

**RADIATION THERAPY ONCOLOGY GROUP**

**RTOG 94-13**

**A PHASE III TRIAL COMPARING WHOLE PELVIC IRRADIATION  
FOLLOWED BY A CONEDOWN BOOST TO BOOST IRRADIATION ONLY  
AND COMPARING NEOADJUVANT TO ADJUVANT  
TOTAL ANDROGEN SUPPRESSION (TAS)**

**Chairmen**

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## RADIATION THERAPY ONCOLOGY GROUP

### RTOG 94-13

#### A Phase III Trial Comparing Definitive Whole Pelvic Irradiation Followed by a Conedown Boost to Boost Irradiation Only and Comparing Neoadjuvant to Adjuvant Total Androgen Suppression (TAS)

<u>Stage</u>			
1. T1c, T2a			
S 2. T1b, T2b	R	<u>Arm 1:</u> Neoadjuvant TAS 2 months before and during RT	T
3. T2c-T4	A	to the whole pelvis followed by a prostate boost.	
R	N		
A <u>PSA</u>	D	<u>Arm 2:</u> Neoadjuvant TAS 2 months before and during RT.	T
1. $\leq 30$	O	RT to prostate only.	
I 2. $> 30$	M		
F	I	<u>Arm 3:</u> RT to include whole pelvis followed by a boost to	Y
<u>Gleason Score</u>	Z	the prostate and then by 4 months of TAS.	
1. $< 7$	E		
2. 7-10		<u>Arm 4:</u> RT to the prostate only followed by 4 months of	
		TAS.	

**Radiation :** Patients on Arms 1 and 3 will receive whole pelvic irradiation to 50.4 Gy (1.8 Gy/day five times a week x 28 fractions) followed by a 19.8 Gy boost (1.8 Gy/day, five times a week x 11 fractions) to a total dose of 70.2 Gy to the prostate.

**Total: 39 fractions in 8 weeks**

Patients on Arms 2 and 4 will receive RT to prostate only (1.8 Gy/day five days a week x 39 fractions) to a total dose of 70.2 Gy.

**Total: 39 fractions in 8 weeks**

**Total Androgen Suppression (TAS):** Patients on Arms 1 and 2 will receive Flutamide (two 125 mg capsules t.i.d., p.o.) and Zoladex (3.6 mg s.c. monthly x four months) or Lupron, beginning 2 months before RT and continuing until RT is completed.

Patients on Arms 3 and 4 will receive Flutamide and Zoladex (or Lupron) for four months beginning at completion of RT.

**ELIGIBILITY:** (See Section 3.0 for details)

- Histologically confirmed localized adenocarcinoma of the prostate with an elevated PSA. (Section 3.1.1)
- Estimated risk of lymph node involvement  $> 15\%$  (see the risk equation in Section 1.4.3)
- No involved common iliac or para-aortic nodes or distant mets.
- Pathological lymph-node-positive patients are ineligible.
- No prior cryosurgery for prostate cancer.
- Karnofsky performance status  $\geq 70$ .
- No prior or concurrent hormonal therapy (except allowed by Section 3.1.6), radiation or chemotherapy.
- PSA is mandatory; (PSA must be  $\leq 100$ )
- Liver function tests  $\leq 1.2$  x upper limits of normal.
- Must be ineligible for RTOG 94-08
- Treatment must begin within 6 weeks after randomization and within 60 days of surgical staging.
- Must sign a study-specific consent form prior to randomization.
- Previous or concurrent cancers other than superficial basal or squamous cell skin carcinoma unless disease free for at least five years.

**Required Sample Size: 1200**

**10/13/95, 3/1/96, 10/1/96, 7/1/97**

Institution # \_\_\_\_\_  
RTOG 94-13 \_\_\_\_\_  
Case # \_\_\_\_\_

ELIGIBILITY CHECK (9/8/98)

- \_\_\_\_\_ (Y) 1. Is there histologically confirmed adenocarcinoma of the prostate?  
\_\_\_\_\_
- \_\_\_\_\_ (Y/N) 2. What is the T stage?  
\_\_\_\_\_
- \_\_\_\_\_ (NX, N0) 3. Is the estimated risk of lymph node involvement > 15%?  
\_\_\_\_\_ (Y) If no, is the Gleason Score  $\geq 6$  with a T2C-T4?
- \_\_\_\_\_ (Y) 4. What is the N Stage?
- \_\_\_\_\_ (> 4-  $\leq 100$ ) 5. Was a Gleason score assigned? State score \_\_\_\_\_
- \_\_\_\_\_ (Y) 6. What is the PSA level?
- \_\_\_\_\_ ( $\geq 70$ ) 7. Are the liver function tests  $\leq 1.2$  x the upper normal limits?
- \_\_\_\_\_ (N) 8. What is the Karnofsky?
- \_\_\_\_\_ (N) 9. Has the patient has prior hormonal therapy (*excluding proscar and testosterone*)?
- \_\_\_\_\_ (N) 10. Has the patient had prior finasteride < 60 days and/or testosterone < 90 days before registration?
- \_\_\_\_\_ (N) 11. Has the patient had prior radiation or chemotherapy?
- \_\_\_\_\_ (N) 12. Is there evidence of distant mets?
- \_\_\_\_\_ (N) 13. Is there evidence of common iliac and/or periaortic lymph node involvement?
- \_\_\_\_\_ (N) 14. Has the patient had prior radical surgery or crysurgery for prostate carcinoma?
- \_\_\_\_\_ (N/NA) 15. Did the patient have previous or concurrent cancer other than basal or squamous cell skin carcinoma and been disease free for at least 5 years?
- \_\_\_\_\_ (Y) 16. Will treatment begin within the next 42 days and within 60 days of surgical staging?
- \_\_\_\_\_ (N) 17. Are there any major medical or psychiatric illnesses which would prevent completion of treatment and interfere with followup?
- \_\_\_\_\_ (N) 18. Is this patient eligible for RTOG 94-08?  
Specify the reason \_\_\_\_\_
- \_\_\_\_\_ (Y) 19. Has the patient signed a study-specific informed consent?

_____	Patient's Name	_____	Race
_____	Verifying Physician	_____	Social Security Number
_____	Patient ID #	_____	Zip Code ( <i>9-digit if available</i> )
_____	Referring Institution	_____	Method of Payment
_____	Birthdate	_____	Treatment Start Date
_____	VA or Military?	_____	Treatment Assignment

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

## 1.0 INTRODUCTION

Recent studies have demonstrated that, using the tumor marker prostate specific antigen (*PSA*), standard radiotherapy yields results which are worse than previously thought.<sup>1-19</sup> The early results of RTOG 86-10 demonstrated an improvement in the disease-free survival, time to local failure and time to distant failure when androgen suppression (*TAS*) was combined with radiation compared with radiotherapy alone.<sup>20</sup> This study is designed answer the question of what is the appropriate volume to treat as well as the biological question as to what is the optimal way to combine radiation and *TAS*. In RTOG 86-10, all patients received whole pelvic radiotherapy based on the assumption that these patients were all high risk and based on the assumption that whole pelvic irradiation is effective in controlling metastasis to pelvic lymph nodes. Recent studies have demonstrated that the use of the pre-treatment *PSA* and Gleason score as well as clinical stage allows us to more accurately identify patients at high risk for lymph node involvement (*see the discussion below*). Unfortunately, the use whole pelvic radiotherapy increases the cost due to the need for additional treatment simulations and the need to cut more blocks and do more calculations for conedown boost fields. Whole pelvic radiotherapy also increases acute toxicity such as diarrhea requiring more medications to manage and may reduce the total dose of radiation that can be delivered to the prostate without unacceptable rectal toxicity.<sup>21,22</sup> Perez et al. noted a significantly higher incidence of grade 2-3 radiation proctitis among patients receiving whole pelvic compared to prostate only irradiation, 10% vs 3% respectively.<sup>22</sup> Furthermore, recent studies from Memorial Sloan Kettering suggest that that there may be no benefit to whole pelvic irradiation<sup>23</sup> (*see Section 1.4 for more discussion*).

### 1.1 Radiotherapy - Results of Standard Treatment

A number of retrospective and prospective studies support the efficacy of radiation therapy in the management of localized prostate cancer.<sup>1,2</sup> Based on these early studies, the local control rate following external beam irradiation (*XRT*) was estimated to be between 70% and 90%. The end points of these studies were based primarily on a clinical assessment of "local control". These endpoints are now known to underestimate the local failures because of the presence of occult cancer in clinically controlled patients. In the past, positive biopsies were thought to be of questionable significance.<sup>3,4</sup> Recent studies have demonstrated that when positive biopsies are associated with a rising *PSA* the outcome is unfavorable.<sup>5-11</sup> Many patients once thought to be controlled locally by physical exam, do in fact have persistent disease if assessed by *PSA* and/or biopsy. Table 1 summarizes the incidence of positive biopsies reported in selected series.

Table 1: Selected Biopsy Following XRT Series

First Author ( <i>year</i> )	Stages (%) A / B1 / B2 / C	+biopsy (%)	Comments
Nachtsheim (78)	10 / 24 / 66	52% **	How were patients selected?
Leach (82)	11 / 7 / 14 / 68	~65%	'local control'=96% + Bx makes no difference
Cox (83)	0 / 0 / 100	~19%#	+ Bx makes no difference
Freiha (84)	2 / 3 / 47 / 48	61% **	89% + if abnl exam
Schellhammer (87)	10 / 6 / 51 / 34	33% ** (25-41%)	+Bx predicts local and distant failure
Scardino (88)*	16 / 40 / 18 / 26	32%	+Bx predicts for local failure
Kabalin (89)***	11 / 11 / 44 / 22	93%	How were patients selected?
Dugan (91)	0 / 0 / 0 / 100	38% ##	Pts. clinically NED
Crook (93)	19 / 24 / 36 / 21	21%	100 consecutive patients
Kuban (92)	10 / 6 / 49 / 29	10%	Pts. who by exam were clinically controlled.

\* modified from reference 24 , \*\*≥ 18 months, # at 15-18 months, ## >1 yr, \*\*\*11% had stage D disease. and >24 months post treatment and no endocrine therapy.

The wide range in the incidence of positive biopsies almost certainly reflects differences in selection bias among the various series. If patients with locally advanced disease or with palpable regrowth of disease are biopsied the incidence of positive biopsies approaches 90%.<sup>11,12</sup> If patients with low pre-treatment PSAs or patients with clinically controlled disease and stable PSAs are biopsied, the incidence of positive biopsies is much lower on the order of < 30%.<sup>13,14</sup> The post-treatment PSA is more sensitive, but a less specific endpoint for treatment failure than biopsy, because distant failures can contribute to a rising level.<sup>12</sup> These data underscore the need for improvement in the treatment of these patients.

**1.2 Pre-Treatment PSA and Gleason Scores as Prognostic Factors**

Several published series provide sufficient information to allow estimates to be made of the risk of biochemical relapse (*BCR, a rising PSA*) following XRT using the pre-treatment PSA. <sup>14-17</sup> Figure 1 graphically displays the risk of PSA failure at 1, 2, and three years following radiotherapy as a function of the pretreatment PSA (*estimated by combining the data from Stanford, MD Anderson, and the Mayo Clinic*).<sup>13-15</sup> These data highlight the need to stratify patients by their pre-treatment. Note patients with a PSA > ~ 20ng/ml have a risk of PSA experiencing biochemical relapse (*PSA failure*) in excess of 50% at 5 years.

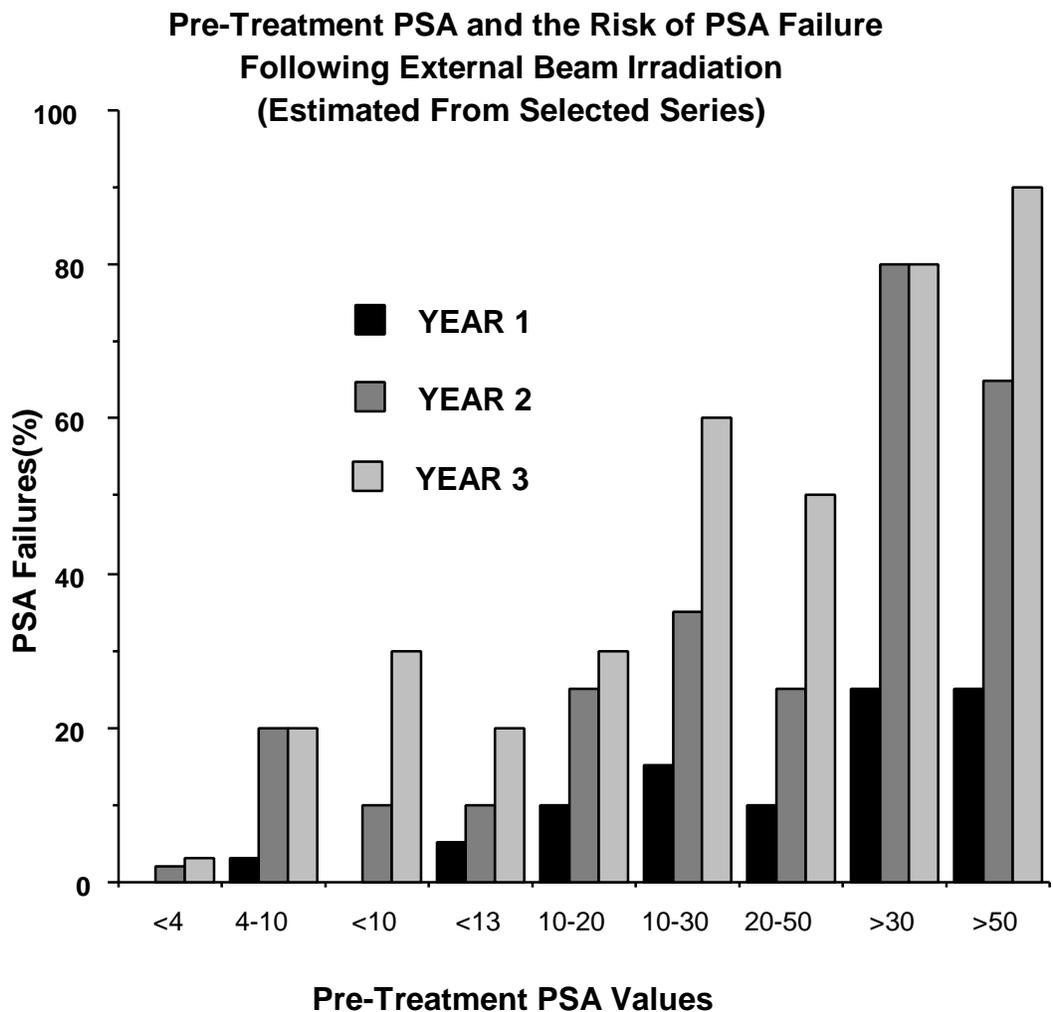


Figure 1. Pre-treatment PSA and the risk of biochemical (*PSA*) failure following radiotherapy at 1, 2, and 3 years based on combined data reported by Zagars et al., and Kaplan et al.

Data from Stanford suggest that the Gleason score also appears to be a major factor for identifying patients at high risk of PSA failure. Figure 2 demonstrates that as the Gleason score rises to a score of 6 or more, the failure rate again exceeds 50% at 3 years. Despite these alarming observations, a similar percentage of patients appear to be disease free following conventional radiotherapy as following a retropubic radical prostatectomy at 1, 2, 3 and 10 years .<sup>18,19</sup>

In addition to pre-treatment PSA and Gleason Score being prognostic factors for failure following radiotherapy, they are also prognostic factors useful for predicting the pathologic stage (*see Section 1.4.3 for the discussion*).

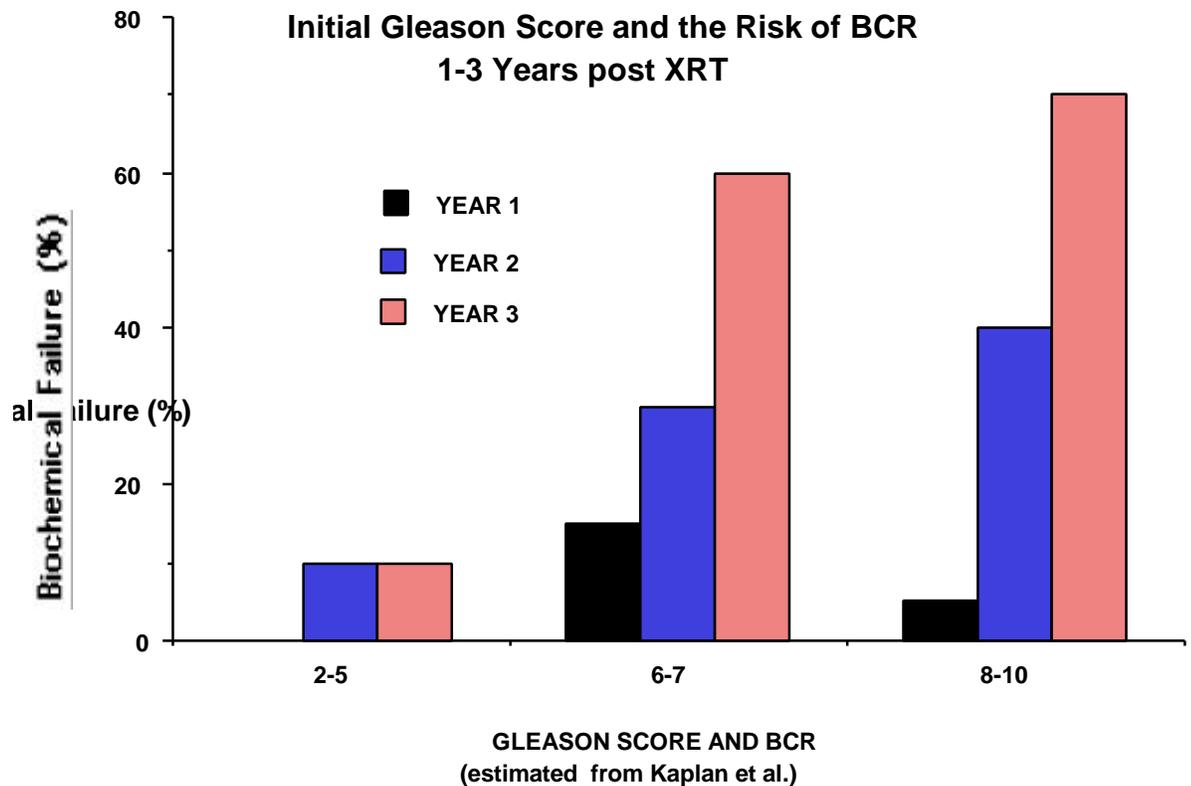


Figure 2. Gleason score and the risk of PSA failure

### **1.3 Total Androgen Suppression (TAS) and Radiotherapy:**

The rationale for using TAS with radiotherapy is supported by a number of studies.<sup>20,24-29</sup> First, an enhanced biological effect has been suggested with the use of complete as opposed to partial androgen block.<sup>24</sup> Secondly, TAS with surgery may have a beneficial effect on disease free and overall survival, even among patients with lymph node involvement if delivered early.<sup>25</sup> For example, Zincke et al. reported on the benefits of androgen deprivation on disease progression and survival even in patients with positive pelvic nodes following a lymphadenectomy. For the 52 patients who were not treated with adjunct hormonal manipulation, the overall five year rate without progression was only 18.5%. Patients, however, who received adjunct hormonal manipulation had a five year rate of non-progression of 95%. Cyto-reduction followed by radiotherapy was performed by Green and colleagues. Twenty-five patients were treated with estrogen cyto-reduction using 3mg of diethylstilbestrol prior to external beam radiotherapy and these patients were compared to a control group of 11 patients treated with external beam radiotherapy alone.<sup>26</sup> The local control rate was 72% and 55% respectively for the group receiving neoadjuvant estrogens as compared to the group receiving external beam radiotherapy alone. RTOG has performed a study (*RTOG 83-07*) which compared the use of Megace to diethylstilbestrol as cyto-reductive agents prior to radiotherapy.<sup>28</sup> Good cyto-reduction with local control being achieved in over 90% of

patients in either arm with reduced toxicity in the group receiving Megace therapy. Similarly a Canadian study was reported by Porter et al. using Cyproterone Acetate induced cyto-reduction for 12 weeks prior to the initiation of external beam radiotherapy in patients with bulky stage B2 or C prostate cancer.<sup>29</sup>

#### **1.4 Rationale and Study Design:**

##### **1.4.1 Neoadjuvant vs Adjuvant TAS**

The rationale for four months of TAS is supported by a retrospective analysis of RTOG 75-06 and the results of RTOG 86-10. The retrospective review of RTOG 75-06 demonstrated that patients who received hormonal therapy within 60 days of radiation experienced an improvement in the time to distant failure, as well as the disease free and overall survival. A multivariate analysis demonstrated an improvement in local control. The rationale for a "head to head" comparison of neoadjuvant TAS vs. adjuvant TAS arises from the early results of RTOG 86-10 and 85-31. This study suggests that the results of treating patients (*clinical stages T2B-T3*) with TAS plus radiotherapy (*XRT*) is superior to XRT alone in terms of local control, by the percentage of patients with normal (<4.0) and/or by non-rising PSAs.<sup>20</sup> The question remains which form of TAS is better. Some radiation oncologists have discouraged the use of hormones prior to and during radiation because of concern that the tumor cells would be forced into G<sub>0</sub> (*a portion of the cell cycle thought to be more radiation resistant*).<sup>30</sup> If this does in fact occur, the use of neoadjuvant and concurrent irradiation might not work as well as adjuvant irradiation. Recently, studies have suggested that since radiation and hormonal therapy may both cause death of prostate cells by the induction of apoptosis, it is possible that induction and concurrent therapy might be superior to adjuvant treatment.<sup>31</sup>

##### **1.4.2 Value of Whole Pelvic Irradiation**

The second question addressed by this study is the value of whole pelvic irradiation in patients with locally advanced disease. RTOG 77-06 suggested that, for patients at very low risk for lymph node involvement, there is no value to whole pelvic irradiation.<sup>32</sup> Small but significant improvements could have resulted from the use of whole pelvic irradiation if higher risk patients had been compared however. Furthermore, the major endpoint for this study was clinical exam which may have been too insensitive to detect differences that could have been detected by PSA. RTOG 75-06 included whole pelvic irradiation in both arms and may have included some low risk patients as well so it also does not resolve this issue (*although it did suggest that hormonal therapy was beneficial when delivered in close proximity to XRT*).<sup>33</sup> Since studies can be found for and against whole pelvic irradiation and the practicing radiotherapy community is evenly divided, it seems appropriate to answer this question with a prospective randomized trial.<sup>23,34</sup>

##### **1.4.3 Defining High Risk Patients with PSA, Gleason Score and Clinical Stage**

This study will assess the value of whole pelvic irradiation in patients at high risk for lymph node involvement defined using the pre-treatment PSA and Gleason score.<sup>35,36,37</sup> Partin et al. reported data from Johns Hopkins based on over 700 patients who underwent radical prostatectomies and demonstrated that the use of both the pre-treatment PSA and Gleason score can allow us to predict the pathologic stage more accurately than ever before.<sup>35</sup> Roach described a set of simple equations derived from Partin's nomograms that appear to obviate the need to use the nomograms. These equations also facilitate retrospective testing of various cut-off points and are easily applied to computerized data bases. The value of one of these equations in identifying patients at high risk for lymph node involvement has recently been confirmed by Roach et al.<sup>37</sup> This equation is:

$$\text{Risk of +LN} = 2/3 \text{ PSA} + [(\text{GS}-6) \times 10]$$

Where the PSA value is the highest PSA prior to treatment using the monoclonal assay with a normal range of 0-4 ng/ml. PSA's 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 for use in this equation.<sup>38</sup> Note that the nine possible Gleason Score values are empirically grouped into five major scoring categories, ≤ 4=4, 5=5, 6=6, 7=7, and ≥ 8=8. Based on this data and data described above, the patients to be included in this study will be at high risk for lymph node involvement with an overall risk of ~40% (*range >15%-100*) and for PSA failure at 3 years ~ 50%.<sup>14,15,37</sup>

We hypothesize that the use of early hormonal therapy in patients at high risk for lymph node mets will be synergistic with radiation and that this will result in an increase in survival. This effect would be similar to the observation reported by Isaacs et al. in which in an animal model system, early

orchiectomy resulted in a statistically significant prolongation of survival.<sup>39</sup> We also test the value of whole pelvic irradiation since distant mets may have already occurred, and since eliminating its use would reduce cost and morbidity.

## **2.0 OBJECTIVES**

- 2.1** To test the hypothesis that TAS and whole pelvic irradiation followed by a conedown boost to the prostate improves the progression-free survival (*an "early endpoint"*) by at least 10% at 5 years compared to TAS and prostate only irradiation.
- 2.2** To test the hypothesis that induction (*neoadjuvant*) and concurrent TAS and RT, improves the progression-free survival (*an "early endpoint"*) compared to adjuvant TAS and RT by at least 10% at 5 years. (10/13/95)
- 2.3** Secondary objectives include comparing treatments with regard to local control, time to distant failure and overall survival. Survival will be evaluated as a "late endpoint".

## **3.0 PATIENT SELECTION**

### **3.1 Conditions for Patient Eligibility (10/13/95, 3/1/96, 10/1/96, 7/1/97)**

- 3.1.1** Patients with histologically confirmed adenocarcinoma of the prostate at significant risk for lymph node involvement and therefore for local failure and/or systemic failure will be candidates for this phase III trial. The estimated risk for biochemical relapse (*BCR*), defined by a rising PSA in these patients, is estimated to be  $\geq 50\%$ . To be eligible for this trial, these patients must have either:
  - 1. Any stage with estimated risk of lymph node involvement  $>15\%$  (*based on the pre-treatment PSA and Gleason Score [GS]*), or
  - 2. Must be ineligible for RTOG 94-08. Clinical stages T2c (*palpable in both lobes*) through T4 with Gleason  $\geq 6$  are eligible for this study.An estimated risk of lymph node involvement of  $> 15\%$  corresponds to patients with a GS of 7 and a PSA of  $> 7.5$ , a GS of 6 would require a PSA of  $> 22.5$  or a GS of 5, a PSA  $> 37.5$  ng/ml. The PSA value used should be the highest PSA prior to treatment using the monoclonal assay with a normal range of 0-4 ng/ml. PSA's 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.<sup>38</sup> Note that the nine possible Gleason Score values are empirically grouped into five major scoring categories,  $\leq 4 = 4$ ,  $5 = 5$ ,  $6 = 6$ ,  $7 = 7$ , and  $\geq 8 = 8$ .
- 3.1.2** Nodes evaluated negative by imaging methods will be classified as NX. Imaging-positive nodes must be confirmed negative by biopsy. Negative lymph node status can be confirmed only by surgical sampling or fine needle aspiration.
- 3.1.3** Classification by Gleason Score is mandatory prior to randomization.
- 3.1.4** Karnofsky performance status  $\geq 70$ .
- 3.1.5** PSA is mandatory for patient eligibility; maximum level is PSA  $\leq 100$
- 3.1.6** No prior hormonal therapy, radiation or chemotherapy.
- 3.1.6.1** Prior finasteride for prostatic hypertrophy is allowed if discontinued at least 60 days prior to randomization.
- 3.1.6.2** Prior testosterone administration is allowed if at least 90 days have elapsed since last administration (*testosterone effect will have receded by 90 days*).
- 3.1.7** No distant metastases.
- 3.1.8** Liver function tests no greater than 1.2 x upper limits of normal.
- 3.1.9** Treatment must begin within 6 weeks after randomization and within 60 days of surgical staging.
- 3.1.10** Patients must sign a study-specific informed consent form prior to randomization.

### **3.2 Conditions for Patient Ineligibility (10/13/95, 3/1/96, 10/1/96)**

- 3.2.1** Patients with PSA  $\leq 4.0$  or  $>100$  (*by the Hybritech monoclonal assay, see Section 3.1.1 for conversion factor if a polyclonal assay is used*).
- 3.2.2** Evidence of distant metastasis (*MI*).
- 3.2.3** Lymph node involvement outside the pelvis proper (*spread to common iliac and/or periaortic lymph nodes*).
- 3.2.4** Radical surgery or prior crysurgery for carcinoma of the prostate, previous radiation, hormonal manipulation or chemotherapy. See Section 3.1.6 for allowable exceptions.
- 3.2.5** Previous or concurrent cancers other than superficial basal or squamous cell skin carcinoma unless disease free for at least 5 years.
- 3.2.6** Major medical or psychiatric illness which, in the investigator's opinion, would prevent completion of treatment and would interfere with follow-up.

- 3.2.7 Karnofsky Performance Status of < 70.
- 3.2.8 Eligible for RTOG 94-08.
- 3.2.9 Patients with biopsy-proven lymph node involvement.

**4.0 PRETREATMENT EVALUATION (10/13/95, 3/1/96)**

- 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. Gleason scores (*Appendix VI*) are 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 60 days of randomization.** PSA's 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 for use in this equation.<sup>38</sup>
- 4.5 Radiographic studies: Chest x-ray (*if indicated by patient's history*); bone scan (*mandatory, must be done within 90 days prior to randomization*).
- 4.6 Lymph node evaluation is mandatory and can be performed by at least one of the following: Lymphangiogram, CT of the pelvis (*must be done within 90 days prior to randomization*) or exploratory laparotomy with lymph node biopsies or laparoscopic node sampling. Treatment should be started within 60 days of surgical staging.

**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. 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:
  - Patient's Name & ID Number
  - Institution Name & Number
  - Physician's Name
  - Eligibility Criteria Information
  - Stratification Information
  - Demographic Data
  - Treatment Start Date

**6.0 RADIATION THERAPY**

**6.1 Treatment Plan (3/1/96)**

Arm	Initial Therapy weeks 1-8	Weeks 9-16	Weeks 17-24	Week 25+ Follow-up
1		Whole Pelvic + Boost RT		
	Z + F	Z + F		
2		Prostate Only RT		
	Z + F	Z + F		
3	Whole Pelvic + Boost RT			
		Z + F	Z + F	
4	Prostate Only RT			
		Z + F	Z + F	

RT = Radiotherapy, Z = Zoladex (*or Lupron*), F = Flutamide

## **6.2 Dose**

**6.2.1** Arms 1 and 3: Radiation will include treatment to the whole pelvis with 50.4 Gy to regional lymphatics delivered at 1.8 Gy/day, five times a week x 28 fractions followed by a boost to the prostate given at 1.8 Gy/day, five times a week x 11 fractions to a total of 70.2 Gy in 39 fractions in eight weeks.

**6.2.2** Arms 2 and 4: Radiation will include treatment to only the prostate at 1.8 Gy/day five days a week to a total of 70.2 Gy in 39 fractions in eight weeks.

## **6.3 Physical Factors**

Megavoltage equipment is required with effective photon energies  $\geq 6$  MeV. Minimum source-to-axis distance is 100 cm. The minimum source-to-skin distance is 80 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 Volumes (10/1/96, 7/1/97) - For patients receiving whole pelvic irradiation, the minimum initial unblocked field size will be 16 x16 cm. Patients who are surgically staged positive for pelvic node involvement are not eligible for this study.

**A urethrogram will be used as part of the simulation for all patients to define the inferior portion of the field.**<sup>41</sup> The inferior margin of the pelvic target column will be placed at least 1.0 cm below the highest point where the contrast narrows to a point ("*the apex of the urethra*").<sup>41</sup> 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.<sup>41</sup> The lateral margins will be 2.0 cm lateral to the pelvic brim. A four-field technique is used, care should be taken to adequately cover external and internal iliac node 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.

**6.4.2** Prostate Boost Target Volume (7/1/97) will include the prostate with margins sufficiently wide to encompass all of the tumor extensions into the surrounding tissues. Final boost volume does not require including the entire seminal vesicles to 70 Gy. A conedown to the prostate and proximal seminal vesicles is strongly recommended to reduce the risk of excessive rectal morbidity. 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. For patients receiving prostate only irradiation (*Arms 2 and 4*), the maximum initial unblocked field size will be 11 x11 cm.

**6.4.3** Films: Portal films of each treatment field and simulation films must be submitted to RTOG Headquarters for review.

## **6.5 Dose Specification**

**6.5.1** The prescribed doses are defined on the central axis at the projected center of the target volumes if using conventional treatment planning techniques. If 3D conformal treatment planning technology is used, the protocol dose may be prescribed as "minimum tumor dose". However, the maximum dose must not exceed the specified values given in Sections 6.5.1.6 and 6.5.1.10. The dose at the center of the target volume and the maximum dose must be reported to RTOG Headquarters on the relevant forms. All patients will require isodose plans at the central axis of both the pelvic and prostate treatment volumes. The dose will be uncorrected for tissue inhomogeneities. For the following portal arrangements, the protocol will be specified as follows:

**6.5.1.1** For an arrangement of two or more co-axial beams at the intersection of the central ray of the beams. If 3-D conformal treatment planning technology is used, the dose may be prescribed at the periphery as a "minimum tumor dose".

**6.5.1.2** For complete rotation or arc therapy: in the plane of rotation at the isocenter of rotation.

**6.5.1.3** Other or complex treatment arrangements: at the center of the target area (*Note: there may be several target areas*).

**6.5.1.4** Regional lymphatics will receive a total of 50.4 Gy. (*Arms 1 and 3*).

**6.5.1.5** The minimal dose to the regional lymphatic target volume, identified in the central plane fields dose distribution, will be  $\geq 47.9$  Gy (*95% of the protocol dose*).

**6.5.1.6** The maximal target dose (*defined as the greatest dose in target volume which is delivered to an area greater than 2 cm<sup>2</sup>*) to the regional lymphatics target volume, identified in the central plane

- pelvic fields dose distribution will be  $\leq 105\%$  of the protocol prescribed dose of 50.4 Gy.
- 6.5.1.7** The prostatic target volume on Arms 1 and 3 will receive a boost of 19.8 Gy bringing the total prescribed dose to that volume to 70.2 Gy.
- 6.5.1.8** The prostate only target volume on Arms 2 and 4 will receive a protocol prescribed dose to that volume of 70.2 Gy.
- 6.5.1.9** The minimal prostate target dose to the prostatic target volume, identified in the central plane of the prostatic fields dose distribution, will be  $\geq 66.7$  Gy (*95% of the protocol dose*).
- 6.5.1.10** The maximal prostate target dose (*defined as the greatest dose in target volume which is delivered to an area greater than 2 cm<sup>2</sup>*) to the prostatic target volume, identified in the central plane of the prostatic field dose distribution, will be  $\leq 105\%$  or  $\leq 73.7$  Gy.

## **6.6 Critical Normal Structures (7/1/97)**

- 6.6.1** The bladder will receive the same dose as the regional lymphatics. 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. Rectal blocks should be used on lateral fields. 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, hemochezia,
- 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.

## **7.0 DRUG THERAPY**

### **7.1 Zoladex (NSC# 606864)**

#### **7.1.1 Description:**

Zoladex 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: (3/1/96, 7/1/97)**

**Zoladex is commercially available.** For indigent patients who cannot afford the four months of 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.

#### **7.1.2.1 Lupron 7.5 mg IM may be used instead of 3.6 mg Zoladex. This should be clearly specified on the RTOG Flowsheets if administered in place of Zoladex.**

#### **7.1.2.2 One 3-month depot plus one single dose depot of Zoladex or Lupron may be used in place of four single doses.**

#### **7.1.3 Preparation and Storage:**

The Zoladex depot is supplied preloaded with 3.6 mg Zoladex 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:**

Zoladex will be administered to patients on all four treatment arms. The patients on Arms 1 and 2 will receive neoadjuvant therapy while the patients on Arms 3 and 4 will receive adjuvant Zoladex. 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 1cm, 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. The tear off portion of the depot package label will be removed and affixed to the appropriate data form as part of the patient's permanent record. All patients will receive four monthly injections of Zoladex with an overall treatment time of 112 days.

**7.1.4.1** Neoadjuvant Therapy (Arms 1 and 2)

Zoladex depot will be injected every four weeks for four months beginning two months prior to radiation therapy. In the event of radiotherapy treatment interruptions, the drug administration will be continued. Administration of drug will be suspended only if there is an apparent or suspected reaction to the drug.

**7.1.4.2** Adjuvant Therapy (Arms 3 and 4)

Administration of Zoladex on an adjuvant basis will begin upon completion of radiation. Administration of Zoladex will be continued every four weeks for four months but may be terminated if signs of disease progression appear while the patient is receiving the drug.

**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** Flutamide (NSC# 147834)

**7.2.1** 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.

**7.2.2** Supply:

Flutamide is commercially available.

**7.2.3** 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.

**7.2.4** 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*).

Arms 1 and 2: Flutamide will begin 2 months prior to radiotherapy and continue throughout radiotherapy. Administration of the drug will be suspended only if there is an apparent or suspected reaction to the drug. Administration of Flutamide will be terminated on the last day of radiotherapy or on day 112, whichever occurs first. During radiotherapy interruptions the drug will be continued.

Arms 3 and 4: Flutamide will begin upon completion of radiation and continue for 112 days. Administration of the drug will be suspended only if there is an apparent or suspected reaction to the drug.

**7.2.5** 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>17</sup> One death from liver failure occurred in RTOG 92-02 among the first 1000 patients.

**7.2.6** 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.**

### **7.3 Adverse Reaction Reporting**

**7.3.1** The following ADR's attributed to commercial agent(s) should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days:

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

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

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

**7.3.1.4** The ADR Report should be documented on Form FDA 3500 and mailed to:

**Investigational Drug Branch**

**Box 30012**

**Bethesda, MD 20824**

**(301) 230-2330 (24 hours)**

**fax # 301-230-0159**

## **8.0 SURGERY**

### **8.1 Prostate Re-biopsy**

**8.1.1** A biopsy will be performed for all patients with evidence of "PSA failure" or growth of a palpable abnormality. 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 post-treatment follow-up visit (*3 months after completing hormonal treatment*). A PSA failure is defined as a consistent and significant rise in the PSA. A consistent rise is defined as three consecutive increases in the PSA. A consistent rise is defined as three consecutive increases in the PSA, each separated by at least one month. A significant rise is defined as a rate of rise of 20% or more 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. Patients with slowly rising PSA's, (*e.g. < 20% per year*) will be considered free from PSA failure as long as their PSA remains less than 4 ng/ml. *Among patients with no evidence of failure, biopsies are not mandatory.*

**8.1.2** Biopsies are strongly recommended for patients with evidence of distant failure to assist in accurately determining the "true" local control rate. In the absence of a biopsy, such patients will be considered local failures if their exam is abnormal. If their exam is normal or if they are post orchiectomy they will be censored at the last point in time they were considered locally controlled and considered "inevaluable" for further assessment of local control.

## **9.0 OTHER THERAPY**

Does not apply to this study.

## **10.0 PATHOLOGY (7/1/97)**

**10.1** Central pathology review of the diagnostic and post treatment biopsy (*as applicable, per Section 8.1.1*) are planned for this study. Central reviews on previous prostate studies have demonstrated a 34% discrepancy in histological grading. H & E stained sections and representative tissue of all pathologic material, the pathology report and a pathology submission form will be submitted to the RTOG Tissue Bank:

**LDS Hospital**

**Department of Pathology**

**E.M. Laboratory**

**8th Avenue and C Street**

**Salt Lake City, UT 84143**

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

- selected post-therapy biopsies.
- 10.1.2** Post-therapy biopsies will be evaluated for the presence or absence of residual tumor. All post-therapy biopsies will be centrally reviewed by two pathologists.
- 10.1.3** Immunocytochemical studies will be performed on all cases for evidence of neuroendocrine differentiation (*chromagranin A, neuron specific enolase*).
- 10.2** To encourage compliance, your Pathology Department can be reimbursed for obtaining blocks or cutting slides.
- 10.3** Patient consent form should give the Pathology Department authority and responsibility to comply with this request (*pathology blocks belong to the patient from whom tissue has been removed*).

## **11.0 PATIENT ASSESSMENTS**

### **11.1 Study Parameters (10/13/95, 7/1/97)**

<b>Parameter</b>	<b>Pretreatment</b>	<b>At completion of Hormonal Tx</b>	<b>At Completion of Radiotherapy</b>	<b>Followup (See Sec. 11.2)</b>
History & Physical, KPS	X	X	X	X
Tumor size in cm in two dimensions ( <i>phys. exam</i> )	X			X
Gleason Score	X <sup>a</sup>			X <sup>b</sup>
Sexual function status	X	X	X	X
Chest X-ray	X <sup>g</sup>			
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>	X <sup>d</sup>
CBC	X	X <sup>e</sup>	X <sup>e</sup>	X <sup>e</sup>
Lymph Node Assessment	X			
Prostatic-Specific Antigen( <i>PSA</i> )	X	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 during hormone therapy. If liver functions rise to  $\geq 4$  x normal, flutamide will be discontinued and the study chairman contacted.
- e. At each followup for the first 6 months.
- f. All PSA determination (*minimum of q 6 months*) within a followup period must be reported on the followup forms (*FI*).
- g. As indicated by patient's history

### **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.
- 11.2.5** The patient will be asked whether he is able to achieve an erection and/or ejaculation and if he is able to have sexual relations. This assessment must be done at the beginning and end of treatment and at each follow-up visit.

### **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*) by the day of discontinuation of hormonal therapy.
- 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 (*3 months after completing hormonal treatment*). 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. Patients with slowly rising PSA's, (*e.g. < 20% per year*) will be considered free from PSA failure as long as their PSA remains less than 4 ng/ml.
- 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 their exam is normal or if they are post orchiectomy, they will be censored at the last point in time they were considered locally controlled and considered "inevaluable" for further assessment of local control.
- 11.4.3** Time to Distant Failure: The time to distant failure will be measured from the date of randomization to the date of documented metastatic 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 (7/1/97)**

<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)*	
* <i>If node dissection or sampling was performed</i>	
<u>Preliminary Dosimetry Information:</u>	Within 1 week of start of RT
RT Prescription (Protocol Treatment Form) (T2)	
Films ( <i>simulation and portal</i> ) (T3)	
Calculations (T4)	
Interim Report (F9) ( <i>Arms 1 &amp; 2</i> )	
Hormone Flowsheet (M1)	Monthly during drug

Radiotherapy Form (T1)	Within 1 week of RT end
<u>Final Dosimetry Information:</u>	
Daily Treatment Record (T5)	
Isodose Distribution (T6)	
Boost Films ( <i>simulation and portal</i> ) (T8)	
Hormone Flowsheet (M1)	Upon completion of radiotherapy, thereafter with each Follow-up Form for 6 mos. following completion of hormones.
Follow-up Form (F1)	Upon completion of radiotherapy, 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 death.	at
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 Study Design**

The objectives of the trial are described in Section 2.0 They can be met by a 2 x 2 design with hormonal sequencing as one factor and radiation field as the other factor. These factors are not expected to show any statistical interaction with treatment, so the two objectives will be addressed by grouping patients across one or the other factor and comparing two large groups.

Treatment allocation will be done by randomized permuted blocks within strata to balance for prognostic factors. Stratification will be done by T stage (*T1c and T2a, versus T1b and T2b, versus T2c-T4*), PSA (*£ 30 versus >30 ng/ml*), Gleason score (*< 7 versus 7-10*).

#### **13.2 Sample Size and Accrual**

The primary endpoint upon which the sample size is based is progression-free survival. For the estimation of sample size, the design of the trial is viewed as a 2-arm study, in which whole pelvis irradiation versus prostate irradiation would be tested by combining the different hormonal arms, and hormonal sequencing would be tested by combining the different irradiation areas. In order to detect a difference between distributions with 40% and 50% 5-year progression-free probabilities, **a sample size of 1200 patients is needed.** This estimate assumes uniform accrual for 2.5 years at the rate of 40 patients per month, exponentially distributed progression-free survival, and 3 years of additional follow-up. An analysis using a log-rank test at a two-sided alpha level of 2.5% would have 80% power. The assumes a rate of 10% unevaluables.

After 2 years of further follow-up (*a total of 5 years of follow-up after accrual ends*), there will be over 80% power to detect a difference between 64% and 72% 5-year survival, which is on the order of the difference that has been observed in breast cancer.

#### **13.3 Analysis Plans**

Analyses of survival and progression-free survival will use the log-rank test and the Cox proportional hazards model; analyses of cause-specific failure endpoints such as time to local failure will use methods appropriate for cumulative incidence<sup>42</sup>. All hypothesis testing will be two-sided. Exploration of the effects of pretreatment prognostic factors such as stage, Gleason score, PSA and nodal status will be done using the Cox proportional hazards model. It will be important to examine the patterns of failures comprising the progression-free survival endpoint<sup>45</sup>, because an effect of hormonal sequencing would be expected to impact local events, whereas an effect of whole pelvic irradiation would be expected to impact distant events.

Interim accrual and morbidity reports will be done at least semi-annually prior to the RTOG group meeting. The report will describe accrual by institution and project completion of accrual. It will give the distribution of pretreatment characteristics and a tabulation of toxicities.

In addition to the semi-annual reports, reporting will be done for the RTOG Data Monitoring Committee

(DMC). The report will address whatever concerns that the DMC chooses to raise, but it is expected to contain interim blinded efficacy results with adjustment for multiple group sequential testing using an O'Brien-Fleming alpha-spending function<sup>43,44</sup>, and it is planned to take place when approximately 50% and 100% of the patients have been accrued. The expected number of events that will be observed by the final analysis is 530. The expected cumulative numbers of events that will be observed by the two interim analyses are 60 and 200. Under this scenario, the alpha levels to be used for treatment comparisons at the two planned interim analyses are less than 0.0001 for the first analysis (*the Z-value cutoff is 5.53*) and 0.0002 for the second. The final analysis would then be done using an alpha level of 0.0249.

#### **13.4 Inclusion of Women and Minorities (10/1/96)**

In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, we have considered the possible interaction between race and treatments.

Analysis of three prior RTOG studies failed to show such a significant difference<sup>46</sup> and so this study was not designed to test for treatment differences within race. A sensitivity analysis was done with the targeted sample size by racial groups in testing for treatment differences. If 88% of the patients recruited in this study are white/other, the statistical power to detect an improvement in the 5-year progression free survival rate from 40% to 50% is .77. If 12% of the patients recruited in this study are Afro-Americans, the statistical power to detect a reduction in the 5-year progression free survival rate from 40% to 50% is .13. The analysis for reporting the initial treatment results will include treatment comparisons within each race for progression free survival and for overall survival.

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\* 10/1/96

## APPENDIX I

### RTOG 94-13

#### **A Phase III Trial Comparing Whole Pelvic Irradiation Followed by a Conedown Boost to Boost Irradiation Only and Comparing Neoadjuvant to Adjuvant Total Androgen Suppression (TAS)**

#### **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 and hazards involved. This disclosure is not meant to frighten or alarm me; it is simply an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

#### **PURPOSE OF THE STUDY (7/1/97)**

It has been explained to me that I have prostate cancer. My doctor feels that my participation in this study may be helpful. This study involves evaluation of drugs Zoladex (*or* Lupron) and Flutamide used before, during, and after a course of radiotherapy. There are two purposes of this study. The first purpose of this study is to determine whether the timing of these drugs may improve the probability of tumor control when used in conjunction with radiotherapy. The second purpose is to determine whether giving radiation to the lymph nodes in my pelvis is better than just treating the prostate. If I agree to participate in this program, I would be assigned to receive Zoladex, or Lupron, and Flutamide together with radiotherapy in one of four combinations. Radiotherapy will be given daily over approximately 2 months. Approximately 1200 men will be involved in this study which involves random (*by chance*) assignment to one of the four methods of treatment.

#### **DESCRIPTION OF PROCEDURES (7/1/97)**

It is not clear at the present time which of the four regimens is better. For this reason the therapy which is to be offered to me will be based upon a method of selection called randomization. Randomization means that my physician will call a statistical office which will assign me one of the four regimens by computer. The chance of my receiving one of the four therapies is approximately equal. Lupron may be substituted for Zoladex. Both are also available as a 3 month dose. I will be assigned to one of the following treatments:

**Treatment 1:** Prior to radiation, I will receive two injections of Zoladex (*once a month for two months*) under my upper abdominal skin, and six Flutamide capsules daily for two months. Radiation to my pelvis and prostate will be given once a day, 5 days a week for almost eight weeks. During radiation, Zoladex and Flutamide will be given on the same schedule as it was given before radiation began.

**Treatment 2:** I will receive two injections of Zoladex (*once a month for two months*) under my upper abdominal skin, and six Flutamide capsules daily for two months. Radiation to only my prostate will be given once a day, 5 days a week for almost eight weeks. During radiation Zoladex and Flutamide will continue to be given on the same schedule as it was given before radiation began.

**Treatment 3:** Radiation to my pelvis and prostate will be given once a day, 5 days a week for almost eight weeks. I will then receive four injections of Zoladex (*once a month for four months*) under my upper abdominal skin, and six Flutamide capsules daily during the same period.

**Treatment 4:** Radiation to only my prostate will be given once a day, 5 days a week for almost eight weeks. I will then receive four injections of Zoladex (*once a month for four months*) under my upper abdominal skin, and six Flutamide capsules daily during the same period.

Also, at the time of my diagnosis by biopsy, all or 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 the 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 procedure or expense to me. The tumor tissue's cells will be examined to see if any special "markers", tests which predict how a patient with tumors like mine responds 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 (7/1/97)**

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 and Lupron** frequently lead 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%) : 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, anxiety, or depression. The relationship of these adverse reactions to therapy is uncertain. The symptoms may reverse upon cessation of treatment. Zoladex and 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 any of the following symptoms; intense itching, dark urine, loss of appetite, yellow skin or eyes, abdominal tenderness or "flu-like" symptoms. If I have any of these symptoms, the Flutamide may be discontinued.

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

My physician will be checking 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 treatments for side effects caused by the study treatment.

There is also the unknown risk that the delay before starting radiation therapy may allow the tumor to grow larger.

### **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**  
**Prostate, AJC 4th Edition, 1992**

**DEFINITION OF TNM**

**Primary Tumor (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 (*e.g., because of elevated PSA*)  
**T2** Tumor confined within prostate\*  
    **T2a** Tumor involves half of a lobe or less  
    **T2b** Tumor involves more than half of a lobe but not both lobes.  
    **T2c** Tumor involves both lobes.  
**T3** Tumor extends through prostatic capsule\*\*  
    **T3a** Unilateral extracapsular extension  
    **T3b** Bilateral extracapsular extension  
    **T3c** Tumor involves the seminal vesicle(s).  
**T4** Tumor is fixed or invades adjacent structures other than the seminal vesicles.  
    **T4a** Tumor involves any of: bladder neck, external sphincter, or rectum  
    **T4b** Tumor involves levator muscles and/or is fixed to the pelvic wall

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

\*\*Note: Invasion into the prostatic apex 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 a single lymph node, 2 cm or less in greatest dimension  
**N2** Metastasis in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, metastases, none more than 5 cm in greatest dimension  
**N3** Metastasis in a lymph node more than 5 cm in greatest dimension

**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.

**APPENDIX III (cont'd)**

**Histopathologic Grade (G) (3/1/96)**

- GX** Grade cannot be assessed
- G1** Well differentiated, slight anaplasia
- G2** Moderately differentiated, moderate anaplasia
- G3-4** Poorly differentiated or undifferentiated, marked anaplasia

**STAGE GROUPING**

<b>Stage 0</b> T1a	N0	M0	G1	
<b>Stage I</b> T1a	N0 T1b, T1c, T1	M0 N0	G2, G3-4 M0	Any G
<b>Stage II</b> T2	N0	M0	Any G	
<b>Stage III</b>	T3	N0	M0	Any G
<b>Stage IV</b>	T4 Any T Any T	N0 N1, N2, N3 Any N	M0 M0 M1	Any G Any G Any G

## APPENDIX V

### ADVERSE REACTION REPORTING GUIDELINES

#### A. GENERAL GUIDELINES

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

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

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

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

#### B. RADIATION TOXICITY GUIDELINES

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

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

An adverse reaction is a toxicity or an undesirable effect usually of severe nature. Specifically, this may include major

organ toxicities of the liver, kidneys, cardiovascular system, central nervous system, skin, bone marrow, or anaphylaxis. These undesirable effects may be further classified as "known" or "unknown" toxicities.

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

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

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

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

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

### **Investigational Agents**

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

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

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

- |   |   |
|---|---|
| - All deaths during therapy with the agent.                                 | Report <b>by phone</b> within 24 hours 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> ).          | Report by <b>phone within 24 hours</b> to IDB <u>drug</u> monitor and RTOG Headquarters.<br>**A written report may be required. |

ii. Phase II, III Studies Utilizing Investigational Agents

- |   |  |
|---|--|
| <ul style="list-style-type: none"><li>- All fatal (grade 5) and life threatening (grade 4) <u>known</u> adverse reactions due to investigational agent.</li></ul>   | <p>Report <b>by phone</b> to RTOG Headquarters and the Study Chairman within 24 hours<br/>**A written report must be sent to RTOG within working days with a copy to IDB.<br/>(Grade 4 myelosuppression not reported to IDB)</p> |
| <ul style="list-style-type: none"><li>- All fatal (grade 5) and life threatening (grade 4) <u>unknown</u> adverse reactions resulting from or suspected to be related to investigational agent.</li></ul> | <p>Report <b>by phone</b> to RTOG Headquarters, the Study Chairman and IDB within <b>24 hours</b>.<br/>**A written report to follow within 10 working days.</p>  |
| <ul style="list-style-type: none"><li>- All grade 2, 3 <u>unknown</u> adverse reactions resulting from or suspected to be related to investigational agent.</li></ul>                                     | <p>**Report <b>in writing</b> to RTOG Headquarters and IDB within 10 working days.</p>   |

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

## APPENDIX VI

### GLEASON CLASSIFICATION

Histologic patterns of adenocarcinoma of the prostate

<b>Pattern</b>	<b>Margins Tumor Areas</b>	<b>Gland Pattern</b>	<b>Gland Size</b>	<b>Gland Distribution</b>	<b>Stromal Invasion</b>
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 predominal 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.