A PHASE III TRIAL OF THE USE OF LONG TERM TOTAL ANDROGEN SUPPRESSION FOLLOWING NEOADJUVANT HORMONAL CYTOREDUCTION AND RADIOTHERAPY IN LOCALLY ADVANCED CARCINOMA OF THE PROSTATE

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RADIATION THERAPY ONCOLOGY GROUP  
RTOG 92-02  
A PHASE III TRIAL OF THE USE OF LONG TERM TOTAL ANDROGEN SUPPRESSION FOLLOWING NEOADJUVANT HORMONAL CYTOSEROPTION AND RADIOTHERAPY IN LOCALLY ADVANCED CARCINOMA OF THE PROSTATE

**SCHEMA**

<table>
<thead>
<tr>
<th>S</th>
<th>Stage</th>
<th>R</th>
<th>Arm 1</th>
<th>Neoadjuvant TAS* 2 months before, and during RT</th>
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<tbody>
<tr>
<td>T</td>
<td>1. T2c</td>
<td>A</td>
<td>Neoadjuvant TAS* 2 months before, and during RT</td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>2. T3</td>
<td>N</td>
<td>before, and during RT, then Zoladex alone for 2 years</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>3. T4</td>
<td>D</td>
<td>beginning after RT ends.</td>
<td></td>
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<tr>
<td>Y</td>
<td>PSA</td>
<td>I</td>
<td>PSA &lt; 30 Zoladex alone for 2 years</td>
<td></td>
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<tr>
<td>F</td>
<td>1. ≤ 30</td>
<td>Z</td>
<td>begin after RT ends.</td>
<td></td>
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<tr>
<td>Y</td>
<td>PSA</td>
<td>2. &gt; 30</td>
<td>Zoladex alone for 2 years</td>
<td></td>
</tr>
</tbody>
</table>

**Grade (Differentiation)**
1. well
2. moderately
3. poorly or undifferentiated

**Nodal Status (Pathologic)**
1. negative
2. positive
3. not done

**Radiation**: 44-46 Gy (1.8 - 2.0 Gy/day four to five times a week) to regional lymphatics followed by 20-29 Gy (1.8 - 2.0 Gy/day) for a total of 65-70 Gy to the prostate for stage T2c and 67.5 - 70 Gy for stages T3 and T4.

**Total Androgen Suppression (TAS)**: Patients will receive Flutamide (two 125 mg capsules t.i.d., p.o.) and Zoladex, (3.6 mg s.c. monthly), beginning 2 months before RT and continuing until RT is completed. Randomization will assign half the patients to additional Zoladex to begin after the completion of RT and continuing monthly for two years.

**ELIGIBILITY**: (See Section 3.0 for details)
- Histologically confirmed locally advanced adenocarcinoma of the prostate.
- Confirmed bulky tumors confined to the prostate, clinical stage T2c-T4.
- No involved common iliac or para-aortic nodes.
- Karnofsky performance status ≥ 70.
- No prior hormonal therapy, radiation or chemotherapy.
- No distant mets.
- Must sign a study-specific consent form.
- PSA is mandatory; (must be PSA < 150)

Required Sample Size: 1508  
Revised 9/21/92, 11/9/92, 12/17/93, 8/15/94
Is there histologically confirmed locally advanced adenocarcinoma of the prostate?  

What is the T stage?  

What is the disease status by imaging of the pelvic lymph nodes? (1. positive or 2. negative)  

If positive, was a lymph node biopsy done?  

Is there evidence of positive common iliac or para-aortic nodes?  

What is the KPS?  

Has the patient signed a study-specific informed consent?  

Has a PSA been done?  

Did an abnormal PSA lead to further investigation and the eventual diagnosis of prostate cancer?  

Has the patient had prior hormonal, radiation or chemotherapy?  

Does the patient have distant mets?  

Has the patient had prior radical surgery for prostate carcinoma?  

Has the patient had previous or concurrent cancer, other than basal cell skin carcinoma?  

Are there any major medical or psychiatric illnesses which would prevent completion of treatment and interfere with follow-up?  

Patient's Name  

Verifying Physician  

Patient ID #  

Referring Institution  

Grade (1. Well vs. 2. moderately vs. 3. poorly or undifferentiated)  

Nodal Status (pathologic) (1. negative vs. 2. positive vs. 3. not done)  

Method of Payment  

Treatment Start Date  

Completed by  

Date  

Revised  

11/9/92  

2/15/93  

12/17/93  

8/15/94
1.0 INTRODUCTION

The treatment of bulky prostatic cancer remains controversial. Loco-regional failure although unusual in early stage small tumors is frequently observed in locally advanced bulky primary lesions. In a series from Washington University School of Medicine 50% of patients with massive pelvic tumors had persistent or recurrent tumors following irradiation. Some of the difficulties in achieving good local control may be reflected in the tumor volumes being treated in this category of patients. One must be cognizant of the fundamental principles of external beam radiotherapy, in particular, the dose response curve which implies that as the dose of radiation delivered increases, so will the tumor control, but in parallel, so will the complication rate. Recent data from the U.S. Patterns of Care suggest that prostate cancer also has a dose response curve and that the central prostate dose required to prevent 90% of infield failures for stage C prostate cancer will require doses of between 71.0 and 79.0 Gy. It is also recognized that doses in excess of 70.0 Gy may cause unacceptable normal tissue morbidity. Biopsy data from Freiha and Bagshaw have alerted us to the fact that in patients who have stage C prostate cancer, approximately 75% will have positive biopsies to 31 months after external beam radiation. This data tends to confirm the volume dependency of histological control. For many years the question as to whether a positive biopsy following external beam therapy implies reduced survival and reduced local control has been considered a controversial area in radiotherapy. Data from several authors suggest that it appears that patients that do have a positive biopsy following external beam radiotherapy do significantly worse in terms of the development of local and distant failure.

It is not clear however, whether this is just a reflection of the potential biology of the tumor system, or of failure of the treatment utilized. There is some data in the literature to address the question of whether a patient whose tumor is histologically sterilized has an improved chance of survival. Kuban and her associates has shown that a five year survival which is much reduced in patients who have persistent tumors after both external beam therapy and iodine therapy as compared to patients achieving local control. For example in patients with poorly differentiated stage B2 and C prostate cancers treated with external beam radiotherapy the five year survival was only 56% for those who had persistent disease as compared to 85% for those who had no residual disease on clinical palpation. A further study that lends weight to this argument to that of Griffin et al. who looked at the potential for improving local control by using a mixed beam containing neutrons and photons. A recent analysis performed at 10 years demonstrated a significantly improved patient survival and local control in the arm treated with the mixed beam therapy as compared to the arm treated with the photon therapy. Data from the brachytherapy groups in which high doses of radiation are delivered to small volumes have demonstrated increases in histological sterilization. Several authors have demonstrated that with Iridium brachytherapy, negative biopsy rates between 75 and 85% have been achieved for stage C prostate cancer. Martinez has recently reported an improved survival rate in a series of patients undergoing this form of brachytherapy as compared to the standards reported in the literature.

Further approaches that can be used in the attempt to control the tumor histologically include therefore, brachytherapy, particle therapy with either neutrons or protons, or hormonal cytoreduction prior to external beam radiotherapy.

Endocrine or hormonal therapy for carcinoma of the prostate was introduced by Huggins in 1941 and is based on the dependence of prostatic epithelial cells and prostatic carcinoma cells on androgenic hormones. Androgen deprivation induced by orchectomy or the administration of estrogens can produce dramatic and often prolonged systematic improvement in a large percentage of patients. The first work on cytoreduction was performed by Green and colleagues when 25 patients were treated with estrogen cytoreduction 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. Seventy-two% of local control was reported in the group receiving neoadjuvant estrogens as compared to 55% local control in the group receiving external beam radiotherapy alone. Pilepich and his colleagues have performed a RTOG study which compared the use of Megace to diethylstilbestrol as cytoreductive agents prior to radiotherapy. Currently available data has shown good cytoreduction with local control being achieved in over 90% of patients in either arm with reduced toxicity in the group receiving Megace therapy. Porter has reported on the Canadian cytoreduction study in which Cyproterone Acetate is used as a cytoreductive agent for 12 weeks prior to the initiation of external beam radiotherapy in patients with bulky stage B2 or C prostate cancer.

The use of hormonal manipulation as a cytoreductive means has drawn considerable attention in recent years as the interaction of hormonal manipulation and radiotherapy may be affected significantly by the sequence of administration. It is generally agreed that the proportion of cells within a tumor which otherwise appears responsive to androgen manipulation will show little or no hormonal dependence. For this reason hormonal manipulation is unlikely to permanently eradicate residual tumor after irradiation. However, if applied as a cytoreductive agent prior to irradiation, hormonal manipulation may reduce the tumor cell burden and enhance the probability of tumor eradication by irradiation.
In recent years considerable interest has been generated by the appearance of LHRH agonists. These agents when given either intranasally or subcutaneously block LH secretion and reduce testosterone level to an anorchid level\textsuperscript{13}. This reduction is preceded by a brief increase in LH secretion. The main advantage of LHRH agonists is an apparent lack of toxicity. The potential disadvantage of these agents is an initial increase in testosterone level which may produce a flare of disease. To circumvent this problem and also to block the action of adrenal steroids a combination of LHRH agonists and the anti-androgen [Flutamide] which blocks androgen receptors at the cellular level has been tested. While LHRH agonists alone produce a response rate over approximately 70 to 75\% comparable to that seen with estrogen therapy, the combined LHRH agonist plus Flutamide administration has been reported to produce subjective responses in close to 100\% of previously untreated patients\textsuperscript{6,12}.

One of the disadvantages of earlier LHRH agonist was the route of administration by either intranasal spray or daily subcutaneous injections. These problems have been solved by the appearance a depot preparation of Zoladex which is administered subcutaneously on a monthly basis\textsuperscript{13}.

The RTOG has tested a Zoladex plus Flutamide combination as a cytoreductive means prior and during radiotherapy in a phase II trial. The recorded related toxicity has been acceptable and consisted predominantly of hot flashes. Some patients develop gastrointestinal disturbances in form of diarrhea and abdominal cramps necessitating discontinuation of Flutamide. With this phase II data in hand the RTOG began a phase III (RTOG 86-10) study of the use of Zoladex and Flutamide as cytoreductive agents in locally advanced carcinoma of the prostate treated with definitive radiotherapy. In essence, this study involved patients with bulky B2 and stage C prostate cancer who after appropriate stratification, were randomized to receive either Zoladex and Flutamide for two months prior to the initiation of radiotherapy or to receive radiotherapy alone with end points that evaluated not only survival but local and distant control parameters as well. Four hundred and seventy one patients were accrued to this study which was closed in April 1991. No apparent imbalances by treatment have been shown in five variables: differentiation, Gleason score, nodal status, total serum acid, acid phosphatase, or prostatic acid phosphatase, and clinical stage. Toxicities have been analyzed. There have been three grade 4 complications in two patients in the control arm, and no grade 4 complications in the experimental arm, and there have been 12 grade 3 toxicities on the control arm and nine grade 3 toxicities on the experimental arm. Drug compliance has been good with only six patients assigned to Zoladex and 22 patients assigned to Flutamide having had to terminate their medications.

In 1984, Zincke first reported from the Mayo Clinic an apparently striking effect of elective androgen deprivation on disease progression and survival in patients with positive pelvic nodes following a lymphadenectomy. The series dealt with 100 patients who underwent pelvic lymphadenectomy and a radical retropubic prostatectomy and were found at time of surgery to have positive pelvic lymph nodes\textsuperscript{14}. Forty-eight patients received hormonal manipulation in the form of an orchiectomy or estrogen administration but the remaining patients received hormonal manipulation only at the time of relapse. 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\%. Although this was not a randomized study the two treatment groups appeared to be comparable and the results indicated an apparent dramatic effect on both disease progression and survival. Analysis of previous RTOG data base collaborates the findings that the use of hormonal management in conjunction with definitive radiotherapy may have a beneficial effect on disease free survival and overall survival\textsuperscript{16}. Isaacs has studied\textsuperscript{6} the effect of androgen ablation in an animal model system and has also documented a statically significant prolongation of survival with the use of early orchietomy. In 1985 the RTOG developed RTOG 85-31 to test the hypotheses generated by the Mayo Clinic data in patients who had clinical stage C disease or stage A2 and B disease with regional lymph node involvement demonstrated at lymphadenectomy. These patients were randomized after suitable stratification to either radiation therapy plus expectant therapy with Zoladex of the time of relapse or radiation therapy, and on completion of radiotherapy adjunct long-term Zoladex therapy. Over 900 patients were randomized to the study. Compliance to long term Zoladex has been good with only 14\% of patients terminating their drug prior to at least a year because of patient refusal.
3.1.2 Nodes evaluated negative by imaging methods will be classified as NX. Nodes evaluated negative by surgical sampling will be classified as N0. Imaging positive nodes must be confirmed by biopsy. Positive lymph node status can be determined only by surgical sampling or fine needle aspiration. Patients with regional lymph node involvement will be eligible provided the involved nodes are below the common iliac level (involved common iliac and/or para aortic lymph nodes will not be eligible).

3.1.3 Karnofsky performance status ≥ 70. Patients must sign a study-specific informed consent form.

3.1.4 PSA is mandatory for patient eligibility; maximum level is PSA < 150 (revised 11/92)

3.1.5 No prior hormonal therapy, radiation or chemotherapy.

3.1.6 No distant mets.

3.2 Conditions for Patient Ineligibility

3.2.1 Stage ≤ T2b disease. (revised 12/17/93)

3.2.2 Evidence of distant metastasis. (M1)

3.2.3 Lymph node involvement outside the pelvis proper (spread to common iliac and/or periaortic lymph nodes).

3.2.4 Radical surgery for carcinoma of the prostate, previous radiation, hormonal manipulation or chemotherapy.

3.2.5 Previous or concurrent cancers other than basal cell skin carcinoma.

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.

4.0 PRETREATMENT 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. Tumors must be graded (well-differentiated, moderately differentiated, or poorly differentiated). Gleason scores (Appendix VI) should be provided when possible.

4.4 Mandatory laboratory studies: CBC, SGOT and SGPT, serum acid phosphatase, serum testosterone levels, alkaline phosphatase and a prostatic-specific antigen (PSA) study are mandatory for all patients.

4.5 Radiographic studies: Chest x-ray; bone scan (mandatory).

4.6 Lymph node evaluation is mandatory and can be performed by at least one of the following: Lymphangiogram, CT of the pelvis/abdomen or exploratory laparotomy with lymph node biopsy (sampling).

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 Radiation will start two months following initiation of drug administration. 44-46 Gy (1.8 - 2.0 Gy/day four to five times a week) to regional lymphatics followed by 20-29 Gy (1.8 - 2.0 Gy/day) for a total of 65-70 Gy to the prostate for stage T2c and 67.5 - 70 Gy for stages T3 and T4. (revised 12/17/93)

6.2 Physical Factors

Megavoltage equipment is required with effective photon energies ≥ 4 MeV (≥ 6 MeV is preferable). Minimum source-to-axis distance is 80 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.

6.3 Target Volumes

The volumes defined in the ensuing paragraphs 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.

6.3.1 Regional Lymphatics Target Volumes

Patients with no evidence of tumor spread to the pelvic lymphatics may be treated electively to a target volume to include pelvic nodes to the level of the L5-S1 interspace. Patients who are surgically staged and negative for pelvic node involvement should be treated with a volume encompassing the prostate only. Although the inferior margin will usually project at the bottom (calculated at one cm below the tuberosity) of the ischial tuberosity this structure may not be an appropriate landmark in patients with a
flat or elongated pelvis. A more reliable landmark is the superior margin of the symphysis. The inferior margin of the pelvic target volume will be placed at least 5 cm (but no more than 6 cm) from the superior margin of the symphysis. The lateral margins will be 2.0 cm lateral to the pelvic brim. An AP-PA technique is not acceptable except with ≥ 24 MeV photons. If 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 rectum may need to be included in the lateral fields. In patients with evidence of pelvic lymph node involvement, the regional lymphatics target volume will include not only pelvic but also common iliac nodes. The inferior and lateral pelvic margins will be the same as in the section above. The superior margin may extend to the L4-L5 interspace.

6.3.2 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.

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

6.4 Doses (revised 4/5/93)
6.4.1 The prescribed doses are defined on the central axis at the projected center of the target volumes. All patients will require isodose plans at the central axis of both the pelvic and prostate treatment volumes.

6.4.3.1 For two opposed coaxial equally weighted beams: on the central ray at mid-separation of beams.
6.4.3.2 For an arrangement of 2 or more intersection beams: at the intersection of the central ray of the beams.
6.4.3.3 For complete rotation or arc therapy: in the plane of rotation at the center of rotation.
6.4.3.4 For a single beam: on the central ray at the center of the target area.
6.4.3.5 For two opposing coaxial unequally weighted beams: on the central ray at the center of the target area.
6.4.3.6 Other or complex treatment arrangements: at the center of the target area (Note: there may be several target areas).

6.4.2 Regional lymphatics will receive a total of 44-46 Gy. Doses of up to 50 Gy will be acceptable.
6.4.3 The prostatic target volume will receive a boost of 20-29 Gy bringing the total prescribed dose to that volume to 65-70 Gy for T2C and 67.5-70 Gy for T3-4.
6.4.4 The minimal target dose to the regional lymphatics will be 44 Gy.
6.4.5 The minimal target dose to the prostatic target volume will be 65 Gy for T2 and 67.5 Gy for T3-4.
6.4.6 The maximal target dose defined as the greatest dose in target volume which is delivered to an area greater than 2 cm² shall be 50 Gy for the regional lymphatics target volume and 70 Gy for the prostate boost target volume.

6.5 Fractionation
Daily tumor doses will be 1.80-2 Gy given once a day four to five times a week.

6.6 Critical Normal Structures
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. 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.

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: The drug will be supplied by the manufacturer and will be distributed by the NCI. Drug orders (NIH-986) should be limited to an eight week supply.
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: The administration of Zoladex will take two components, the first component will be the neoadjuvant therapy which all patients will receive. The second component will be the adjuvant component which only the arm randomized (Arm 2) to long-term Zoladex therapy will receive.

7.1.4.1 Neoadjuvant Therapy (Arms 1 and 2) (revised 2/15/93)
Zoladex depot will be injected every four weeks beginning two months prior to radiation therapy. 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. 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. The tear off portion of the depot package label will be removed and affixed to the appropriate case report 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. 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 Zoladex (Arm 2) (revised 8/15/94)
Administration of Zoladex on an adjuvant basis will begin four weeks after the fourth neoadjuvant Zoladex injection. Administration of Zoladex will be continued for 24 months but may be terminated if signs of disease progression appear while the patient is receiving the drug.

7.1.5 Toxicity: (4/195) 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: This drug will be supplied by the manufacturer and distributed by the NCI. Drug orders (NIH-986) should be limited to an eight week supply.

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. (revised 9/21/92)

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 beginning 2 months prior to radiotherapy and continuing throughout radiotherapy. (revised 9/21/92)
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. 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 and mild elevation of SGOT without alteration in serum bilirubin and without clinical manifestations. Refer to package insert for additional information. A high percentage of patients treated with Flutamide alone developed gynecomastia within 2-8 months. One death from liver failure has been reported in the first 1000 patients. (8/15/94, 9/30/94)

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 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.
7.3 Adverse Reaction Reporting
7.3.1 Grades 4 and 5 unknown reactions. Phone report to RTOG, Study Chairman, and IDB within 24 hours. A written report to follow within 10 working days.
7.3.2 Grades 4 and 5 known reactions and Grades 2 and 3 unknown reactions. Written report to IDB within 10 working days. Copies to Study Chairman and RTOG.
7.3.3 Phone report to Investigational Drug Branch (IDB) within 24 hours (301/230-2330, available 24 hours, recorded after hours) (revised 9/21/92)
7.3.4 Address for submitting ADR reports:
   Investigational Drug Branch
   Box 30012
   Bethesda, MD 20824
7.3.5 Further information for reporting Adverse Drug Reactions is detailed in Appendix V.

8.0 SURGERY (revised 2/15/93)
8.1 Prostate Re-biopsy
8.1.1 A prostate biopsy will be done at two months (see Section 8.1.3) after randomization (pre RT) and at 24 months. The two-year biopsy will be performed for any patient who has achieved a clinical complete response (CR) or an equivocal disease response (ER) unless there is a medical contraindication to rebiopsy or definite evidence of local progression by clinical physical exam.
8.1.2 If the patient has distant metastatic disease or is post orchiectomy, the biopsy will not be performed.
8.1.3 An additional complementary case credit will be given for the pre RT biopsy when done.

9.0 OTHER THERAPY
Does not apply to this study.

10.0 PATHOLOGY
Central pathology review of the diagnostic and pre RT biopsies and of the 2-year biopsy are planned for this study. Central reviews on previous prostate studies have demonstrated a 34% discrepancy in histological grading. H & E stained sections and tissue blocks of all pathologic material, the pathology report and a pathology submission form will be submitted to the pathology coordinator at RTOG headquarters.
10.1 Blocks will be returned upon completion of the study (slides prepared by Dr. Grignon from the blocks will be retained). 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-hormonal therapy and post-radiotherapy biopsies.
10.2 All cases will be graded histologically according to Gleason. Where possible, post-hormonal therapy and post-radiotherapy biopsies will also be histologically graded.
10.3 Immunocytochemical studies will be performed on all cases for evidence of neuroendocrine differentiation (chromogranin A, neuron specific enolase).
10.4 Post-hormonal biopsies will be evaluated for the presence or absence of residual tumor.
10.5 Post-radiotherapy biopsies will be evaluated for the presence or absence of residual tumor. All post-radiotherapy biopsies will be centrally reviewed by two pathologists.

11.0 PATIENT ASSESSMENTS (9/30/94)
11.1 Study Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pretreatment</th>
<th>At Completion of Radiotherapy</th>
<th>Follow-up (See Section11.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History &amp; Physical, KPS</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Tumor size in cm in two dimensions</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Tumor Biopsy</td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Sexual status</td>
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<td>Chest X-ray</td>
<td>X</td>
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<td>Bone Scan</td>
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<tr>
<td>Acid Phosphatase, Alk. Phos.</td>
<td>X</td>
<td>yearly</td>
<td></td>
</tr>
<tr>
<td>LFT's, CBC</td>
<td>X&lt;sup&gt;c&lt;/sup&gt;</td>
<td>X&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Serum Testosterone</td>
<td>X</td>
<td>X</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lymph Node Assessment</td>
<td>X&lt;sup&gt;f&lt;/sup&gt;</td>
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<tr>
<td>Prostatic-Specific Antigen (PSA)</td>
<td>X</td>
<td>X&lt;sup&gt;g&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

a. Diagnostic biopsy and pre RT rebiopsy.
b. A two-year post-tx biopsy will be required (See Section 8.1).c. As indicated.d. Following administration of drugs.e. Serum testosterone will be repeated at the time of the first followup in all patients. If elevated, serum testosterone will be repeated until it returns to normal range, or (in patients with below normal pretreatment values) to pretreatment value ± 10%, or until 2 years elapse, whichever occurs first. Must also be done at
In order to ensure the proper continuation and monitoring of Zoladex therapy, specific procedures are outlined below:

- Imaging-positive nodes must be confirmed by biopsy.
- At each Followup assessment.
- LFT's must be repeated at 4 weeks after Flutamide is started.

### 11.2 Follow-up Schedule (revised 9/21/92)

- **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 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** Prostate/prostate tumor dimensions in cm should be calculated from physical exam and must be recorded on the diagrams found on the data collection forms for initial and follow-up evaluation 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 Complete Response (CR):** Complete disappearance of clinical evidence of disease.
  - **11.3.2.2 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.
  - **11.3.2.3 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.
  - **11.3.2.4 Minor Response (MR):** Tumor regression that is greater than 25% but less 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. An elevated PSA in the absence of identifiable distant metastases should be recorded but is not an indication for institution of additional treatment.

### 11.4 Other Response Parameters

- **11.4.1 Time to Complete Response (CR):** time in months from completion of radiotherapy to documentation of complete tumor regression.
- **11.4.2 Duration of Clinical Response:** The duration of clinical response will be measured from the date of documentation of first response to the date of documentation of the first progression or until the date of death if progression does not occur.
- **11.4.3 Disease-Free Interval:** The disease-free interval will be measured from the date of documentation of complete response to the date of documentation of progression or until the date of death.
- **11.4.4 Time to Local Progression:** The time to progression will be measured from the date of first treatment to the date of documented local progression as determined by clinical exam.
- **11.4.5 Time to Distant Failure:** The time to distant failure will be measured from the date of first treatment to the date of documented metastatic disease.
- **11.4.6 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 (revised 9/21/92)

**Item** | **Time of Submission**
--- | ---
Demographic Form (A5) | Within 1 week of study entry
On Study Form (I1) | Within 2 weeks of registration
Pathology Report (P1) | 
Pathology Blocks (P2) | 
Surgical Operative Report (S2)* | 
Surgical Pathology Report (S5)* | 
* If node dissection or sampling was performed
Preliminary Dosimetry Information:  
Within 1 wk of start of RT
- RT Prescription (Protocol Treatment Form) (T2)
- Films (simulation and portal) (T3)
- Calculations (T4)
- Interim Report (F9)
- Hormone Flowsheet (M1)

Pathology Report: Rebiopsy #1 (P1)  
Pathology Blocks: Rebiopsy #1 (P2)

Within 4 weeks of second biopsy.

Radiotherapy Form (T1)  
Within 1 week of RT end

Final Dosimetry Information:  
- Daily Treatment Record (T5)
- Isodose Distribution (T6)
- Boost Films (simulation and portal) (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 at death.

Pathology Report: Rebiopsy #2 (P1)  
Pathology Blocks: Rebiopsy #2 (P2)

At 2 years post RT

Autopsy Report (D3)  
As applicable.

13.0 STATISTICAL CONSIDERATIONS

13.1 Randomization
Treatment allocation will be done by a randomized permuted block within strata to balance for patient factors other than institution. The strata in this protocol are histological differentiation (grade well, moderately, or poor/undifferentiated), PSA (>30 vs. <30) and T stage (T2b, T3, T4), and nodal status (negative, positive, unknown).

13.2 Endpoints and Sample Size Estimates, Projection of completion of accrual.
13.2.1 Major endpoints will be local regional control, disease free survival, survival, and effect on sexual function. For purposes of comparing the two treatment arms, total recurrence free survival will be used, assuming we seek at 10% improvement at 5 years from date of randomization, from 40% to 50%. Total recurrence free is defined as negative biopsy at 2 years, PSA <= 10, and no clinical evidence of disease. If a=0.05, one sided and power = .80, a study with 4 years of accrual plus 2 additional years of follow-up will require 350 patients in each arm. Allowing for 10% patients with invaluable data, the total requirement is then (350 + 350) / .9 = 778 patients. Previous RTOG studies 8531 and 8610 accrued nearly 30 patients/month combined. So even at 22 patients/month this requirement should actually be met in less than 3 years.

13.2.2 Non Compliance Adjustment
Studies 8531 and 8610 were adjusted for as much as a 15% noncompliance rate in taking the drugs. Whether that will be a problem is difficult to estimate with these new drug regimens. However, at 22 patients/month, the total accrual could be 1056 if the study is allowed to run the full 4 years, providing ample room for an adjustment in total sample size, if needed.

The non-compliance adjustment will be accomplished by the formula (Pajak - RTOG 85-03):

\[ Sm = Ce \times Se + (1- Ce) \times Sc \]

where if \( m \) = mixture, \( e \) = experimental and \( c \) = control and

\[ Sm = \text{Success rate for mixture population assigned Zoladex} \]
\[ Ce = \text{Compliance rate for the patients assigned to Zoladex} \]
\[ Se = \text{Success rate hypothesized for compliers to Zoladex} \]
\[ Sc = \text{Success rate hypothesized for non-compliers to Zoladex, which is the same as the control arm}. \]

This is a proportional adjustment. The sample size estimate (Section 13.2.1) would then be recalculated using \( Sm \) instead of 50%.
The definition of non-compliance to be used is the evaluation made on the drug flow sheets (M6 form) and the study chairman’s review (M5 form) which indicate if the patient terminated Zoladex prior to 2 years from the start of treatment due to a treatment related problem or refusal. This will be checked at the time of the first and second designated timepoints for evaluation of outcome. See Section 13.3.2.

For example, if $C_e = .85$ and $1 - C_e = .15$ for non-compliance and $S_e = .50$, $S_c = .40$, then

$$S_m = .85 (.50) + .15 (.40) = .485$$

That is, the hypothesized difference of 40% to 50% in total recurrence free survival becomes 40% to 48.5% with the adjustment. The total sample size requirement for this adjustment would be 1052 patients rather than 778.

13.2.3 Revised Sample Size (added 12/17/93)

Accrual to this trial has been more rapid than anticipated. In order to take advantage of this, the target sample size of the trial will be increased to make survival the primary endpoint for sample size calculation. The expected 5-year survival is 64% which was estimated from RTOG 7506. Breast cancer trials have shown a 6-8% improvement in 5-year survival rates with appropriate hormonal therapy. With two years of accrual at 45 patients per month, a total of $N=1080$ patients will be entered onto RTOG 92-02. Assuming a 10% unenrollment rate, with 3.5 years of follow-up there will be over 80% power using a one-sided $\alpha=0.05$ log rank test to detect a survival advantage in the range observed in breast cancer. A study of this size will have a 90% power to detect a difference between 40% and 50% 5-year recurrence-free survival between the two treatments.

13.2.4 Revised Sample Size (added 8/15/94)

Previous analyses of three mature RTOG studies could neither "conclusively prove nor disprove the assertion that race is an independent prognostic factor for survival from prostate cancer" (Roach et al, IJROBP 24:441-449, 1992). When data from RTOG 86-10 and RTOG 85-31 are mature, more information will become available. The enthusiastic accrual to RTOG 92-02 provides an opportunity to expand a data base that will eventually provide more definitive answers to research questions regarding race. This trial is the first RTOG trial that collects baseline PSA data, so it will be the first RTOG dataset that allows testing of race as a prognostic factor independent of PSA. When accrual stopped on June 20, 1994, there were 135 Blacks entered onto the trial. If a total of 175 Blacks were accrued, there would be 80% statistical power to detect a 10% 5-year recurrence-free survival difference between Blacks and Whites after 3.5 years of follow-up with a one-sided 0.05 level test. There would be lower (67%) statistical power to detect the smaller (8%) survival differences that RTOG 92-02 was designed to detect. Further follow-up would increase the statistical power. An additional 428 patients are required for a total sample size of 1508.

13.3 Frequency of Reports

13.3.1 Interim accrual and morbidity reports will be prepared on at least a semi-annual basis prior to each RTOG meeting and will contain the following items:

13.3.1.1 Projections for completion of accrual phase, based on patient accrual rates observed during the last year and/or for the whole study.

13.3.1.2 Patient accrual by institution.

13.3.1.3 Disposition of all the cases entered into the study with respect to analysis. Analyzable cases are those eligible as confirmed by the submitted on-study pretreatment data. Ineligible and cancelled/ineligible cases are identified along with reasons for exclusion.

13.3.1.4 Distribution of stratifying variables used in randomization and of other important prognostic variables for each assigned treatment regimen. A tabulation of toxicities reported up to date will be included.

13.3.2 Interim response and survival analyses including endpoints such as initial response rate, local control, time to progression, disease free survival and survival, will be performed as soon as 50% (first designated timepoint), 75% (second designated timepoint), and 100% (third designated timepoint) of the required sample size has been obtained and one year following completion of accrual, with consideration of reporting results if they are significant at the .005 level. This schedule is suggested due to the slow development of the disease, and the need for follow-up data. Otherwise results will be reported at the end of the planned follow-up period using a significance level of .046.²⁶

13.4 Monitoring Committee

In order to effectively monitor the study, a committee is created consisting of the principal study chairman, the responsible statistician, the GU Site Committee Chairman, the RTOG Group Chairman, the RTOG Group Statistician and designated representatives for ICI and Shearing-Plough. This Committee will receive the accrual and toxicity results unblinded, and the response and survival data blinded. Based on the results, the Committee can make one of the following three decisions: 1) continue the study as it is; 2) revise the study because of toxicity or execution problems; 3) close the study before it has realized its accrual objectives because of insufficient patient accrual, or a highly significant advantage observed on the experimental arm, or because of the extremely low probability of observing the lack of difference for an experimental arm if the hypothesized difference is, in fact, true. See early stopping rules below.
13.5  

**Early Stopping Rules**

13.5.1 If an experimental arm shows a highly significant difference in total overall survival from the standard arm (p<.003 at the first designated time point and p<.004 at the second designated time point), the recommendation will be made to drop the appropriate arm. These p-levels are selected in order to preserve an overall significance level of .05.26

13.5.2 If an experimental arm fails to show any improvement over the standard arm, recommendation will be made to drop the experimental arm. Judgement will be based on rules similar to the methods of Wieand.27
References


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

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 and Flutamide used before and during a course of radiotherapy. The purpose of this study is to determine whether these drugs may improve the probability of tumor control when used in conjunction with radiotherapy. If I agree to participate in this program, I would be assigned to receive Zoladex and Flutamide together with radiotherapy. Radiotherapy will be given daily over approximately 2 months. This study involves at random (by chance) assignment to one of the two arms.

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

DESCRIPTION OF PROCEDURES

The treatment to be given to me is as follows:

**Treatment 1:** I will receive two monthly injections of Zoladex under my upper abdominal skin, and six Flutamide capsules daily for two months. Radiation will be given once a day, 4-5 days a week for almost eight weeks. The Zoladex and Flutamide will be given on the same schedule during radiation as it was given before radiation began. *(revised 9/21/92)*

**Treatment 2:** I will receive monthly injections of Zoladex under my upper abdominal skin, and six Flutamide capsules daily for two months. Radiation will be given once a day, 4-5 days a week for almost eight weeks. The Zoladex and Flutamide will continue to be given again on the same schedule during radiation as it was given before radiation began. After radiation treatments end, Zoladex injections (without Flutamide) will continue monthly for two years. *(revised 9/21/92, 8/15/94)*

After two months of hormones and again at two years following radiotherapy, I will be requested to have a biopsy of my prostate to evaluate microscopically the response to treatment.

The Division of Cancer Treatment at the National Cancer Institute will provide me with these agents free of charge for this study as long as the pharmaceutical manufacturer is willing to make such supplies available. When these agents are commercially available, however, I may be asked to purchase subsequent doses of the medicine.
RISKS AND DISCOMFORTS (8/15/94, 4/1/95)

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 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: 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 Zoladex therapy is uncertain. The symptoms may reverse upon cessation of Zoladex treatment. Zoladex may occasionally produce irritation at the site of injection. Very rarely, allergic reactions, generalized skin rash or vasculitis (inflammation of the tissue beneath the skin) have been reported.

Flutamide has been reported to cause diarrhea, swelling and tenderness of the breasts and changes in certain tests which evaluate the liver. One death from liver failure has been reported in the first one thousand patients.

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. 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 or receive other compensation. For more information concerning the research and research-related risks or injuries, I can notify Dr.____________________________ at _______________________. 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 developments occur that indicate the treatment is not in my best interest, or should my physician feel that this treatment is no longer in my best interest, the treatment would be stopped. Further treatment would be discussed.

ALTERNATIVES

Alternatives which could be considered in my case include radiation therapy alone, surgery, 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 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. I will be provided with a written list of procedures related solely to research which would not otherwise be necessary. These will be explained to me by my physician. 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 (revised 2/15/93)

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 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 the 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, may be sent to a central office for review and research investigation associated with this protocol. I have read all of the above, asked questions, received answers concerning areas I did not understand, and willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

____________________________  __________________________
Patient Signature (or Legal Representative)  Date
**APPENDIX II**

**KARNOFSKY PERFORMANCE SCALE**

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

DEFINITION OF TNM (revised 8/16/93)

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 (con’d)

Histopathologic Grade (G)

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

STAGE GROUPING

<table>
<thead>
<tr>
<th>Stage</th>
<th>T1a</th>
<th>N0</th>
<th>M0</th>
<th>G1</th>
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<tbody>
<tr>
<td>Stage I</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
<td>G2, G3-4</td>
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<tr>
<td></td>
<td>T1b, T1c, T1</td>
<td>N0</td>
<td>M0</td>
<td>Any G</td>
</tr>
<tr>
<td>Stage II</td>
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<td>M0</td>
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<td>Stage III</td>
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<tr>
<td>Stage IV</td>
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<td>M0</td>
<td>Any G</td>
</tr>
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<td>Any T</td>
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<td>M0</td>
<td>Any G</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>Any G</td>
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</tbody>
</table>
APPENDIX V

ADVERSE DRUG REACTION REPORTING GUIDELINES

General Toxicity Reporting 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.

1. The Principal Investigator will report to the RTOG Group Chairman, the details of any unusual, significant, fatal or life-threatening protocol treatment reaction. In the absence of the Group Chairman, the report should be made to the Headquarters Data Management Staff (215/574-3150).

2. The Principal Investigator will also report to the Study Chairman by telephone the details of the significant reaction.

3. When directed, a written report containing all relevant clinical information concerning the reported event will be sent by the Principal Investigator to RTOG Headquarters. This must be mailed within 10 working days of the discovery of the toxicity unless specified sooner by the protocol.

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), when feasible, 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 (Adverse Reaction Reports or Drug Experience Reports) submitted to NCI, IDB, FDA, or to another Cooperative Group (in the case of RTOG sponsored intergroup studies) must also be submitted to RTOG Headquarters when written documentation is required.

6. When telephone reporting is required, the Principal Investigator should have all relevant material available. See attached reporting form for the information that may be requested.

7. See the specific protocol for criteria utilized to grade the severity of the reaction.

8. The Principal Investigator when participating in RTOG sponsored intergroup studies is obligated to comply with all additional reporting specifications required by the individual study.

9. Institutions must also meet their individual Institutional Review Board (IRB) policy with regard to their toxicity reporting procedure.

10. Failure to comply with reporting requirements in a timely manner may result in suspension of participation, of application for investigational drugs or both.

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.

An unknown adverse reaction is a toxicity thought to have resulted from the agent but had 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. Form 3500 is to be used in reporting details (see attached). 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 and 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 only a reasonable suspicion.

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

i. Phase I Studies Utilizing Investigational Agents

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

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

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

- First occurrence of any toxicity (regardless of grade).  
  Report by phone within 24 hours to IDB drug monitor and RTOG Headquarters.  
  **A written report may be required.
Phase II, III Studies Utilizing Investigational Agents

- All fatal (grade 5) and life threatening (grade 4) known adverse reactions due to investigational agent.
  
  **Report by phone to RTOG Headquarters and the Study Chairman within 24 hours.**
  
  **A written report must be sent to RTOG within working days with a copy to IDB.**
  
  (Grade 4 myelosuppression not reported to IDB)

- All fatal (grade 5) and life threatening (grade 4) unknown adverse reactions resulting from or suspected to be related to investigational agent.
  
  **Report by phone to RTOG Headquarters, the Study Chairman and IDB within 24 hours.**
  
  **A written report to follow within 10 working days.**

- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent.
  
  **Report in writing to RTOG Headquarters and IDB within 10 working days.**

**See attached NCI Adverse Drug Reaction Reporting Form**
## APPENDIX VI

### GLEASON CLASSIFICATION

Histologic patterns of adenocarcinoma of the prostate

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

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)