

**RADIATION THERAPY ONCOLOGY GROUP**

**RTOG 96-08**

**A PHASE III TRIAL OF TOTAL ANDROGEN SUPPRESSION VERSUS  
TOTAL ANDROGEN SUPPRESSION PLUS DEFINITIVE EXTERNAL BEAM IRRADIATION  
FOR PATHOLOGIC LYMPH NODE POSITIVE (pN+) ADENOCARCINOMA OF THE  
PROSTATE**

**Chairmen**

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## RADIATION THERAPY ONCOLOGY GROUP

### RTOG 96-08

#### A PHASE III TRIAL OF TOTAL ANDROGEN SUPPRESSION VERSUS TOTAL ANDROGEN SUPPRESSION PLUS DEFINITIVE EXTERNAL BEAM IRRADIATION FOR PATHOLOGIC LYMPH NODE POSITIVE (pN+) ADENOCARCINOMA OF THE PROSTATE

##### Schema

<b>S</b>	<b>PSA</b>	<b>R</b>	
<b>T</b>	1. $\leq 30$ ng/ml	<b>A</b>	
<b>R</b>	2. $> 30$ ng/ml	<b>N</b>	<b>Arm 1:</b> Total Androgen Suppression Alone
<b>A</b>		<b>D</b>	
<b>T</b>	<b>Stage</b>	<b>O</b>	<b>Arm 2:</b> Total Androgen Suppression Plus
<b>I</b>	1. T <sub>1</sub> or T <sub>2</sub> , N+	<b>M</b>	External Beam Irradiation
<b>F</b>	2. T <sub>3</sub> or T <sub>4</sub> , N+	<b>I</b>	
<b>Y</b>		<b>Z</b>	
	<b>Nodal Status (first detection)</b>	<b>E</b>	
	1. Clinically-detected involved lymph nodes		
	2. Microscopic only (+) lymph nodes		

##### Radiation:

Patients on Arm 2 will receive whole pelvis irradiation to 50.4 Gy (1.8 Gy/day, 5 times/week x 28 fractions) followed by a 18-19.8 Gy boost to the prostate (1.8 Gy/day, 5 times/week for 10-11 fractions, depending on T stage). T<sub>1</sub> and T<sub>2</sub> will get an 18 Gy boost, and T<sub>3</sub> and T<sub>4</sub> will get a 19.8 Gy boost for a total of 68.4 - 70.2 Gy to the prostate.

##### Total Androgen Suppression (TAS):

All patients will receive either

- orchiectomy plus Flutamide t.i.d. p.o. or Casodex 50 mg qd **OR**
  - LHRH analog (*Zoladex* or *Lupron*) plus Flutamide t.i.d. p.o. or Casodex 50 mg qd.
- TAS will be given indefinitely or until disease progression or inability to tolerate toxicity

Eligibility: (see Section 3.0 for details)

- Histologically confirmed adenocarcinoma of the prostate with elevated PSA
- Histologically-confirmed pelvic lymph node involvement;
- CT showing no periaortic or common iliac lymph node involvement.
- Negative bone scan and chest x-ray;
- Karnofsky Performance Status  $\geq 70$ ;
- PSA  $\geq 4.0$  is mandatory (*the highest PSA within 45 days prior to randomization is the eligible level*);
- Liver function tests  $\leq 1.2$  times the upper limits of normal;
- Treatment must begin 60 days after randomization and within 90 days of surgical staging;
- Orchiectomy if done, must be  $\leq 90$  days prior to randomization (*may be performed  $\leq 60$  days post randomization*); chemical hormones may be started prior to randomization but must begin  $\leq 90$  days before study entry;
- Patients must sign a study-specific consent form;
- No prior chemotherapy or radiation;
- No distant mets.

**Required Sample Size: 750 patients**

**3/17/98**

**Institution #** \_\_\_\_\_  
**RTOG 96-08**  
**Case #** \_\_\_\_\_

**ELIGIBILITY CHECK (7/1/97, 3/17/98)**  
*(page 1 of 2)*

- \_\_\_\_\_(Y) 1. Is there histologically confirmed adenocarcinoma of the prostate?
- \_\_\_\_\_(T1-T4) 2. What is the T stage?
- \_\_\_\_\_(Y) 3. Is there histologically confirmed pelvic lymph node involvement?
- \_\_\_\_\_(N1-N3) 4. What is the N stage?
- \_\_\_\_\_(Y) 5. Was a Gleason score assigned?
- \_\_\_\_\_(≥ 70) 6. What is the Karnofsky?
- \_\_\_\_\_(≥4) 7. What is the PSA level?
- \_\_\_\_\_(N) 8. Has the patient had prior chemotherapy, pelvic radiation, or anti-androgen hormone as specified in Section 3.2.5?
- \_\_\_\_\_(N) 9. Has the patient had prior radical surgery or cryosurgery for prostate carcinoma?
- \_\_\_\_\_(N) 10. Any evidence of distant mets?
- \_\_\_\_\_(Y) 11. Are the liver function tests  $\leq 1.2$  x the upper normal limits?
- \_\_\_\_\_(N) 12. Is there evidence of periaortic or common iliac lymph node involvement?
- \_\_\_\_\_(Y) 13. Was a CT of the abdomen and pelvis done within the last 90 days?
- \_\_\_\_\_(Y) 14. Will treatment begin within the next 60 days and within 90 days of surgical staging?
- \_\_\_\_\_(N) 15. Are there any major medical or psychiatric illnesses which would prevent completion of treatment and interfere with follow-up?
- \_\_\_\_\_(Y/N) 16. Did the patient have an orchiectomy?  
\_\_\_\_\_(Y) If yes, was it done within the last 90 days?
- \_\_\_\_\_(N) 17. Is this patient eligible for RTOG 94-08 or 94-13?  
Specify the reason: \_\_\_\_\_
- \_\_\_\_\_(Y/N) 18. Is there a history of a previous or concurrent cancer other than superficial basal or squamous cell skin cancer?

*continued on page 2*

**Institution #** \_\_\_\_\_  
**RTOG 96-08**

**ELIGIBILITY CHECK (7/1/97, 3/17/98)**

Case # \_\_\_\_\_

(page 2 of 2)

\_\_\_\_\_(Y) 19. If yes, has the patient been free of disease for at least 5 years?

\_\_\_\_\_(Y) 20. Has the patient signed a study-specific informed consent?

**The following questions will be asked at Randomization:**

\_\_\_\_\_(Y) 1. Has the Eligibility Checklist (*above*) been completed?

\_\_\_\_\_(Y) 2. Is the patient eligible for this study?

\_\_\_\_\_  
Patient's Name

\_\_\_\_\_  
Verifying Physician

\_\_\_\_\_  
Patient ID #

\_\_\_\_\_  
Referring Institution # (*if different*)

\_\_\_\_\_  
PSA ( $\leq 30$  ng/ml vs.  $> 30$  ng/ml)

\_\_\_\_\_  
Stage (*T1 or T2, N + vs. T3 or T4, N+*)

\_\_\_\_\_  
Node Status, First Detection (*clinically vs. microscopic only*)

\_\_\_\_\_  
Birthdate

\_\_\_\_\_  
Sex

\_\_\_\_\_  
Race

\_\_\_\_\_  
Social Security Number

\_\_\_\_\_  
Zip Code (*9 digit if available*)

\_\_\_\_\_  
Method of Payment

\_\_\_\_\_  
Will any component of the patient's care be given at a military or VA facility?

\_\_\_\_\_  
Treatment Start Date

\_\_\_\_\_  
Treatment Assignment

Completed by \_\_\_\_\_

Date \_\_\_\_\_

## **1.0 INTRODUCTION**

Currently, much controversy exists over the role of definitive external beam irradiation therapy in pathologic pN+ (*positive pelvic lymph nodes or D<sub>1</sub>*) adenocarcinoma of the prostate. Table I shows clinical progression-free survival rates at 5 and 10 years with different treatment approaches. Delayed hormones provide the lowest progression-free survival among the treatment options listed. Yet, data regarding hormones up-front versus surgery alone versus radiation therapy alone are not very different (*Table I*).

**Table I**

<u>Treatment</u>	<u>Results (Progression-free Survival)</u>	
	<u>5 Years</u>	<u>10 Years</u>
Delayed Hormonal Therapy	20-30% <sup>10,11</sup>	5% <sup>10,11</sup>
Hormones Upfront	55% <sup>5,9,12</sup>	20-25% <sup>5,9,12</sup>
Surgery Alone	20-40% <sup>13,14,15</sup>	10-30% <sup>13,14,15</sup>
XRT Alone	50-60% <sup>1,2</sup>	30-50% <sup>1,2</sup>

Some authors maintain that regional treatment may be curative in some of these patients.<sup>1,2</sup> The data at the Medical College of Wisconsin on 56 patients treated definitively with external beam irradiation shows a 61% 5 year clinical disease-free survival and 48% 10 year disease-free survival.<sup>1</sup> Yet other authors have shown no benefit to regional irradiation in what would appear to be the a similar cohort of patients.<sup>3,4</sup>

Patients with pN+ disease who are not treated with external beam irradiation are usually treated with androgen ablation. Zagars et al. recently published a series of 179 such patients who received early androgen ablation and found 5 and 8 year actuarial rates of freedom from disease progression to be 55% and 25%, respectively.<sup>5</sup> Their dataset also shows that local progression of disease occurred as often as metastatic disease which, presumably, external beam irradiation could help to control.<sup>5</sup>

Two separate groups have recently reported the results of combined hormonal management and external beam irradiation for patient with positive pelvic lymph nodes.<sup>6,7</sup> In the series from Philadelphia, 41 patients received definitive irradiation and hormonal manipulation concurrently.<sup>6</sup> Overall and relapse-free survival at 5 years for this group of patients was 91% and 81%, respectively.<sup>6</sup> Five patients in this same time period received radiation therapy alone and refused hormonal manipulation.<sup>6</sup> All five relapsed within 18 months.<sup>6</sup> Data from M.D. Anderson shows 181 patients with positive lymph nodes treated with hormones alone between 1984 and 1992, and 27 patients treated with hormones and external beam radiation therapy.<sup>7</sup> Actuarial incidence of rising PSA at 4 years in the hormone only group was 53%, while there were no PSA failures in the radiation therapy and hormone group.<sup>7</sup> This data, combining radiation therapy and hormones for locally advanced disease, as well as the encouraging results of RTOG 85-31 and 86-10, suggest that hormones and radiation does improve disease-free and may improve cause-specific survival in a group of patients previously thought to be destined to rapid disease progression and death.<sup>8,9</sup> Therefore, this study will attempt to show that external beam radiation therapy and hormonal manipulation is superior to hormonal manipulation alone.

## **2.0 OBJECTIVES**

- 2.1 To test the results of the addition of pelvic radiation therapy to TAS in patients with lymph-node positive adenocarcinoma of the prostate. Endpoints of overall survival, disease specific survival, and disease free survival will be addressed.
- 2.2 To assess the differences in toxicity with the addition of pelvic radiation therapy to TAS. Endpoints of gastrointestinal toxicity and genitourinary toxicity will be utilized.

## **3.0 PATIENT SELECTION**

### **3.1 Conditions for Patient Eligibility**

- 3.1.1 Patients with histologically confirmed localized adenocarcinoma of the prostate with histologically confirmed pelvic lymph node metastasis with no evidence of other disseminated disease, T1-T4, N1-N3.
- 3.1.2 Grading of the tumor by Gleason is mandatory.
- 3.1.3 Karnofsky Performance Status of  $\geq 70$ .
- 3.1.4 PSA is  $\geq 4.0$  is mandatory for patient eligibility. The PSA value used should be the highest PSA prior to randomization (*but within 45 days*) using the monoclonal assay with a normal range of 0-4 ng/ml. PSAs measured using a polyclonal assay (*e.g., Yang*), with a normal range of ~0.0-2.5 ng/ml, may need

to be divided by a conversion factor of approximately 1.5.

- 3.1.5 No prior therapy, per Section 3.2.5.
- 3.1.6 No distant metastases.
- 3.1.7 Liver function tests  $\leq 1.2$  times the upper limits of normal.
- 3.1.8 CT of abdomen and pelvis within 90 days prior to randomization.
- 3.1.9 Treatment must begin within 60 days after randomization and within 90 days of surgical staging.
- 3.1.10 If orchiectomy was done, it must be within 90 days prior to randomization; if chemical hormones have begun, the start date must also be within 90 days prior to study entry and must not be different from what the patient would receive after study entry (*Zoladex, Lupron, and Flutamide*).
- 3.1.11 Patients must sign a study-specific consent form prior to randomization.

### **3.2 Conditions for Patient Ineligibility**

- 3.2.1 Patients with PSA  $< 4.0$  (*by the Hybritech monoclonal assay; see Section 3.1.4 for conversion factor if a polyclonal assay is used*).
- 3.2.2 Evidence of distant metastasis (*MI*).
- 3.2.3 Patients who are surgically staged negative for pelvic node involvement.
- 3.2.4 Lymph node involvement of periaortic or common iliac region.
- 3.2.5 Radical surgery for carcinoma of the prostate, (*i.e. prostatectomy*) previous pelvic radiation therapy, cryosurgery, chemotherapy. Anti-androgen hormones  $> 90$  days prior to study entry (*prior testosterone administration is acceptable if completed  $> 90$  days before study entry*).
- 3.2.6 Previous or concurrent cancers unless NED free  $\geq 5$  years, other than superficial basal or squamous cell skin carcinoma.
- 3.2.7 Major medical or psychiatric illness which, in the investigator's opinion, would prevent completion of treatment and would interfere with follow-up.
- 3.2.8 Karnofsky Performance Status of  $< 70$ .
- 3.2.9 Eligible for RTOG 94-08, or 94-13.

## **4.0 PRE-TREATMENT EVALUATION**

- 4.1 History, physical examination (*to include tumor measurements*) and Karnofsky Performance Status evaluation.
- 4.2 Sexual history (*assessment of potency status*) is mandatory.
- 4.3 Histological evaluation. Grading by Gleason is mandatory.
- 4.4 Mandatory laboratory studies: CBC, SGOT and SGPT, bilirubin, serum testosterone levels, alkaline phosphatase and a prostatic specific antigen (*PSA*) study are mandatory for all patients. The PSA value is the highest PSA prior to treatment using the monoclonal assay with a normal range of 0-4 ng/ml. The PSA value used must have been obtained within 45 days of randomization. PSAs measured using a polyclonal assay (*e.g., Yang*), with a normal range of  $\sim 0.0$ -2.5 ng/ml, may need to be divided by a conversion factor of approximately 1.5 for use in this equation.
- 4.5 Chest x-ray and bone scan are mandatory.
- 4.6 Histological evaluation of pelvic lymph nodes is mandatory. CT of abdomen and pelvis (*mandatory; must be done within 90 days prior to randomization*) to rule out abnormal extrapelvic lymph nodes.

## **5.0 REGISTRATION PROCEDURES**

- 5.1 Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday 8:30 am to 5:00 pm ET. Patients may also be registered via computer modem 24 hours a day, 7 days a week. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The following information must be provided:
  - Institution Name & Number
  - Patient's Name & ID Number
  - Verifying Physician's Name
  - Medical Oncologist's Name
  - Eligibility Criteria Information
  - Stratification Information
  - Demographic Data
  - Treatment Start Date

## **6.0 RADIATION THERAPY (ARM 2 ONLY)**

### **6.1 Treatment Plan**

Arm 1 - Total Androgen Suppression (TAS) alone (*i.e., no radiation*).

Arm 2 - Total Androgen Suppression plus whole pelvis external beam radiation therapy to 50.4 Gy at 1.8 Gy/day, five fractions/week, followed by a boost to the prostate.

## **6.2 Dose**

**6.2.1** Arm 2 will receive radiation to the whole pelvis with 50.4 Gy to regional lymphatics delivered at 1.8 Gy/day, five days/week, times 28 fractions, followed by a boost to the prostate given at 1.8 Gy/day, five days/week, times 10 or 11 fractions to a total of 68.4 - 70.2 Gy in 38 - 39 fractions in eight weeks.

**6.2.2** T<sub>1</sub> and T<sub>2</sub> tumors will get a total of 68.4 Gy in 38 fractions, while T<sub>3</sub> and T<sub>4</sub> tumors will get a total of 70.2 Gy in 39 fractions.

## **6.3 Physical Factors**

Megavoltage equipment is required with effective photon energies  $\geq 6$  MeV. Minimum source-to-axis distance is 100 cm. Any treatment technique (*field arrangement*) capable of producing the dose distribution specified by the protocol will be acceptable with the exception of perineal boost.

## **6.4 Target Volumes**

The volumes defined are for the purpose of dose prescription. The actual radiation treatment fields used must have adequate margins to allow the delivery of the prescribed dose to the defined target volume. The total irradiated volume will depend on the treatment unit and the treatment techniques employed.

**6.4.1** Regional Lymphatics Target Volume For patients receiving whole pelvic irradiation, the minimum initial unblocked field size will be 16 x 16 cm. A urethrogram will be used to define the inferior portion of the field. The inferior margin of the pelvic target volume will be placed at least 1.0 cm below the highest point where the contrast narrows to a point (*"the apex of the urethra"*). Simply adding margins of 1.2 cm below the ischial tuberosity would result in unnecessary irradiation to portions of the penis, rectum and/or urethra for a significant number of patients and is not recommended. The lateral margins will be 2.0 cm lateral to the pelvic brim. If a four-field technique is used, care should be taken to adequately cover external and internal iliac nodal chains and extensions of the primary tumor into the seminal vesicles and/or perirectal tissues. To achieve these goals, a major part of the rectum may need to be included in the lateral fields. Upper border will be at the L4-5 interspace.

**6.4.2** Prostate Boost Target Volume will include the prostate with margins sufficiently wide to encompass all of the tumor extensions into the surrounding tissues. The prostatic boost target volume will measure at least 9.0 cm in longitudinal (*craniocaudal*) diameter and at least 8.0 cm in transverse and sagittal diameter. Depending on tumor size, considerably larger target volumes will be required. The size and the position of the prostatic boost target volume in these patients is optimally defined by the use of CT scan.

### **6.4.3** Films

Portal films of each treatment field and simulation films must be submitted to RTOG Headquarters.

## **6.5 Dose Specifications**

**6.5.1** If using conventional treatment planning techniques, the prescribed doses are defined on the central axis at the center of the regional lymphatics target volume for the regional lymphatics and to the center of the prostate for the dose delivered to the prostate. If 3D conformal treatment planning technology is used, the protocol dose may be prescribed as "minimum target volume dose". However, if this approach is used, the maximum dose must not exceed the specified values given in Sections 6.5.3.3 and 6.5.4.3. The dose to the center of both target volumes and the maximum dose must be reported on the relevant forms. The dose will be uncorrected for tissue inhomogeneities.

**6.5.2** The dose will be specified as follows for the following portal arrangements:

**6.5.2.1** At the intersection of the central rays of two or more co-axial beams.

**6.5.2.2** At isocenter for arc or complete rotation techniques.

**6.5.2.3** At the center of each target volume for other treatment arrangements.

**6.5.2.4** If 3D-CRT treatment planning technology is used, the dose may be prescribed at the periphery as a "minimum target volume dose".

### **6.5.3** Dose to Regional Lymphatics

**6.5.3.1** The dose to the regional lymphatics is 50.4 Gy, to be delivered 1.8 Gy/day, 5 days/week, for 28 fractions.

**6.5.3.2** The minimal dose to the regional lymphatic target volume, as identified in the central plane for this target volume, will be  $\geq 47.9$  Gy, which is 95% of the protocol dose.

**6.5.3.3** The maximal target volume dose (*defined as the greatest dose in the target volume which is delivered to an area greater than 2cm<sup>2</sup>*) to the regional lymphatics target volume, will be  $\leq 52.9$  Gy, which is 105% of the protocol dose.

### **6.5.4** Dose to Prostate

- 6.5.4.1 The dose from the whole pelvis field to the center of the prostate must be calculated. The boost dose to the prostate will be added to this dose. In rare cases, it is expected that the dose to the center of the prostate from the regional lymphatic field will be less than 47.9 Gy. In such cases, it will be necessary to increase the number of fractions for the boost. In all cases, the dose to the boost will be 1.8 Gy/day.
- 6.5.4.2 The prostatic target volume will receive a boost of 18 Gy for T1 and T2 tumors or 19.2 Gy for T3 and T4 tumors. Thus the total prescribed dose for T1 or T2 tumors will be 68.4 Gy and for T3 or T4 tumors will be 70.2 Gy. These values assume that the prostate received at least 47.9 Gy from the regional lymphatic field.
- 6.5.4.3 The minimal dose to the prostatic target volume, as identified in the central plane for this target volume, will be  $\geq 68$  Gy for T1 or T2 tumors or will be  $\geq 70$  Gy for T3 and T4 tumors.
- 6.5.4.4 The maximal prostatic target volume dose (*defined as the greatest dose in the target volume which is delivered to an area greater than 2cm<sup>2</sup>*), as identified in the central plane for this target volume, will be  $\leq 105\%$  of the protocol dose.

## **6.6 Critical Normal Structures**

- 6.6.1 The bladder will receive the same dose as the regional lymphatics. The base of the bladder will be included in the prostate target volume and will receive the same dose as the prostate. Every attempt should be made to keep the bladder distended during administration of the boost in order to avoid irradiation of the superior portion of the organ.
- 6.6.2 Doses to the whole rectum shall not exceed 55 Gy. Portions of the anterior wall will, by necessity, receive the same dose as the prostate.

## **6.7 Radiation Toxicity**

- 6.7.1 All patients will be seen weekly by their radiation oncologist during radiation therapy. Any observations regarding radiation reactions will be recorded (*See Appendix IV for grading*) and should include attention toward the following potential side effects:
  - 6.7.1.1 Skin reactions;
  - 6.7.1.2 Small bowel or rectal irritation manifesting as abdominal cramping, diarrhea, rectal urgency, hematochezia;
  - 6.7.1.3 Bladder complications including urinary frequency, dysuria, hematuria, urinary tract infections, and incontinence;
  - 6.7.1.4 Impotence in previously potent patients.

## **6.8 Dose Documentation**

- 6.8.1 CT based dosimetry is required even for conventional planning. The entire pelvis will be imaged using 10 mm thick, contiguous slices. Contrast will be used to define the bladder and the rectum.
- 6.8.2 Isodose distributions are required on each CT image which displays the prostate. This will result in a total of approximately 6 axial dose distributions. The prostate, the rectum, and the bladder will be outlined on each slice on which they occur. The following dose levels will be displayed on these axial dose distributions: 105% of the prescription dose to the prostate, 95% of the prescription dose to the prostate, 55 Gy, 50 Gy, 45 Gy, and 40 Gy. In addition, one isodose distribution of the regional lymphatic field at the approximate level of the superior most port of the external iliac node is required. This distribution should contain an outline of the bony anatomy at this level and display the 50 Gy, 48 Gy, 45 Gy, and 40 Gy isodose distributions.

## **6.9 Compliance Criteria**

- Compliance will be scored in relation to field borders, radiation dose, fractionation, elapsed days, and dosimetry documentation. Each parameter will be scored as being 1) per protocol, 2) a variation (*acceptable*), or 3) a deviation (*unacceptable*).
- 6.9.1 Field Borders
    - Per protocol: actual field borders that either exceed or fall short by less than or equal to 1 cm those borders stated in the protocol.
    - Variation: actual field borders that either exceed or fall short by less than or equal to 2 cm those by more than 2 cm those borders stated in the protocol.
    - Deviation: actual field borders that either exceed or fall short by more than 2 cm those borders stated in the protocol.
  - 6.9.2 Radiation Dose
    - Per protocol: actual dose is within 5% of the specified dose.
    - Variation: actual dose is within 10% of the specified protocol dose.
    - Deviation: actual dose deviates by more than 10% from the specified protocol dose.
  - 6.9.3 Minimum Dose Coverage

Per protocol: the target structures are covered by the 95% isodose surface as a minimum. Variation: the target structures are covered by greater than or equal to the 90% isodose surface, but less than the 95% isodose surface.

Deviation: the target structures are covered by less than 90% isodose surface.

**6.9.4** Maximum Isodose

Per protocol: 105% or less.

Variation: greater than 105% but less than 110%.

Deviation: greater than or equal to 110%.

**6.9.5** Elapsed Days

Per protocol: no more than a 3 day break.

Variation: 4 to 7 day break.

Deviation: a break of 8 days or more.

**6.9.6** Dosimetry Documentation

Per protocol: as requested in Section 6.8.

Variation: none.

Deviation: less than requested in Section 6.8.

**7.0** DRUG THERAPY (3/17/98)

If chemical castration is selected over orchiectomy, either Zoladex or Lupron monthly injections can be used as the LHRH analog along with Flutamide or Casodex. The 3-month depot is also acceptable. Hormones may be administered as follows:

- Flutamide plus Zoladex or
- Flutamide plus Lupron or
- Flutamide plus orchiectomy or •
- Casodex plus Zoladex or
- Casodex plus Lupron or
- Casodex plus orchiectomy

**7.1** Zoladex (NSC# 606864)

**7.1.1** Description

Zoladex (*Goserelin*) is an LHRH analog with substitutions for the L-amino acid Glycine in positions 6 and 10. These substitutions produce an analog with 50-100 times the potency and longer duration of action than the naturally occurring peptide when assessed in acute animal tests.

**7.1.2** Supply

Zoladex is commercially available. For indigent patients who cannot afford the neoadjuvant Zoladex, RTOG investigators may contact their local Zeneca sales representative to request compassionate use of Zoladex for an individual patient. Zeneca reserves the right to terminate this program for administrative reasons at any time with 30 days advance notice.

**7.1.3** Preparation and Storage

The Zoladex depot is supplied preloaded with 3.6 mg Zoladex (*monthly*) or 10.8 mg (*3-month*) in a disposable syringe with a 16 gauge needle. The unit is sterile and comes in a sealed, light- and moisture-proof package.

The pack should be stored at approximately 25° C (*room temperature*). Before being opened, each package must be inspected for damage in which case the syringe must not be used. Being sterile, the syringe should be removed from its package only by the physician/nurse immediately before needed.

**7.1.4** Administration

If Zoladex is selected as the route of androgen suppression, administration is as follows. If requested by the patient, a local anesthetic, i.e., 0.2 to 0.5 ml of 1% lidocaine hydrochloride may be given intradermally. Zoladex will be injected subcutaneously using an aseptic technique. Insert the needle to its full length, pull it back 1 cm, then inject. The manufacturer recommends inserting the needle into the subcutaneous fat then changing the direction of the needle so that it parallels the abdominal wall before inserting the needle to its full length. This will create a little pocket for the Zoladex plug so that it does not extend when the needle is withdrawn. After checking to ensure that the depot has been discharged, the used syringe will be discarded in a safe manner. One can ensure that the depot has been discharged by ensuring the tip of the plunger is visible within the tip of the needle. Subcutaneous injection will occur every four weeks (*every three months if using the 10.8 mg depot*) indefinitely or until there is disease progression or patient is unable to tolerate toxicity.

**7.1.5** Toxicity

During routine screening of Zoladex, no significant pharmacological activity was apparent in the cardiovascular, respiratory, central nervous, renal, metabolic, coagulation or gastric acid secretory

systems. The acute toxicity of Zoladex has been found to be very low in relation to its pharmacological potency. Studies have shown that serum levels of testosterone can be reduced and maintained within the castrate range resulting in objective evidence of tumor regression. Other than the occasional transient worsening of cancer symptoms (*tumor flare*) due to an initial temporary rise in testosterone serum levels on initiating therapy, no significant toxicity apart from that attributed to castration (*hot flashes, decreased erections, impotence*) has been reported. Reports show that the incidence of localized or generalized rash with patients receiving Zoladex is 6%. There have been no reports of bronchospasm in the United States Clinical Trials program. In general, allergic reactions have been extremely uncommon with Zoladex therapy. There have been isolated reports of urethral obstruction, urticaria, or spinal cord compression. Shortness of breath, cardiac arrhythmia, hyperglycemia, severe back pain, acute kidney failure, pneumonia, confusion, weakness, pancreatitis and diabetes mellitus were reported in four men. No episodes of anaphylaxis as a result of Zoladex therapy have occurred in the past.

## **7.2 Lupron Depot (Leuprolide acetate)**

### **7.2.1 Description**

Lupron depot is a synthetic nonapeptide analog of LHRH. The chemical name is 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (*salt*). The analog, like Zoladex, possesses greater potency than the natural hormone.

### **7.2.2 Supply**

Lupron depot is commercially available in a vial containing sterile lyophilized microspheres, which, when mixed with the accompanying vial of diluent, become a suspension which is intended as a monthly, or 3 month, intramuscular injection. Monthly dose is 7.5 mg; three month dose is 22.5 mg.

### **7.2.3 Preparation and Storage**

No refrigeration is required but this product should be protected from freezing.

### **7.2.4 Administration**

a. Lupron depot: monthly formulation, should be administered as follows (*recommended dose = 7.5 mg incorporated in a depot formulation*):

1. Using a syringe with a 22 gauge needle, withdraw 1 mL of diluent from the ampule and inject into the vial (*extra diluent is provided; any remaining should be discarded*).
2. Shake well to thoroughly disperse particles to obtain a uniform suspension. The suspension will appear milky.
3. Withdraw the entire contents of the vial into the syringe and inject it at the time of reconstitution. Discard suspension if not used immediately.
4. Intramuscular injection will occur every four weeks indefinitely until there is disease progression or the patient is unable to tolerate toxicity.

b. Lupron depot: 3 month formulation should be administered as follows (*recommended dose = 22.5 mg incorporated in a depot formulation*):

1. Using a 22 gauge needle withdraw 1.5 mL diluent from ampule and inject into the vial.
2. Shake well to thoroughly disperse particles to obtain a uniform suspension. It will appear milky.
3. Withdraw entire contents of the vial into the syringe and inject immediately. Discard suspension if not used immediately.
4. Intramuscular injection will occur every 12 weeks indefinitely unless patient is unable to tolerate toxicity or has evidence of progression of disease.

### **7.2.5 Toxicity**

Adverse reactions to Lupron depot have been reported but, fortunately, the incidence is small.<sup>16</sup> In a study of 56 patients, the following percentage exhibited these reactions:

Cardiovascular System -	Edema	(12.5%)
Gastrointestinal System -	Nausea/Vomiting	(5.4%)
Endocrine System -	Decreased testicular size	(5.4%)
	Hot flashes	(58.9%)
	Impotence	(5.4%)
Central/Peripheral Nervous System -		(7.1%)
Respiratory System -	Dyspnea	(5.4%)
Miscellaneous -	Asthenia	(5.4%)

There has been a report of an anaphylactic reaction to Lupron depot in the medical literature.<sup>16</sup>

In addition to the toxicities noted above, lupon 3-month depot has the following toxicities:

varicose veins	< 5% incidence
testis disorders	< 5% incidence
pleural effusion	< 5% incidence
dry eyes	< 5% incidence

### **7.3 Flutamide (NSC# 147834)**

#### **7.3.1 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 anti-androgen that is metabolized into a hydroxylated derivative which effectively competes with the hydrotestosterone for androgen receptor sites.

#### **7.3.2 Supply**

Flutamide is commercially available.

#### **7.3.3 Storage**

Flutamide is supplied as 125 mg capsules. Flutamide should be stored at temperatures ranging from 2°-30° C (36°-86° F) and be protected from excessive moisture.

#### **7.3.4 Administration**

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

#### **7.3.5 Toxicity**

The reported side effects of treatment include diarrhea, anemia, and mild elevation of SGOT without alteration in serum bilirubin and without clinical manifestations. A high percentage of patients treated with Flutamide alone developed gynecomastia within 2-8 months.<sup>16</sup> One death from liver failure occurred in RTOG 92-02 among the first 1000 patients.

#### **7.3.6 Dose Modification Schedule**

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

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

If liver functions increase  $\geq 4$  x normal, the Flutamide must be discontinued and the study chairman contacted.

### **7.4 Casodex (3/17/98)**

#### **7.4.1 Description**

Casodex (*bicalutamide*) is a nonsteroidal antiandrogen which has no androgenic or progestational properties. The chemical name is Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]- 3- [(4-fluorophenyl)sulphonyl]- 2- hydroxy- 2- methyl, (+,-). Casodex is a racemic mixture with the antiandrogen activity residing exclusively in the (-) or (*R*) enantiomer. Casodex 50 mg has the status of an approved new drug, 150 mg is experimental. Casodex has a long half-life compatible with once-daily dosing. Casodex is well tolerated and has good response rates in phase II trials (*Kennealey and Furr, 1991, Tyrrell 1994*).

#### **7.4.2 Supply**

Casodex is commercially available.

#### **7.4.3 Storage**

Casodex is supplied as 50-mg green film-coated tablets and should be stored in a dry place at room temperature between 68°-77° F.

#### **7.4.4 Administration**

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

#### **7.4.5 Toxicity**

In animal experiments, birth defects (*abnormal genitalia, hypospadias*) were found in male offspring from female animals dosed with Casodex during pregnancy. Although offspring from male animals dosed with Casodex did not show any birth defects, patients are advised to neither cause pregnancy nor

to donate sperm while receiving therapy or during the first 3 months after cessation of therapy. The use of barrier contraceptives is therefore advised.

**7.4.6** Dose Modification Schedule

Casodex should be discontinued in instances of chemical liver toxicity. If the bilirubin rises > 1.5 x the institutional upper limit of normal or if the SGOT (or SGPT) rises > 2.5 x the institutional upper limit of normal, Casodex may be stopped at the investigator's discretion. Casodex can be restarted when the bilirubin and SGOT are within normal range.

**7.5** Disease Progression (3/17/98)

**7.5.1** Continuing with TAS after documented progression will be at the treating physician's discretion.

**8.0** SURGERY

**8.1** Simple bilateral orchidectomy through transverse or bilateral scrotal incision is to be performed under general or local anesthetic at patient and surgeon's choice.

**8.2** Surgery may have been performed no more than 90 days prior to start of protocol treatment, and within 60 days after randomization.

**9.0** OTHER THERAPY

Does not apply to this study.

**10.0** PATHOLOGY

**10.1** Central pathology reviews of both the diagnostic and post treatment prostate biopsies are planned for this study. Central reviews on previous prostate studies have demonstrated a 23% discrepancy (*difference in Gleason score of 2 or more*) in histological grading (*see Section 13.2*).

**10.2** H & E stained slides and a representative tissue block of the diagnostic biopsy and a lymph node containing metastatic carcinoma, the pathology report(s) and a pathology submission form will be submitted to the RTOG Tissue Bank:

**LDS Hospital  
Department of Pathology  
E.M. Laboratory  
8th Avenue at C Street  
Salt Lake City, UT 84143**

**10.2.1** If paraffin block is not available, submit 10 unstained slides. Block/slides must be clearly labeled with the pathology identification number that agrees with the Pathology Report.

**10.2.2** Pathology report documenting that submitted block or slides contain tumor must be enclosed.

**10.2.3** A Pathology Submission Form must be included and must clearly identify the enclosed materials.

**10.3** To encourage compliance, your Pathology Department can be reimbursed for obtaining a tissue block.

**10.4** 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*).

**10.5** All cases will be graded histologically according to Gleason. Where possible, post-therapy biopsies will also be histologically graded. In selected cases, the DNA content and proliferation rate will be assessed by image cytometry. This will be performed on pre-treatment biopsies and may also be performed on selected post-therapy biopsies.

**10.6** Post-therapy biopsies will be evaluated for the presence or absence of residual tumor. In cases with residual tumor, the degree of therapy effect will be assessed.

**10.7** Submitted pathology materials will be retained.

**11.0** PATIENT ASSESSMENTS

**11.1** Study Parameters

<u>Parameter</u>	<u>Pretreatment</u>	<u>At Completion of Radiotherapy</u>	<u>Followup</u> (See Sec. 11.2)
History & Physical, KPS	X	X	X
Tumor size in cm in two dimensions ( <i>phys. exam</i> )	X		X
Gleason Score <sup>a</sup>	X		X <sup>b</sup>

Sexual function status	X	X	X
CT of Abdomen and Pelvis	X		
Chest X-ray	X		
Bone Scan	X		X <sup>c</sup>
Alk Phosp, Serum Testosterone	X		yearly
SGOT, SGPT, Bilirubin	X	X <sup>d</sup>	X <sup>d</sup>
CBC	X	X	X <sup>e</sup>
Lymph Node Assessment	X		
Prostatic-Specific Antigen(PSA)	X	X	X <sup>f</sup>

- a. Diagnostic biopsy and post-treatment rebiopsy.
- b. Post-tx biopsy as indicated (*abnormal exam or rising PSA*).
- c. As clinically indicated, e.g. rising PSA or bone pain.
- d. Every two weeks x 4, then monthly during hormone therapy. If liver functions rise to  $\geq 4$  x normal, flutamide will be discontinued and Dr. Lawton must be contacted.
- e. At each follow-up for the first 6 months.
- f. At each follow-up.

## **11.2 Follow-up Schedule**

- 11.2.1** Every 3 months for the remainder of the first year.
- 11.2.2** Every 4 months during the second year.
- 11.2.3** Every 6 months for years 3-5 then annually for the remainder of the patient's life.
- 11.2.4** A bone scan will be performed on any patient who presents with complaints of bone pain that cannot be attributed to any intercurrent disease. Discretionary plain films may be needed to evaluate lesions seen on bone scan to confirm the diagnosis of metastatic disease.

## **11.3 Measurement of Effect**

- 11.3.1** PSA levels and prostate tumor dimensions in cm must be recorded on the diagrams on the data collection forms for initial and follow-up evaluations of the patient.
- 11.3.2** After study entry, disease activity evaluations will be made and recorded using the following criteria:
  - 11.3.2.1** PSA Complete Response (PSA-CR): A PSA-CR will be declared if the PSA becomes undetectable ( $< 0.3$  ng/ml).
  - 11.3.2.2** Clinical Complete Response (CR): A clinical CR will be declared if there is a complete resolution of all palpable abnormalities. *Note*: patients with non-palpable lesions will not be considered in this category.
  - 11.3.2.3** Equivocal Disease (ER): This rating will be assigned if the changes observed in the prostate are abnormal due to treatment and felt not to represent tumor.
  - 11.3.2.4** Partial Response (PR): Tumor regression that is greater than 50% of the product of the two largest perpendicular diameters of the prostate tumor and that is present for at least one month as measured clinically.
  - 11.3.2.5** Stable Disease(SD): There is no change in the size of the tumor or less than or equal to 25 % decrease in the product of the two largest perpendicular diameters of the prostate tumor.
  - 11.3.2.6** Progressive Disease (PD): This rating will be assigned when there is clinical evidence in the prostate gland of disease progression or recurrence measured by a 25% or greater increase in the product of the two largest perpendicular diameters of the prostate.

## **11.4 Other Response Parameters**

- 11.4.1** Freedom from biochemical (PSA) failure  
For this study, the "PSA nadir" will be defined as the lowest PSA value reached immediately preceding a "PSA failure", from the time of the first required follow-up visit. A PSA failure is defined as a consistent and significant rise in the PSA, each separated by at least one month. A significant rise is defined as a rate of 20% or more if in excess of 1.5 ng/ml. For PSA values of  $\leq 1.5$  ng/ml, a significant rise is  $\geq 0.3$  ng/ml. A second consecutive PSA rise is required for PSA failure unless there is obvious evidence of disease.
- 11.4.2** Time to Local Progression: The time to progression will be measured from the date of randomization to the date of documented local progression. Patients who have a normal exam and no evidence of having a PSA failure will be considered controlled locally. Patients with a residual abnormality or a rising PSA shall undergo biopsy to distinguish between local and distant failures. If patient refuses biopsy, wait for an increase in PSA or obvious digital progression.

- 11.4.3** *Time to Distant Failure:* The time to distant failure will be measured from the date of randomization to the date of documented metastatic disease by bone scan or CT evidence of progression of nodal or other distant disease. Patients with evidence of a biochemical relapse (*rising PSA*) but a negative biopsy will be considered to have experienced only a distant failure.
- 11.4.4** *Disease-Free Survival:* The progression-free survival will be measured from the date of randomization to the date of documentation of progression or until the date of death. This endpoint includes all measures of disease including physical exam, PSA, bone scans and biopsies.
- 11.4.5** *Survival:* The survival time will be measured from the date of first treatment 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 should be sent to RTOG.

## **12.0 DATA COLLECTION**

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

<u>Item</u>	<u>Date Due</u>
Demographic Form (A5)	Within 2 weeks of randomization
On Study Form (I1)	
Pathology Report (P1)	
Pathology Blocks (P2)	
Surgical Operative Report (S2)*	
Surgical Pathology Report (S5)*	
* Node dissection or sampling	
Hormone Flowsheet (M1)	
(if hormones start before randomization)	
<u>Preliminary Dosimetry Information:</u> (Arm 2)	Within 1 week of start of RT
RT Prescription ( <i>Protocol Treatment Form</i> ) (T2)	
Films ( <i>simulation and portal</i> ) (T3)	
Calculations (T4)	
Radiotherapy Form (T1)	
<u>Final Dosimetry Information:</u> (Arm 2)	Within 1 week of RT end
Daily Treatment Record (T5)	
Isodose Distribution (T6)	
Boost Films ( <i>simulation and portal</i> ) (T8)	
Follow-up Form (F1)	At 6 and 10 weeks from study entry, then every 3 mos during year 1, every 4 mos. during year 2 every 6 mos during years 3-5 then annually. Also at progression/relapse and at death.
Pathology Report (P1)	Biopsy, as applicable
Pathology Blocks (P2)	( <i>rising PSA, local regrowth</i> )
Autopsy Report (D3)	As applicable

## **13.0 STATISTICAL CONSIDERATIONS**

### **13.1 Endpoints**

- 13.1.1** Overall survival (*Failure: death from any cause*)
- 13.1.2** Disease Specific Survival (*Failure: death from prostate cancer*)
- 13.1.3** Disease-free Survival (*defined in Section 11.4.4*)
- 13.1.4** Time to PSA failure (*defined in Section 11.4.1*)
- 13.1.5** Time to local failure (*defined in section 11.4.2*)
- 13.1.6** Time to Distant Metastasis (*Failure: first appearance of distant metastasis*)
- 13.1.7** Toxicity

### **13.2 Overview**

The trial is designed to test the addition of definitive external beam irradiation to total androgen suppression (TAS). The primary endpoint to test for efficiency is overall survival. The disease specific

survival will be used as a secondary endpoint will be used for efficacy evaluation. For planning purposes, the survival of the patients with histologically positive nodes who were assigned to RT + Zoladex on RTOG 85-31 will be used as an estimate for experiment arm in this protocol. This 5 year estimate is 59% (*Personal communication*) and the survivals are assumed to be exponentially distributed. It is hypothesized that the addition of RT with TAS accounts for at least 10% absolute improvement in the 5 year survival rate. So the sample size will be calculated to test for an absolute improvement of 10% in the 5 year survival rate from 49% (TAS) to 59% (TAS + RT). Since TAS is more intense hormonal treatment than Zoladex alone, the survival rates may be underestimated. If that is the case, the statistical power would, in fact, be increased with higher survival rate for the TAS alone control arm.

Grade: (*Differentiation*): (*Well vs Moderate vs Poor*) has been shown to be important prognostic variable. Since this is cooperative group study, the concordance rate between the contributing institutional pathologists and the central review pathologist in grading was examined in the histologically staged D-1 patients in RTOG 85-31. For analysis, well differentiation was defined as Gleason sums 2, 3, 4, and 5; moderate differentiation, sums of 6 and 7; poorly differentiation, sums of 8, 9, and 10. When the contributing institutional pathologists scored the patients with the Gleason sum of 2, 3, 4, or 5, the central pathologist would put these patients in this stratum 8% of the times. For the stratum with the sums of 6 and 7, the agreement was 68% and for stratum with the sums of 8, 9, and 10, the agreement was 72%. In light of these data, grade was not be used as stratification variable prior to randomization and the central pathologist's sum will be used as the stratification variable for analyses of treatment effect.

### **13.3 Sample Size**

Given the assumptions made, it is projected that the addition of RT to TAS will reduce the yearly death rate by at least 25.9% from .143 to .106. Patients will enter the study uniformly over 4 years with 4 additional years follow up. For significance level of .05, statistical power of .80, and a two sided test, a total of 682 patients will be required, 341 in each treatment arm.<sup>17</sup> Guarding against an ineligibility/unevaluability (*no data*) rate up to 10%, **a total of 750 patients will be entered.**

### **13.4 Accrual for the Study**

It is anticipated that this study will be done as an RTOG Study with a projected accrual rate of approximately 185 patients per year. If less than 150 patients are entered after 18 months, the possibility of making the study an intergroup will be explored.

### **13.5 Randomization**

The treatment allocation scheme described by Zelen will be used because it balances patient factors other than institution.<sup>19</sup> The stratifying variables are Stage: ( $T_1$  or  $T_2$ ,  $N+$  vs.  $T_3$  or  $T_4$ ,  $N+$ ); pretreatment PSA ( $\leq 30$  ng/ml vs.  $> 30$  ng/ml) and method of first detection of positive nodes (*clinical/CT scanning vs. surgical/lymph node sampling*).

### **13.6 Analyses Plan**

#### **13.6.1 *Methods for Estimation and Testing***

Gelman et al.<sup>20</sup> and Gaynor et al.<sup>21</sup> pointed out in their respective papers that the Kaplan Meier methods tend to overestimate the cause specific survival, time to PSA failure, time to local failure and time to distant metastases. So the cumulative incidence approach will be used to estimate them as a function of time because this approach specifically accounts for competing risks such dying without a recurrence from the prostate cancer.<sup>22</sup> Their distributions between the two arms will be compared a method especially developed for the task by Gray.<sup>23</sup> Overall survival will be estimated by the usual Kaplan-Meier method<sup>24</sup> and the survival between the two arms will be compared with log rank test.<sup>25</sup>

#### **13.6.2 *Interim Analyses to Monitor the Study Progress:***

Interim reports with statistical analyses will be prepared twice a year until the initial paper reporting the treatment results has been submitted. The interim reports will usually contain information about the patient accrual rate with a projected completion date for the accrual phase, data quality, compliance rate of treatment delivery with the distributions of important prognostic baseline variables and the frequencies and severity of the toxicities by treatment arm. The interim reports will not contain the results from the treatment comparisons with respect to the efficacy endpoints, such as overall survival. These endpoints will be reported in a blinded fashion only to the RTOG Data Monitoring Committee (DMC) until all the required patients have been entered on-study and completed their assigned treatment.

#### **13.6.3 *Significance Testing for Early Termination (3/17/98)***

Three interim significance testings of treatment difference are planned. The first two interim analyses will be performed for the first RTOG semi-annual meeting after 50% and 100% of the target sample size has been accrued. The third one will be performed for the first RTOG semi-annual meeting two

years after the last patient has been randomized. The results will be reported to RTOG DMC with treatment blinded.

The significance level for each interim analysis will be calculated using the O'Brien-Fleming alpha spending function. The maximum number of deaths required for the study is 363. Under the alternative hypothesis given in 13.3, the projected numbers of deaths at the time of these three interim analyses are 40, 146 and 266, respectively. Thus, the corresponding nominal significance levels are <.0001, .001, and .018. It must be noted that the nominal significance level will be recalculated at time of interim analysis based on the observed number of deaths. If the difference is significant at level specified, the study statistician will recommend to the RTOG DMC that the randomization be discontinued (*if applicable*) and study be immediately written up for publication.

**13.6.4 Analysis for Reporting the Initial Treatment Results: (3/17/98)**

This major analysis will occur after each patient has been potentially followed for a minimum of 4 years unless the study is stopped earlier. It will include tabulation of all cases entered, and those excluded from the analyses with the reasons, the distribution of the important prognostic baseline variables, and observed results with respect to the endpoints mentioned in Section 13.1 The primary hypothesis for the study is whether the control and the experimental arms have different effects on overall survival. All eligible patients randomized will be included in the comparison. All eligible patients randomized will be grouped by assigned treatment arm in the analysis. The significance level of 0.044 will be used in this analysis to preserve an overall significance level of .05 for the study. The primary hypothesis of treatment benefit will be tested using the Cox proportional hazard model with the three stratification factors included as fixed covariates.<sup>26</sup> Additional analyses of treatment effect will include modifying factors such as age, race, and other patient characteristics. These analyses will also use the Cox proportional hazard model. The treatment comparison on disease specific survival, time to PSA failure, and time to distant metastases will be analyzed in a similar fashion. The treatment comparison on the patterns of treatment failures and of 3+ grade toxicity will use the z-statistic for testing binomial proportions.

**13.7 Inclusion of Women and Minorities (3/17/98)**

In conformance with the National Institute of Health (*NIH*) Revitalization Act of 1993 with regard to inclusion of woman and minority in clinical research, we have also considered the possible interaction between race and treatments. Analysis of three prior RTOG studies failed to show a significant difference.<sup>18</sup> On the basis of prior RTOG studies, the protocol population is projected to be 12% black and 88% white/other. If 88% of the patients recruited in this study are white/other and they are evenly distributed between the two arms, than the statistical powers to detect an increase in the 5 year survival rate from 49% to 59%, 64%, and 69% will be respectively .75, .98, .99 for a two sided test of significance at 0.05. If 12% of patients required in this study are black, the corresponding statistical powers are .16, .31, and .49 respectively.

In conformance with this act the treatment comparisons will be done for overall survival within each race. Projected minority accrual is estimated in the following table:

	<b>American Indian or Alaskan Native</b>	<b>Asian or Pacific Islander</b>	<b>Black, not of Hispanic Origin</b>	<b>Hispanic</b>	<b>White, not of Hispanic Origin</b>	<b>Other or Unknown</b>	<b>Total</b>
Female							
Male	2	5	150	24	561	8	750
Unknown							
Total	2	5	150	24	561	8	750

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## APPENDIX I

### RTOG 96-08

#### **A Phase III Trial of Total Androgen Suppression Versus Total Androgen Suppression Plus Definitive External Beam Irradiation for Pathologic Lymph Node Positive (*pN+*) Adenocarcinoma of the Prostate**

#### **Sample Patient Consent Form**

### RESEARCH STUDY

I have the right to know about the procedures that are used in my participation in clinical research so as to afford me an opportunity to make the decision whether or not to undergo the procedure after knowing the risks, benefits and alternatives. This disclosure is an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

### PURPOSE OF THE STUDY

It has been explained to me that I have prostate cancer. The study involves evaluation of external beam radiation plus drugs Zoladex (*or Lupron*) and Flutamide or orchiectomy (*surgical removal of the testicles*) plus Flutamide to treat my prostate cancer. The purpose of this study is to evaluate the effect of external beam radiation on patients with positive lymph nodes all of whom receive drugs or surgery and drugs to reduce the male hormones. If I agree to participate in this program, I would be assigned to receive either radiotherapy or no radiotherapy along with whichever form of hormone treatment I choose (*either drugs alone [two different drugs] or one drug plus surgical removal of the testicles*). Approximately 750 men will be involved in this study.

### DESCRIPTION OF PROCEDURES (3/17/98)

It is not clear at the present time which of the two regimens is best. For this reason the treatment which is to be offered to me will be based upon a method of selection called randomization. Randomization means that my physician will call a statistical office which will assign me one of the two regimens by computer. The chance of my receiving one of the two therapies is approximately equal. I will be assigned to one of the following treatments:

Treatment 1: Hormones alone

Treatment 2: Hormones with radiation therapy

Hormones reduce the male hormones in one of two ways. I can choose: monthly injections of the drug Zoladex or Lupron along with six capsules of the drug Flutamide or 1 tablet of Casodex daily. These drugs would be given indefinitely. Zoladex and Lupron are also available as a three month injection (*one injection every 3 months*). The other form of hormone reduction would be one drug (*Flutamide, six capsules daily or Casodex, 1 tablet daily*) along with surgical removal of the testicles. Again the Flutamide or Casodex would be continued indefinitely. External beam irradiation which would be given once a day five days a week for almost eight weeks.

Also, at the time of my diagnosis by biopsy, some of my 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, remaining tumor samples were stored in the Pathology Department. I am being asked for permission to use the remainder of my tumor for additional tests. Since this tissue was removed at the time of surgery or biopsy, the permission to use my tissue will not involve any additional procedures or expense to me. The tumor tissue cells will be examined to see if any special "marker" tests which predict how a patient with tumors like mine respond to treatment, can be identified.

I may be requested to have an additional biopsy of my prostate to evaluate it microscopically if my PSA level begins to go up, or if my physician feels an abnormality in my prostate after my treatment is over.

### RISKS AND DISCOMFORTS (3/17/98)

Cancer treatments often have side effects. The treatment used in this program may cause all, some, or none of the side

effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.

Zoladex or Lupron frequently leads to hot flashes, sexual dysfunction and decreased erections. A brief but temporary flare-up of tumor-related symptoms (*if any*) may also occur. The following have been reported as possible reactions (1-5%) to Zoladex or Lupron: acute kidney failure, back pain, mental confusion, pressure on my spinal cord, spasms of the windpipe, chest pain, pneumonia, lung clots and cough or breathlessness, chills, fever, irregular heartbeat, elevated or low blood sugar, and weakness, nausea and vomiting, anxiety, or depression. The relationship of these adverse reactions to Zoladex or Lupron therapy is uncertain. The symptoms may reverse upon stopping Zoladex or Lupron treatment. Zoladex or Lupron may occasionally produce irritation at the site of injection. Very rarely, allergic reaction, generalized skin rash or vasculitis (*inflammation of the tissue beneath the skin*) has been reported.

Flutamide has been reported to cause diarrhea, anemia, swelling and tenderness of the breasts and changes in certain tests which evaluate the liver. There have been rare reports of death following severe liver damage from Flutamide. It is important to call my doctor immediately if I experience "flu-like" symptoms or any of the following symptoms; intense itching, dark urine, loss of appetite, yellow skin or eyes, abdominal tenderness. If I have any of these symptoms, the Flutamide should be discontinued.

Casodex principal discomforts are breast tenderness, breast swelling, and hot flashes. Approximately 2% of patients had constipation, diarrhea, or nausea. The most frequently reported discomforts have been fatigue, back pain, and fluid retention. Casodex has been associated with changes in liver function, though these are infrequent, less than 2%, and rarely with jaundice (*yellowing of skin*). Many of these changes improved or went away despite continuation of Casodex therapy. In animal experiments birth defects (*abnormal external sex organs*), were found in male offspring from female animals dosed with Casodex during pregnancy. Although offspring from male animals dosed with Casodex did not show any birth defects, patients enrolled in this trial are advised to neither cause pregnancy nor to donate sperm both while receiving trial therapy and during the first 3 months after stopping the medication. The use of barrier contraceptives is therefore advised.

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

Orchiectomy, if chosen, is the surgical removal of the testicles with either local or general anesthetic. I would go home that same day or after a minimal stay. Bleeding and infection are possibilities, but unlikely. Removal of the testicles will cause a lowering of the male hormone testosterone, and will lead to decreased erections, hot flashes, and fatigue. Loss of libido and impotence are common.

My physician will be checking me closely to see if any of these effects are occurring. Appropriate tests will be done to monitor the effects of treatment. If needed, appropriate medications will be prescribed to keep the side effects under control. I understand that the use of medications to help control side effects could result in added costs. This institution is not financially responsible for treatment for side effects caused by the study treatment.

### **CONTACT PERSONS**

In the event that injury occurs as a result of this research, treatment will be available. I understand, however, I will not be provided with reimbursement for medical care other than what my insurance carrier may provide nor will I receive other compensation. For more information concerning the research and research-related risks or injuries, I can notify Dr. \_\_\_\_\_ the investigator. In addition, I may contact \_\_\_\_\_ at \_\_\_\_\_ for information regarding patients' rights in research studies.

### **BENEFITS**

It is not possible to predict whether or not any personal benefit will result from the use of the treatment program. I understand that the information which is obtained from this study may be used scientifically and possibly be helpful to others. The possible benefits of this treatment program are greater shrinkage and control of my tumor and prolongation of my life but I understand this is not guaranteed.

I have been told that should my disease become worse, should side effects become very severe, should new scientific

findings occur that indicate this treatment is not in my best interest, or should my physician feel that this treatment is no longer in my best interest, the treatment would be stopped. Further treatment would be discussed.

### **ALTERNATIVES**

Alternatives which could be considered in my case include surgery, radiation therapy alone or with Zoladex and Flutamide (*but not on study*), chemotherapy or treatments to make me feel better, but not necessarily cure me or make my disease less. An additional alternative is no further therapy, which would probably, but not definitely, result in continued growth of my tumor. I understand that my doctor can provide detailed information about my disease and the benefits of the various treatments available. I have been told that I should feel free to discuss my disease and my prognosis with the doctor. The physician involved in my care will be available to answer any questions I have concerning this program. In addition, I understand that I am free to ask my physician any questions concerning this program that I wish in the future.

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

### **VOLUNTARY PARTICIPATION**

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

### **CONFIDENTIALITY**

I understand that records of my progress while on the study will be kept in a confidential form at this institution and also in a computer file at the headquarters of the Radiation Therapy Oncology Group (*RTOG*). The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (*FDA*), the National Cancer Institute (*NCI*), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in the conduct of this study may have access to medical records which contain my identity. However, no information by which I can be identified will be released or published. Histopathologic material, including tissue and/or slides or blocks, will be sent to a central office for review and research investigation associated with this protocol. A representative tissue sample may be kept by the reviewing pathologist for additional tests. All samples and their associated information will be kept confidential.

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

\_\_\_\_\_  
Patient Signature (*or Legal Representative*)

\_\_\_\_\_  
Date

## APPENDIX II

### **KARNOFSKY PERFORMANCE SCALE**

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

### APPENDIX III

#### AJCC STAGING SYSTEM PROSTATE, 1997

##### DEFINITION OF TNM

###### Primary Tumor, Clinical (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor not palpable or visible by imaging
T1a	Tumor incidental histologic finding in 5% or less of tissue resected
T1b	Tumor incidental histologic finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy ( <i>e.g., because of elevated PSA</i> )
T2	Tumor confined within prostate*
T2a	Tumor involves one lobe
T2b	Tumor involves both lobes
T3	Tumor extends through prostate capsule**
T3a	Extracapsular extension ( <i>unilateral or bilateral</i> )
T3b	Tumor involves the seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than the seminal vesicles: bladder neck, external sphincter, rectum, levator muscles and/or pelvic wall

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

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

###### Regional Lymph Nodes (N)

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

###### Primary Tumor, Pathologic (pT)

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

\*\*\*Note: There is no pathologic T1 classification

###### Distant Metastasis\*\*\*\* (M)

MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Non regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s)

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

pM1c is most advanced

**Histopathologic Grade (G)**

GX	Grade cannot be assessed
G1	Well-differentiated ( <i>slight anaplasia</i> )
G2	Moderately differentiated ( <i>moderate anaplasia</i> )
G3-4	Poorly undifferentiated or undifferentiated ( <i>marked anaplasia</i> )

**Stage Grouping**

Stage I	T1a	N0	M0	G1
Stage II	T1a	N0	M0	G2, G3-4
	T1b	N0	M0	Any G
	T1c	N0	M0	Any G
	T1	N0	N0	Any G
	T2	N0	M0	Any G
Stage III	T3	N0	M0	Any G
Stage IV	T4	N0	M0	Any G
	Any T	N1,	M0	Any G
	Any T	Any N	M1	Any G

## APPENDIX V

### ADVERSE REACTION REPORTING GUIDELINES

#### A. GENERAL GUIDELINES

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

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

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

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

#### B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (grade 5) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
2. All life-threatening (grade 4) toxicities resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

#### C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

An adverse reaction is a toxicity or an undesirable effect usually of severe nature. Specifically, this may include major organ toxicities of the liver, kidneys, cardiovascular system, central nervous system, skin, bone marrow, or anaphylaxis.

These undesirable effects may be further classified as "known" or "unknown" toxicities.

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

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

### **Commercial and Non-Investigational Agents**

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

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

### **Investigational Agents**

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

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

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

- |   |  |
|---|--|
| - All deaths during therapy with the agent.                                 | <b>Report by phone within 24 hours</b> to IDB and RTOG Headquarters.<br>**A written report to follow within 10 working days. |
| - All deaths within 30 days of termination of the agent.                    | As above   |
| - All life threatening ( <i>grade 4</i> ) events which may be due to agent. | As above   |
| - First occurrence of any toxicity ( <i>regardless of grade</i> ).          | <b>Report by phone within 24 hours</b> to IDB drug monitor and RTOG Headquarters.<br>**A written report may be required.     |

#### **ii. Phase II, III Studies Utilizing Investigational Agents**

- |  |   |
|--|---|
| -All fatal ( <i>grade 5</i> ) and life | <b>Report by phone</b> to RTOG Headquarters |
|--|---|

threatening (*grade 4*) known  
adverse reactions due to

-All fatal (*grade 5*) and  
life threatening (*grade 4*)  
unknown adverse reactions  
resulting from or suspected

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

and the Study Chairman within 24 hours  
\*\*A written report must be sent to RTOG  
investigational agent. within working days with a  
copy to IDB.  
(*Grade 4 myelosuppression not reported to IDB*)

Report by phone to RTOG Headquarters,  
the Study Chairman and IDB within 24  
hours.  
\*\*A written report to follow within  
to be related to 10 working days.  
investigational agent.

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

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

## APPENDIX VI

### GLEASON CLASSIFICATION

#### Histologic patterns of adenocarcinoma of the prostate

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

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

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

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

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

Gleason, D.F. et al: Prediction of prognosis for prostatic carcinoma by combined histologic grading and clinical staging. J Urol 111:58, 1974.