RADIATION THERAPY ONCOLOGY GROUP

RTOG 85-31

PHASE III STUDY OF ZOLADEX ADJUVANT TO RADIOTHERAPY IN UNFAVORABLE PROGNOSIS CARCINOMA OF THE PROSTATE

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**SCHEMA**

<table>
<thead>
<tr>
<th>S</th>
<th>a) Histological diff. (well, moderately, poorly, diff, ca or Gleason 2-5-6-7, 8-10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>b) Nodal status and extent of nodal involvement (none below common iliacs, common iliacs, (periaortic)</td>
</tr>
<tr>
<td>R</td>
<td>c) Acid phosphatase status (not elevated, elevated)</td>
</tr>
<tr>
<td>A</td>
<td>d) Radical prostatectomy (yes vs. no)</td>
</tr>
<tr>
<td>T</td>
<td></td>
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<table>
<thead>
<tr>
<th>R</th>
<th>1. Radiation Therapy + Zoladex (q. 4 wks., s.c.)</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>2. Radiation Therapy + Observation - &gt; Zoladex at the time of relapse</td>
</tr>
<tr>
<td>N</td>
<td></td>
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<td>D</td>
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</table>

**Patients Assigned to Adjuvant Zoladex** will start receiving the drug during the last week of the radiation therapy course, patients on the observation arm will start receiving the drug only at the time of documented disease progression (relapse).

**Radiation Therapy**: 44-46 Gy (1.80 - 2.00 Gy/day) to regional lymphatics followed by 20-25 Gy (1.80-2.00 Gy/day) to a total of 65-70 Gy to the prostate. In patients who are treated post-operatively (following radical prostatectomy) the prostatic bed will receive 60-65 Gy.

**Eligible**: Patients with unfavorable prognosis adenocarcinoma of the prostate including those with clinical Stage A2, B with regional lymph node involvement (- D1), those with gross extension of the palpable primary tumor beyond the prostate (clinical stage C) with or without evidence of nodal involvement and those irradiated post-operatively (following radical prostatectomy) in whom there is pathologically documented penetration through the prostatic capsule in the margin of resection and/or seminal vesicle involvement.

**Ineligible**: Patients who have received any type of hormonal management. Patients with evidence of metastatic disease (spread beyond the pelvic and periaortic lymphatics). Patients with concomitant cancer or history of cancer other than basal cell skin cancer. Patients with bulky primary lesions defined as those with a product of tumor dimensions (in centimeters) of 25 or more will not be eligible for this study but for the cytoreduction protocol (RTOG 86-10). Exception will
be patients in whom there is evidence of spread to regional lymphatics outside the pelvis proper (spread to common iliac and periaortic lymph nodes).
1. Is disease histologically confirmed adenocarcinoma of the prostate?
2. Report stage of the primary tumor.
3. If stage is A2, B1 or B2 is there radiographic or histological evidence of spread to the regional lymph nodes?
4. If the product of tumor dimensions is ≥ 25 cm, is there spread to the common iliac or periaortic nodes?
5. If the patient has had radical surgery for carcinoma of the prostate is there histologically documented penetration through the prostatic capsule to the margin of resection and/or seminal vesicle involvement?
7. Has patient signed informed consent?
8. Is there evidence of distant metastases?
9. Is there lymph node involvement beyond the periaortic area?
10. Has patient received prior radiation therapy?
11. Has patient received hormonal manipulation?
12. Has patient had orchiectomy?
13. Has patient received prior chemotherapy?
14. Is there a history of previous or concurrent cancers other than basal cell skin carcinoma?
15. Does patient have major medical or psychiatric illness, which in the investigator’s opinion, would prevent completion of treatment or interfere with follow-up?

Stratification

1. Differentiation/Gleason
   - Well or Gleason 2-5; moderately or gleason 6-7; poorly undifferentiated or Gleason 8-10
2. Nodal Status
   - Not involved; below common iliacs; common iliacs; periaortic
3. Acid phosphatase status
   - Not elevated; elevated
4. Radical Prostectomy
   - No; yes

(Amended 4/27/90)
1.0 **INTRODUCTION**

1.1 Endocrine therapy for carcinoma of the prostate was introduced by Huggins\textsuperscript{5} in 1941 and is based on the dependence of the prostatic epithelial cells and the prostatic carcinoma cells on androgenic hormones. Androgen deprivation induced by either orchiectomy or administration of Estrogens can produce dramatic and often prolonged symptomatic improvement in a large percentage of patients. Some forms of hormonal manipulation have been associated with considerable morbidity. This refers to Estrogen therapy which is associated with an increased incidence of cardiovascular problems including thromboembolic phenomena and fluid retention. As shown in the VA cooperative studies, the incidence of these complications is dose dependent.\textsuperscript{13,14}

1.2 In spite of the wide spread use of hormonal manipulation in the treatment of carcinoma of the prostate, properly conducted studies testing its effect on disease progression and survival are surprisingly scarce. The VA studies did document a beneficial effect on disease progression and survival in certain subpopulations of patients and also significant morbidity associated with administration of Estrogens.\textsuperscript{2,3,4,13,14} This morbidity seems to have counteracted the apparent beneficial effect of hormonal manipulations. It appears appropriate to conclude that less toxic ways of the hormonal manipulation may produce not only a significant improvement in disease free survival but also survival, in a population of patients who are at a high risk of progression and tumor related death.

Recent publications from Mayo Clinic indicate an apparent striking effect of elective Androgen deprivation on disease progression and survival in patients with positive pelvic lymphadenectomy.\textsuperscript{17} The series deals with 100 patients who underwent pelvic lymphadenectomy and radical retropubic prostatectomy and were found to have positive pelvic lymph nodes. Forty-eight patients received hormonal manipulation in the form of orchiectomy or Estrogen administration. The remaining patients received hormonal manipulation only at the time of relapse. For the 52 patients who were not treated with adjuvant hormonal manipulation, the overall five year rate for non-progression was only 18.5%. Patients who received adjuvant orchiectomy had a five year non-progression rate of 95%. Adjuvant bilateral orchiectomy was associated with projected 5 and 10 year survival rates of 94 and 80% respectively. Although this was not a randomized study, the two treatment groups seem to be comparable and the results indicate an apparent dramatic effect on disease progression and survival.

Analysis of RTOG data\textsuperscript{7} corroborates the contention that the use of hormonal management in conjunction with definitive radiotherapy may have a beneficial effect on disease-free survival and survival. Although the patients who received concomitant hormonal management had significantly higher proportion of unfavorable lesions than the population that received no hormonal manipulation, the incidence of distant metastases appeared comparable. Isaacs\textsuperscript{6} studied the effect of timing of Androgen ablation in an animal model and documented a statistically significant prolongation of survival with the use of early orchiectomy.

1.3 In the recent years considerable interest has been raised by the appearance of LH-RH agonists.\textsuperscript{1,10,12,15,16} These agents given either intranasally or subcutaneously block LH secretion and reduce Testosterone level to an anorchid level production “medical orchiectomy”. This reduction is proceeded by a brief increase in LH secretion. The main advantage of LH-RH agonists is an apparent lack of toxicity. One of the disadvantages of LH-RH agonists has been the route of administration either intranasal spray or daily subcutaneous injections. These problems have been solved by the appearance of a Depo preparation\textsuperscript{15,16} (Zoladex, manufactured by Stuart Pharmaceuticals) which is administered subcutaneously on a monthly basis.

2.0 **OBJECTIVES**

2.1 Evaluation of the relative effectiveness of elective versus therapeutic Androgen deprivation with Zoladex on disease progression and survival, in a population of patients with carcinoma of the prostate who are at high risk of relapse and tumor related death. These include patients with evidence of involvement of regional lymphatics or extension of the primary tumor beyond the prostate as determined by palpation (=clinical stage C) or histological examination of the radical prostastectomy specimen (=pathological stage C). (Analysis of RTOG data indicates that gross extraprostatic extension of the primary tumor has, in patients who are irradiated to the pelvis, the same prognostic and therapeutic implications as nodal involvement.\textsuperscript{7,8}

2.2 Documentation of the potential side effects (or the lack of side effects) associated with the long term administration of Zoladex.
3.0 PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Eligible patients will be those with histologically confirmed adenocarcinoma of the prostate with regional lymphatic involvement or GROSS extension of the palpable primary tumor beyond the prostate (clinical stage C). Included will be patients with clinical Stage A2 and B in whom there is either radiographic or histological evidence of spread to the regional lymph nodes (obturator, external and/or internal iliac, common iliac and periaortic lymph nodes) and patents with clinical stage C disease regardless of the status of the regional lymphatics.

3.1.2 Patients with bulky primary lesions defined as those with a product of tumor dimensions (in centimeters) of 25 or more will not be eligible for this study but for cytoreduction protocol (RTOG #86-10). Exception will be patients in whom there is evidence of spread to regional lymphatics outside the pelvis proper (spread to common iliac and/or periaortic lymph nodes).

3.1.3 Patients who are irradiated postoperatively (following radical prostatectomy) are eligible if there is histologically documented penetration through the prostatic capsule to the margin of resection and/or seminal vesicle involvement.

3.1.4 Karnofsky performance status must be equal to or greater than 60%.

3.1.5 All institutional, state and federal guidelines must be followed. Patients must sign and informed consent prior to being placed on the study.

3.2 Ineligibility Criteria

3.2.1 Evidence of distant metastasis.

3.2.2 Lymph node involvement beyond the periaortic area.

3.2.3 Previous irradiation, hormonal manipulation or chemotherapy.

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

3.2.5 Major medical or psychiatric illness which, in the investigator’s opinion, would prevent completion of treatment and would interfere with follow-up.

3.2.6 Performance status of less than 60% on Karnofsky scale.

3.2.7 See Section 3.1.2.

4.0 PRETREATMENT EVALUATION

4.1 History, physical examination and Karnofsky status evaluation.

4.2 Histological evaluation. The degree of histological differentiation should be defined by the assignment of either grade (well-differentiated, moderately differentiated, or poorly differentiated) or Gleason score (2-5, 6-7, 8-10).

4.3 Mandatory laboratory studies: Serum acid phosphatase, complete blood count including platelets, serum testosterone (in patients assigned to Zoladex arm), prostatic-specific antigen (PSA). (Amended 7/13/90).

4.4 Radiographic studies: Chest x-ray and bone scan. (Amended 9/8/87)

4.5 Lymph node evaluation is mandatory and can be performed by one of the following: Lymphangiogram, computerized tomography of the pelvis (abdomen), with or without needle biopsy, or exploratory laparotomy with lymph node biopsy (sampling). The purpose of nodal evaluation in clinical stage A2 and B disease in documentation of nodal involvement and its extent. In patients with clinical stage C disease the purpose of nodal evaluation is determination of the extent of nodal involvement (if present).

5.0 REGISTRATION AND RANDOMIZATION

Within one week (5 fx) of the start of radiation therapy (11/11/88) patients will be registered and randomized by calling RTOG Headquarters at 215-574-3191, Monday through Friday, from 8:30 am to 5:00 pm ET. The following information must be supplied:

a. Institution
b. Patient’s name
c. Patient’s identification or Social Security Number
d. Person responsible for the eligibility review.
e. Clinical stage, histological differentiation, presence and extent of nodal involvement, acid phosphatase status and pathological evaluation of primary tumor extent in patients treated following radical prostatectomy.

6.0 RADIATION THERAPY
6.1 Physical Factors
Megavoltage equipment is required with effective photon energies higher than 1 MV. Minimum source to skin or source to isocenter 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. Simulation procedures are mandatory.

6.2 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.

6.2.1 Regional Lymphatics Target Volumes
6.2.1.1 Patients with evidence of tumor spread to the pelvic lymphatics (obturator, external and internal iliac lymph nodes) will be treated to a target volume that would include pelvic nodes to the level of the L_5-S_1 interspace. The inferior margin will be at the bottom of the ischial tuberosity. In some patients ischial tuberosity may not be an appropriate landmark (patients with flat or elongated pelvises) since it projects too low or too high. In these cases superior margin of the symphisis will be used as a landmark. The inferior margin of the target volume will be placed at least 5 cm (but no more than 6 cm) from the superior margin of the symphisis. The lateral margins will be 2.0 cm lateral to the pelvic brim.

If a four field technique is used, care should be taken to adequately cover external and internal iliac 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.

6.2.1.2 In patients with evidence of nodal spread to the common iliac chain, the regional lymphatics target volume will include not only pelvic but also periaortic nodes up to the level of L_2–L_3 interspace. The inferior and lateral pelvic margins will be the same as in the section above. The lateral margins of the target volume in the periaortic will extend at least 4.5 cm from the midline.

6.2.1.3 In patients with evidence of spread to the periaortic area the upper border of the regional lymphatics target volume will extend to T_11 vertebra. Other margins will be the same as in 6.2.1.2.

6.2.1.4 In post-operatively (following radical prostatectomy) irradiated patients in whom staging lymphadenectomy revealed no evidence of nodal involvement irradiation of the regional (pelvic) lymphatics may be avoided.

6.2.2 The prostate boost target volume will include the prostate (prostatic bed) with margins sufficiently wide to encompass all of the tumor extensions into the surrounding tissues. The prostatic boost target volumes will measure at least 9.0 cm in longitudinal (craniocaudal) diameter and at least 8 cm in transverse diameter. In patient with massive tumors considerably large target volumes will be required. The size and the position of the prostatic boost target volume is optimally defined by the use of the CT scan (see reference #9 for detailed discussion).

6.3 Doses
The prescribed doses are defined on the central axis at the projected center of the target volumes.

6.3.1 Standard Physics Specifications
a) For two opposed coaxial equally weighted beams: on the central ray at mid-separation of beams.
b) For an arrangement of 2 or more intersecting beams: at the intersection of the central ray of the beams.
c) For complete rotation or arc therapy: in the plane of rotation at the center of rotation.
d) For a single beam: on the central ray at the center of the target area.
e) For two opposing coaxial unequally weighted beams: on the central ray at the center of the target area.
f) Other or complex treatment arrangements: at the center of the target area (Note: there may be several target areas).

6.3.2 Regional lymphatics will receive a total of 44.00-46.00 Gy. Doses up to 50 Gy will be acceptable.

6.3.3 The prostatic target volume will receive a boost of 20.00 25.00 Gy bringing the total prescribed dose to that volume to 65.00-70.00 Gy. In post-operatively treated patients the prostatic target volume will receive a total prescribed dose of 60.00-65.00 Gy.
6.3.4 The minimal target dose to the regional lymphatics will be 44.00 Gy.

6.3.5 The minimal target dose to the prostatic target volume will be 65.00 Gy in definitively treated patients and 60.00 Gy in post-operatively irradiated patients.

6.3.6 The maximal target dose defined as the greatest dose in target volume (area) which is delivered to an area greater than 2 cm² shall be 50.00 Gy for the regional lymphatic target volume and 72.00 Gy for the prostate boost target volume in definitively treated patients and 66.50 Gy for post-operatively treated patients.

6.3.7 The allowed variation of dose across the target volume shall be ± 5% relative to the prescribed dose.

6.4 Fractionation

Daily tumor doses will be 1.80-2.00 Gy given four to five times a week.

6.5 Critical Normal Structures

6.5.1 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.

6.5.2 Dose to the whole rectum shall not exceed 55.00 Gy. Portions of the anterior wall will, by necessity, receive the same dose as the prostate.

6.6 Radiation Adverse Event Reporting (7/28/05)

AdEERS provides a radiation therapy (RT)-only pathway for events experienced involving RT only, both with and without a drug component arm. Events that occur on the RT-only arm of a study with a drug component must be reported for purposes of comparison. Events that occur on an RT-only study without a drug component also must be reported. These types of events involving RT only must be reported via the AdEERS RT-only pathway.

The following must be reported via the AdEERS RT-only pathway:

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<tr>
<th>Unexpected</th>
<th>Expected</th>
<th>4 &amp; 5 Unexpected</th>
<th>4 &amp; 5 Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td>Unlikely</td>
<td>Not Required</td>
<td>Not Required</td>
<td>Not Required</td>
</tr>
<tr>
<td>Possible</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>24 Hour: 5 Calendar Days</td>
</tr>
<tr>
<td>Probable</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td>Definite</td>
<td>Not Required</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
</tr>
</tbody>
</table>

Note:
- *AdEERS 24-hour notification followed by complete report within 5 calendar days for: Grade 4 and Grade 5 unexpected events
- All grade 4 and 5 adverse events (AEs) that occur during or within 30 days after the completion of radiation therapy (RT), regardless of causation, must be reported within 5 days;
- Grade 4 and 5 AEs that occur in follow up (beyond 30 days after the completion of RT but still within the timeframe of follow up of the patient on study) and that are thought to be probably or definitely related to RT (e.g., radiation-induced spinal cord myelopathy) must be reported within 5 days.

7.0 DRUG THERAPY

Administration of Zoladex (NSC #606864) (IND #28059) will be started during the last week of the radiotherapy course in the patients randomized to receive the drug as an adjuvant and at the time of documented disease progression (relapse) in the patients randomized to observation arm (see section 11.3.1.c). Administration of Zoladex will be continued indefinitely but may be terminated if signs of disease progression appear while the patient is receiving the drug.

7.1 Patients Assigned Zoladex

Administration of Zoladex will be started during the last week of the radiotherapy course in the patients randomized to receive the drug as an adjuvant. Administration of Zoladex will be continued indefinitely but may be terminated if signs of disease progression appear while the patient is receiving the drug.

7.2 Patients Assigned Observation Following Radiation

Patients randomized to observation will receive Zoladex only at the time of documented disease progression or relapse whether local (see 11.3.1c) regional or distant. Administration of Zoladex
will be continued indefinitely but may be terminated if signs of disease progression appear while the patient is receiving the drug.

### 7.3 Description and Toxicity

Zoladex is an LH-RH 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. During routine screening of Zoladex, no significant pharmacological activity was apparent in the cardiovascular, respiratory, central nervous, renal and 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. Intravenous doses of up to 6 mg/kg (more than 5000 times the active dose) were without any adverse effects in animals. Except for predictable involutional changes in the reproductive organs, no significant pathology has been found in subacute (3 month) toxicity studies. Six, twelve, and twenty-four month rat studies have revealed an incidence of benign pituitary adenomas which is higher in Zoladex treated groups than in controls. Pituitary changes have not been noted in other species and the phenomena is believed to be species-specific.

Similar effects have been reported with other LH-RH agonists.

The following adverse experiences concerning the drug ZOLADEX have been reported to ICI Pharmaceuticals Group and the Food and Drug Administration (Amended 6/12/1989).

- A 28 year old female, with advanced breast cancer, developed an acute compression of the right ureter and acute renal failure three days following her first injection of Zoladex therapy (3.6 mg/month). A percutaneous right nephrostomy was performed which resulted in good urinary flow. The nephrostomy tube was removed after one month. The patient was able to continue on Zoladex.

- A 59 year old female, with advanced breast cancer involving the skeleton was prescribed Zoladex (3.6/month) after previously receiving tamoxifen and progesterone. She was hypercalcemic (2.9 mmol/L) at the start of treatment, but without any symptoms attributable to the elevated calcium levels. Fourteen days after the initial injection of Zoladex, she experienced mental confusion and was in poor health. Her calcium level was 3.3 mmol/L and she was treated with disphosphonate. The patient received a second injection of Zoladex one month after the first, but subsequently deteriorated and died three weeks later from progressive disease.

- A 75 year old male, receiving Zoladex for prostate cancer, developed myopathy after approximately one year of therapy and was hospitalized. Zoladex therapy had been discontinued several months prior to the identification of myopathy. Since myopathy could possibly be due to prostate cancer, the physician described the reaction as being possibly secondary to Zoladex therapy.

- A male receiving Zoladex for prostate cancer, developed a generalized rash and bronchospasms after his second or third depot injection. The reaction subsided a few days after the injection and Zoladex therapy was continued. The reaction was described by the investigator as severe and possibly related to Zoladex therapy.

- ICI reports that the incidence of localized or generalized rash with patients receiving Zoladex is 6%. There have been no other reports of bronchospasm in the United States Clinical Trials program. In general, allergic reactions have been extremely uncommon with Zoladex therapy. No episodes of anaphylaxis as a result of Zoladex therapy have occurred in the past. The international database indicates that urticaria has been reported in 5 instances.

**Additional adverse experiences concerning the drug Zoladex have been reported to ICI Pharmaceuticals and the FDA:** (Amended 4/27/90, 12/21/90).

- An Australian male with advanced prostatic cancer received a 28 day depot formulation of Zoladex. Approximately seven days later he developed a rash on the legs, upper back, wrist and trunk. He was examined by a dermatologist who described the lesions as annular induced dermal plaques. Biopsy samples confirmed vasculitis. Steroid therapy was started and the rash rapidly reduced. Zoladex therapy was stopped and there were no new lesions.

- This is the first report of vasculitis in patient receiving the 28 day depot formulation of Zoladex. There was one additional report from a pilot study evaluating a longer acting depot formulation of Zoladex. The reaction which was diagnosed as allergic vasculitis occurred five weeks after therapy and persisted for four weeks. The reaction resolved spontaneously and patient remained on study. The patient subsequently received a 28 day depot of Zoladex and no occurrence of the vasculitis was noted.

- A 70 year old white male began Zoladex therapy as treatment for his advanced prostate cancer. The gentleman was enrolled in the Zoladex Quality of Life Study. This gentleman

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suffered a pulmonary embolism and died 11 months later. The gentleman had a history of diabetes. An autopsy was performed and the investigator did not consider the death to be drug-related.

- An elderly male developed a cough and breathlessness in May, 1990, having been treated with Zoladex for prostate cancer since early 1990. He was admitted to the hospital for investigation of interstitial lung changes in July; however, a positive diagnosis was never made. He was treated with anti-tubercular chemotherapy, erythromycin, and high doses of steroids. His condition improved and he continued on cortisone alone. There have been no previous reports of interstitial lung changes in any patient receiving Zoladex, and a relationship to Zoladex therapy has not been established.

7.3.1 Adverse Drug Reactions (Amended 10/15/87) (7/28/05)
Zoladex is an investigational agent and prompt reporting of drug reactions in compliance with the NCI and the RTOG guidelines is mandatory.

7.3.1.1 Adverse Events (7/28/05)
This study will utilize Toxicity Criteria (Appendix V) and Combined Radiosensitizer/Radioprotector/Chemotherapy Toxicity Criteria (Appendix VI) for grading of all adverse events.

All adverse events (AEs) as defined in the tables below will be reported via the AdEERS (Adverse Event Expedited Reporting System) application accessed via the CTEP web site (https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup).

Serious adverse events (SAEs) as defined in the tables below will be reported via AdEERS. Sites also can access the RTOG web site (http://www.rtog.org/members/toxicity/main.html) for this information.

7.3.1.2 Adverse Events (AEs) — RTOG AE PHONE: 215-717-2762; 800-227-5463 ext. 4189 (available 24 hours/day)
Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

The following guidelines for reporting adverse events (AEs) apply to all NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported via AdEERS. Use the patient’s case number as the patient ID when reporting via AdEERS. AEs reported using AdEERS also must be reported on the follow-up form (see Section 12.0). NOTE: If the event is a Serious Adverse Event (SAE) [see next section], further reporting may be required. Reporting AEs only fulfills Data Management reporting requirements.

7.3.1.3 Serious Adverse Events (SAEs) — All SAEs that fit any one of the criteria in the SAE definition below must be reported to RTOG (SAE PHONE: 215-717-2762; 800-227-5463 ext. 4189, available 24 hours/day) within 24 hours of discovery of the event.
Definition of an SAE: Any adverse drug experience occurring at any dose that results in any of the following outcomes:
- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE drug experience, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

Outside of regular business hours (8:30-5:00 EST), leave a message that includes the study/case numbers and the caller’s contact information. A Data Manager will return the call the next business day requesting details of the event and also will inform the caller which type of report is required for that study (5 or 10 day AdEERS). The required report must be completed in AdEERS within 5 or 10 calendar days of the initial phone report, as directed by the
Data Manager taking the call. SAEs reported using AdEERS also must be reported on the follow-up form (see Section 12.0).

Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported to RTOG via the AE/SAE telephone line within 24 hours of discovery. An expedited report, if applicable, will be required within 5 or 10 calendar days.

All supporting source documentation, if applicable or if being faxed to NCI, must be properly labeled with the study/case numbers and the date of the adverse event and must be faxed to the RTOG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTOG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTOG trial. All forms (and supporting source documentation) submitted to RTOG Headquarters must include the RTOG study/case numbers; non-RTOG intergroup study and case numbers must be included, when applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient’s case number as the patient ID when reporting via AdEERS.

SAE reporting is safety related and separate and in addition to the Data Management reporting requirements as outlined in the previous AE reporting section. Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as “expedited reporting NOT required” must still be reported for safety reasons and to fulfill the obligations of RTOG to the pharmaceutical company/companies supporting the RTOG trial. Sites must bypass the “NOT Required” assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment. Note: Sites must print the AdEERS report and fax it to the FDA, FAX 1-800-332-0178.

7.3.1.4 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)
AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the NCI/CTEP Secondary AML/MDS Report Form available at http://ctep.cancer.gov/forms/index.html. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification (RTOG study/case numbers). This form will take the place of a report via the AdEERS system and must be faxed to the Investigational Drug Branch, FAX 301-230-0159, and mailed to RTOG Headquarters (address below) within 30 days of AML/MDS diagnosis.

<table>
<thead>
<tr>
<th>RTOG Headquarters</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML/MDS Report</td>
</tr>
<tr>
<td>1818 Market Street, Suite 1600</td>
</tr>
<tr>
<td>Philadelphia, PA 19103</td>
</tr>
</tbody>
</table>

7.3.1.5 AdEERS Expedited Reporting Requirements
Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days\(^1\) of the Last Dose of the Investigational Agent [Zoladex] in this Study

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 3</th>
<th>Grades 4 &amp; 5(^2)</th>
<th>Grades 4 &amp; 5(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexpected</td>
<td>Unexpected</td>
<td>Expected</td>
<td>Unex-</td>
<td>Expected</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Adverse Events Reporting Requirements

<table>
<thead>
<tr>
<th>Expected</th>
<th>Unexpected</th>
<th>Expected with Hospitalization</th>
<th>Unexpected with Hospitalization</th>
<th>Expected without Hospitalization</th>
<th>Unexpected without Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated</td>
<td>Not Required</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td>Unlikely</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>24-Hour; 5 Calendar Days</td>
</tr>
<tr>
<td>Probable</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td>Definite</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows: AdEERS 24-hour notification followed by complete report within 5 calendar days for:
   - Grade 4 and Grade 5 unexpected events
   - Grade 3 unexpected events with hospitalization or prolongation of hospitalization
   - Grade 5 expected events

2. Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Please see exceptions below under section entitled “Additional Instructions or Exceptions.”

---

**Note:** All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. “On study” is defined as during or within 30 days of completing protocol treatment.

- Expedited AE reporting timelines defined:
  - “24 hours; 5 calendar days” – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - “10 calendar days” - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.

- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

---

**Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP-IND [or Non-CTEP IND]:**

Not applicable.
7.3.1.6 Institutions must follow their Institutional Review Board policy with regard to reporting toxicities to the IRB.

7.4 Clinical Experience

Preliminary clinical studies have involved patients with advanced carcinoma of the prostate treated with various dose levels of aqueous (bolus) and Depot (long acting) formulations of Zoladex administered subcutaneously. These 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 symptoms (tumor flare) on initiating therapy, no significant toxicity apart from that attributed to castration has been reported.

7.5 The Preparation

Zoladex Depot is supplied as a totally biodegradable lactic glycolic acid copolymer impregnated with 3.6 mg Zoladex in a disposable syringe device mounted on a #16 gauge hypodermic needle. The unit is sterile and comes in a sealed, light and moisture proof package. For long term storage the pack should be refrigerated at approximately 4 °C (not frozen). Before being opened, each package must be inspected for damage in which case the syringe should not be used. Being sterile, the syringe should be removed from its package by the physician/nurse only immediately before it’s needed.

7.6 Administration

Zoladex Depot will be injected during the last week of radiotherapy and every 4 weeks thereafter. Whenever possible, attempt to schedule subsequent injections on the same day of the week to avoid the treatment day coinciding with a weekend.

After cleaning with an alcohol swab, a small area of skin on the anterior abdominal wall will be anesthetized by injecting 0.2-3 ml of 1% Lidocaine hydrochloride intraderamally. Zoladex will then be injected subcutaneously using an aseptic technique. Insert the needle to its full length, pull the needle back 1 cm then inject. (This technique creates a little pocket for the Zoladex plug so that it will not be expelled when the needle is withdrawn). Different abdominal sites will be used for subsequent injections.

After checking to insure that the Depot has been discharged the used syringe will be broken irrevocably and discarded in a safe manner. The tear-off portion of the Depot package label will be removed and affixed to the appropriate case report and made part of the patient’s permanent record.

After injecting Zoladex Depot for the first time only, the overlying skin will be permanently marked with a single spot (e.g. tattoo or permanent marker). In the unlikely event of the Depot needing to be surgically removed, this mark will facilitate the procedure.

7.7 Manufactured By:
Stuart Pharmaceutical, ICI Americas Inc., Wilmington, DE.

7.8 Supplied By:
National Cancer Institute. To order Zoladex a Clinical Drug Request Form (NIH #986) must be completed and sent to NCI as directed. Please allow four weeks for delivery of drug. Drug should be ordered when the patient begins radiation therapy.

8.0 SURGERY

Patients who have undergone either retropubic, suprapubic or perineal radical prostatectomy are eligible provided the criteria is defined in Section 3.1.3 are satisfied.

9.0 OTHER THERAPY

Does not apply to this study.

10.0 PATHOLOGY

Central pathology review is planned for this study to confirm histology. Five unstained slides and the Pathology Submission Form must be received at Headquarters within four weeks of randomization. The Pathology Report is due within 1 week of randomization.
11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (Amended 9/8/87, 7/13/90)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pretreatment</th>
<th>Follow-up (See Section 11.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and Physical (including and estimate of tumor size in cm in 2 dimensions)</td>
<td>X</td>
<td>X (See Section 11.2)</td>
</tr>
<tr>
<td>Karnofsky Status</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>X</td>
<td>X(a)</td>
</tr>
<tr>
<td>Bone Scan</td>
<td>X</td>
<td>X(a)</td>
</tr>
<tr>
<td>Acid Phosphatase</td>
<td>X</td>
<td>every 6 months</td>
</tr>
<tr>
<td>Prostate-specific antigen (PSA)</td>
<td>X</td>
<td>every 6 months</td>
</tr>
<tr>
<td>Lymph Node Assessment</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Serum Testosterone(b)</td>
<td>X(b)</td>
<td>3,6,12,24 months(b)</td>
</tr>
</tbody>
</table>

(a) as indicated
(b) patients receiving Zoladex

11.2 Follow-up Schedule (revised 2/15/93)

11.2.1 Every 3 months during the first year.
11.2.2 Every 4 months during the second and third year.
11.2.3 Every 6 months to year 5, then annually for the remainder of the patient's life.

11.3 Specific Endpoints to be Measured

11.3.1 Primary tumor response will be measured by palpation in the following way. Length (apex to base) and width distances of each nodule or tumor mass estimated by the examining finger will be recorded in addition to pictures on anatomic diagrams.

The following definitions of response will be used:

a) Complete regression of primary: complete disappearance of primary tumor.

b) Partial regression of primary: at least 50% decrease in the product of the length and width of the tumor mass or nodule (in the case of more than one nodular tumor mass, the sum of the products be used).

c) Increase in the size of measurable tumor at the primary site (prostate and the periprostatic area) at any time, will be labeled as recurrence (local failure).

11.3.2 Time to clinical manifestation of progression (loco regional failure or distant metastases) disease-free interval.

11.3.3 Absolute survival.

11.3.4 Toxicity of treatment

11.4 Removal from Zoladex Therapy

11.4.1 If patient developed allergic reactions to Zoladex (notify study chairman), the drug will be discontinued.

11.4.2 When patient progresses or relapses (locally, regionally and/or distantly) the drug will be discontinued.

11.4.3 Follow-up on patients where relapse is mandatory.

11.4.4 Evaluation of Zoladex. If a patient is randomized to the RT + Zoladex arm dose take the drug for one year, that case will be counted as evaluable and included in the group designated as "in compliance." Patients who stop taking the drug within a year, due to either refusal or a treatment-related problem, will be designated as "not in compliance." (Amended 4/27/90).

12.0 DATA COLLECTION

<table>
<thead>
<tr>
<th>Item</th>
<th>Time of Submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>On Study Form</td>
<td>Within 1 week of registration</td>
</tr>
<tr>
<td>Diagram of primary tumor</td>
<td></td>
</tr>
<tr>
<td>Pathology Report</td>
<td></td>
</tr>
<tr>
<td>Operative Pathology Report (if applicable)</td>
<td></td>
</tr>
<tr>
<td>Operative Report</td>
<td></td>
</tr>
<tr>
<td>Pathology Slides</td>
<td>Within 4 weeks of registration</td>
</tr>
<tr>
<td>Preliminary Dosimetry Information</td>
<td>Within 1 week of start of RT</td>
</tr>
</tbody>
</table>
Flow Sheet*  
With each follow-up form while receiving Zoladex for 6 months following discontinuation of drug. A column must be completed for each dose of Zoladex and at the onset and clearance of any toxicity. After five years of Zoladex, flowsheets will no longer be collected. This info will be captured on the follow-up form (F1).

Upon completion of treatment

Follow-up Forms  
At completion of RT, then every 3 mos during first year, q 4 mo during 2nd and 3rd year, then q 6 mo until year 5 then yearly, at relapse, progression and death.

* All persons assigned drug and those who receive Zoladex upon progression.

13.0 STATISTICAL CONSIDERATIONS (Amended 11/11/88)

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, nodal status and extent of nodal involvement, acid phosphatase status and prior radical prostatectomy.

13.2 Endpoints and Sample Size Estimates (Revised 4/27/90)
The primary endpoints of the study to be used to compare the group assigned RT + Zoladex vs. the group with RT alone are disease progression and survival. Survival is adopted as the primary endpoint to be used in sample size calculation. Assuming that the study should have significant accrual to determine a 10% difference in absolute survival at 5 years, from 65% to 75%, one sided, and with power -.80, then 287 patients in each group will be required. This is based on a 5 year accrual period + two additional years of follow-up, utilizing the methods of Schoenfeld. 

13.2.1 Non Compliance Adjustment
Preliminary examination of cases for final review by the study chairman has revealed an approximate 15% non-compliance rate in the RT + Zoladex arm, as defined in Section 11.4, termination of taking the drug within one year. A proportional adjustment to the 10% desired difference, assuming the 15% of RT + Zoladex cases actually receive RT alone, narrows the difference to 8.4%, from 65% to 73.4% survival at 5 years.

13.2.2 Total Sample Size with Non-Compliance Adjustment
The required sample size for the 8.4% difference is 419 in each arm. Assuming 10% invaluable cases, then a total of 931 will be needed. If disease-free survival is considered, and it is desired to distinguish between 40% and 50% with a proportional adjustment for 15% non-compliance to Zoladex, this sample size will provide power of approximately .76 for this comparison as well.

13.2.3 Projection
The study has accrued 460 cases as of 3/27/90, and accrual per month has been 18.5 in the last 6 months. In order to add 471 more cases and reach the revised requirement of 931, the study should remain open until May, 1992.

13.3 Frequency of Reports
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 Projections for completion of accrual phase, based on patient accrual rates observed during the last year and/or for the whole family.
13.3.2 Patient accrual by institution.

13.3.3 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 with submitted treatment data. Cancelled and ineligible patients excluded from analysis are identified by their unique case number and reasons for their exclusion are generally provided.

13.3.4 Distribution of stratifying variables used in randomization and of other important prognostic variables for each assigned treatment regimen. 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% and 75% of the required sample size has been obtained.

A “final” analysis of initial treatment results will be performed shortly after the closure of the study with consideration of reporting results if they are significant at the .005 level. Otherwise results will be reported at the end of the planned follow-up period using a significance level of .046.

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 Group Chairman of the RTOG and the Group Statistician of the RTOG. The 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 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

If an experimental arm shows a highly significant improvement over the standard arm (p < .003 at the first interim response report and p < .004 at the second interim response report), recommendation will be made to drop the standard arm. These p-levels are selected in order to preserve an overall significance level of .05.

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

14.0 ADDITIONAL THERAPY

Therapy is to be administered as detailed in Sections 6.0 and 7.0. Subsequent therapy shall proceed at the discretion of the patient’s responsible physician. Indications for subsequent therapy and the therapy performed should be documented in the patient’s follow-up records.
REFERENCES


APPENDIX I

RTOG 85-31

PHASE III RANDOMIZED STUDY OF ZOLADEX ADJUVANT TO RADIOTHERAPY

I, ____________________________, willingly agree to participate in this study which has been explained to me by Dr. ____________________________. This research study is being conducted by the Radiation Therapy Oncology Group and by ____________________________.

PURPOSE OF THE STUDY

It has been explained to me that I have cancer of the prostate. My doctor feels that my participation in this study may be helpful. This study involves evaluation of an agent Zoladex used after a course of radiotherapy. The purpose of this study is to determine whether the regimen is likely to improve the probability of tumor control and to confirm the reported lack of serious toxicity for Zoladex.

DESCRIPTION OF PROCEDURES

This study involves assigning patients to receive either radiation therapy immediately followed by a course of Zoladex or receive radiation therapy and then receive the Zoladex if my tumor should relapse. Zoladex is given monthly (every 28 days) on a permanent basis (indefinitely).

It is not clear at the present time which of the two therapies is better. For this reason, the option which is to be offered to me will be based upon chance using a method of random selection called randomization. Randomization means that my physician will call a statistical office which will assign one of the options to me, and that the chances of my receiving any one of the two offered therapies are approximately equal.

The Division of Cancer Treatment, National Cancer Institute will provide me with the agent Zoladex free of charge for this study. Should this agent become commercially available during the course of the study, however, I may be asked to purchase subsequent doses of the medicine (added 9/9/91).

RISKS AND DISCOMFORTS (Amended 9/8/87, 1/22/88, 6/12/89, 4/27/90, 7/13/90, 12/21/90).

The drug 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.

An increased incidence of benign pituitary adenomas has been seen in rats receiving large doses of Zoladex for one year; in addition, other manufacturers have reported the appearance of pancreatic islet adenomas, ovarian adenomas, adrenal gland adenomas in rats receiving large doses of LHRH analogs for two years. There is no evidence to date however, that LHRH analogs such as Zoladex are associated with benign or malignant tumors in humans.

The following have been reported as possible reactions to Zoladex: acute kidney failure, mental confusion, generalized skin rash, spasms of the windpipe, vasculitis (inflammation of the tissue beneath the skin), lung clots, myopathy (muscle weakness), and cough or breathlessness.

Zoladex may produce irritation at the site of the injection and hot flashes and is likely to cause impotence. Any symptoms due directly to prostate cancer may be temporarily aggravated during the first few days of Zoladex therapy.

Side effects of radiotherapy are temporary fatigue, 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 which may cause pain, bleeding, bowel obstruction etc. any may require further medical or surgical management.

My physician will be checking closely to see if any of these side 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 caused by the study treatment.
CONTACT PERSONS

In the event that injury occurs as a result of this research, treatment for injury will be available. I understand, however, I will not automatically be provided with reimbursement for medical care or receive other compensation. For more information concerning the research and research-related injuries, I can notify Dr. ________________, the investigator in charge 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. Possible benefits include an increased probability of tumor clearance and control. 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 the use of radiotherapy alone. 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 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, if any related solely to research which would otherwise be necessary. These will be explained to me by my physician. Some of these procedures may result in added costs and some of these costs may not 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 record of my progress while on the study will be kept in a confidential form at ________________ and also in a computer file at Headquarters of the Radiation Therapy Oncology Group. 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) and Stuart Pharmaceuticals 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 slides, may be sent to a central office for review.

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          Date

Witness Signature          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

Staging of Carcinoma of the Prostate

Numerous staging systems for carcinoma of the prostate have been proposed. The so-called American Urological Staging System (developed after Whitmore and Jewett) has not been defined formally, but is utilized widely.

American Urological Staging System

Stage A – Latent incidentally detected tumor in operative specimen
  A1 – Focal, well-differentiated carcinoma
  A2 – Diffuse, multifocal and/or high-grade carcinoma

Stage B – Tumor confined within prostate
  B1 – Solitary nodule occupying ≤ 1.5 cm.
  B2 – Tumor occupying > 1.5 cm or multifocal tumor

Stage C – Tumor extending beyond the prostate, invading periprostatic tissues, seminal vesicles, bladder or rectum

Stage D – Carcinoma of the prostate with demonstrable metastases
  D1 – Metastatic spread limited to pelvic lymph nodes
  D2 – Tumor metastatic to distant sites of lymph nodded outside the pelvis.

* * * * *

For Protocol 85-31

For the purpose of this protocol, the patients will be labeled as clinical Stage A, B or C with or without evidence of lymph node involvement, Stage D1 designation will not be used (see explanatory notes below).

Explanatory Notes

Assessment of tumor extent and assignment of stage can be:

1. Clinical – Clinical staging in carcinoma of the prostate as a minimum involves:
   a) Physical (rectal) examination, aimed at determination of size and extent of the primary
   b) Standard radiographic evaluation including bone scan and/or bone survey, aimed at exclusion of distant metastases
   c) Clinical assessment of the tumor extent and assignment of stage will be based on results from the physical (rectal) examination, cystoscopy (if done) and proctoscopy (if done), aimed at determination of size and extent of the primary.

2. Clinical with radiographic evaluation of regional lymphatics (by lymphangiogram or computerized tomography)

3. Pathological (Surgical) – Pathological staging usually refers to histological evaluation of regional (pelvic) lymphatics. In patients undergoing prostatectomy, the primary lesion can also be staged pathologically, e.g., a clinical Stage B tumor becomes surgical (pathological) Stage C if there is histological evidence of penetration through the capsule.

Stage D1 is defined either radiographically or pathologically, a tumor classified as Stage A, B or C clinically is, if there is radiographic or histological evidence of pelvic lymph node involvement, reclassified as Stage D1, or alternatively, labeled as (clinical) Stage A, B, or C with pelvic lymph node involvement.
## APPENDIX IV

### GLEASON CLASSIFICATION

Histologic patterns of adenocarcinoma of the prostate

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Margins 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 rounded 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>or 3</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>or 5</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)

### APPENDIX V

**TOXICITY CRITERIA FOR RTOG 85-31**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Minor symptoms requiring no treatment.</td>
</tr>
<tr>
<td>2</td>
<td>Symptoms responding to simple out-patient management, life style (performance status) not affected.</td>
</tr>
<tr>
<td>3</td>
<td>Distressing symptoms altering patient’s life style (performance status), hospitalization for diagnosis or surgical intervention.</td>
</tr>
<tr>
<td>4</td>
<td>Major surgical intervention (such as laparotomy, colostomy, cystectomy) or prolonged hospitalization are required.</td>
</tr>
<tr>
<td>5</td>
<td>Fatal complications.</td>
</tr>
</tbody>
</table>