver function will be checked monthly while you are taking the agent. It is important to call your doctor immediately if you experience any of the following symptoms; intense itching, dark urine, loss of appetite, nausea and vomiting, yellow skin (*jaundice*) or eyes, abdominal tenderness or "flu-like" symptoms. There have been rare reports of death following severe liver damage from flutamide. Flutamide may cause photosensitivity. Avoid prolonged exposure to the sun and other ultraviolet light. Use sunscreens and wear protective clothing until tolerance is determined. Many of these changes improve or go away despite continuation of therapy.

Your physician will be checking you closely for these side effects. Side effects usually disappear after the treatment is stopped. In the meantime, your doctor may prescribe medication to keep these side effects under control.

You must use adequate birth control measures to prevent pregnancy while participating in this study. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study.

COSTS

Routine blood tests and scans will be done to evaluate the effects of treatment. There may also be laboratory testing and procedures required by this study for research purposes. These additional tests may increase your medical bills although the impact will be dependent on your insurance company. If injury occurs as a result of this research, treatment will be available. The use of medication to help control side effects could result in added costs. This institution is not financially responsible for the treatment of side effects caused by the study treatment. You will not be reimbursed for medical care other than what your insurance carrier may provide. You will not be paid for your participation in this research study.

CONTACT PERSONS

(This section must be completed)

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

_____ Name

_____ Telephone Number

For information about this study, you may contact:

_____	_____
Name	Telephone Number

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

_____	_____
Name	Telephone Number

ALTERNATIVES

Other treatments that could be considered for your condition may include the following: (1) radiation therapy; (2) chemotherapy; (3) surgery; or (4) no treatment except medications to make you feel better. With the latter choice, your tumor would continue to grow and your disease would spread.

These treatments could be given either alone or in combination with each other.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments. You should discuss your condition and the expected outcome with your doctor. Your doctor will be available to answer any questions. You are encouraged to ask your doctor any questions you have about this research study and the choices of treatment available to you. If you have any questions at all, please ask your doctor.

If your disease becomes worse, if side effects become very severe, or if developments occur that indicate the research study is not in your best interest, the treatment would be stopped. Further treatment would be discussed at that time.

BENEFITS

It is not known whether the treatment you will be given in this research study will help your condition more than the another treatment for this disease would. The information from this study may also help others by providing information about your type of cancer and its response to treatment. The information will be used scientifically. A possible personal benefit of this research study may be a decrease in the size of your tumor and a longer survival. None of these possible benefits is certain or guaranteed.

VOLUNTARY PARTICIPATION

You do not have to take part in this research study. You are free to withdraw or withhold your consent from taking part in this research study at any time. If you refuse to participate, there will be no penalty or loss of benefits. You may seek care from a doctor of your choice at any time. If you do not take part in this study or if you withdraw from the study, you will continue to receive care.

CONFIDENTIALITY (8/25/00)

Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (***RTOG***). The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (***FDA***), the National Cancer Institute (***NCI***), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in this study may have access to medical records that contain your identity. 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. However, no information by which you can be identified will be released or published.

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

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

Patient Signature *(or legal Representative)*

Date

TISSUE AND BLOOD TESTING (RTOG 99-10)

I agree to the use of my tissues/other samples for research studies related to my cancer.

Yes

No

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

ZUBROD PERFORMANCE SCALE

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

APPENDIX III

AJCC STAGING SYSTEM PROSTATE, 5th Edition

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 the 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

APPENDIX III *(continued)*

**AJCC STAGING SYSTEM
PROSTATE, 5th Edition**

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

****Note: When more than one site of metastasis is present, the most advanced category is used.
pM1c is most advanced

Histopathologic Grade (G)

GX	Grade cannot be assessed
G1	Well-differentiated (<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 EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES (6/07/04)

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

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/717-0990) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.
 - a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.
2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone.
3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).
4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.
5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

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

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.
7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.
8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (grade 5) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
2. All life-threatening (grade 4) toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

C. ADVERSE DRUG REACTIONS DRUG AND BIOLOGICS

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

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

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

Commercial and Non-Investigational Agents

- i. Any fatal (*grade 5*) or life threatening (*grade 4*) adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters' Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.
- ii. Unknown adverse reactions (\geq *grade 2*) resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters' Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.
- iii. All neurotoxicities (\geq *grade 3*) from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.
- iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

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

Investigational Agents

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

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

i. Phase I Studies Utilizing Investigational Agents

- All deaths during therapy with the agent.

Report **by phone** within 24 hours to IDB and RTOG Headquarters.
**A written report to follow within 10 working

days.

- All deaths within 30 days of termination of the agent. As above

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

- First occurrence of any toxicity (*regardless of grade*). Report by **phone within 24 hours** to IDB drug monitor and RTOG Headquarters. ****A written report may be required.**

ii. Phase II, III Studies Utilizing Investigational Agents

- All fatal (*grade 5*) and life threatening (*grade 4*) known adverse reactions due to investigational agent. Report **by phone** to RTOG Headquarters and the Study Chairman within 24 hours ****A written report must be sent to RTOG within 10 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 SCORE CLASSIFICATION⁶¹

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 system of histologic grading is based on an overall pattern of tumor growth at relatively low-magnification (40X - 100X). Five patterns of growth are recognized and numbered in order of increasing malignancy. Because of histologic variation in the tumor, two patterns are recorded for each case, a primary or predominant pattern and a secondary or lesser pattern. The Gleason score is the sum of the primary and secondary patterns; for example: Primary = 2, Secondary = 1; Gleason score = 3. If only one pattern is present, the primary and secondary pattern receive the same designation; for example: Primary = 2, Secondary = 2; Gleason score = 4.