

RADIATION THERAPY ONCOLOGY GROUP

RTOG P-0011

PHASE III RANDOMIZED STUDY OF ADJUVANT THERAPY FOR HIGH RISK pT2-3N0 PROSTATE CANCER

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CTSU (RP-0011)

Activation Date:

July 13, 2001

Closure & Termination Date:

May 7, 2004

Update Date:

April 28, 2004

Version Date:

March 18, 2004

Includes Revision 1-3

(Broadcast April 26, 2004)

This protocol was designed and developed by the Radiation Therapy Oncology Group (RTOG) of the American College of Radiology (ACR). It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by RTOG nor does RTOG assume any responsibility for unauthorized use of this protocol.

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**RADIATION THERAPY ONCOLOGY GROUP
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HIGH RISK pT2-3N0 PROSTATE CANCER**

SCHEMA (12/9/02, 3/18/04)

S	<u>Seminal Vesicle Invasion</u>	R	<u>Arm 1</u>
	1. No		LH-RH agonist x 2 years
T	2. Yes	A	Plus Radiation Therapy to 63.0-66.6 Gy
R	<u>Preoperative PSA</u>	N	<u>Arm 2</u>
	1. ≤ 10 ng/ml		Radiation Therapy to 63.0-66.6 Gy
A	2. > 10 ng/ml	D	
T	<u>Surgical Grade (Gleason Score)</u>	O	<u>Arm 3 CLOSED 2/12/03</u>
	1. 2-6		LH-RH agonist x 2 years
I	2. 7	M	
	3. 8-10	I	
F	<u>Positive Surgical (inked) Margins (M+)</u>	Z	
Y	1. No	E	
	2. Yes		
	<u>Neoadjuvant Hormonal Therapy</u>		
	1. No		
	2. Yes		

- a. Radiation Therapy: 63.0-66.6 Gy in 35-37 fx (1.8 Gy in 5 daily sessions per week) to the original prostate volume, the tumor resection bed, and the proximal membranous urethra.
- b. LH-RH agonist: Patients will receive an LH-RH agonist for two years beginning immediately upon the initiation of irradiation plus one month of oral antiandrogen (*flutamide* or *bicalutamide*).

Eligibility: (See Section 3.0 for details) [6/10/02]

- Patients will have pathologic stage T2-3N0M0 prostate cancer at high-risk for PSA relapse. T2 patients must have GS ≥ 7 , preoperative PSA > 10 ng/ml, and positive surgical margins. T3 patients must have GS ≥ 7 and one or more of the following: 1. preoperative PSA > 10 ng/ml; 2. positive surgical margins; 3. seminal vesicle invasion. If Gleason score < 7 , then two or more of the above factors.
- Patients who have negative LN status by lymph node sampling or LN dissection will be eligible. If pathologic LN status is unknown, the risk of involvement must be less than 15 % as determined by the Roach formula.³⁶
- Undetectable postoperative PSA (≤ 0.2)
- Gleason Score classification is mandatory prior to randomization.
- Pre-operative PSA is mandatory and must have been ≤ 40.0 .
- Zubrod Performance Status 0-1
- ALT must be within 3 x normal limits.
- Prior hormones are allowed if started no more than 10 months before randomization.
- Prior finasteride is allowed if discontinued at least 60 days prior to randomization.
- Prior testosterone administration is allowed if last administered at least 90 days prior to randomization.
- Treatment must begin within 6 weeks after randomization.
- No concurrent invasive cancers other than superficial non-melanomatous skin cancers or prior invasive cancers, unless disease-free for at least five years.
- No prior pelvic RT or orchiectomy
- No previous chemotherapy within five years
- Patients must sign a study-specific informed consent form prior to randomization.

Required Sample Size: 1398 (12/9/02)

RTOG Institution # _____

RTOG P-0011

ELIGIBILITY CHECK (6/10/02)

RTOG Case # _____

(page 1 of 2)

- _____(Y) 1. Does the patient have pathological stage T2-3N0M0 prostate cancer?
- _____(Y) 2. If the patient is T2, does the patient have Gleason score ≥ 7 , pre-op PSA > 10 , and positive surgical margins?
- _____(Y/N) 3. If the patient is T3, is the Gleason score ≥ 7 ?
- _____(Y/NA) If yes, does patient have ONE or more of the following:
- a) Pre-op PSA > 10 ?
 - b) Positive surgical margins?
 - c) Seminal vesicle invasion?
- _____(Y/NA) If no, does patient have TWO or more of the following:
- a) Pre-op PSA > 10 ?
 - b) Positive surgical margins?
 - c) Seminal vesicle invasion?
- _____(Y) 4. Was the pre-op PSA ≤ 40.0 ?
- _____(Y) 5. Is post-op PSA ≤ 0.2 ?
- _____(Y) 6. Is Zubrod status 0-1?
- _____(Y/N) 7. Are lymph nodes negative by lymph node sampling or lymph node dissection?
- _____(Y) If no, is the risk involvement as calculated by the Roach formula less than 15%?
- _____(≥ 3) 8. What is the WBC? (x 1000)
- _____(≥ 130) 9. What is the platelet count? (x 1000)
- _____(≥ 11.4) 10. What is the hgb?
- _____(≤ 2.5) 11. What is creatinine?
- _____ 12. What is ALT? (*within 3 x normal*)
- _____(Y) 13. Will treatment begin within 6 weeks of randomization?
- _____(N) 14. If patient was receiving finasteride, has it been administered 60 days prior to this randomization?
- _____(N) 15. If patient was receiving testosterone, has it been administered 90 days prior to this randomization?
- _____(N) 16. Has any prior pharmacologic androgen ablation for prostate cancer been initiated greater than 10 months before randomization?
- _____(N) 17. Any prior pelvic radiation therapy or orchiectomy?
- _____(N) 18. Any previous chemotherapy within the last 5 years?
- _____(Y) 19. Have all mandatory lab studies been done?
- _____(Y/N) 20. Any prior or concurrent malignancy other than non-melanoma skin cancer?
- _____(Y) If yes, disease free for 5 years?

RTOG Institution # _____

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ELIGIBILITY CHECK (4/28/04)

RTOG Case # _____

(page 2 of 2)

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. Patient's Country of Residence
- _____ 12. Zip Code
- _____ 13. Patient's Insurance Status
- _____ 14. Will any component of the patient's care be given at a military or VA facility?
- _____ (Y/N) 15. Does the patient have seminal vesicle invasion?
- _____ (≤ 10 or > 10) 16. Specify pre-operative PSA
- _____ (2-10) 17. Specify Gleason score
- _____ (Y/N) 18. Are there positive surgical (*inked*) margins?
- _____ (Y/N) 19. Did patient receive neoadjuvant hormonal therapy?
- _____ 20. Treatment Start Date
- _____ 21. Treatment Assignment

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.

Completed by _____

Date _____

1.0 INTRODUCTION

The efficacy of early adjuvant radiation therapy in pathologic pT3N0 (*capsular penetration and negative pelvic lymph nodes*) adenocarcinoma of the prostate is controversial. Historically, several authors have reported that postoperative radiation therapy reduces the risk of local recurrence but does not influence overall survival.¹⁻³ The results of these studies are difficult to interpret since they antedated the prostate-specific antigen (PSA) era and thus included patients who had biochemical evidence of residual disease. The outcome of adjuvant postoperative radiation therapy may be more clearly elucidated if administered in the setting of adverse prognostic features and an undetectable postoperative PSA level. Recently, we evaluated early adjuvant radiation therapy in this group of patients as compared to matched controls.⁴ The data at Thomas Jefferson University Hospital on 72 patients after radical prostatectomy show an 83% reduction in PSA failure with the use of adjuvant radiation therapy without the addition of hormonal therapy. Other authors have noted a similar benefit for men with pT3N0 prostate cancer.^{5,6} Whether these results are sustained with longer follow-up remains to be seen. In any event, the PSA era has allowed us to define a new group of patients in which to re-evaluate the benefit of early adjuvant therapy.

Initially, the availability of PSA allowed clinicians to adopt salvage post-prostatectomy therapy after observing for future biochemical progression instead of initiating adjuvant therapy for adverse features.⁷ This approach seems most justifiable in men who are at low risk for disease progression, provided salvage therapy is initiated early at the time of PSA relapse. Recent long-term follow-up data demonstrated poor sustained responses for most men undergoing this approach and puts into question salvage therapy. Investigators at Johns Hopkins University noted that less than 20% of men remain free of second biochemical progression 5 years after salvage radiation therapy.⁸ In men with seminal vesicle involvement or Gleason score greater than 7, the probability of salvage is lower.^{8,9} Recognition of the poor outcome with salvage radiation therapy led to the development of RTOG 96-01, a prospective randomized study evaluating androgen therapy combined with radiation therapy. The current state-of-affairs indicate that the “wait and watch policy” of salvage post-prostatectomy radiation therapy has limited durable efficacy in men with high-risk prostate cancer. Thus, an approach of immediate adjuvant therapy is worthy of clinical investigation.

In recent years, attention has been directed at identifying and defining subsets of patients who would benefit from adjuvant systemic treatment in addition to local therapy. Two cooperative groups have evaluated combined hormonal therapy and radiation therapy for patients with locally advanced prostate cancer. Phase III RTOG trials 86-10 and 85-31 have shown an improved disease-free survival benefit for men receiving adjuvant hormonal therapy as opposed to radiation therapy alone.^{10,11} Similarly, the EORTC reported a local control, disease-free survival, and overall survival advantage for adjuvant hormonal therapy and radiation therapy.¹² These studies indicate the greatest benefit of adjuvant hormonal therapy and radiation therapy is potentially for men with high-risk prostate cancer (*e.g., capsular penetration, seminal vesicle invasion, and/or Gleason score > 7*).

In RTOG 85-31 a subgroup analysis of men after prostatectomy was carried out.¹³ One hundred thirty-nine men had indications for adjuvant treatment after prostatectomy (*e.g., capsular penetration and seminal vesicle involvement*). Seventy-one patients received radiation therapy with immediate androgen suppression (*luteinizing hormone-releasing hormone (LHRH) agonist*); 68 patients received radiation therapy alone with hormonal manipulation instituted only at time of relapse. The patients receiving treatment after prostatectomy were irradiated to 60 to 65 Gy in 1.8 to 2.0 Gy fractions. Patients were randomized to receive RT and androgen suppression initially or at the time of relapse. Administration of Goserelin (*3.6 mg*) was to begin during the last week of RT on arm I, and at the time of relapse on arm II. In the group of post-prostatectomy patients, freedom from biochemical relapse (*< 0.5 ng/ml*) at 5 years was 65% for men who received combination therapy versus 42% for those treated by RT alone (*with hormones reserved for relapse*). On multivariate analysis, the use of RT plus immediate hormonal therapy was an independent factor predictive of likelihood of remaining free of biochemical failure. Acute and late toxicities were according to the RTOG schema. There was no statistically significant difference in toxicity between the two treatment groups. There were only three grade 4 toxicities. Although this approach seems safe and promising, this trial provides only indirect information from which to assess the effect on survival of adjuvant hormonal therapy or radiation therapy for pT3 prostate cancer patients.

More recently, Messing et al. reported the results of an ECOG study evaluating immediate hormonal therapy versus observation in men with pTN1M0 prostate cancer.¹⁴ They found that immediate hormonal therapy in

these men improves survival and reduces the risk of recurrence. The results of this study and similar studies have resulted in enthusiasm and further testing of androgen suppression either in adjunct to radiotherapy or as adjuvant monotherapy. Thus, the proposed study will test the superiority of combining adjuvant hormonal therapy and radiation therapy over either adjuvant radiation therapy alone or hormonal therapy alone for men with high-risk pT3N0 prostate cancer.

The main rationale for the proposed study is that high-risk prostate cancer patients are identifiable after prostatectomy and may benefit from combined modality therapy. In an analysis of 379 patients treated with prostatectomy alone for clinically localized prostate cancer, Stamey et al. noted that the factors, Gleason grade and prostate volume were independently associated with biochemical relapse risks.¹⁵ They also found that capsular penetration, seminal vesicle invasion, positive surgical margins, and preoperative PSA were highly correlated with cancer volume. Using Gleason score, preoperative PSA, positive margins, and seminal vesicle invasion, Lowe et al. identified pT3N0 patients at high risk for early PSA failure after prostatectomy.¹⁶ Lowe et al. were able to separate patients into low and high-risk groups, with distinct relapse probabilities at 5 years after radical prostatectomy (9.8% and 41.2%, respectively; $p < 0.0001$). The patients who would be eligible for this protocol would have similar pre-treatment and postoperative prognostic factors to those in the high-risk group identified by Lowe et al.

Other investigators at multiple other institutions have noted similar findings.¹⁶⁻²⁴ A study by D'Amico et al. examined a series of 862 patients treated with radical prostatectomy and found that, by multivariate analysis, pretreatment PSA > 10 and Gleason Score of 7 or higher were adverse prognostic factors when biochemical control was used as an endpoint.²⁰ Kupelian et al. noted similar findings in a cohort of 337 consecutive patients treated with radical prostatectomy alone; preoperative PSA, Gleason Score, extracapsular extension, and surgical margin status were all independent prognostic factors by multivariate analysis.¹⁹

Although surgical techniques, patient populations, and definitions of biochemical control may have varied between different institutions, there are remarkable consistencies in the findings that patients with elevated PSA at presentation, high Gleason Scores, and advanced surgical stage have relatively poor prognosis when compared with other patients. We believe that the results obtained with delayed treatment for these patients are sufficiently poor to justify the exploration of early adjuvant approaches in an attempt to improve therapeutic results. Because of the importance of prognostic factors in predicting outcome in studies, we believe that a randomized, controlled, phase III study is the best way to determine if early androgen suppression will add to the control rates obtained with immediate postoperative RT.

In patients with high risk for progression after radical prostatectomy, combined RT and androgen suppression should be tested. We thus propose an investigational study to see if androgen suppression with RT may result in improved control and survival rates over those obtained with radiotherapy or androgen suppression alone.

(12/9/02) From July 2001 to August 2002, the study accrued at a slower pace than expected with only 9 cases entered to the study. With the goal of 2850 cases unlikely to be reached within the originally projected five years, the Data Monitoring Committee (DMC) recommended adjusting the study design by dropping the androgen suppression only arm.

2.0 OBJECTIVES (12/9/02)

2.1 Primary Objectives

- 2.1.1** The revised study design will test if the addition of androgen suppression to radiation therapy in patients with unfavorable pathologic stage pT3N0M0 prostate cancer leads to better overall survival than radiation therapy alone.

2.2 Secondary Objective

- 2.2.1** To determine disease-free survival, freedom from PSA failure, and freedom from distant metastases of patients with pT2-3N0M0 prostate cancer treated with adjuvant androgen suppression and radiation therapy compared to those patients treated with adjuvant radiation therapy alone.
- 2.2.2** To compare the qualitative and quantitative toxicities of patients with pT2-3N0M0 prostate cancer treated adjuvantly with androgen suppression and radiation therapy to that of adjuvant radiation therapy.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility (6/10/02)

- 3.1.1** Patients will have pathologic stage T2-3N0M0 prostate cancer at high-risk for PSA relapse.
- 3.1.1.1** T2 patients must have a Gleason score ≥ 7 , preoperative PSA > 10 ng/ml and positive surgical margins.
- 3.1.1.2** T3 patients must have a Gleason score ≥ 7 and one or more of the following:
- Preoperative PSA > 10 ng/ml
 - Positive surgical margins
 - Seminal vesicle invasion (*Appendix III*)
- Or if Gleason score < 7 , then two or more of the above factors.
- 3.1.2** Surgical Gleason Score classification is mandatory prior to randomization. Preoperative PSA is mandatory and must have been ≤ 40.0 .
- 3.1.3** Patients who have negative LN status by lymph node sampling or LN dissection will be eligible. If pathologic LN status is unknown, the risk of involvement must be less than 15% as determined by the Roach formula.³⁶ An estimated risk of lymph node involvement $< 15\%$ (*based on preoperative PSA and surgical Gleason score*): risk of +LN = $2/3 \text{ PSA} + ([\text{GS}-6] \times 10)$.
- 3.1.4** Undetectable post-operative PSA (≤ 0.2)
- 3.1.5** Zubrod Performance Status 0-1 (*Appendix II*).
- 3.1.6** ALT must be within 3 x normal limits.
- 3.1.7** Hematologic parameters must be within the following limits:
- 3.1.7.1** WBC ≥ 3000
- 3.1.7.2** Plt $\geq 130,000$
- 3.1.7.3** Hgb ≥ 11.4 g/dl
- 3.1.7.4** Creatinine ≤ 2.5 g/dl
- 3.1.8** Treatment must begin within 6 weeks after randomization.
- 3.1.9** Prior finasteride is allowed if discontinued at least 60 days prior to randomization.
- 3.1.10** Prior testosterone administration is allowed if last administered at least 90 days prior to randomization.
- 3.1.11** Prior pharmacologic androgen ablation for prostate cancer will be allowed only if the onset of androgen ablation is ≤ 10 months prior to the date of randomization. This is allowable since there is no clear therapeutic benefit to neoadjuvant hormonal therapy in patients undergoing prostatectomies. At the time of study entry, the patient must be converted to protocol-specified androgen ablation. If the patient has been receiving hormone therapy at the time of randomization and is then randomized to Arm 2 (*RT only*), hormone therapy must be discontinued.
- 3.1.12** Patient must have completed all pretreatment evaluations per Section 4.0.
- 3.1.13** Patients must sign a study-specific informed consent form prior to randomization.
- 3.2** **Conditions for Patient Ineligibility**
- 3.2.1** Patients with preoperative PSA > 40 ;
- 3.2.2** Evidence of M1 metastatic disease;
- 3.2.3** Pathologically positive lymph nodes;
- 3.2.4** Prior pelvic RT or orchiectomy;
- 3.2.5** Previous chemotherapy within the last 5 years;
- 3.2.6** Concurrent invasive cancers other than superficial non-melanomatous skin cancers or prior invasive cancers unless disease-free for at least 5 years;
- 3.2.7** Major medical or psychiatric illness, which, in the investigators opinion, would prevent completion of treatment and would interfere with follow-up.

4.0 PRETREATMENT EVALUATION (12/9/02)

- 4.1** History and Physical examination and Zubrod Performance Status (*Appendix II*);
- 4.2** Histologic evaluation. Surgical Gleason Score is mandatory (*Appendix VI*);
- 4.3** Mandatory laboratory studies: CBC with platelets, PSA, bilirubin, serum ALT, alkaline phosphatase, BUN, creatinine, testosterone, urinalysis within four weeks prior to randomization;
- 4.4** Bone scan; pelvic MRI or CT scan within six months prior to randomization;
- 4.5** Pelvic lymph node assessment by pelvic lymph node dissection or sampling procedure (*either via laparotomy or laparoscopically*); If pathologic lymph node status is unknown, the risk of involvement must be less than 15% as determined by the Roach formula;³⁶ **(6/10/02)**
- 4.6** Sexual function status.

5.0 REGISTRATION PROCEDURES

5.1 RTOG Institutions

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 Cancer Trials Support Unit (CTSU) Investigators (12/9/02)

5.2.1 CTSU Address and Contact Information

- For Patient Enrollment or To Report Adverse Events:
Phone – 1-888-462-3009
Fax – 1-888-691-8039
- To mail forms or data:
Westat
CTSU Data Operations Center
1441 W. Montgomery Avenue
Rockville, MD 20850-2062
- 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 ctsusupport@westat.com. All inquiries will be triaged to the appropriate CTSU representative.
- The CTSU public web site is located at: www.ctsu.org
- The CTSU member web site is located at: <http://members.ctsu.org>

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

Requirements for RTOG-P-0011 site registration:

- CTSU IRB Certification
- IRB/Regulatory Approval Transmittal Sheet
- IRB-approved consent form
- Personnel contact list for protocol
- Radiation Therapy Facility Inventory Form (NOTE: Radiation therapy facilities must participate in the RPC monitoring program to participate in studies sponsored by the CTSU.)

Requirements for patient enrollment on RTOG-P-0011:

- Patient must meet all inclusion criteria and no exclusion criteria should apply.
- Patient has signed and dated the consent.
- All baseline laboratory tests and prestudy evaluations performed.

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. Complete the following forms:

- CTSU Patient Enrollment Transmittal Sheet
- Eligibility Checklist

Fax these forms 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, that all regulatory requirements have been met, and that the enrollment forms are completed. The CTSU Registrar will follow up with the site to resolve any discrepancies.

Once investigator and patient eligibility are confirmed, the CTSU Registrar will contact the RTOG to obtain a randomization assignment and assignment of a unique patient ID. The CTSU Registrar 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, data submission calendar, and case-specific labels with the patient ID number.

5.3 NCIC CTG Investigators (6/10/02)

5.3.1 Investigator Requirements

All investigators (*principal and additional investigators*) must have on file with the NCIC CTG a current curriculum vitae (*updated within the past 2 years*). In addition, all principal investigators must have on file with the NCIC CTG a Health Canada "Qualified Investigator Undertaking".

Because this is an U.S. NCI-affiliated study, all investigators participating on the study must have completed human subjects protections education as mandated by the U.S. National Institute of Health. Documentation of this completed education must be on file with the NCIC CTG.

5.3.2 Ethical and Regulatory Requirements

This study will be conducted under a Clinical Trial Application (*CTA*), formerly called an Investigational New Drug (*IND*) application, in Canada. The principal investigator will ensure this study is conducted in compliance with the protocol, NCIC CTG requirements, ICH-Good Clinical Practice Guidelines and Division 5 of the Canada Food and Drug Regulations.

The following documentation must be on file at the NCIC CTG central office prior to randomization (*also see Section 5.3.1 for documentation required for investigators*):

- Documentation of full board REB approval of the protocol and consent form and REB receipt of the investigator's brochure for the investigational agent used in this study.
- A completed Health Canada 'Research Ethics Board Attestation' form. If an REB prefers, it may include the following language in the protocol specific REB approval letter/form (*signed by the REB chair*) instead of completing the Health Canada form:
 - The membership of this Research Ethics board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations
 - This Research ethics Board carries out its functions in a manner consistent with Good Clinical Practice and
 - This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent for the trial, which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.
- A copy of the REB approved consent form (*on institutional letterhead*)

Please note: The REB approved consent form must include all required NCI US and ICH-GCP elements. Upon request and time permitting, consent forms may be reviewed by the NCIC CTG central office prior to REB submission.
- REB membership (*consistent with ICH-GCP and OHRP membership requirements*)
- A completed NCIC CTG Confirmation of Initial Ethical Approval Form
- A completed NCIC CTG participant's list
- Lab certification and lab normal values
- A current Cooperative Project Assurance (*CPA*) or Federal Wide Assurance (*FWA*) number

Documented annual re-approval of the study is required as long as there are patients being followed on the study. Annual re-approval must be full board until accrual is complete and all patients have completed protocol treatments and/or protocol mandated interventions.

If an REB refuses to approve the initial protocol or an amendment at anytime during the conduct of the study, the NCIC CTG must be notified immediately of the refusal, the date of the refusal, and the rationale.

If your centre stops participating on this trial at anytime prior to study closure, the NCIC CTG must be notified immediately of the discontinuation and the rationale.

Central Office Contacts (12/16/03):

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E-mail: wparulekar@ctg.queensu.ca

5.3.3 Randomization Procedure

Randomizations for all NCIC CTG centres will be done through the NCIC CTG Central Office. Randomizations will be accepted on Monday to Friday between 8:00 AM and 6:00 PM Eastern Time. The eligibility checklist must be completed prior to randomisation. Randomizations may be done by telephone (613-533-6430) or by fax (613-533-2812). Once eligibility is confirmed by the NCIC CTG, the Radiation Therapy Oncology Group (RTOG) will be contacted by the NCIC CTG between 8:30 AM and 5:00 PM Eastern Time to obtain the treatment assignment. The NCIC CTG will then relay the treatment assignment to the centre and confirm it in writing.

6.0 RADIATION THERAPY NOTE: IMRT IS NOT ALLOWED ON THIS STUDY. (3/18/04)

6.1 Physical Factors

Megavoltage equipment is required with effective photon energies ≥ 10 Mv is preferred. Equipment with photon energies of 6-10 MV can be used only if the anterior/posterior separation is ≤ 24 cm. Minimum source-to-axis distance is 100 cm. The treatment technique (*field arrangement*) will be by a 4 field (*anterior, posterior, right and left lateral*) coplanar technique with blocks designed for all fields to protect adequately uninvolved structures. Focused block techniques should be used to minimize the penumbra around the photon field.

6.2 Treatment Volumes

6.2.1 Calculation of the Clinical Target Volumes (CTV) will be primarily based upon: (1) the histopathologic information of the prostate size and the tumor extent to specific inked boundaries of the surgical resection and (2) the imaging information available at the time of simulation which requires (a) 30cc of Cystocon dye introduced into a empty bladder followed by a retrograde urethrogram demonstrating the apex or beak of dye at the GU diaphragm and (b) rectal marker in the distal rectum; the location of the external end of the anal canal marked is optional if CT based planning is used. The preoperative TRUS and pelvic

tomographic studies (*if available*) may be of secondary assistance. The CTV calculation will be based on the estimated location of the preoperative prostate tumor volume plus sites of microscopic tumor extension. The superior margin for the CTV will be, in patients judged to have a normal-size prostate prior to surgery (*i.e. then a prostatic urethral length of 4.0 cm*), 5.5 cm superior to the beak of the urethrogram. This is the sum of 4.0 cm (*the urethral length*) plus 1.0 cm (*the usual but not consistent distance between the beak and the inferior extent of the prostatic urethra*) plus 0.5 cm (*for possible superior extension of the capsule of the median lobe above the proximal prostatic urethra*). The anterior border of the CTV will be 3 cm posterior to the anterior tip of the symphysis. The posterior extent of the CTV will be at the anterior rectal wall. The original volume of seminal vesicles will not be considered target if they were not microscopically involved with tumor. If there was microscopic involvement of the seminal vesicles, then the distal 1½ cm of the seminal vesicles will be considered target. The inferior, right, and left extent of the CTV will be determined by the pre-operative imaging studies (*if available*) or the CT-based plan.

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

6.2.3 Field Borders will add 1.5 cm outside the PTV. The individually shaped anterior, posterior, right and left lateral fields will have the following radiation field borders when the patient is judged to have had a normal sized prostate (*prostatic urethral length of 4.0 cm*) prior to surgery and have had no microscopic involvement of the seminal vesicles (*Appendix VII*).

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

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

Posteriorly: 2.5 cm posterior to the most anterior portion of the anterior rectal wall.

Anteriorly: 1.0 cm posterior to the anterior tip of the symphysis laterally.

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

6.2.4 Films

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

6.3 Radiation Doses

Daily tumor doses will be 1.8 Gy given once a day, five sessions a week. The dose shall be prescribed at the intersection of the central rays of the beams. The prescribed doses to the intersection of the central rays of the beams may range from 63.0-66.6 Gy given in 35-37 fractions of 1.8 Gy. The minimal dose to the CTV shall not be less than 95% of the prescribed dose; the maximum, not more than 105% of the prescribed dose.

6.4 Critical Normal Structures

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

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

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

6.5 Radiation Toxicity

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

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

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

6.5.1.3 Impotence in previously potent patients.

6.5.1.4 Reaction within 90 days of treatment start date will be scored using 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*).

6.6 Compliance Criteria

6.6.1 Field Borders

- Per protocol: within 1 cm of the borders as stated in the protocol
- Variation, acceptable: > 1 to 2 cm beyond borders as stated in protocol

- Deviation, unacceptable: > 2 cm beyond borders as stated in protocol
- 6.6.2** Dose
 - Per protocol: ≤ 5% of protocol specified dose
 - Variation, acceptable: > 5 to 10% of protocol specified dose
 - Deviation, unacceptable: > 10% of protocol specified dose
- 6.6.3** Minimum and Maximum Allowances
 - Per protocol: 95% isodose coverage
 - Variation, acceptable: < 95 to 90% isodose coverage
 - Deviation, unacceptable: < 90% isodose coverage
 - Per protocol maximum 105%
 - Variation, acceptable: > 105 to 110%
 - Deviation, unacceptable: > 110%
- 6.6.4** Fractionation
 - Will be directed by dose score
- 6.6.5** Elapsed Days
 - Per protocol: 1 to 7 break days
 - Variation, acceptable: 8 to 14 days
 - Deviation, unacceptable: > 14 days

7.0 DRUG THERAPY (ARM 1) [12/9/02, 3/18/04]

- 7.1** In the revised study design patients will be randomized to one of two arms; Arm 3 has been closed as of 2/12/03. Arm 2 does not involve any hormone/drug therapy. Arm 1 involves the administration of LH-RH agonist therapy (*choice of dose frequency and drug at the discretion of physician*) for two years beginning immediately upon initiation of irradiation plus one month of oral antiandrogen therapy (*either flutamide or bicalutamide*) to prevent the possibility of an LH “flare” reaction.
- 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 analogs 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 analogs should be stored as directed by the commercial supplier.
- 7.2.4** Administration
LHRH analogs are administered with a variety of techniques, including subcutaneous insertion of a solid plug in the 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 analogs 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 vertebral metastases and/or urinary obstruction or hematuria which, if aggravated, may lead to neurological problems such as temporary weakness and/or paresthesia of the lower limbs or worsening of urinary symptoms.
- 7.4** **Eulexin (flutamide)**
- 7.4.1** Description
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. Flutamide is a non-steroid antiandrogen that is metabolized into a

hydroxylated derivative, which effectively competes with the hydrotestosterone for androgen receptor sites.

7.4.2 Supply

Flutamide is supplied as 125 mg capsules and is commercially available.

7.4.3 Storage

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

7.4.4 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*).

Flutamide will begin immediately upon initiation of radiotherapy and will continue for one month. Administration will be suspended only if there is an apparent or suspected reaction to the drug. See Section 7.4.6. During radiotherapy interruptions, flutamide will be continued.

7.4.5 Toxicity

The reported side effects of treatment include diarrhea, anemia, hot flashes, decreased libido, impotence and mild elevation of ALT without alteration in serum bilirubin and without clinical manifestations. 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.

7.4.6 Dose Modification Schedule

If gastrointestinal disturbances (*cramps, diarrhea*) occur, 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.

7.5 Casodex (bicalutamide)

7.5.1 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*).

7.5.2 Supply

Casodex is commercially available as a 50 mg tablet.

7.5.3 Storage

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

7.5.4 Administration

Casodex is administered orally at a dose of one 50 mg tablet per day. Casodex will begin immediately upon initiation of radiotherapy and will continue for one month. Administration will be suspended only if there is an apparent or suspected reaction to the drug. During radiotherapy interruptions, Casodex will be continued.

7.5.5 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 bicalutamide therapy are breast tenderness, breast swelling, and hot flashes. Adverse events not directly related to the pharmacological properties of bicalutamide were infrequent. Nonpharmacological adverse events, reported in the trial using bicalutamide 50 mg as monotherapy include asthenia, pelvic pain, peripheral edema, pruritus, rash, constipation, impotence, dyspnea, nausea, hypertension, dizziness, paresthesia, insomnia, sweating, diarrhea, increased liver enzyme tests, nocturia, hematuria, UTI, hyperglycemia, weight loss, anemia, and chest pain (*Kaisary 1994*). There has been no observed change in cardiac parameters during long-term administration of bicalutamide 50 mg daily.

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

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

7.6.1 The revised NCI Common Toxicity Criteria Version 2.0 (3/98) will be used to score hormonal therapy and acute radiation (≤ 90 days) toxicities. A copy of the CTC version 2.0 can be downloaded from the CTEP home page (<http://ctep.info.nih.gov>). This study will be monitored by the Clinical Data Update System (CDUS) version 1.1. 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 guidelines for reporting adverse drug reactions (ADRs) apply to any research protocol which uses commercial anticancer agents. The following ADRs experienced by patients accrued to these protocols and attributed to the commercial agent(s) should be reported to RTOG within 10 working days and telephoned to RTOG Headquarters Data Management and to the Study Chair within 24 hours of discovery:

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

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

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

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

7.6.2 The ADR report should be documented on Form FDA 3500 and mailed to the address on the form, to RTOG Headquarters and to:

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

7.6.3 Drug death, regardless of cause, which occurs during protocol treatment must be reported to RTOG Headquarters by telephone within 48 hours of discovery (*See Appendix V*).

7.7 Cancer Trials Support Unit (CTSU) Investigators - Adverse Event (AE) Reporting (12/9/02)

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 guidelines is available on the CTSU web site. 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 (888-691-8039). These will be forwarded to RTOG for formal review. RTOG will then distribute the documents internally and to the appropriate regulatory agencies. For those adverse events requiring **24-hour phone notification**, the CTSU investigator is responsible for reporting the event within 24 hours to the following persons/agencies:

- CTSU Data Operations Center at 1-888-462-3009
- RTOG Headquarters' Data Management
- NCI Investigational Drug Branch at 301-230-2330

Secondary AML/MDS reporting:

CTSU investigators will submit the NCI Secondary AML/MDS Report Form and supporting documentation to the CTSU. The CTSU will forward this information to the RTOG, who will then forward the information to the IDB.

Your local Investigational Review Board must be informed of all reportable serious adverse reactions.

All adverse event reports submitted to the CTSU should be accompanied by a completed CTSU Data Transmittal Form.

If the sexual partner of a patient becomes pregnant while receiving protocol therapy, the CTSU Patient Registrar should be notified immediately. The CTSU will then notify RTOG.

7.8 NCIC CTG Investigators – Reporting Adverse Events (6/10/02)

7.8.1 Investigator Reporting Responsibilities to NCIC CTG

NCIC CTG investigators are to report all serious adverse events by telephone (613-533-6430) and/or fax (613-533-2812) within 24 hours to the NCIC CTG central office. Written reports must be submitted on the NCIC CTG Serious Adverse Event Form. Please see the “Safety Reporting” section of the protocol for the definition of reportable serious adverse events.

In addition, since this study will be conducted under a CTA in Canada, any adverse events (*i.e., toxicities*) considered serious and unexpected and related to protocol treatment must be reported to NCIC CTG

"Serious" adverse events include any untoward medical occurrence that at any dose:

- results in death
- is life threatening
- requires hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect

"Unexpected" toxicities include those that are not consistent in terms of nature or severity with the protocol agent information contained in the investigator brochure or product monograph.

"Related" toxicities include any toxicities possibly, probably, or definitely related to protocol treatment.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Any second malignancies or myeloid dysplasia must also be reported in writing on the NCIC CTG Serious Adverse Event Form within 15 working days of when the diagnosis is known to the investigator.

7.8.2 NCIC CTG Reporting Responsibilities

Expedited serious adverse events will be forwarded by the NCIC CTG to the RTOG Office. In addition, any events considered serious, unexpected and at least possibly related to protocol therapy (*ie. a causal relation cannot be ruled out*) will be reported in an expedited manner to the Therapeutic Products Directorate of Health Canada by NCIC CTG.

7.8.3 Investigator Responsibilities for Reporting Serious Adverse Events to Local Research Ethics Boards

NCIC CTG will notify all Investigators of all Serious Adverse Events that are reportable to regulatory authorities in Canada from this trial or from other clinical trials as reported to the NCIC CTG by RTOG. This includes all serious events that are unexpected and related to protocol treatment. Investigators must notify their Research Ethics Board (*REB*) and file the report with their Investigator Drug Brochure. Documentation from the REB of receipt of these reportable serious adverse events must be kept on file in the centre.

In addition to reporting SAE's sent by the NCIC CTG for reporting, all expedited adverse events occurring within a centre should also be reported to local REBs.

7.8.4 Quality Assurance

NCIC CTG on-site auditing will be conducted at active participating centres at least once every three years during the course of the study. The auditors will require access to REB files and patient medical records to verify appropriate ethical review and the data submitted on CRFs.

8.0 SURGERY

8.1 There is no planned surgery for any non-progressing patients.

8.2 Unplanned surgery for bladder neck stricture: Because these patients are at a 5% to 20% risk of developing a bladder neck stricture following radical prostatectomy, this possibility should be continually monitored by clinicians if their patients develop progressive urinary frequency during radiation therapy. This can be well

- corrected by minimally invasive procedures with a minimal, if any, radiation treatment break; however, it would be better to anticipate this problem, if possible, and to correct it prior to starting protocol therapy.
- 8.3** As is outlined in the treatment algorithm in Section 9.1 for patients developing a PSA progression, prostate bed/vesical-urethral anastomotic re-biopsy may be indicated. This will be done using conventional TRUS-guided biopsy procedures.
- 8.4** For PSA progression in some special categories (*see Section 9.0*), castration by orchiectomy (*or by LHRH analog*) will be recommended.

9.0 OTHER TREATMENT

9.1 Subsequent PSA Progression

If the patient is found to have subsequent PSA progression (*a PSA increase of greater than 0.5 ng/ml at 6 or more months after entry; see Section 11.3*), the patient will be evaluated by bone scan. If metastases are demonstrated, the patient will be recommended to have maximum androgen blockade. Maximum androgen blockade will be the combination therapy of castration (*either orchiectomy or LHRH analogs*) plus antiandrogen (*either Casodex 50 mg qd., or Eulexin 250 mg t.i.d.*). If no metastases are found on bone scan, the patient will be observed. If another PSA increase of 0.5 or greater is subsequently detected, the patient will first undergo an abdominal and pelvic CT scan. If there is evidence of metastatic disease in the lymph nodes, he will be recommended to have maximum androgen blockade. If there are no metastases found on CT scan, he will undergo a TRUS-guided rebiopsy of his anastomosis. If the biopsy documents histologic tumor persistence, the patient will be recommended to have maximum androgen blockade. If neither of these evaluations detect disease, the patient will be observed. If during observation the patient subsequently develops a PSA of greater than 4.0 ng/ml, then he will be recommended to undergo maximum androgen blockade. If in the above algorithm the patient is recommended to have maximum androgen blockade, and the progression has occurred while the patient is on study medication, the following steps are suggested to prevent a patient, who may have an altered androgen receptor, from being at increased risk if he is maintained on antiandrogen therapy. The patient should stop the study medication and have his PSA assessed 6 weeks later. If the PSA decreases, no therapy need be instituted until there is another PSA rise. At that point orchiectomy or an LHRH antagonist is recommended. If the PSA remains stable or increases, maximum androgen blockade should be employed.

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

If a patient in Arm 3 (*hormones alone; closed 2/12/03*) has a rising PSA on two or more separate measurements, is found to have a biopsy-proven local recurrence, and has no evidence of distant metastases on bone scan or CT scan, prostatic bed irradiation may be considered.

10.0 PATHOLOGY (12/9/02)

10.1 Central Review

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

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

- 10.1.3** RTOG will reimburse submitting institutions \$200 per case for materials submitted for central review. After confirmation from the RTOG Tissue Bank that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution. Pathology payment

cycles are run on a quarterly basis and will appear on the institution's check summary report with the regular treatment case reimbursement.

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

10.1.5 H & E stained slide(s) and block (s) will be retained for the special studies.

10.1.6 If a block will not be released, submission of 10-15 unstained sections and mounted on sialinized (or other "sticky slides") may be substituted.

10.2 All tumors will be graded according to Gleason Score Classification (see Appendix VI)

10.3 DNA content and proliferation rate may be assessed in selected cases by image analysis (Feulgen staining) and immunocytochemistry (MIB-1 antibody).

10.5 Cancer Trials Support Unit (CTSU) Investigators (12/9/02)

All pathology materials and associated forms and reports are to be submitted directly to the RTOG Tissue Bank within two weeks of randomization. A copy of the completed Pathology Submission Form(s) and Pathology Report(s) also should be sent to the CTSU. Refer to Section 10.0 of the protocol (*above*) for further details on collection and submission. Reimbursement to CTSU sites is handled per Section 10.1.3 above.

10.6 NCIC CTG Institutions: Central Pathology Review (6/10/02)

Pathology materials are due following randomization as described in section 10.0 of the protocol. The blocks are to be clearly marked with the patient's initials and NCIC CTG and RTOG patient and study numbers. **DO NOT INCLUDE PATIENT NAMES ON THE BLOCKS.** Please do not submit materials directly to RTOG. Please send the blocks with a completed RTOG Pathology Submission form and operative and pathology reports to:

The NCIC CTG National Tumour Bank
C/O Department of Pathology
Queen's University
Richardson Labs, Stuart Street
Kingston, Ontario K7L 2V6
Attention: Mr. Troy Feener

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (12/9/02)

Parameter	Pretreatment	Weekly During RT	At end of XRT	Follow-up (per Sec. 11.2)
History and Physical	X			X
Histological evaluation; Gleason Score	X			
Performance Status	X		X	X
PSA	X ^c		X	X
Alkaline phosphatase, ALT, Bilirubin, BUN	X ^c		X ^a	X ^a
Serum Testosterone	X ^c			
CBC with platelets	X ^c		X	X
Creatinine, Urinalysis	X ^c			
Rectal exam; sexual function/bladder status	X		X	X
Bone scan; pelvic MRI or CT scan	X ^f			X ^b
Pelvic lymph node assessment ^d	X			
TRUS-guided biopsy				X ^c
Check for toxicity		X		

a. Three weeks after beginning XRT, at the completion of XRT, then every 3 months during follow-up (*Section 11.2*); Serum ALT at termination of antiandrogens. **(6/10/02)**

b. As clinically indicated, and at 30 months after study entry

c. See Section 9.1.

- d. By pelvic lymph node dissection or sampling procedure (*either via laparotomy or laparoscopically*); If pathologic lymph node status is unknown, the risk of involvement must be less than 15% as determined by the Roach formula.³⁶ (6/10/02)
- e. Within 4 weeks prior to randomization
- f. Within 6 months prior to randomization

11.2 Follow-up Schedule (12/9/02)

- 11.2.1 Patients should be evaluated one month following completion of the radiation therapy; thereafter, patients will be seen every 3 months for one year. The investigator or designee will see the patient (*Arm 1*) prior to prescribing new drug supplies in order to evaluate the patient's side effects, compliance, and continuation of drug. Then, until month 60, patients will be seen at 6-month intervals. Then, after month 60, the patient will be seen at 12-month intervals for the remainder of the patient's life.
- 11.2.2 A bone scan will be performed on any patient who presents with complaints of bone pain that cannot be attributed to any intercurrent disease. Discretionary plain films may be needed to evaluate lesions seen on bone scan to confirm the diagnosis of metastatic disease. A bone scan should be done 30 months after entry (*6 months after termination of adjuvant treatment*) as a new baseline.
- 11.2.3 The patient will be asked whether he is able to achieve an erection and if he is able to have sexual relations. This assessment and that of bladder function must be done prior to the start of radiation therapy and at the end of treatment and at each follow-up visit.

11.3 Measurement of Response and Freedom from Progression

- 11.3.1 Time to PSA Progression
This will be measured from the date of randomization to the date of developing a PSA of 0.5 ng/ml or greater over the entry PSA. Changes in serum PSA alone are not considered evidence of objective progression. Subjects with rises in PSA may be treated according to the algorithm in Section 9.1 or at the discretion of the investigator. When additional treatment is considered, combination therapy of castration (*either orchiectomy or LHRH analogues*) plus antiandrogen (*either Casodex 50 mg or Eulexin 250 mg t.i.d.*) is recommended. Subjects will be followed up until the first date of clinical progression is documented and subsequently will be monitored for survival.
- 11.3.2 Time to Local Progression
Time to local progression will be measured from the date of randomization to the date of documented local progression as determined by clinical exam.
- 11.3.3 Time to Distant Failure
The time to distant failure will be measured from the date of randomization to the date of documented metastatic disease.
- 11.3.4 Time to Clinical Progression
 - 11.3.4.1 The time to clinical progression will be measured from the date of randomization to the date of documented local progression or distant failure.
 - 11.3.4.2 Any of the following will be sufficient evidence for clinical progression of disease:
 - a) evidence of objective progression, e.g., by bone scan, computer tomography (*CT*) scan, magnetic resonance imaging (*MRI*), biopsy, etc.
 - b) local or symptomatic progression:
 - the development of a palpable mass in the prostatic fossa that on biopsy is positive for prostate cancer;
 - ureteric obstruction either by primary tumor or pelvic nodal disease;
 - lymphedema of lower extremities due to pelvic nodal involvement;
 - recurrent vesical obstruction, bleeding or pain due to growth of primary tumor (*not due to radiation therapy*).

NB: if these symptoms are reported, assessments as in item (a) above should be made to seek confirmation of objective progression.
- 11.3.5 Survival
The survival time will be measured from the date of randomization to the date of death. All patients will be followed for survival. Every effort should be made to document the cause of death. Post-mortem examination will be carried out when feasible and a copy of the final autopsy report sent to RTOG.

12.0 DATA COLLECTION (3/18/04)

(RTOG, 1101 Market Street, Suite 1400 Philadelphia, PA 19107)

12.1 Summary of Data Submission (12/9/02)

<u>Item</u>	<u>Due</u>
Demographic Form (A5)	Within 2 weeks of study entry
Initial Evaluation Form (I1)	
Pathology Report (P1)	
Pathology Blocks/Slides (P2)	
<u>Preliminary Dosimetry Information:</u>	Within 1 week of start of RT
RT Prescription (<i>Protocol Treatment Form</i>) (T2)	
Films (<i>simulation and portal</i>) (T3)	
Calculations (T4)	
<u>Final Dosimetry Information:</u>	Within 1 week of RT end
Daily Treatment Record (T5)	
Isodose Distribution (T6)	
Initial Follow-up Form (FS)	At 3 months from start of RT
Follow-up Form (F1)	At 6, 9, and 12 months; then q 6 months x 4 years, then annually; Also at progression/relapse and at death.
Hormone Summary (TF)	At 24 months or at completion of hormones
Long Term Follow-up Form (FF)	Yearly after 5 years in place of the F1 form, as applicable; See FF form for instructions.
Pathology Report (P1), rebiopsy	As applicable
Pathology Blocks/Slides (P2), rebiopsy	
Autopsy Report (D3)	As applicable

12.2 Cancer Trials Support Unite (CTSU) Investigators (12/9/02)

12.2.1 Data Submission

Data Forms: All data forms for this study are available for download from the CTSU member web site (<http://members.ctsu.org>). CTSU sites 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 and RTOG study/case labels should be affixed to all documentation.

- Patient registration forms should be *faxed* to the CTSU Data Center (1-888-691-8039) according to instructions in the registration procedures section of the protocol (*See Section 5.2*).
- 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 (*see Section 10.0*). A copy of the RTOG Pathology Submission Form(s) and Pathology Report(s) also should be sent to the CTSU Data Operations Center for tracking purposes.
- Dosimetry forms should be sent to the RTOG Dosimetry Department.
- All other forms are to be mailed directly to the CTSU Data Operations Center at the address below. The CTSU will forward all information to the RTOG.

**Westat
CTSU Data Operations Center
1441 W. Montgomery Avenue
Rockville, MD 20850-2062**

12.2.2 Radiation Therapy Documentation Submission

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 12.0 of the protocol. See Section 12.1 of the protocol for a complete inventory and schedule of dosimetry items to be submitted.

Any dosimetry questions should be directed to the Dosimetry Department at RTOG Headquarters (215) 574-3219.

12.3 NCIC CTG Investigators (6/10/02)

12.3.1 Data Submission

RTOG Case Report Forms (CRFs), with the header modified by the NCIC CTG for their use, will be used by all NCIC CTG institutions.

A single set of case report forms (CRFs) will be sent to each centre (*for photocopying and use*) following local activation. CRFs should be completed and submitted to the NCIC CTG Central Office (*see Section 5.3.2 for mailing address*) according to the submission schedule in Section 12.0 of the protocol. In addition to the required forms as listed, a copy of the signed consent form must be submitted for each patient. RTOG and NCIC CTG patient numbers as well as patient initials must be recorded on each form. CRFs will be forwarded to the RTOG by the NCIC CTG. Do not send CRF's directly to RTOG.

12.3.2 Radiation Therapy Documentation Submission

NCIC CTG investigators will submit radiation therapy data listed in section 12.0 of the protocol (*preliminary and final dosimetry information*) directly to RTOG at the address listed in section 12.1 of the protocol. Please do not submit dosimetry information to NCIC CTG. Any dosimetry questions should be directed to the Dosimetry Department at the RTOG headquarters, telephone (215) 574-3219.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary

- Overall survival

13.1.2 Secondary

- Disease-free survival
- Distant failure
- Biochemical failure (*detectable PSA*)

13.2 Randomization

The treatment allocation scheme described by Zelen²⁵ will be used at randomization to balance risk factors within institutions. The stratifying variables are Seminal vesicle invasion (*yes, no*), pre-operative serum PSA (≤ 10 , > 10), operative Gleason Score (2 – 6, 7, 8 – 10), Positive Surgical (*inked*) Margins (*yes, no*) and neoadjuvant hormone treatment (*yes, no*).

13.3 Sample Size

The primary hypothesis of this trial is whether the 2-year androgen ablation plus radiation will improve survival compared with radiation therapy alone or androgen ablation alone for patients following prostatectomy. There are two sets of data that are available to provide some estimates on the survival rates and potential treatment effect. Since the biochemical failure is an intermediate event to the survival, we designed the study using the novel approach proposed by Lu²⁶, which deals with potential lag time effect²⁷ and provides a more reasonable extrapolation of the long-term survival.

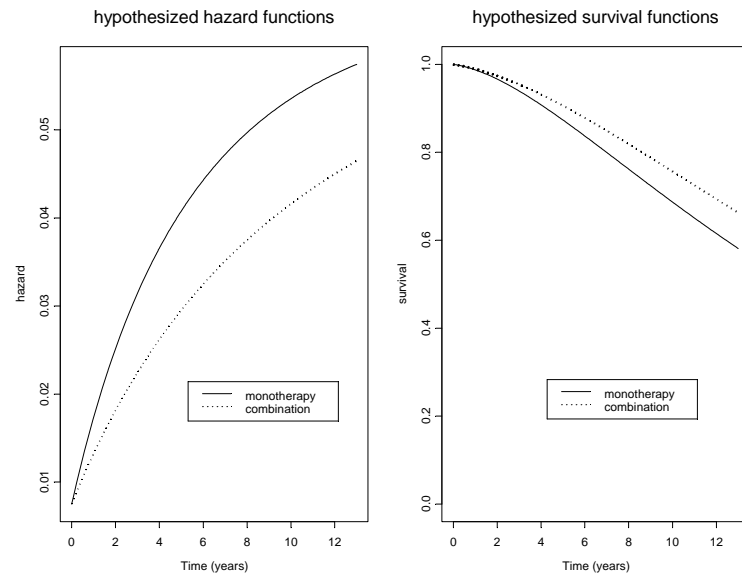
A subset of 139 patients in RTOG 8531 received either radiation alone or adjuvant hormone therapy plus radiation following prostatectomy.

- The estimated yearly hazard rate for biochemical failure is $\lambda_s = 0.195$ for the radiation alone arm. And the estimated hazard ratio of the combined therapy to radiation alone for biochemical failure is

$h_s = 0.42$ based on Cox model. For the study design, we assume the hazard ratio for biochemical failure to be $h_s = 0.5$.

- The estimated yearly hazard rate for all cause mortality without or before biochemical failure was $\lambda_1 = .0075$, whereas the hazard rate for all cause mortality given biochemical failure was estimated to be $\lambda_2 = .0645$.
- The unconditional hazard for all cause mortality can be numerically estimated by $\lambda(t) = \lambda_2 - (\lambda_2 - \lambda_1) \exp[-(\lambda_s + \lambda_1)t] / S(t)$, where $S(t)$ is the unconditional survival function for all cause mortality. Thus, the projected survival for radiation alone arm is 87% and 69% at 5 year and 10 year, respectively.
- If the biochemical failure is a surrogate to the mortality, the potential survival benefit by the combination arm will be captured by the prolongation of the biochemical control. However, the RTOG 8531 suggested that while there was no difference in λ_1 between the two arms, the combination arm had a somewhat higher conditional hazard (λ_2) for mortality given biochemical failure than the radiation alone arm with a hazard ratio of 2.0 (95% confidence interval of [1.76, 5.5]). Considering the salvage hormone treatment is mandatory in RTOG 8531, such a ratio for the new study will be smaller. For the study design, we assume the hazard ratio of the combination arm to the radiation alone arm is 1 and 1.1, for λ_1 and λ_2 respectively. Thus, the projected survival for the combination arm is 91% and 76% at 5 year and 10 year, respectively. See the figure for the projected hazard functions and survival functions.
- Though the hazard ratio is not a constant over the time, we can compute the “effective” hazard ratio that leads to the same statistical power as if the proportional hazards assumption were met. With the previous assumptions, the “effective” hazard ratio for the study is 0.745.

Messing et al.²⁸ has published a randomized study comparing hormone therapy alone vs. observation following prostatectomy for node positive patients. They reported a 5-year survival of 88% (*picked up from the curve*) for hormone therapy alone arm. Since it is not much different from radiation alone group of RTOG 8531, the previous assumption may be applicable to the comparison between hormone alone arm and the combination arm.



With four interim analyses of overall survival planned and the “effective” hazard ratio of 0.745, a maximum of 528 deaths are required to detect such a survival benefit by the combination arm compared to radiation alone or hormone therapy alone arm with a one-sided significance level of 0.025 and a statistical power of 90%. Using the projected hazard functions, we required a sample size of 898 per arm to be accrued uniformly within 5 years and be followed for additional 8 years. Considering about 5% ineligible and lack-of-data cases, **a total of 2850 cases will be required.**

13.3.1 (6/10/02) Pathological T2 patients with a Gleason score ≥ 7 , preoperative PSA > 10 ng/ml and positive surgical margins have a similar survival experience as those from RTOG 85-31 and Messing et al²⁸;

inclusion of these patients will not impact the statistical design as originally written. Therefore, the sample size will not need to be adjusted to meet the study objectives.

13.3.2 Sample Size (12/9/02)

From July 2001 to August 2002, the study accrued at a slower pace than expected with only 9 cases entered to the study. With the goal of 2850 cases unlikely to be reached within the originally projected five years, the Data Monitoring Committee (DMC) recommended adjusting the study design by dropping the androgen suppression only arm.

The original primary objective of the study was to test if the addition of androgen suppression to radiation therapy will lead to improve overall survival than to each treatment used separately. The original design called for two one-sided tests each with a significance level of 0.025. The revised design will use a one-sided test with a significance level of 0.05. Without changing the other assumptions in the hypothesized hazard ratio and median survival of the control arm, a total of 435 deaths are required to have statistical power of 90%. Thus, we required a sample size of 665 per arm to be accrued uniformly within 5 years and to be followed for additional 8 years. Considering about 5% ineligible and lack-of-data cases, a total of 1398 cases will be required.

13.4 Analysis plans

13.4.1 Statistical Methods

Overall and disease-free survivals will be calculated by the Kaplan-Meier method.²⁹ The treatment effect with respect to all endpoints will be done with the logrank test statistics.^{30,31} All eligible and evaluable patients will be included in the intent-to-treat analysis. The cumulative incidence method³¹ will be used to estimate the 5-year rates of biochemical failure and the clinical patterns of tumor recurrence. The primary analysis focuses on the pair-wise comparison of the combination arm to either the RT alone or the hormonal treatment arm. These will be conducted as per our one-sided test as discussed in section 13.3 above. A secondary analysis will be the comparison of the hormonal treatment versus RT alone arms. Since we are not hypothesizing the direction of the outcome (See RTOG 8531 and Messing et al.²⁸), this comparison will be via a two-sided test at the 0.05 level preserving the power of approximately 0.90.

13.4.1.1 Statistical Methods (12/9/02)

The statistical methods of the revised study design will remain as described in Section 13.4.1, with the exception of the primary analysis. In the revised plan, the primary analysis will be conducted per our one-sided test as discussed in section 13.3.2. The planned secondary analysis comparing hormonal treatment to RT alone will not be necessary in the revised design.

13.4.2 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 the toxicity

13.4.3 Interim Treatment Analysis for Early Stopping

Four such interim treatment comparisons of overall survival shall be performed when we observe 103, 175, 288, and 409 deaths in each of the comparison pairs (*radiation alone vs. combination, or hormone alone vs. combination*). The projected nominal significance level is .0005, .0005, .0028, and .0103 at each of these four interim analyses, respectively. However, the first two nominal levels will be truncated at 0.001.³⁷ The first interim analysis is projected to take place when 100% of total accrual is reached and each patient has been followed at least half a year. 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*). The fourth interim analysis is projected to take place at the seventh year after the closure (*6 years of follow-up*).

For each of these interim analyses for early stopping and/or reporting of results, the toxicity, treatment delivery, and efficacy statistics will be reported to RTOG Data Monitoring Committee (DMC). If the difference with respect to the primary endpoint is highly significant, i.e., the p-value is less than the nominal value specified in a sequential design or the conditional power is extremely small, the statistician responsible for the study recommends early stopping and/or reporting of the results. In making that recommendation, the accrual rate, treatment compliance, safety of the treatments, and importance of the study are taken into consideration along with the p-value and the conditional power. The DMC then makes its recommendation about the study to the study chair, who generally accepts that recommendation. The boundary of each comparison 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'Brien-Fleming alpha spending function approach.^{32, 33}

We decided not to set up a sequential lower boundary for the lack of efficacy because all interim analyses will be performed after all patients have been entered to the study. Early stopping due to seemingly lack of efficacy has no considerable clinical implication other than saving some collection of follow-up data. More importantly, the inclusion of lower boundary based on proportional hazards assumption will cause a significant loss of statistical power depending on the severity of the potential lag time effect. Instead, conditional power for alternative hypotheses outlined in Section 13.3 given the observed data will be calculated at the third and fourth interim analyses. The low conditional power suggests the low probability of significant treatment benefit even if the future follow-up data are distributed as assumed by alternative hypotheses. Such a conditional power will be reported to RTOG DMC for evaluation.

13.4.3.1 Interim Treatment Analysis for Early Stopping (12/9/02)

In the revised design, four interim treatment comparisons will be performed when we observe 85, 144, 237, and 337 of the 435 deaths. The projected nominal significance level is .0005, .0011, .0085, and .0237 at each of these four interim analyses, respectively. However, the first two nominal levels will be truncated at 0.001.³⁷ The first interim analysis is projected to take place when 100% of total accrual is reached and each patient has been followed at least half a year. 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*). The fourth interim analysis is projected to take place at the seventh year after the closure (*6 years of follow-up*).

13.4.4 Initial Analysis for Reporting Treatment Effects

This analysis will be carried out after the end of the follow-up period or 528 deaths in each of the comparison pairs are observed unless the criteria for early stopping are met. The survival difference between a monotherapy arm and the combination arm will be tested by log-rank statistic at the significance level of 0.021 given four interim analyses carried out according to Section 13.4.3. The potential survival difference between the two monotherapy arms will be estimated by the hazard ratio with a 95% confidence interval using Cox model.³⁴ The proportional hazards assumption will be tested using the approach proposed by Grambsch and Therneau.³⁵

13.4.4.1 Initial Analysis for Reporting Treatment Effects (12/9/02)

In the revised study design, this analysis will now be carried out after the end of the follow-up period or when 435 deaths are observed unless the criteria for early stopping in Section 13.4.3.1 are met.

13.5 Patient Accrual

The patient accrual is projected to be about 40-50 cases per month. We expect to complete the accrual in 5 years. The accrual may be extended to 6 or 7 years if the patient entry is somewhat slower than it is anticipated, in which case the minimum follow-up will be adjusted to meet the requirement of maximum number of deaths. However, if the average monthly accrual rate during the first year beyond the first six months of quiet period (*due to administrative reasons*) is below 30 cases per month, the study will be re-evaluated for its feasibility.

13.5.1 Patient Accrual (12/9/02)

With the revisions to this study, we expect to accrue approximately 23-25 cases per month and to complete accrual in 5 years. If the average monthly accrual rate during the first year beyond the activation of the revised protocol is below 20 cases per month, the study will be re-evaluated for its feasibility.

13.6 Inclusion of Minorities

In conformance with the National Institute of Health Revitalization Act of 1993 with regard to inclusion of women and racial/ethnic minority in clinical research, we have also considered the possible interaction between race and treatments. Based on the latest accrual statistics from RTOG 9413 and 9408, 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 82% and 37% for white and black, respectively.

Planned Gender and Minority Inclusion

	American Indian or Alaskan	Asian or Pacific Islander	Black, not of Hispanic	Hispanic	White, not of Hispanic	Other or Unknown	Total
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	Native		Origin		Origin		
Male	5	11	655	85	2080	14	2850

13.6.1 *Inclusion of Minorities (12/9/02)*

The statistical power for detecting the hypothesized difference for white and black is 80% and 40%, respectively, in the current study design. The revised Planned Gender and Minority Inclusion Table is below:

Planned Gender and Minority Inclusion

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown	Total
Male	3	5	321	42	1020	7	1398

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APPENDIX I

RTOG P-0011

SAMPLE CONSENT FOR RESEARCH STUDY

(12/9/02) *Note: CTSU investigators must include the following text in the consent form: You will be entered onto this study as part of the Cancer Trials Support Unit (CTSU), a pilot project sponsored by the National Cancer Institute (NCI) to provide physicians and patients with greater access to NCI-sponsored phase III clinical trials.

STUDY TITLE

PHASE III RANDOMIZED STUDY OF ADJUVANT THERAPY FOR HIGH RISK pT2-3N0 PROSTATE CANCER

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, "Taking Part in Clinical Trials: What Cancer Patients Need To Know," is available from your doctor.

You are being asked to take part in this study because you have prostate cancer.

WHY IS THIS STUDY BEING DONE? (12/9/02)

The purpose of this study is to compare the effects (good and bad) of radiation therapy alone or hormonal therapy given during and after radiation therapy on you and your prostate cancer to see which treatment is better.

This research is being done because you are at risk for your prostate cancer to come back. Prostate cancer cells may remain after your surgery. Additional treatment with radiation therapy to the prostate area or a combination of radiation and hormonal therapy may be used as appropriate treatment. It is not known which of these is the best treatment.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY (12/9/02)

About 1,398 men will take part in this study.

WHAT IS INVOLVED IN THE STUDY? (12/9/02, 3/18/04)

You will be “randomized” into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. A computer will determine into which group you are placed. Neither you nor the researcher will choose what group you will be in. You will have an equal chance of being placed in either group.

Group 1: You will receive radiation therapy five days a week for approximately 7 weeks. Your radiation treatments will be given as an outpatient at your institution. You will also receive hormonal therapy for 2 years beginning at the start of radiation treatment.

Group 2: You will receive radiation therapy alone for five days a week for approximately 7 weeks. Your radiation treatments will be given as an outpatient at your institution.

For Group 1 Your doctor will prescribe a standard hormonal drug regimen for you and administer the drug per the package instructions.

and

Eulexin (Flutamide) **or** Casodex (Bicalutamide)

Eulexin is a pill. You will take 2 pills three times a day for one month. Casodex is also a pill. You will take one pill once a day for one month. You will receive either Eulexin or Casodex.

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

Schedule

Prior to study entry

Procedure

Physical exam with medical history

Blood tests-

(to include a CBC, PSA, liver and kidney function tests and a testosterone level.)

Bone scan

CT of the pelvis

Pelvic lymph node assessment

During radiation treatment

Blood tests –

(every three weeks from beginning of radiation treatment and at the end of radiation treatment.)

Physical exam - including rectal exam one month following the end of radiation therapy

During hormonal therapy

Physical exam – including a rectal exam (every three months for 1 year, then every six months for the following year and as indicated by your physician.)

Blood tests – (monthly during Eulexin or Casodex treatment, then every three months for 2 years and as indicated by your physician.)

At each follow-up appointment:

(every 6 months for 4 years, then annually)

Physical exam – including a rectal exam

Blood tests

Bone scan – (at 2 ½ years from start of treatment and as indicated by your physician.)

CT scan of the pelvis- (at 2 ½ years from start of treatment and as indicated by your physician.)

Biopsy – (if indicated to evaluate your cancer.)

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 a portion 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. A portion of this tissue will be sent to a central office for review and research investigation associated with this protocol.

HOW LONG WILL I BE IN THE STUDY? (12/9/02)

Group 1 will receive radiation treatments once a day for about 7 weeks with hormonal treatment for 2 years.

Group 2 will receive radiation treatments once a day for about 7 weeks.

Your physician will see you one month following the end of radiation therapy, then you will have follow-up visits with your physician every three months for one year, then every 6 months for 4 years, then yearly for the rest of your life.

The researcher may decide to stop your treatment if it is in your *medical* best interest, your condition worsens, or new information becomes available, and this information suggests the treatment will be ineffective or unsafe for you; however, you still will be seen in follow-up visits, and data about your treatment will be included in the study results.

It is unlikely, but the study may be stopped due to lack of funding or participation. You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

WHAT ARE THE RISKS OF THE STUDY?

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

Risks Associated with Radiation Therapy

Very Likely

Reddening or tanning of the skin in the treated area
Hair loss in the treated area
Fatigue
Diarrhea
Abdominal cramps
Nausea and vomiting
Bladder irritation causing urinary frequency; urinary tract infection; painful or difficult urination

Less likely, but Serious

Injury to the bladder causing blood in the urine
Inability to hold urine
Injury to the bowel and pelvis area
Permanent inability to achieve an erection

Risks Associated with Hormone Therapy (3/18/04)

Very likely

Hot flashes
Sweats
Dizziness
Breast swelling and tenderness
Inability to achieve an erection (impotence)

Less likely

Unusual taste in your mouth
Diarrhea
Increased skin redness
Hives and/or rash
Bone pain
Increased thirst
Increased urination and difficulty in urination
Decreased bone density
Fatigue
Weakness
Sleeplessness
Shortness of breath
Decreased hunger
Nausea and vomiting
Fluid retention
Infection
Increased blood pressure
Depression
Headache
Nervousness
Muscle pain
Anemia
Blood clots
Injection site reaction
Loss of sexual desire (libido)
Neuromuscular disorder
Shrinking of testicles

Less likely, but Serious

Allergic reaction including a skin rash and difficulty breathing
Temporary weakness following injection
Difficulty breathing
Heart failure

Your doctor will discuss the side effects that apply to the drug you receive.

Risks Associated with Eulexin and Casodex

Very likely

Hot flashes
Breast swelling and/or tenderness
Back pain
Fatigue
Fluid retention
Decrease in red blood cell count
Anemia
Inability to achieve an erection
Loss of sexual desire

Less likely

Rash
Constipation or diarrhea
Nausea
Sweating
Dizziness
Sensitivity to light
Weight loss
Urinary tract infection
Increased urination at night
Blood in the urine
Increased blood pressure
Chest pain
Increased blood sugar

Rare, but Serious

Changes in liver function which can cause severe, possibly life-threatening damage: Liver symptoms could include intense itching, dark urine, loss of appetite, nausea and/or vomiting, yellow skin or eyes, abdominal tenderness, and flu-like symptoms. Your liver function will be checked before you start this hormone and one month later.

The side effects described above are risks associated with a combination of the two drugs. Your doctor will discuss which risks apply to the drug you choose.

Reproductive risks: Because the drugs and/or radiation in this study can affect an unborn baby, you should not father a baby while on this study. You must use adequate birth control measures to prevent pregnancy while participating in this study.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with prostate cancer in the future.

The possible benefits of taking part in the study are the same as receiving radiation therapy and hormonal treatment without being in the study.

WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: (1) radiation therapy; (2) hormone therapy; or (3) no additional treatment except medications to make you feel better. With the latter choice, 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.

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

Please talk to your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (*RTOG*). If you are participating in this trial through the Cancer Trials Support Unit (*CTSU*), a record of your progress will also be kept by the *CTSU*. Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (*FDA*), the National Cancer Institute (*NCI*), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in this study.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. You or your insurance company will be responsible for the cost of the drugs and radiation treatments given during this study. Please ask about any expected added costs or insurance problems.

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

You or your insurance company will be charged for continuing medical care and/or hospitalization. (Medicare is considered a health insurance provider.)

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

WHAT ARE MY RIGHTS AS A PARTICIPANT?

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

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

A Data Safety Monitoring Board an independent group of experts, will be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

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

Name

Telephone Number

For information about this study, you may contact:

Name

Telephone Number

For information about your rights as a research subject, you may contact:

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

Name

Telephone Number

You may also call the Project Office of the NCI Central Institutional Review Board (CIRB) at 888-549-0715 (from the continental U.S. only) or 800-937-8281, Ext. 4445 (from sites outside the continental U.S.).

WHERE CAN I GET MORE INFORMATION?

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

Visit the NCI's Web sites for comprehensive clinical trials information
<http://cancertrials.nci.nih.gov> or for accurate cancer information including PDQ
<http://cancernet.nci.nih.gov>.

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

SIGNATURE

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

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

Patient Signature (*or legal Representative*)

Date

TISSUE AND BLOOD TESTING (*RTOG P-0011*)

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 with prostate*
T2a	Tumor involves one lobe
T2b	Tumor involves both lobes
T3	Tumor extends through prostate capsule**
T3a	Extracapsular extension (<i>unilateral or bilateral</i>)
T3b	Tumor involves the seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than the seminal vesicles: bladder neck, external sphincter, rectum, levator muscles and/or pelvic wall

*Note: Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c

**Note: Invasion into the prostatic apex or into (*but not beyond*) the prostatic capsule is not classified as T3, but as T2.

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node or nodes

Primary Tumor, Pathologic (pT)

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

***Note: There is no pathologic T1 classification

Distant Metastasis**** (M)

MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis

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

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

APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

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

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/574-3214) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.
 - a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.
2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone.
3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).
4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.
5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

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

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

B. RADIATION TOXICITY GUIDELINES

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

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

C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

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

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

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

Commercial and Non-Investigational Agents

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

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

Investigational Agents

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

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

i. Phase I Studies Utilizing Investigational Agents

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

of termination of the agent.

- 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 CLASSIFICATION

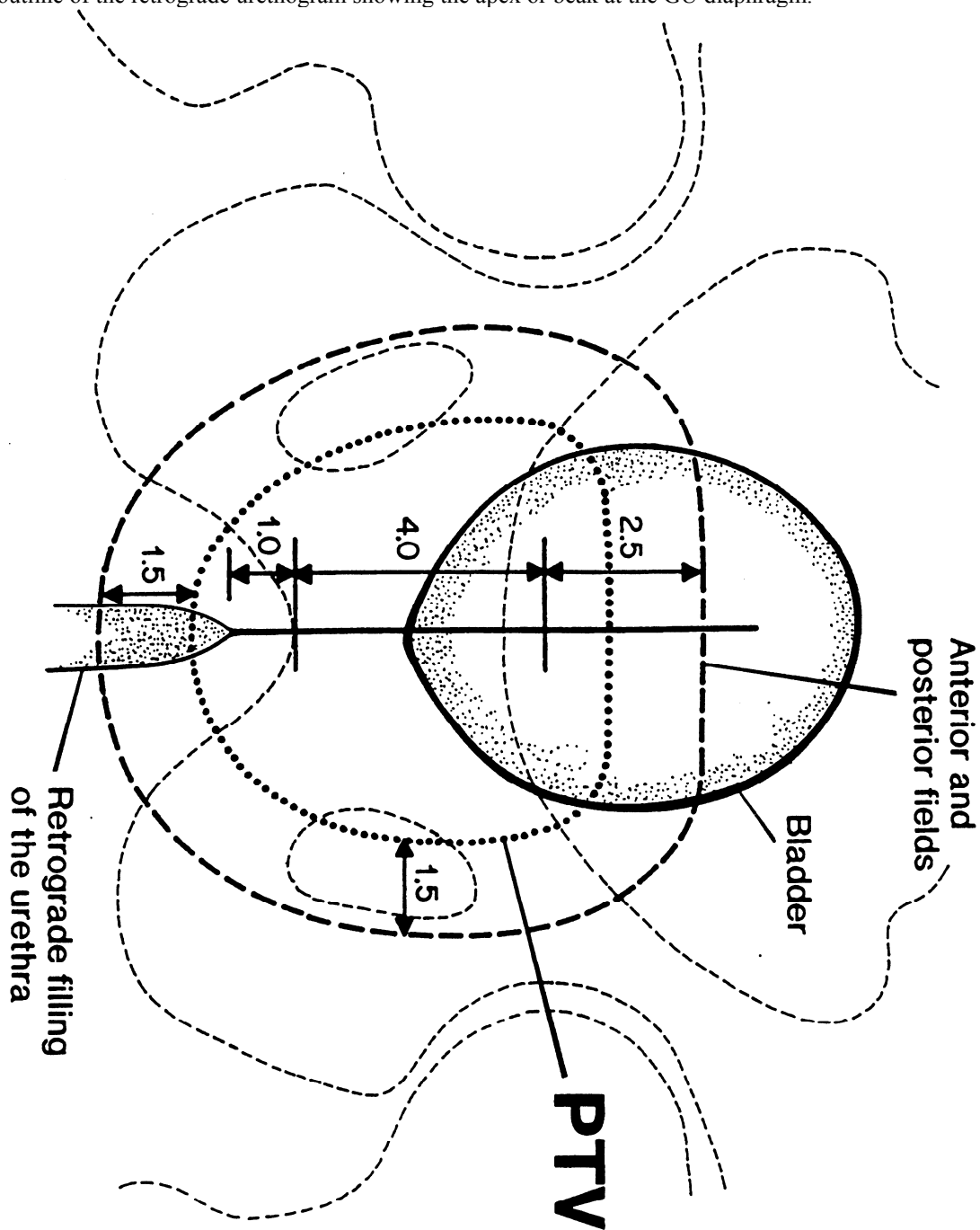
Pattern	Margins Tumor Areas	Gland Pattern	Gland Size	Gland Distribution	Stromal Invasion
1	Well defined	Single, separate, round	Medium	Closely packed	Minimal, expansile
2	Less definite	Single, separate rounded but more variable	Medium	Spaced up to one gland diameter, average	Mild, in larger stromal planes
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.

APPENDIX VII

Figure 1

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



APPENDIX VII (continued)

Figure 2

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

