RADIATION THERAPY ONCOLOGY GROUP

RTOG 99-02

A PHASE III PROTOCOL OF ANDROGEN SUPPRESSION (AS) AND RADIATION THERAPY (RT) VS AS AND RT FOLLOWED BY CHEMOTHERAPY WITH PACLITAXEL, ESTRAMUSTINE, AND ETOPOSIDE (TEE) FOR LOCALIZED, HIGH-RISK, PROSTATE CANCER

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**CTSU (R99-02)**

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This protocol was designed and developed by the Radiation Therapy Oncology Group (RTOG) of the American College of Radiology (ACR). It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by RTOG nor does RTOG assume any responsibility for unauthorized use of this protocol.
This study is supported by the NCI Cancer Trials Support Unit (CTSU) [1/31/07]

Institutions not aligned with the RTOG will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix.

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at http://members.ctsu.org

- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.

- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.

- Data management will be performed by the RTOG. **Case report forms** (with the exception of patient enrollment forms), **clinical reports, and transmittals** must be sent to RTOG Headquarters unless otherwise directed by the protocol. Do not send study data or case report forms to CTSU Data Operations.

- **Data query and delinquency reports** will be sent directly to the enrolling site by the RTOG. Please send query responses and delinquent data to the RTOG and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and RTOG Headquarters.
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RADIATION THERAPY ONCOLOGY GROUP
RTOG 99-02

A PHASE III PROTOCOL OF ANDROGEN SUPPRESSION (AS) AND RADIATION THERAPY (RT) VS AS AND RT FOLLOWED BY CHEMOTHERAPY WITH PACLITAXEL, ESTRAMUSTINE, AND ETOPOSIDE (TEE) FOR LOCALIZED, HIGH-RISK, PROSTATE CANCER

SCHEMA (11/16/01, 6/3/02, 3/16/04)

S   R  Arm 1
T   PSA   A  AS (LHRH agonist and Casodex or Eulexin) x 8 weeks followed by RT
     1. ≤ 10 Androgen suppression will continue for a total of 24 months from initiation
     R  2. >10 to ≤ 100 N of all treatment. Oral antiandrogen will be discontinued at the end of RT.

A Tumor Stage  D  Arm 2
T 1. T1-2  AS (LHRH agonist and Casodex or Eulexin) x 8 weeks followed by RT
     2. T3-4  to 70.2 Gy with concurrent AS (LHRH agonist and Casodex or Eulexin).
     I 1. 7  Androgen suppression will continue for a total of 24 months from initiation
     M 2. 8-10  plus
     A Four cycles of TEE chemotherapy will be delivered concurrently with androgen suppression beginning 28 days after completion of RT:
     Y 1. No  Oral Emcyt 280 mg t.i.d. x 14 days q 21 days
     2. Yes  Oral VP-16, 50 mg/m2* in divided doses b.i.d x 14 days q 21 days
         and
         Taxol 135 mg/m2 i.v. over 1 hour (on day 2 of each cycle) q 21 days. Premedication for Taxol with corticosteroids and H2 blocks is required
         and
         Coumadin® (warfarin) to keep INR > 1.5 and < 2.5. Coumadin® will begin with the start of chemotherapy and will be given continuously until 4 weeks after the end of the fourth cycle of chemotherapy.
         * Patients with a creatinine clearance between 15-50 mL/min will have their etoposide dose decreased by 25%. This will equal a dosing of 50 mg etoposide b.i.d. alternating with 50 mg etoposide qd.

Eligibility:  (See Section 3.0 for details)
- Histologically-confirmed prostate cancer with either PSA 20-100 and GS ≥ 7 (any T stage)
  or clinical stage ≥ T2 and GS ≥ 8 (PSA ≤ 100) (M0).
- Clinically negative lymph nodes as established by imaging (pelvic CT, MR, or LAG), or pathologically negative by LN sampling or dissection.
- Gleason score classification.
- Performance Status 0-1.
- ALT must be within 2 X upper normal limits.
- WBC ≥ 3000, Platelets ≥ 130,000, Hemoglobin ≥ 11.4g/dl, Creatinine ≤ 2.5 mg/dl. Creatinine clearance must be ≥ 15 ml/min.
- Treatment must begin within 6 weeks after randomization.
- No prior radical prostatectomy or cryosurgery for prostate cancer.
- No prior pelvic RT or orchiectomy.
- Prior hormones are allowed if started no more than 30 days before randomization.
- No previous or concurrent invasive cancers other than superficial non-melanomatous skin cancers unless disease free for at least five years.
- No previous chemotherapy for malignancy within five years.
- Signed study-specific informed consent prior to randomization.
- No prior history of thromboembolic events or contraindications to Coumadin® (warfarin) therapy.

Required Sample Size: 1440
RTOG Institution # ________
RTOG 99-02
RTOG Case # ________

**ELIGIBILITY CHECK (11/16/01, 6/3/02)**
(page 1 of 2)

_______(Y) 1. Is there histologically confirmed prostate cancer?

_______(Y/N) 2. Is PSA 20-100 and Gleason score ≥ 7 (any T-stage)?

_______(Y) If no, is clinical stage ≥ T2 and Gleason score ≥ 8 (PSA ≤ 100)?

_______(Y) 3. Is patient M0?

_______(Y) 4. Have clinically negative lymph nodes been established by imaging (pelvic CT, MR, or LAG) or pathologically negative by sampling or dissection?

_______(Y) 5. Has the study entry PSA been done prior to randomization and prior to start of any hormone therapy?

_______(Y) 6. Is Zubrod performance status 0-1?

_______(Y) 7. Are lab values as defined in 3.1.6 and 3.1.7?

_______(Y) 8. Was a medical oncology consultation done?

_______(N) 9. Has the patient had a prior radical prostatectomy or cryosurgery for prostate cancer?

_______(N) 10. Was there prior pelvic RT or orchiectomy?

_______(Y/N) 11. Has the patient received hormones for prostate cancer?

_______(Y) If yes, have they been started no more than 30 days before randomization?

_______(N) 12. Any prior or concurrent malignancy other than superficial non-melanomatous skin cancer unless disease free for at least 5 years?

_______(N) 13. Has there been previous chemotherapy for malignancy within last 5 years?

_______(N) 14. Has the patient had prior finasteride (< 60 days) and/or testosterone (< 90 days) before randomization?

_______(N) 15. Does patient have any major medical or psychiatric illness which would prevent completion of treatment and would interfere with follow-up?

_______(N) 16. Does the patient have any history of thromboembolic events or contraindications to Coumadin® use as per Sections 3.2.9 and 3.2.10 of the protocol?

The following questions will be asked at Study Registration:

___________ 1. Name of institutional person registering this case?

___________(Y) 2. Has the Eligibility Checklist (above) been completed?

___________(Y) 3. Is the patient eligible for this study?  

(con’t on next page)
4. Date the study-specific Consent Form was signed? (must be prior to study entry)

5. Patient’s Name

6. Verifying Physician

7. Patient’s ID Number

8. Date of Birth

9. Race

10. Social Security Number

11. Patient’s Country of Residence

12. Zip Code

13. Patient’s Insurance Status

14. Will any component of the patient’s care be given at a military or VA facility?

15. Medical Oncologist’s Name

16. PSA Value ($\leq 10$ vs. $>10$ to $100$)

17. T Stage ($T1-2$ vs. $T3-4$)

18. Combined Gleason ($7$ vs. $8-10$)

19. Prior Hormones ($no$ vs. $yes$)

20. Hormone Start Date, if yes ($must$ be $<30$ days before randomization)

21. Proposed RT Start Date ($See$ Section 6.1)

22. Date of Randomization

23. Treatment Assignment

The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by  ________________________________  Date  ________________________________
1.0 INTRODUCTION

Prostate cancer is an increasingly common cause of cancer morbidity and mortality in the United States. In 1998, there will be an estimated 184,500 new cases of prostate cancer and 39,200 prostate cancer deaths in the US. As prostate cancer becomes more commonly diagnosed in this country, there has been increasing awareness of the clinical heterogeneity of the disease. Some patients present with metastatic disease, while there are subsets of patients whose disease is quite indolent and may be observed. Other subsets of patients may be treated with curative local therapies, such as radical prostatectomy, external beam radiation therapy, or interstitial radiotherapy.

In recent years, attention has been directed at identifying and defining subsets of patients who would benefit from adjuvant systemic treatment in addition to local therapy. RTOG 86-10 demonstrated an improvement in local control and progression free survival (but not overall survival) in patients with large (>25 cc) prostate tumors, for patients treated with RT + goserelin vs. RT alone. RTOG 85-31 examined adjuvant goserelin (Zoladex) in a group of patients estimated to be at high risk for failure for prostate cancer. In this trial, patients were randomized to adjuvant goserelin prior to radiation therapy versus radiotherapy alone with goserelin at relapse. There is statistically significant improvement in local recurrence, in metastasis, and disease-free survival in the patients who received adjuvant goserelin. There was a five year survival advantage (66% versus 55%) for the patients with Gleason score of 8-10 (P=.03). In a European randomized study, Bolla et al. demonstrated a local control and survival benefit to 3 years of androgen suppression plus RT vs. RT alone.

The results of these and similar studies have resulted in enthusiasm and further testing of androgen suppression in adjunct to radiotherapy. The exact combination of hormonal agents, sequencing of hormonal therapy with radiation therapy, radiation therapy field sizes, appropriate subsets of patients in whom hormonal therapy will be acceptable, and duration of hormonal therapy continue to be subjects of active investigations (RTOG 92-02, 94-08, 94-13). RTOG 92-02 which completed accrual of over 1500 patients in 1995, randomized patients to a four month course of total androgen suppression (Zoladex + Flutamide) given for 2 months prior to and then concurrently with RT (70.2 Gy) vs. four months of TAS + RT followed by androgen suppression with Zoladex alone for 2 years. The standard arm of this trial is similar to the experimental arm of that trial, based in part on the results of Bolla et al., which noted a survival advantage to prolonged androgen suppression. The regimen of TAS has been associated with mild anemia, and the addition of flutamide to the anti-androgen regimen has been noted to be associated with some hepatotoxicity. Closer monitoring of LFTs has been performed in subsequent trials (e.g. RTOG 94-08, RTOG 94-13). In RTOG 94-13, which is due to complete accrual in 1999, patients with intermediate to high risk prostate cancer are all treated with 4 months of TAS + RT (70.2 Gy), with a double randomization: half of the patients are treated with TAS prior to and concurrent with RT, and half with TAS after RT. In addition, half of the patients are treated to a pelvic field with a prostate boost volume, and half are treated to a small volume for the entire course of treatment. These trials should help to answer questions regarding the optimal nature, duration, and sequence of anti-androgen therapy for prostate cancer, however, there is a realization, based on multiple studies of prognostic factors in prostate cancer (vide infra) that there are subsets of patients who remain at high risk of failure and who may benefit from more aggressive treatment approaches, including cytotoxic chemotherapy.

There are high-risk subsets of prostate cancer patients with poor prognosis that can be identified for treatment failure after radiation therapy. In an analysis of 500 patients treated with RT alone for clinically localized prostate cancer, Pisansky et al. noted that the factors of clinical tumor stage, Gleason Score, and pre-treatment PSA level were all independently associated with clinical or biochemical relapse risks. Using these factors they were able to separate patients into low, intermediate, and high risk groups, with distinct relapse-free probabilities at 5 years after RT (92%, 67% and 24%, respectively; p<0.0001). The patients who would be eligible for this protocol would have similar pre-treatment prognostic factors to those in the high-risk group identified by Pisansky et al.

Other investigators at multiple other institutions have noted similar findings. A study by Horwitz et al. examined a series of 470 patients treated with RT and found that, by multivariate analysis, pretreatment PSA > 20 and Gleason Score of 7 or higher were adverse prognostic factors when biochemical control was used as an endpoint. Hanks et al. noted similar findings in a cohort of 456 consecutive patients treated with conformal RT; PSA, Clinical T-Stage, and Gleason Score were all independent prognostic factors by multivariate analysis. 5-year bNED rate for patients with pre-treatment PSA was only 28%, as opposed to a 5-year bNED rate of 61% for the entire cohort. Other series which have presented 5 year biochemical control rates for prostate cancer with PSA >20 include: Kuban et
al., bNED rate 20%;9 Zagars et al., bNED rate 38%;10 Sandler et al., bNed rate 20%,11 and Zelefsky et al., bNED rate 37%.12

Although treatment techniques, patient populations, and definitions of biochemical control may have varied between different institutions, there are remarkable consistencies in the findings that patients with elevated PSA at presentation, high Gleason Scores, and advanced T-Stage have relatively poor prognosis when compared with other patients. We believe that the results obtained with conventional treatment for these patients are sufficiently poor to justify the exploration of more aggressive approaches for these patients in an attempt to improve therapeutic results. Because of the importance of pre-treatment prognostic factors in predicting for outcome in studies of prostate cancer patients, we believe that a randomized, controlled, phase III study is the best way to determine if cytotoxic chemotherapy will add to the control rates which can be obtained with RT + androgen suppression alone.

Until recently, the role of cytotoxic chemotherapy in prostate cancer has been limited to the treatment of patients with advanced disease refractory to treatment with androgen suppression.13,14 However, clinical experience from other disease sites suggests that chemotherapy may be more effective if used earlier in the course of disease. When used in the adjuvant setting, the tumor burden may be lower and there is less chance for malignant cells to develop resistance to therapeutic agents. Chemotherapy may also be able to target hormonally resistant cells, complementing the ability of androgen suppression to target hormonally sensitive cells.

We propose an investigational study to see if cytotoxic chemotherapy with paclitaxel, etoposide, and estramustine, in addition to androgen suppression plus radiotherapy may result in improved control and survival rates over those obtained with androgen suppression plus radiotherapy. Paclitaxel (Taxol), a diterpene antineoplastic agent, targets tubulin to stabilize microtubules, and has also been shown to have a marked cytotoxic effect on prostatic cancer cells in vitro.15 A synergistic effect has been demonstrated with the combination of paclitaxel and estramustine using estramustine-resistant and sensitive, wild-type human prostatic carcinoma cell lines.16

Oral etoposide (VP-16) is from a family of antineoplastic agents, which inhibit DNA replication. These agents, such as amsacrine, teniposide, and etoposide, work selectively at the nuclear matrix. Specifically, etoposide is thought to interact with the topoisomerase II - DNA complex and cause DNA strand breakage.17,18,19

Estramustine phosphate (EMP), an agent which combines estradiol with nitrogen mustard, has been shown to have activity against prostate cancer cells which is independent of its hormone moiety and its alkylating moiety.20,21,22,23 EMP is preferentially taken up by prostate epithelial cells and binds at the nuclear matrix.24,25 The significance of this interaction is unknown, however, it is thought that EMP may bind to the nuclear matrix and act as a physical block to the DNA replication process.

Hudes et al. have evaluated the two drug combination of paclitaxel and oral estramustine in metastatic hormone refractory prostate cancer, and noted a >50 % PSA response in 17/32 (53%) of patients.26 Pienta et al. performed a phase II trial of the two drug combination of oral estramustine and oral etoposide and noted that 54% of patients had a >50% PSA response.27

The TEE three drug combination has been evaluated in patients with hormone refractory prostate cancer by Pienta et al. In vitro data demonstrated that the three drug combination significantly inhibited cell growth as compared with any of the single or dual drug combinations. In vivo data, using rats injected with Dunning rat prostate adenocarcinoma MLL cells, showed that the TEE combination inhibited tumor growth 90% when compared with controls. Preliminary results in phase II clinical trials in patients with hormone refractory disease demonstrated good response rates, with 57% of patients responding to therapy as measured by a > than 50% decrease in pre-treatment PSA levels. The regimen was generally well tolerated. All patients had alopecia; neutropenia was the other predominant toxicity, with 10% of patients having grade 3 neutropenia, and another 10% having grade 4 neutropenia.28,29 The 50% reduction in PSA levels measured has been shown to correlate with measurable disease response and increased survival in studies using the two drug combination of estramustine and etoposide in patients with hormone-refractory prostate cancer.30
Prostate cancers are heterogeneous collection of cells. Combination therapy with TEE may help to kill hormone refractory prostate cancer cells early in the course of therapy. Treatment with hormonal agents, such as total androgen suppression may kill hormone sensitive cells or make them sensitive to radiation induced killing during the course of external beam radiation therapy. There are numerous examples in oncology literature where agents which are found to have limited activity as single agents in advanced disease are found to have significant activity when used early in the course of therapy before treatment resistant clonogens are selected out or induced by previous cytotoxic therapy.

The potential for increased toxicity with chemotherapy and radiation are of concern. Myelotoxicity is the major potentially life-threatening toxicity associated with the TEE chemotherapy. However, we believe that by keeping the radiation therapy treatment volume smaller than was standard in previous RTOG trials for high-risk prostate cancer, and by treating patients sequentially, with chemotherapy to follow RT rather than concurrently, that these interactions can be limited. However, the potential for added toxicity, hematologic and otherwise, will need to be carefully monitored, especially in view of the mild anemia, which can be produced by androgen suppression.

Radiation therapy field sizes and doses will follow from previous RTOG trials. The total dose to the prostate will be 70.2 Gy, the same dose used in RTOG 92-02 and 94-13. Higher doses have been used in RTOG 94-06, but that trial is a conformal trial, with treatment volumes limited to the prostate, SVs, and immediately surrounding tissues only. Furthermore, it is a trial with limited institutional participation, with special institutional credentialing required. The patients to be enrolled in this study will have a significant risk of lymph node involvement, so we do not believe that treatment of the prostate alone is indicated. In this situation, where conformal technique will not be used for the entire course of treatment (although it is strongly recommended for the boost volume), and where there is the potential for chemotherapy to add to the morbidity associated with external beam radiation, we do not feel comfortable using a higher RT dose than had been used in previous randomized RTOG trials in which pelvic lymph nodes have been treated electively. However, we believe it is prudent to reduce the nodal treatment volumes to include only the first echelon lymph nodes (obturator, and internal and external iliac LN lying below the SI joints). The upper borders of the pelvic fields will be at the bottom of the SI joints in this study, rather than at the L5-SI interspace, so that a significant amount of pelvic bone marrow will be spared, and the volume of bowel treated will be reduced. RTOG 94-13 is currently accruing patients to address the question as to the importance of pelvic lymph node RT in prostate cancer, but results of this investigation are not expected to be available for several years.

Because of an increased incidence of deep venous thrombosis observed early in this study (23%), the protocol has been modified to intensify the anticoagulation employed in the chemotherapy arm. Rather than use 1 mg per day of Coumadin® (warfarin) as prophylaxis only during the delivery of estramustine, the Coumadin® will be adjusted to keep the INR > 1.5 and < 2.5 continuously during the 12 weeks of chemotherapy and for 4 weeks after the chemotherapy is completed. This change was made after discussion with the RTOG Data Monitoring Committee and with the approval of that committee. (6/3/02)

2.0 OBJECTIVES
2.1 To assess the relative efficacy of the combination of androgen suppression + RT followed by androgen suppression vs. AS + RT followed by TEE chemotherapy + androgen suppression in a population of patients with clinically-localized prostate cancer with unfavorable prognostic factors. The primary endpoint will be survival, but biochemical control (freedom from PSA failure), local control, disease free survival, and freedom from distant metastasis will also be assessed.

2.2 To assess the differences in toxicity between the two treatment arms.

3.0 PATIENT SELECTION
3.1 Conditions for Patient Eligibility (11/16/01)
3.1.1 Patients will have histologically-confirmed prostate cancer at high-risk for relapse as determined by either:
   - PSA 20-100 and Gleason score ≥ 7 (any T Stage) or
   - Clinical stage ≥ T2 (Appendix III) and Gleason score ≥ 8 (PSA ≤ 100).

3.1.2 Patients will have clinically negative lymph nodes (LN) as established by imaging (pelvic CT, MR or LAG). Patients with imaging positive LN should be confirmed by biopsy. LN which are equivocal or questionable by imaging will be permitted entry at the investigator’s discretion if LN are ≤ 1.5 cm in
size. Patients who have negative LN status by lymph node sampling or LN dissection will be eligible. Patients with + LN by capromab pendetide (ProstaScint) scans will be eligible unless a corresponding LN > 1.5 cm can be identified by CT, MR, or LAG imaging, in which case they will be ineligible.

3.1.3 Gleason Score classification is mandatory prior to randomization.
3.1.4 Pre-treatment serum PSA is mandatory prior to randomization and must be obtained prior to any hormone therapy.
3.1.5 Zubrod Performance Status 0-1 (Appendix II).
3.1.6 ALT must be within 2 X upper normal limits.
3.1.7 Hematologic parameters must be within the following limits:
3.1.7.1 WBC ≥ 3000
3.1.7.2 Plt ≥ 130,000
3.1.7.3 Hgb ≥ 11.4 g/dl
3.1.7.4 Creatinine ≤ 2.5 mg/dl and creatinine clearance ≥ 15ml/min (Cockroft-Gault formula).
3.1.8 Medical Oncology consultation prior to randomization.
3.1.9 Treatment must begin within 6 weeks after randomization.
3.1.10 Prior finasteride for prostatic hypertrophy is allowed if discontinued at least 60 days prior to randomization.
3.1.11 Prior testosterone administration is allowed if last administered at least 90 days prior to randomization.
3.1.12 Prior pharmacologic androgen ablation for prostate cancer will be allowed only if the onset of androgen ablation is ≤ 30 days prior to the date of randomization. At the time of study entry, the patient must be converted to protocol-specified androgen ablation.
3.1.13 Patients must sign a study-specific informed consent form prior to randomization.

3.2 Conditions for Patient Ineligibility (11/16/01, 6/3/02)
3.2.1 Patients with PSA >100.
3.2.2 Evidence of M1 metastatic disease.
3.2.3 Pathologically positive lymph nodes.
3.2.4 Prior radical prostatectomy, cryosurgery for prostate cancer
3.2.5 Prior pelvic RT or orchietomy.
3.2.6 Previous chemotherapy for malignancy within the last 5 years.
3.2.7 Previous or concurrent invasive cancers other than superficial non-melanomatous skin cancers unless disease-free for at least 5 years.
3.2.8 Major medical or psychiatric illness which, in the investigators opinion, would prevent completion of treatment and would interfere with follow-up.
3.2.9 History of thromboembolic events (deep venous thrombosis, symptomatic cerebrovascular events, or pulmonary embolism).
3.2.10 History of bleeding disorders that would contraindicate Coumadin® (warfarin) including esophageal varices and clotting factor defects.

4.0 PRETREATMENT EVALUATION (11/16/01)
4.1 History and Physical examination (to include tumor measurements) and Zubrod Performance Status, Height and Weight
4.2 Histologic evaluation. Gleason Score is mandatory.
4.3 Mandatory laboratory studies (obtained within 8 weeks prior to randomization): CBC with platelets, PSA, bilirubin, ALT, alkaline phosphatase, BUN, creatinine, testosterone.
4.4 Bone scan within 3 months prior to randomization.
4.5 Pelvic lymph node assessment (within 3 months prior to randomization) by one of the following procedures: pelvic CT, pelvic MR, lymphangiogram, or pelvic lymph node dissection or sampling procedure (either via laparotomy or laparoscopically)

5.0 REGISTRATION PROCEDURES (9/28/01, 8/22/03)
5.1 Study Requirement
Each institution must submit a Study Agent Shipment Form (Appendix VI) to the CTSU Regulatory Office (215-579-0206) as soon as the individual responsible for the study agent has been identified. This must be done prior to registration of the institution’s first case. Canadian Institutions must submit the Study Agent Shipment Form and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300). Allow adequate processing time (7-10 days) before calling to register your first case.
5.2 RTOG Institutions

Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated Checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/RTOG audit.

5.3 CTSU Logistics (1/31/07)

5.3.1 ADDRESS AND CONTACT INFORMATION FOR RTOG-99-02

<table>
<thead>
<tr>
<th>To submit site registration documents:</th>
<th>For patient enrollments:</th>
<th>Submit study data directly to the RTOG unless otherwise specified in the protocol:</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTSU Regulatory Office</td>
<td>CTSU Patient Registration</td>
<td>RTOG Headquarters</td>
</tr>
<tr>
<td>1818 Market Street, Suite 1100</td>
<td>Voice Mail – 1-888-462-3009</td>
<td>1818 Market Street, Suite 1600</td>
</tr>
<tr>
<td>Philadelphia, PA 19103</td>
<td>Fax – 1-888-691-8039</td>
<td>Philadelphia, PA 19103</td>
</tr>
<tr>
<td>Phone - 1-888-823-5923</td>
<td>Hours: 8:00 AM – 8:00 PM Eastern Time, Monday – Friday (excluding holidays)</td>
<td>Please do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.</td>
</tr>
<tr>
<td>Fax – 215-569-0206</td>
<td>[For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301-704-2376. Please use the 1-888-462-3009 number for ALL other CTSU patient enrollments.]</td>
<td></td>
</tr>
</tbody>
</table>

For patient eligibility questions: Contact the RTOG Research Associate for Protocol, Data Management section at 215-574-3214.

For treatment-related questions: Correspond by e-mail (preferred) or by phone with the study chair designated on the protocol cover page.

For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail:

CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

The CTSU Public Web site is located at: www.ctsu.org

The CTSU Registered Member Web site is located at: http://members.ctsu.org

5.3.2 Registration/Randomization, CTSU Investigators:

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

Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol before they can enroll patients. Note that, for this protocol, each CTSU investigative site must complete a Study Agent Shipment Form (Appendix VI of protocol) and submit it to the CTSU Regulatory Office in Philadelphia along with other site registration documents prior to
registration of their first patient case. The Study Agent Shipment Form can be found under the site registration materials section of the protocol web page. Please allow adequate processing time (at least 10 days) before calling to register your first case.

Patients can be registered only after pre-treatment evaluation (Section 4.0 of protocol) is complete, all pertinent documents are approved and on file with the CTSU, and all eligibility criteria are met. All forms and documents associated with this study can be downloaded from the RTOG-99-02 Web page on the CTSU registered member Web site (http://members.ctsu.org).

Requirements for RTOG-99-02 site registration:
• CTSU IRB Certification
• IRB/Regulatory Approval Transmittal Sheet
• IRB-approved consent form
• Radiation Therapy Facility Inventory Form
  NOTE: Radiation therapy facilities must participate in the RPC monitoring program to participate in studies sponsored by the CTSU.
• Study Agent Shipment Form (Appendix VI of protocol)

CTSU Procedures for Patient Enrollment:
Contact the CTSU Patient Registration Office by calling 1-888-462-3009 to alert the CTSU Patient Registrar that an enrollment is forthcoming. Complete the following forms:
• CTSU Patient Enrollment Transmittal Form
• RTOG-99-02 Eligibility Checklist

Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 8:00 a.m. and 5:00 p.m. Eastern time, Mon-Fri. The CTSU registrar will verify that the investigator is CTSU credentialed, that the enrollment forms are complete, and that all regulatory and patient eligibility requirements have been met. The CTSU registrar will follow-up with the CTSU investigative site to resolve any discrepancies.

Once investigator eligibility is confirmed and enrollment documents are reviewed for completeness, the CTSU registrar will contact the RTOG to obtain a randomization assignment and assignment of a unique patient ID. The CTSU registrar will then contact the enrolling site and convey the patient ID number (to be used on all future forms and correspondence) and the patient’s treatment assignment. An RTOG-generated confirmation of registration e-mail will be forwarded by the CTSU to the enrolling site.

6.0 RADIATION THERAPY NOTE: INTENSITY MODULATED RT (IMRT) IS NOT ALLOWED (03/16/04)
6.1 Treatment Arms
Radiation therapy (RT) will be delivered identically to patients in both Arm 1 and Arm 2. Radiation will begin 8 weeks following the initiation of hormone administration: 46.8 Gy to the regional lymphatics followed by a 23.4 Gy boost to the prostate to bring the total dose to the prostate to 70.2 Gy. Daily tumor doses will be 1.8 Gy per day, 5 days per week x 7-8 weeks.

6.2 Physical Factors
Megavoltage equipment is required with photon energies of ≥ 6 MV (≥ 10 MV is preferred). The minimum source-to-axis (SAD) distance will be 100 cm. Any treatment technique (field arrangement) capable of producing the required dose distribution will be acceptable, with the following exceptions: (1) Perineal boost will not be permitted, and (2) AP/PA technique will not be permitted except for photon energies ≥ 24 MV photons. Typical field arrangements will be four-field technique for the regional lymphatic volume, and 4 or 6 field technique for the prostate boost volume.

6.3 Target Volumes
6.3.1 Regional Lymphatics Target Volumes
The superior border of the regional lymphatic volume will be at the bottom of the SI joints. Lateral borders will be at least 2 cm lateral to the pelvic brim. Inferior borders will be generally near the inferior border of the ischial tuberosity. If CT treatment planning is used, the border should be set at
least 2 cm below the most inferior aspect of the prostate. If a urethrogram is used, the border should be set at least 1.5 cm below the apex of the urethrogram.

6.3.1.2 In the lateral fields, care should be made to adequately cover the internal and external iliac lymph nodes below the SI joints and to include the posterior extension of the seminal vesicles.

6.3.1.3 The use of CT treatment planning may be of assistance in designing the regional nodal volumes, and is highly recommended for the design of the prostate boost volume.

6.3.2 Prostate Boost Target Volume
Optimal definition of the prostate boost volume is obtained with the use of CT treatment planning. The prostate boost volume should be designed to conform to the prostate volume, as determined by CT, with a 1.5 cm margin around the prostate gland. Seminal vesicles will be included in the boost volume only if the patient has seminal vesicle involvement (T3b). CT treatment planning and conformal technique is recommended. A representation of the prostate should appear on the simulation films.

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

6.4 Doses

6.4.1 For conventional (non-CT based) treatment planning: 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 nodal volume and the prostate treatment volumes.
For conformal treatment planning (highly recommended for boost volumes): the dose should be prescribed to the minimum target dose (i.e. to the highest isodose line, which encompasses the target volume).

6.4.2 Regional lymphatics will receive a dose of 46.8 Gy.

6.4.3 Prostate target volume will receive a boost of 23.4 Gy to bring the total dose to 70.2 Gy. If conformal technique is used as recommended, the treatment volume will include the prostate plus a 1.5 cm margin in all dimensions.

6.4.4 If seminal vesicles are clinically or radiographically involved with tumor (T3b disease, Appendix III), an intermediate dose boost to a dose of 55.8 Gy to a treatment volume including the prostate + SV + 1.5 cm margin should be used. CT treatment planned conformal technique is highly recommended.

6.5 Critical Normal Structures

6.5.1 The bladder will receive the same dose as the regional lymphatics. The base of the bladder will be included in the prostate boost target volume and will receive the same dose as the prostate. Every effort should be made to keep the bladder distended.

6.5.2 Doses to the entire rectum shall not exceed 55 Gy. Portions of the anterior rectal wall will, by necessity, receive the same dose as the prostate.

6.6 Radiation Toxicity

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

6.6.1.1 Skin reactions.
6.6.1.2 Small bowel or rectal irritation manifesting as abdominal cramping, diarrhea, rectal urgency, hematochezia.
6.6.1.3 Bladder complications including urinary frequency, dysuria, hematuria, urinary tract infections, and incontinence.
6.6.1.4 Acute morbidity will be scored using the revised NCI Common Toxicity Criteria Version 2.0. Late effects (> 90 days) will be scored per Appendix IV.

6.7 Compliance Criteria

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Per Protocol</th>
<th>Variation, Acceptable</th>
<th>Deviation, Unacceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Field Borders</td>
<td>up to 1 cm. beyond borders as stated in protocol</td>
<td>&gt; 1 to 2 cm beyond borders as stated in protocol</td>
<td>&gt; 2 cm beyond borders as stated in protocol</td>
</tr>
<tr>
<td>Total Dose</td>
<td>&lt; 5% of protocol specified dose</td>
<td>&gt; 5 to 10% of protocol specified dose</td>
<td>&gt; 10% of protocol specified dose</td>
</tr>
<tr>
<td>Fractionation</td>
<td>Within 0.05 Gy of</td>
<td>&gt; 0.05 Gy to 0.10 Gy</td>
<td>&gt; 0.10 Gy of 1.8 Gy</td>
</tr>
</tbody>
</table>
specify the fraction size of 1.8 Gy/day for 7-8 weeks, to a total dose of 70.2 Gy. For patients who have begun hormone therapy as specified in Section 3.1.12, time to RT (and the 24-month total androgen suppression) will be counted from the start date of first hormone administration. Patients randomized to Arm 2 will receive four cycles of TEE chemotherapy concurrently with AS beginning 28 days after the completion of radiation therapy:

<table>
<thead>
<tr>
<th>Elapsed Days During Radiotherapy</th>
<th>1 to 7 break days</th>
<th>8 to 14 days</th>
<th>&gt; 14 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRUG THERAPY</td>
<td>7.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.1 Treatment Plan (3/16/04)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 7.1.1 Schedule: All patients will receive androgen suppression (LHRH agonist and Casodex or Eulexin [AS]) for 4 months. Radiation therapy will begin eight weeks after the initiation of AS and will be given once a day (1.8 Gy/day), five days a week for 7-8 weeks, to a total dose of 70.2 Gy. For patients who have begun hormone therapy as specified in Section 3.1.12, time to RT (and the 24-month total androgen suppression) will be counted from the start date of first hormone administration. Patients randomized to Arm 2 will receive four cycles of TEE chemotherapy concurrently with AS beginning 28 days after the completion of radiation therapy:

Oral Emcyt 280 mg t.i.d. x 14 days q 21 days plus
Oral VP-16, 50 mg/m² in divided doses b.i.d. x 14 days q 21 days plus
Taxol 135 mg/m² i.v. over 1 hour (on day 2 of each cycle) q 21 days plus Coumadin® (warfarin) to keep INR > 1.5 and < 2.5. Coumadin® will begin with the start of chemotherapy and will be given continuously until 4 weeks after the end of the fourth cycle of chemotherapy. (6/3/02)

In order to minimize hypersensitivity reactions to Taxol, all patients should be premedicated with corticosteroids and H2 blockers.

7.1.2 Doses:

Oral Emcyt 280 mg three times per day x 14 days q 21 days. **
(Patients should take Emcyt with food but without high calcium containing foods or supplements one hour prior to or two hours after taking Emcyt. It is easiest to tell patients to take Emcyt with breakfast, lunch, and dinner.)
(Emcyt comes as 140 mg pills).

plus
Oral VP-16, 50 mg/m²/D x 14 days q 21 days
(In almost all patients this will be a 50 mg pill p.o. bid at breakfast and dinner)

plus
Coumadin® (warfarin) to keep INR > 1.5 and < 2.5

plus
Taxol 135 mg/m² i.v. over 1 hour day 2 q 21 days
(Premeds: Dexamethasone 20 mg i.v. 30 minutes prior to administration, Diphenhydramine 50 mg i.v. and Pepcid 20 mg or Ranitidine 50 mg or Cimetidine 300 mg i.v. 30 minutes prior to administration)

** Patients should be given a 15 day supply of Emcyt and VP-16 so that they can start the next cycle without having to come to the clinic.

Patients will be treated and followed on an ambulatory basis during treatment. CBC, platelets, and PT/INR should be done on days 8, 15, and day 22 (day 2 of the next cycle). When INR is stable and > 1.5 and < 2.5, PT/INR will be analyzed at least every 4 weeks. More frequent analysis may be considered at the discretion of the physician.

(6/3/02)

7.1.3 Dose Modification: (9/28/01)

7.1.3.1 Patients with a creatinine clearance between 15-50 ml/min will have their etoposide dose decreased by 25%. This will equal a dosing of 50 mg etoposide b.i.d. alternating with 50 mg etoposide qd.

7.1.3.2 There is no dose modification for Emcyt. Dose modifications are only done for blood counts and not for other potential toxicities such as fatigue, etc. Dosage modification for VP-16 is based on Day 22 (day 2) granulocyte and platelet count of the preceding cycle for the next and additional courses. Dose modification for paclitaxel is based on Day 22 (day 2) granulocyte and platelet count of the preceding cycle for the next and additional courses. VP-16 and Paclitaxel must not be administered until granulocyte count is > 1,500 cell/mm³ and platelet count ≥ 100,000. If counts are below these levels, recheck weekly and retreat using parameters outlined below. Dose modification is for the next cycle.
and all subsequent cycles. If a patient cannot be treated after holding therapy for 3 weeks, then therapy should be discontinued. (6/3/02)

Day 22 nadir: Granulocytes 1000-1499 and/or platelets 75,000 99,999

VP-16 is decreased to one tab qd alternating with one tab b.i.d.

Taxol dose is decreased by 25%

Granulocytes <1000 and/or platelets < 75,000

VP-16 dose is decreased to one tab p.o. qd

Taxol dose is decreased by 50%

7.1.3.3 If the patient suffers a confirmed thromboembolic event (e.g., DVT, PE, stroke, MI), all chemotherapy will be immediately discontinued. If the patient suffers a bleeding event that requires discontinuation of Coumadin® (warfarin), all chemotherapy will be immediately discontinued. (6/3/02)

7.2 LHRH agonists (such as leuprolide, goserelin, buserelin, triptorelin) (3/16/04)

7.2.1 Description
LHRH agonists are long acting analogs of the native LHRH peptide and are effective at reducing serum testosterone.

7.2.2 Supply
LHRH analogs are commercially available. Currently 4 have been approved by the FDA in the US and are considered similarly effective at reducing serum testosterone.

7.2.3 Storage
LHRH analogs should be stored as directed by the commercial supplier.

7.2.4 Administration
LHRH analogs are administered with a variety of techniques, including subcutaneous insertion of a solid plug in the abdominal wall (Zoladex), intramuscular injection (Lupron), subcutaneous injection (Eligard), or insertion of a long-acting cylinder that slowly releases the agent (Viadur). The manufacturer’s instructions should be followed.

7.2.5 Toxicity
Class related toxicity is generally a manifestation of the mechanism of action and due to low testosterone levels. In the majority of patients testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. The most common side effect of LHRH analogs is vasomotor hot flashes; edema, gynecomastia, bone pain, thrombosis, and GI disturbances have occurred.

Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in patients with vertebral metastases and/or urinary obstruction or hematuria which, if aggravated, may lead to neurological problems such as temporary weakness and/or paresthesia of the lower limbs or worsening of urinary symptoms.

7.4 Eulexin (flutamide)

7.4.1 Description
Flutamide is a substituted anilide. It is a fine, light, yellow powder, insoluble in water but soluble in common organic solvents such as aromatic or halogenated hydrocarbons. Its concentration in plasma can be determined by gas chromatography. Flutamide is a non-steroid anti-androgen that is metabolized into a hydroxylated derivative, which effectively competes with the hydrotestosterone for androgen receptor sites.

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

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

7.4.4 Administration
The drug is administered orally at a dose of two 125 mg capsules three times a day for a total daily dose of 750 mg (six capsules). Flutamide will begin 8 weeks prior to radiotherapy and continue throughout radiotherapy. Administration will be suspended only if there is an apparent or suspected reaction to the drug. See
Section 7.4.6. Flutamide will be terminated on the last day of radiotherapy or on day 112, whichever occurs first. During radiotherapy interruptions, flutamide will be continued.

7.4.5 Toxicity
The reported side effects of treatment include diarrhea and anemia. A high percentage of patients treated with flutamide alone developed gynecomastia within 2-8 months. There have been post-marketing reports of hospitalization, and, rarely, death due to liver failure in patients taking flutamide. Evidence of hepatic injury included elevated serum transaminase levels, jaundice, hepatic encephalopathy, and death related to acute hepatic failure. The hepatic injury was reversible after prompt discontinuation of therapy in some patients. Approximately half of the reported cases occurred within the initial 3 months of treatment with flutamide.

7.4.6 Dose Modification Schedule
If gastrointestinal disturbances (cramps, diarrhea) occur prior to initiation of radiotherapy, flutamide will be withheld until the side effects subside and then reintroduced at a dose of 250 mg/day increasing the dose (at 3 day intervals) to 500 mg/day then to 750 mg/day as tolerated. If gastrointestinal disturbances occur after administration of radiotherapy, it might be difficult to identify their cause. However, if severity of diarrhea exceeds the level commonly observed during pelvic irradiation, the toxicity will be ascribed to flutamide and the drug will be permanently discontinued.
ALT will be measured pretreatment, then monthly during oral antiandrogen therapy. If ALT increases $\geq 2 \times$ upper institutional limit of normal, flutamide must be discontinued. RTOG Headquarters must be notified.

7.5 Casodex (bicalutamide)

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

7.5.2 Supply
Casodex is commercially available as a 50 mg tablet.

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

7.5.4 Administration
Casodex is administered orally at a dose of one 50mg tablet per day. Casodex will begin 8 weeks prior to radiotherapy and continue throughout radiotherapy. Administration will be suspended only if there is an apparent or suspected reaction to the drug. See Section 7.5.6. Casodex will be terminated on the last day of radiotherapy or on day 112, whichever comes first. During radiotherapy interruptions, Casodex will be continued.

7.5.5 Toxicity
In animal experiments, birth defects (abnormal genitalia, hypospadias) were found in male offspring from female animals dosed with Casodex during pregnancy. Although offspring from male animals dosed with Casodex did not show any birth defects, patients enrolled in this trial are advised to neither cause pregnancy nor to donate sperm while receiving protocol therapy or during the first 3 months after cessation of therapy. The use of barrier contraceptives is advised.

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

7.5.6 Dose Modification Schedule
Casodex should be discontinued in instances of chemical liver toxicity. ALT will be measured pretreatment and then monthly during antiandrogen therapy. If the ALT rises $\geq 2 \times$ upper institutional limit of normal, Casodex must discontinued.

7.6 Emcyt (estramustine)

7.6.1 Description
Estramustine phosphate (EMCYT Estracyt), a nitrogen mustard derivative of estradiol-17-b-phosphate, has been studied in several randomized trials by the National Prostate Cancer Project (NPCP) and by the
European Organization for Research on the Treatment of Cancer (EORTC), both as a single agent or in combination with other agents. As initial therapy for advanced disease, an objective response was observed in approximately 80% of patients, a response rate similar to treatment with orchiectomy or estrogens. Treatment of hormone refractory patients with Emcyt appears to have an objective response rate of 0 to 37%. Emcyt in combination with standard chemotherapeutic agents produced similar results. The mechanism of action is unknown. It appears to have antineoplastic activity independent of its alkylating moiety. The initial half-life is approximately 24 hours. The oral formulation has a bioavailability of about 75%. Excretion is split between urine and bile for both the estradiol and nitrogen mustard moieties. Estramustine appears to act as a relatively weak alkylating agent and imports a weak estrogenic activity. The estrogenic portion of the molecule acts as a carrier to facilitate selective uptake of the drug into estrogen receptor-positive cells. Due to the selective steroidal uptake, the alkylating effect of the nitrogen mustard is enhanced in these cells. Estramustine will be given 280 mg t.i.d. Since the drug is supplied as 140 mg capsules, 280 mg t.i.d. is an easy regimen to follow and has been used in previous studies.29

7.6.2 Supply (9/28/01, 8/22/03)
Estramustine is available in 140 mg capsules and will be provided free-of-charge for this study and distributed by I.V. Solutions, Inc. The Study Agent Shipment Form (Appendix VI) must be submitted to the CTSU Regulatory Office (Fax 215-579-0206) as soon as the individual responsible for the study agent has been identified. Canadian Institutions must submit the Study Agent Shipment Form and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300). This must be done prior to registration of the institution’s first case. I.V. Solutions, Inc. will ship an eight-week (two bottle) non-patient-specific supply of Emcyt capsules timed for delivery approximately 8 weeks after the randomization of a patient assigned to Treatment Arm 2. Questions about supply, delivery, and returns should be directed to:

Gary F. Mead, R.Ph, MHA
I.V. Solutions, Inc.
162 North Main Street
Old Forge, PA 18518
(570) 457-9201
Fax (570) 457-0465

7.6.3 Storage
Capsules may be stored in the refrigerator at 2°-8°C and are stable for at least 12 months.

7.6.4 Administration
A total daily oral dose of 280 mg three times a day for 14 days and repeated every three weeks for four cycles.

7.6.5 Toxicity
The principal dose-limiting toxicity is gastrointestinal, with nausea and vomiting reported in approximately 25% of patients. Peripheral edema was demonstrated in 15% of patients. Breast tenderness was described by 70% of patients but was not considered to be dose limiting. Hematologic side effects, as manifested by leukopenia or thrombocytopenia, were reported in only 4% of patients. The maximally tolerated dose is 15 mg/kg/day. Deep venous thrombosis and other cardiovascular events have been noted with estramustine administration; early in this study, the occurrence of these events was approximately 23%. Therefore, continuous Coumadin® (warfarin) administration has been incorporated into this protocol regimen. (6/3/02)

7.6.6 Coumadin® (warfarin) (6/3/02)
7.6.6.1 Description
Coumadin® is an anticoagulant that acts by inhibiting Vitamin K-dependent coagulation factors. Chemically, it is 3-(2-acetonylbenzyl)-4-hydroxycoumarin and is a racemic mixture of the R and S enantiomers.

7.6.6.2 Supply
Coumadin® is commercially available. It is supplied as a sterile, lyophilized powder that is reconstituted with sterile water for injection: 5 mg; or as tablets for oral use in: 1 mg, 2 mg, 2.5 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, and 10 mg strengths.

7.6.6.3 Storage
Store at controlled room temperature (59°-86°F, 15°-30°C) and protect from light.
7.6.6.4 **Administration**

*Coumadin® will be administered to keep INR >1.5 and <2.5. Coumadin® will begin with the start of chemotherapy and will be given continuously until 4 weeks after the end of the fourth cycle of chemotherapy.* The exact dose schedule will be individualized by the treating physician with the goal of attaining the INR as specified above.

7.6.6.5 **Toxicity**

**Special Concerns:** Geriatric clients may be more sensitive to the effects of the drug. Anticoagulant use in patients with the following conditions leads to increased risk: trauma, infection, renal insufficiency, sprue, vitamin K deficiency, severe to moderate hypertension, polycythemia vera, severe allergic disorders, vasculitis, indwelling catheters, severe diabetes, anaphylactic disorders, surgery or trauma resulting in large exposed raw surfaces. Use with caution in patients with impaired hepatic and renal function. Safety and efficacy have not been determined in children less than 18 years of age. Careful monitoring and dosage regulation are required during dentistry and surgery.

**Side Effects:**

*CV:* Hemorrhage is the main side effect and may occur from any tissue or organ. Symptoms of hemorrhage include headache, paralysis, pain in the joints, abdomen, or chest; difficulty in breathing or swallowing; SOB, unexplained swelling or shock. *GI:* nausea, vomiting, diarrhea, sore mouth, mouth ulcers, anorexia, abdominal cramping, paralytic ileus, intestinal obstruction (due to intramural or submucosal hemorrhage). *Hepatic:* Hepatotoxicity, cholestatic jaundice. *Dermatologic:* Dermatitis, exfoliative dermatitis, urticaria, alopecia, necrosis or gangrene of the skin and other tissues (due to protein C deficiency). *Miscellaneous:* Pyrexia, red-orange urine, priapism, leukopenia, systemic cholesterol microembolization (“purple toes” syndrome), hypersensitivity reactions, compressive neuropathy secondary to hemorrhage adjacent to a nerve (rare).

**Laboratory Test Alterations:** False levels of serum theophylline determined by Schack and Waxler UV method (warfarin and dicumarol). Metabolites of indanedione derivatives may color alkaline urine red; color disappears upon acidification.

**Overdose Management:** Symptoms: Early symptoms include melena, petechiae, microscopic hematuria, ooze from superficial injuries (e.g., nicks from shaving, excessive bruising, bleeding from gums after teeth brushing), excessive menstrual bleeding. Treatment: Discontinue therapy. Administer oral or parenteral phytonadione (e.g., 2.5-10 mg p.o. or 5-25 mg parenterally). In emergency situations, 200-250 ml fresh frozen plasma or commercial factor IX complex should be given. Fresh whole blood may be needed in clients unresponsive to phytonadione.

7.6.6.6 **Drug Interactions**

Warfarin is responsible for more adverse drug interactions than any other group. Patients using anticoagulant therapy must be monitored carefully each time a drug is added or withdrawn. Monitoring usually involves determination of PT or INR. In general, a lengthened PT or INR means potentiation of the anticoagulant. Since potentiation may mean hemorrhages, a lengthened PT or INR warrants reduction of the dosage of the anticoagulant. However, the anticoagulant dosage must again be increased when the second drug is discontinued. A shortened PT or INR means inhibition of the anticoagulant and may require an increase in dosage.

7.7 **Etoposide (IND# 61, 009) (9/28/01)**

7.7.1 **Description**

Etoposide (VP-16, VePesid) is a semi-synthetic derivative of podophyllotoxin that is currently a standard component of most regimens for the treatment of germ cell tumors and small cell carcinoma of the lung. An oral formulation of this drug is now available. Approximately 50% of an orally administered dose is absorbed. The major dose-limiting toxicity is myelosuppression, but mild gastrointestinal toxicity is also reported. VP-16 is a semi-synthetic derivative of podophyllotoxin. Although podophyllotoxin acts by binding to tubulin and causing metaphase arrest, VP-16 probably exerts its major effect in late S and G2 phases, with DNA as its major target. Urinary recovery ranges from 44 to 60% of the total intravenous dose with approximately 67% excreted in the form of unchanged drug. Fecal recovery ranges from 2% to 16% over 72 hours. Approximately 94% of the drug are bound to human serum proteins. When combined with estramustine, etoposide has shown activity in patients with metastatic prostate cancer.

7.7.2 **Supply (9/28/01, 6/3/02, 8/22/03)**

Etoposide is supplied in 50 mg capsules and will be provided and distributed free-of-charge for this study by BMS-U.S. The Shipment Form (*Appendix VI*) must be submitted to the CTSU Regulatory
Office (Fax 215-579-0206) as soon as the individual responsible for the study agent has been identified. This must be done prior to registration of the institution’s first case. Canadian Institutions must submit the Study Agent Shipment Form and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300). BMS will ship VP-16 timed for delivery approximately 8 weeks after randomization of a patient to Treatment Arm 2. Sites with defined procedures for study drug destruction may destroy unused Etoposide on site. Questions about supply, delivery, and returns should be directed to:

**Drug Coordinator**
Bristol-Myers Squibb
609-897-2168
FAX 609-897-5846

7.7.3 **Storage**
Oral VP-16 is stable at refrigerated temperatures of 2-8°C.

7.7.4 **Administration**
A total daily oral dose of 50 mg/m² is administered in divided doses b.i.d. for 14 days and repeated every three weeks for four cycles. In almost all patients, this is a dose of one 50 mg pill two times per day.

7.7.5 **Toxicity**
The principal dose-limiting toxicity is myelosuppression. Severe thrombocytopenia can occur in about 4% of the patients. Toxicity is not cumulative. The associated nausea and vomiting is usually mild and controllable with antiemetic therapy. Some less common side effects include: reversible alopecia, anorexia, diarrhea, somnolence, fatigue, liver toxicity, stomatitis, and peripheral neuropathy. The maximally tolerated oral dose is 50 mg/m²/d. There is documentation of a potential drug-drug interaction between paclitaxel and etoposide. Etoposide is an inhibitor of cytochrome P450 isoenzyme CYP2C8 that may increase paclitaxel levels.

7.8 **Paclitaxel (Taxol®)** *(IND #61, 009) (9/28/01)*

7.8.1 **Description**
Paclitaxel (Taxol®) is a poorly soluble plant product from the western yew, Taxus brevifolia. Improved solubility requires a mixed solvent system with further dilutions of either 0.9% sodium chloride or 5% dextrose in water. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 27 hours. A sterile solution concentrate, 6 mg/ml in 5 ml vials (30 mg/vial) in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. The contents of the vial must be diluted just prior to clinical use. Paclitaxel, at the appropriate dose, will be diluted in 1000 ml of D₅W, USP, in 5% polyolefin containers due to leaching of diethylhexphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized. Each bag/bottle should be prepared immediately before administration. NOTE: Formation of a small number of fibers in solution (NOTE: acceptable limits established by the USP Particular Matter Test for LVP's) have been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g.: Millex-GV Millipore Products) into the i.v. fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

7.8.2 **Supply**
7.8.2.1 Paclitaxel is commercially available in the United States.
7.8.2.2 Bristol/Myers Squibb (BMS) Oncology-Canada will provide paclitaxel to Canadian institutions for this study. Contact your local Canadian BMS representative.

7.8.3 **Storage**
Paclitaxel vials should be stored between 2°-25°C (36°-77°F).

7.8.4 **Administration**
Do not give paclitaxel therapy to patients with baseline neutrophil counts of ≤ 1500 cells/mm³. Paclitaxel, at the appropriate dose and dilution, will be given as a 1-hour infusion. See Section 7.1. The paclitaxel is mixed in 500 or 1000 cc of D₅W in non-PVC containers and infused via polyolefin-lined nitroglycerin tubing or low absorption AVI%o with 0.22 m in-line filter. Paclitaxel will be administered via an infusion control device (pump) using non-PVC tubing and connectors, such as the i.v.
administration sets (*polyethylene* or *polyolefin*) which are used to infuse parenteral Nitroglycerin. Nothing else is to be infused through the line through which paclitaxel is administered.

7.8.5 **Toxicity**

- Hematologic: Myelosuppression
- Gastrointestinal: Nausea and vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhlitis, ischemic colitis, neutropenic enterocolitis, increased liver function tests (*SGOT, SGPT, bilirubin, alkaline phosphatase*) hepatic failure, hepatic necrosis.
- Heart: Arrhythmias, heart block, ventricular tachycardia, myocardial infarction (*MI*), bradycardia, atrial arrhythmia, hypotension, hypertension, lightheadedness.
- Neurological: Sensory (*taste*), peripheral neuropathy, seizures, mood swings, hepatic encephalopathy, encephalopathy, sensation of flashing lights, blurred vision, scintillating scotoma.
- Allergy: Anaphylactoid and urticarial reactions (*acute*), flushing, rash, pruritus.
- Other: Alopecia, fatigue, arthralgia, myopathy, myalgia, infiltration (*erythema, induration, tenderness, rarely ulceration*), radiation recall reaction.

- There is documentation of a potential drug-drug interaction between paclitaxel and etoposide. Etoposide is an inhibitor of cytochrome P450 isoenzyme CYP2C8 that may increase paclitaxel levels.

7.9 **RTOG Toxicity Reporting (11/16/01, 3/16/04, 9/29/04)**

7.9.1 The revised NCI Common Toxicity Criteria Version 2.0 (3/98) will be used to score chemotherapy and acute radiation (< 90 days) toxicities. The following guidelines for reporting adverse drug reactions (*ADRs*) apply to any research protocol that uses commercial anticancer agents. The following ADRs experienced by patients accrued to these protocols and attributed to the commercial agent(s) should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, and telephoned to RTOG Headquarters, within 10 working days. This study will be monitored by the Clinical Data Update System (*CDUS*) version 1.X. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and November 16.

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

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

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

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

7.9.2 The ADR report should be documented on Form FDA 3500 and mailed to:

<table>
<thead>
<tr>
<th>Investigational Drug Branch</th>
<th>RTOG Headquarters</th>
</tr>
</thead>
<tbody>
<tr>
<td>P.O. Box 30012</td>
<td>1818 Market Street, Suite 1600</td>
</tr>
<tr>
<td>Bethesda, Maryland 20824</td>
<td>Philadelphia, PA 19103</td>
</tr>
<tr>
<td>(301) 230-2330</td>
<td>(215) 574-3214</td>
</tr>
<tr>
<td>available 24 hours</td>
<td>FAX (215) 717-0990</td>
</tr>
<tr>
<td>FAX (301) 230-0159</td>
<td></td>
</tr>
</tbody>
</table>

7.9.3 **Special Reporting (6/3/02)**

All grades (1-5) of any thromboembolic event (*TIA, CVA, MI, DVT, PE*) experienced by a patient on this protocol must be called to RTOG Headquarters Data Management at the above number within 48 hours of knowledge of such event.

7.10 **CTSU SERIOUS ADVERSE EVENT (SAE) REPORTING (1/31/07)**

7.10.1 1. CTSU sites must comply with the expectations of their local Institutional Review Board (IRB) regarding documentation and submission of adverse events. Local IRBs must be informed of all reportable serious adverse reactions.

2. CTSU sites will assess and report adverse events according to the guidelines and timelines specified in the protocol. You may navigate to the CTEP Adverse Event Expedited Report System (*AdEERS*) from either the Adverse Events tab of the CTSU member homepage (http://members.ctsu.org) or by selecting Adverse Event Reporting Forms from the document center drop down list on the RTOG-99-02 web page.

3. Do not send adverse event reports to the CTSU.
4. Secondary AML/MDS/ALL reporting: Report occurrence of secondary AML, MDS, or ALL via the NCI/CTEP AML-MDS Report Form in lieu of AdEERS. Submit the completed form and supporting documentation as outlined in the protocol.

7.11 **CTSU REGULATORY AND MONITORING**

**Study Audit**

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site’s primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol. Per capita reimbursement will be issued by the credited Group provided they have endorsed the trial, or by the CTSU if the Group has not endorsed the trial.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up are available for download from the CTSU Operations Manual located on the CTSU Member Web site.

**Health Insurance Portability and Accountability Act of 1996 (HIPAA)**

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU website.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US sites.

Clinical Data Update System (CDUS) Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. The sponsoring Group fulfills this reporting obligation by electronically transmitting to CTEP the CDUS data collected from the study-specific case report forms.

8.0 **SURGERY**

8.1 **Prostate Rebiopsy**

8.1.1 A biopsy will be performed for all patients with evidence of biochemical failure or growth of a palpable abnormality. A PSA failure is defined as a consistent and significant rise in the PSA. The ASTRO definition of rising PSA will be used. Thus, when the PSA rises on three consecutive occasions, biochemical failure has occurred and the date of failure is midway between the last non-rising PSA and the first rise in PSA.

8.1.2 Biopsies are strongly recommended for patients with evidence of distant failure to assist in accurately determining the "true" local control rate. In the absence of a biopsy, such patients will be considered local failures if their exam is abnormal. If their exam is normal or if they are post orchiectomy they will be censored at the last point in time they were considered locally controlled and considered "inevaluable" for further assessment of local control.
9.0 OTHER THERAPY
Not applicable to this study.

10.0 PATHOLOGY (03/16/04) (9/29/04)

10.1 Central pathology reviews of the diagnostic and post treatment prostatic biopsies are planned.

10.2 Hematoxylin and eosin (H & E) stained slides and a representative tissue block of all pathologic material, the pathology report, and a Pathology Submission Form will be submitted to the RTOG Tissue Bank:

LDS Hospital
Department of Pathology
E.M. Laboratory
8th Avenue & C Street
Salt Lake City, UT 84143
(801) 408-5626
FAX (801) 321-5020
holly.goold@ihc.com

The collection, storage, and distribution of tissue specimens will conform to guidelines developed by the Intergroup Specimen Banking Committee. Because of the long-term nature of this clinical research effort, emerging (and yet unknown) technologies may have the greatest relevance to the clinical data resources when this becomes available. Thus, the tissue resources will not be released for investigation until such time as deemed appropriate for its association with the clinical endpoints this study aims to assess.

10.2.1 Hematoxylin & eosin (H & E) stained slides will be retained until completion of the analysis of the study. Slides will be returned if specifically requested at that time.

10.2.2 One paraffin block of tumor or 10 unstained slide sections (maximum thickness of 5 microns each) mounted on sialinized (or other “sticky”) slides will be submitted. The block/slides must be clearly labeled with the same pathology identification number as on the institutional pathology report.

10.2.3 A Pathology Submission Form must be included and must clearly identify the enclosed materials as being for the RTOG Tissue Bank.

10.3 All pretreatment biopsies will be assessed for the presence of tumor and graded according to the Gleason system. Additional pathologic features of possible significance including volume of tumor in biopsy specimens and the presence or absence of perineural invasion will be recorded.

10.4 DNA content and proliferation rate will be assessed in all pretreatment biopsies by image cytometry.

10.5 Post therapy biopsies will be assessed for the presence of residual tumor.

10.5.1 All positive biopsies will be histologically graded according to the Gleason scoring system and the degree of therapy effect in the tumor cells will be graded according to Rakozky et al.40

10.5.2 In cases where there is difficulty in diagnosis, immunohistochemical staining for high molecular weight cytokeratin will be performed to aid in the distinction of atypical benign glands from carcinoma.

10.6 RTOG will reimburse pathologists from submitting institutions $100 per case if proper materials are submitted (reimbursement is handled through an invoice submitted to RTOG Administration, ATT: Path Reimbursement).

10.7 Patient consent form should give the Pathology Department authority and responsibility to comply with submission of these materials (pathology blocks belong to the patient from whom tissue has been removed).

10.8 CTSU Pathology Submission (1/31/07)

10.8.1 All pathology materials are to be submitted directly to the RTOG Tissue Bank according to the instructions outlined above. Do not send forms to the CTSU.

10.8.2 Reimbursement for CTSU sites is handled through an invoice submitted to RTOG Administration, Attention: Pathology Reimbursement, Radiation Therapy Oncology Group, 1818 Market St., Suite 1600, Philadelphia, PA 19103.
11.0  PATIENT ASSESSMENTS

11.1  Study Parameters (11/16/01, 6/3/02)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pre-therapy</th>
<th>Weekly during Radiotherapy</th>
<th>Prior to Chemotherapy (post RT)</th>
<th>During Chemotherapy</th>
<th>Post RT&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>H&amp;P and tumor measurement</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Weight and Performance Status</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>χ&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X</td>
</tr>
<tr>
<td>CBC, Platelets</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>PT/INR &lt;sup&gt;(Arm 2)&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Creatinine Clearance</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pre-therapy</th>
<th>Weekly during Radiotherapy</th>
<th>Prior to Chemotherapy (post RT)</th>
<th>During Chemotherapy</th>
<th>Post RT&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Scan&lt;sup&gt;c&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic CT or other lymph node assessment&lt;sup&gt;c&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxicity Assessment</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Prostate Biopsy&lt;sup&gt;e&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

a. CBC and platelets and PT/INR on days 8, 15 and 22 (*day 2 of next cycle*); weight and performance status every 3 weeks. When INR is stable and > 1.5 and < 2.5, PT/INR will be analyzed at least every 4 weeks. More frequent analysis may be considered at the discretion of the physician.

b. Serum ALT, Alk Phos, Bilirubin, BUN, and creatinine every month during oral antiandrogen therapy.

c. At baseline and as clinically indicated afterward.

d. Every 3 months for 2 years, then every 6 months for 3 years, then annually.

e. Must include Gleason score.

f. A biopsy will be performed for all patients with evidence of biochemical failure or growth of a palpable abnormality.

g. Recalculate creatinine clearance if serum creatinine increases by 50% since previous level.

11.2  Follow-up Schedule (11/16/01)

11.2.1  Every 3 months for two years.

11.2.2  Every 6 months for three years, then annually for the remainder of the patient's life.

11.2.3  A bone scan will be performed on any patient with complaints of bone pain that cannot be attributed to any intercurrent disease. Discretionary plain films may be needed to evaluate lesions seen on bone scan to confirm the diagnosis of metastatic disease.

11.3  Measurement of Effect

11.3.1  Prostate tumor dimensions in cm must be recorded on the diagrams on the data collection forms for initial and follow-up evaluations of the patient. All PSA levels done during a follow-up interval will be recorded on the data forms.

11.3.2  After study entry, disease activity evaluations will be made and recorded using the following criteria:

11.3.2.1  **PSA Complete Response (PSA-CR):** A PSA-CR will be declared if the PSA becomes undetectable (<0.3 ng/ml) by the day of discontinuation of hormonal therapy.

11.3.2.2  **Clinical Complete Response (CR):** A clinical CR will be declared if there is a complete resolution of all palpable abnormalities. *Note:* patients with non-palpable lesions will not be considered in this category.

11.3.2.3  **Equivocal Disease (ER):** This rating will be assigned if the changes observed in the prostate are abnormal due to treatment and felt not to represent tumor.

11.3.2.4  **Partial Response (PR):** Tumor regression that is greater than 50% of the product of the two largest perpendicular diameters of the prostate tumor and that is present for at least one month as measured...
clinically.

11.3.2.5 Stable Disease (SD): There is no change in the size of the tumor or less than or equal to 25% decrease in the product of the two largest perpendicular diameters of the prostate tumor.

11.3.2.6 Progressive Disease (PD): This rating will be assigned when there is clinical evidence in the prostate gland of disease progression or recurrence measured by a 25% or greater increase in the product of the two largest perpendicular diameters of the prostate.

11.4 Other Response Parameters

11.4.1 Freedom from biochemical (PSA) failure
For this study, the "PSA nadir" will be defined as the lowest PSA value reached immediately preceding a "PSA failure". A biopsy will be performed for all patients with evidence of biochemical failure or growth of a palpable abnormality. A PSA failure is defined as a consistent and significant rise in the PSA. The ASTRO definition of rising PSA will be used. Thus, when the PSA rises on three consecutive occasions, biochemical failure has occurred and the date of failure is midway between the last non-rising PSA and the first rise in PSA.

11.4.2 Time to Local Progression: The time to progression will be measured from the date of randomization to the date of documented local progression. Patients who have a normal exam and no evidence of having a PSA failure will be considered controlled locally. Patients with a residual abnormality or a PSA failure shall undergo biopsy to distinguish between local and distant failures. If their exam is normal or if they are post orchiectomy, they will be censored at the last point in time they were considered locally controlled and considered "inevaluable" for further assessment of local control.

11.4.3 Time to Distant Failure: The time to distant failure will be measured from the date of randomization to the date of documented metastatic disease. Patients with evidence of PSA failure but a negative biopsy will be considered to have experienced only a distant failure.

11.4.4 Disease-Free Survival: The progression-free survival will be measured from the date of randomization to the date of documentation of progression or until the date of death. This endpoint includes all measures of disease including physical exam, PSA, bone scans and biopsies.

11.4.5 Survival: The survival time will be measured from the date of randomization to the date of death. All patients will be followed for survival. Every effort should be made to document the cause of death. Post-mortem examination will be carried out when feasible and a copy of the final autopsy report should be sent to RTOG.

12.0 DATA COLLECTION (9/29/04)
(RTOG, 1818 Market Street, Philadelphia, PA 19103, FAX #215/928-0153)

12.1 Summary of Data Submission (11/16/01)

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form (A5)</td>
<td>Within 2 weeks of study entry.</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Blocks/Slides (P2)</td>
<td></td>
</tr>
<tr>
<td>Preliminary Dosimetry Information:</td>
<td></td>
</tr>
<tr>
<td>RT Prescription (Protocol Treatment Form) (T2)</td>
<td>Within 1 week of start of RT.</td>
</tr>
<tr>
<td>Films (simulation and portal) (T3)</td>
<td></td>
</tr>
<tr>
<td>Calculations (T4)</td>
<td></td>
</tr>
<tr>
<td>Final Dosimetry Information:</td>
<td>Within 1 week of RT end.</td>
</tr>
<tr>
<td>Radiotherapy Form (T1)</td>
<td></td>
</tr>
<tr>
<td>Daily Treatment Record (T5)</td>
<td></td>
</tr>
<tr>
<td>Isodose Distribution (T6)</td>
<td></td>
</tr>
<tr>
<td>Boost Films (simulation and portal) (T8)</td>
<td>At 8 weeks from study entry, at end of RT, and at 6 weeks from end of RT</td>
</tr>
<tr>
<td>Interim Follow-up Form (FS)</td>
<td></td>
</tr>
<tr>
<td>Treatment Summary (TF) (Arm 2)</td>
<td>After each cycle of chemo, and at 30 days</td>
</tr>
</tbody>
</table>

18
Follow-up Form (F1)

At 6, 9, and 12 months in year 1; q 3 months in year 2; q 6 months x 3 years, then annually.
Also at progression/relapse and at death.

Long Term Follow-up Form (FF)

Yearly after 5 years in place of F1 form, as applicable; see FF form for instructions.

Pathology Report (P1), rebiopsy
Pathology Blocks/Slides (P2), rebiopsy

Autopsy Report (D3) 

As applicable.

12.2 CTSU DATA SUBMISSION AND RECONCILIATION (1/31/07)

1. All case report forms (CRFs) and transmittals associated with this study must be downloaded from the RTOG-99-02 web page located on the CTSU registered member Web site (http://members.ctsu.org). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.

2. Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and transmittals to RTOG Headquarters unless an alternate location is specified in the protocol. Do not send study data to the CTSU.

3. The RTOG Headquarters will send query notices and delinquency reports to the site for reconciliation. Please send query responses and delinquent data to the RTOG and do not copy CTSU Data Operations. Each clinical site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and the RTOG.

4. Please affix the RTOG study/case label to all source documentation and redact the patient’s name.

12.3 Radiation therapy data (preliminary dosimetry information and final dosimetry information) are to be submitted directly to the Dosimetry Department, RTOG, at the address listed in Section 12.0 of the protocol. See Section 12.1 of the protocol for a complete inventory of dosimetry items to be submitted. The Radiotherapy Form (T1) is considered a case report form and should be sent to the CTSU Data Operations Center for forwarding to RTOG. A copy of the Dosimetry Transmittal Form should also be sent to the CTSU for tracking purposes.

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

13.0 STATISTICAL CONSIDERATIONS:

13.1 Study Endpoints

13.1.1 Primary Endpoint

• Overall survival

13.1.2 Secondary Endpoints

• Biochemical control (PSA failure)
• Local progression
• Distant metastasis
• Disease free survival
13.2 Sample Size

13.2.1 Stratification: The treatment allocation scheme described by Zelen will be used at randomization. The stratifying variables are PSA ($\leq 10$, $> 10$ to $\leq 100$), tumor stage ($T1-2$, $T3-4$), Gleason score (7, 8-10), and prior hormone use (no, yes).

13.2.2 Overview: The study is designed to test whether the addition of adjuvant chemotherapy improves the overall survival for this group of prostate cancer patients. Bolla showed a 5-year survival rate of 79% for a similar group of prostate cancer patients treated with external beam radiotherapy plus adjuvant androgen ablation. Assuming the control arm can achieve a 79% 5-year survival rate, the sample size is determined by the hypothesis that the experimental (adjuvant chemotherapy) arm would improve the overall survival rate by an absolute 6%. This 6% improvement in overall survival translates to a 33% reduction in yearly death rate.

Because a potential higher rate of patient refusal in the experimental arm can make the study less powerful, we decided to account for an annual 2% drop-out rate in the sample size calculation. The 2% is based on the experience from RTOG 92-02, in which a total of 6% of cases (accrued in about 3 years) in the long term hormone arm refused further treatment after finishing their radiation therapy (plus 4 months neoadjuvant hormone). The yearly mortality rate for dropout is calculated according to the survival results in RTOG 86-10 which showed a 5-year survival rate of 72% for patients treated with radiation plus 4 months neoadjuvant hormone.

13.2.3 Sample Size Derivation (9/28/01): A two-sided, log rank test with significance level of 0.05 will be used to test the hypothesis. Three interim treatment comparisons are also planned to monitor the study. Assuming exponential distributions for overall survival, 1440 cases are required to be uniformly entered in 6 years and be followed for an additional four years to reject the null hypothesis with 90% power. The projected number of deaths by the time of initial treatment analysis is 340. This sample size takes into account a potential 10% rate of ineligible or lack-of-data cases and an annual 2% patient drop-out rate.

13.3 Toxicity Monitoring

Early chemotherapy studies showed an approximately 20% grade 3 or plus acute toxicity including neutropenia, anemia, DVT, nausea, and thrombocytopenia. To ensure the safety of the experimental therapy, three formal statistical tests against excessive toxicity, i.e. 40%, will be carried out during the first 2-3 years of accrual. Thus, the monitoring procedure is designed to test the null hypothesis of 20% or less toxicity rate against a 40% unacceptable high toxicity rate. A maximum of 262 patients entered in the chemotherapy arm is required with significance level of 0.025 and power of 90%. In another word, the conservative in rejecting the null hypothesis that toxicity rate is 20% or less.

Toxicity Monitoring

We estimate that approximately 5% of the men on the chemotherapy arm of the study will experience a thromboembolic event now using the revised prophylactic treatment with Coumadin® (warfarin). An event rate of 23% is set as the highest acceptable toxicity rate. This rate was based on the observed event rate in the 31 men described above. Fleming’s One-Stage Multiple Testing Procedure is utilized here. We chose a Type I error of 0.05 and a Type II error of 0.10 (i.e. 90% statistical power). We are more concerned with a false negative decision (i.e., failing to detect the increase in toxicity if it exists) than we are with a false positive decision (i.e., deciding the new regimen is more toxic, when in fact it is not). Thirty analyzable patients will be needed.
For planning purposes, we assume a 5% thromboembolic event rate. We wish to ensure that the revised treatment plan is tolerable and does not significantly increase the rate of thromboembolic events. If, at any time, the following boundaries are crossed, all data pertaining to the events will be initially reviewed by the study chairs and by the DMC chair. After this review, the results, along with a recommendation, will be made to the Data Monitoring Committee (DMC) for their consideration. The results of this review will determine the future course of action. If accrual has not been completed, it may be suspended. The following table gives the number of patients with thromboembolic toxicity that is considered unacceptable and acceptable as calculated by the method of Fleming. For example, if two eligible patients with a thromboembolic event are reported in the first 10 patients consecutively entered onto the trial after re-opening of the protocol, the study will immediately undergo special review. If less than two patients have a thromboembolic event, then an additional 10 eligible patients will be observed and thromboembolic toxicity will be assessed again. If there are three or more eligible patients with a thromboembolic event reported in the first 20 patients (consecutively entered after re-opening of the protocol), the study would be reviewed immediately. If there are no reported cases with a thromboembolic event in the first 20 patients, then we can state that we have an “acceptable” thromboembolic toxicity rate and we can discontinue monitoring. However, if one or two patients have a reported thromboembolic event, then we will observe an additional 10 patients for unacceptable toxicity. If three or more patients report a thromboembolic event in the first 30 consecutively entered and eligible patients, the study will be reviewed immediately. If no more than two patients report a thromboembolic event in the same 30 patients, the revised prophylactic treatment will be considered as “acceptable”.

### Number of Patients with Thromboembolic Toxicity

<table>
<thead>
<tr>
<th>Toxicity Unacceptable</th>
<th>Toxicity Acceptable</th>
<th>Total Number Evaluable</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>N/A</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>30</td>
</tr>
</tbody>
</table>

13.4 **Analysis Plan**

13.4.1 **Statistical Methods** (9/28/01)

Overall survival and disease free survival will be calculated by Kaplan-Meier method. The treatment effect by chemotherapy with respect to all the endpoints will be done using log rank test statistics without any stratification. All randomized patients will be included in the intent-to-treat analysis. All eligible patients will be included in a secondary analysis. Cumulative incidence method will be used to estimate 5-year rates of biochemical failure, local progression, and distant metastasis. All the failure time variables are measured by the time interval from the date of randomization to the date of the failure event. However, other time intervals, e.g., from the date of first hormone injection or the date of first radiation therapy to the date of the failure may be calculated for purposes other than testing the primary hypothesis.

Grade 3+ toxicity rate will be computed as the number of grade 3+ maximum toxicity divided by the total number of patients who have completed chemotherapy (Arm 2) or 6-month androgen suppression (Arm 1) after radiation therapy. One-sided Z-test based on normal approximation will be used to test the toxicity hypothesis.

13.4.2 **Interim Reports**

Interim reports are prepared every six months until the closure of the study. In general, the interim reports will include:

- the patient accrual rate including the rates in each stratum;
- protocol compliance and the quality of the submitted data;
- the frequencies and severity of the toxicity.

13.4.3 **Interim Treatment Analysis for Early Stopping**

Three such interim treatment comparisons shall be performed when we observe 25%, 50% and 76% of the 340 required maximum number of deaths. The first interim analysis is projected to take place when 67% total accrual is reached. The second interim analysis is projected to take place when 100% of total...
accrual is reached. The third interim analysis is projected to take place at the third year after the closure (2 years of follow-up). For each of these interim analyses, toxicity, treatment delivery and efficacy statistics will be reported to RTOG DMC. The boundary for early stopping (or the nominal significance level for the test) will be computed based on the observed number of deaths according to the O’Brien-Fleming alpha spending function approach. If the difference is highly significant, i.e., p value less than the nominal level, the responsible statistician will recommend to DMC that the study be closed to patient entry (if open at the time) and be written up for publication.

In addition, three toxicity analyses will be performed when 60, 120 and 262 cases in Arm 2 have completed chemotherapy. The Pocock boundary will be used to detect excessive toxicity rate. If the result is highly significant, i.e., p value less than the nominal level, the responsible statistician will recommend to DMC to suspend or close the study because of excessive toxicity.

13.4.4 The Initial Analysis for Reporting Treatment Effects
This analysis will be done after the end of the follow-up period or 340 deaths are observed unless the criteria for early stopping are met. It will compare the two treatment arms with respect to the endpoints mentioned in Section 13.1.

13.5 Inclusion of Minorities
In conformance with the National Institute of Health Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we have also considered the possible interaction between race and treatments. Based on the latest accrual statistics from RTOG 94-13, we project that 70% of men in the study are white, 25% are black (not of Hispanic origin), 0.3% are Hispanic, 0.5% are Asian or Pacific Islander, 0.5% are American Indian or Alaskan Native, and 1% are others and unknown. The following table lists the projected accrual for each racial group. Assuming no difference among races with respect to survival, the statistical power for detecting the hypothesized difference is 78.5% and 37.5% for white and black, respectively. With 85 deaths in the African American population, we are able to detect a 48% hazard reduction by radiation therapy for the subset with statistical power of 80%. The projected categories are as follows:

<table>
<thead>
<tr>
<th></th>
<th>American Indian or Alaskan Native</th>
<th>Asian or Pacific Islander</th>
<th>Black, not of Hispanic Origin</th>
<th>Hispanic White, not of Hispanic Origin</th>
<th>Other or Unknown</th>
<th>Total</th>
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<tr>
<td>Male</td>
<td>7</td>
<td>7</td>
<td>360</td>
<td>43</td>
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REFERENCES


APPENDIX I

RTOG 99-02

A PHASE III PROTOCOL OF ANDROGEN SUPPRESSION (AS) AND RADIATION THERAPY (RT) VS AS AND RT FOLLOWED BY CHEMOTHERAPY WITH PACLITAXEL, ESTRAMUSTINE, AND ETOPOSIDE (TEE) FOR LOCALIZED, HIGH-RISK, PROSTATE CANCER

SAMPLE CONSENT FOR RESEARCH STUDY

THERE IS A RESEARCH STUDY ABOUT YOUR CONDITION AND ITS TREATMENT. THIS CONSENT FORM WILL TELL YOU ABOUT THIS STUDY AND HOW THE TREATMENT MAY OR MAY NOT HELP YOU.

IT IS IMPORTANT THAT YOU READ AND UNDERSTAND THIS FORM, THE STUDY AND THE TREATMENT BEFORE YOU DECIDE TO BE PART OF THIS STUDY. IF YOU HAVE ANY QUESTIONS ABOUT THIS STUDY, THE TREATMENT OR HOW IT WILL AFFECT YOU, PLEASE ASK YOUR DOCTOR.

RESEARCH STUDY (9/28/01)

You have the right to know about the procedures used in this research study and the risks, benefits and alternatives to the treatment in this study. You should know and understand the treatment proposed in this study, how it will be given, how the treatment may help you, how the treatment may harm you, and the choices available to you. This form will tell you about the study, the benefits, the risks and the alternatives so you can decide whether to be a part of this research study. This research study is being conducted by the Radiation Therapy Oncology Group and by the Cancer Trials Support Unit.

PURPOSE OF THIS STUDY

You have a prostate cancer that may be at risk of spreading outside of the prostate. The kind of treatment that most physicians would consider standard for this stage of prostate cancer combines radiation therapy and hormones. In this study all patients will receive both of these. In addition, half the patients will also receive chemotherapy drugs for about 3-4 months. It is hoped that chemotherapy will be found to provide additional benefit, but chemotherapy has important side effects. The use of chemotherapy needs to be tested to determine if it is worthwhile. This study will also try to find out more about the side effects of the two different treatments.

DESCRIPTION OF PROCEDURES (9/28/01, 6/3/02, 3/16/04)

You will be assigned one of two treatment plans (hormones and radiation or hormones and radiation plus chemotherapy) by chance (at random). Although both plans may be good, it is not known right now which of the two is better. The treatment you get will be assigned by a computer. Your doctor will call a statistical office where a computer will assign you to one of the two treatments. Your chance of receiving one of the two is approximately equal. You will be assigned to one of the following:

**Treatment 1:** Eight weeks before starting your radiation treatments, you will receive one of the commercial hormone treatments currently being used for your condition and daily Eulexin or Casodex capsules. If you are given Eulexin, you will take six (6) pills by mouth every day for two months. If you are given Casodex, you will take one (1) pill by mouth every day for two months. It is important that you take Casodex at the same time each day. After the two months are up, you will have radiation to your pelvis and prostate once a day, 5 days a week, for almost eight weeks. The hormones will be given on the same schedule during radiation as before radiation began. Once radiation is completed, you will stop taking the flutamide or Casodex capsules. Hormone treatment will be prescribed and given per package instructions and continue for about 20 more months.

**Treatment 2:** You will be given the exact same treatment described for Treatment 1. Then beginning 28 days after radiation ends, you will receive three chemotherapy drugs: estramustine (Emcyt), etoposide (VP-16) and paclitaxel (Taxol). The first day you will begin taking Emcyt and VP-16 capsules (pills) by mouth. Take estramustine with water at least one hour before or two hours after meals. Milk, milk products and calcium-rich foods or drugs (i.e., calcium containing antacids) must not
be taken at the same time with estramustine. You will take two Emcyt pills three times a day for 14 days and VP-16 pills two times a day for 14 days. The number of VP-16 pills you take will depend on how much you weigh. The second day you will be given Taxol through a needle in a vein in your arm for one hour. You will be given medication before Taxol to try to prevent serious side effects. These drugs will be repeated every three weeks (21 days) for a total of four times. These drugs will be given as an outpatient. The Emcyt and VP-16 will be provided for you at no cost for this study by the pharmaceutical companies.

Because of the possibility of blood clots forming when you are on this treatment, you will take Coumadin® tablets by mouth. Coumadin® is a drug that helps to prevent blood clots from forming. You will take Coumadin® continuously from the time you start chemotherapy until 4 weeks after your chemotherapy is completed.

Also, at the time of your diagnosis by biopsy, some of your tumor was removed. As is usually done, this tissue went to the hospital’s pathology department for routine testing and diagnosis. After that process was complete, the remaining tumor samples were stored in the pathology department. You are being asked for permission to use the remainder of the tumor samples for additional tests. Since this tissue was removed at the time of surgery or biopsy, your permission to use this tissue will not lead to any additional procedures or expense. This tissue may be sent to a central office for review and research investigation associated with this protocol.

RISKS AND DISCOMFORTS (03/16/04)

Cancer treatments, whether given in a research study or in the ordinary practice of medicine, may often harm you (side effects). The treatment used in this study 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.

**Radiation Therapy** may cause reddening or tanning of the skin, hair loss in the treatment area, temporary tiredness, 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.

**Hormone treatments** can cause hot flashes, sweats, dizziness, breast swelling/tenderness and impotence while taking these drug. Less frequently reported side effects include unusual taste in the mouth, diarrhea, increased skin redness, hives, bone pain and increased thirst and urination. In the first few weeks of treatment, hormones may cause increased difficulty in urination. An allergic reaction of generalized rash and difficulty breathing has been reported while taking these drugs. Your doctor will describe any other side effects described in the package instructions.

**Eulexin (Flutamide) and Casodex (Bicalutamide)** can cause impotence, loss of libido, breast tenderness, anemia, breast swelling, and hot flashes. The most frequently reported discomforts have been fatigue, back pain, and fluid retention. Approximately 2% of patients had constipation, diarrhea, or nausea or changes in liver function, though these are infrequent. Your liver function will be checked monthly while you are taking this agent. It is important to call your doctor immediately if you experience any of the following symptoms; intense itching, dark urine, loss of appetite, nausea and vomiting, yellow skin (jaundice) or eyes, abdominal tenderness or "flu-like" symptoms. There have been rare reports of death following severe liver damage from flutamide. Flutamide may cause photosensitivity. Avoid prolonged exposure to the sun and other ultraviolet light. Use sunscreens and wear protective clothing until tolerance is determined. Many of these changes improve or go away despite continuation of therapy.

**For patients that are randomized to Treatment 2: (6/3/02)**

**Estramustine (Emcyt)** can cause breast tenderness, nausea and vomiting, swelling in the legs and/or arms. Less frequently (4%), Emcyt has been reported to cause lowering of blood counts. This can lead to an increased risk of infection, weakness, easy bruising or bleeding for a longer time. Serious effects from Emcyt include the possibility of blood clots in the legs; blood clots in the lungs that can lead to shortness of breath and possibly, death; blood clots in the heart leading to a heart attack and possibly, death; blood clots in the brain which may lead to stroke and possibly, death. Early in this study, the rate of patients developing blood clots was found to be approximately 23%. This high rate was brought to the attention of the Data Monitoring Committee who suggested changes be made to the study. The study has been changed to include their recommendations. You will now take Coumadin® continuously from the time you start chemotherapy until four weeks after your chemotherapy is completed. Blood tests will be done to monitor the effect of the Coumadin®. We expect the rate of
patients developing blood clots will decrease with these additional measures in place. Due to the possibility of birth defects, use contraceptive measures.

**Etoposide (Vepesid, VP-16)** may lower blood counts, which could lead to an increased risk of infection, weakness, or bleeding complications. You could require hospitalization, treatment with antibiotics, and/or transfusion if these problems are severe. This drug can cause diarrhea, hair loss, chest pain, blood in the urine, or a skin rash. Less common reactions include low blood pressure, liver damage, fever, chills, and muscle cramps.

**Paclitaxel (Taxol)** commonly causes a lowering of blood counts which could lead to an increased risk of infection, weakness and fatigue, or bleeding complications. You might need treatment with antibiotics, require hospitalization, and need transfusions if these problems are severe. Other possible side effects include nausea, mouth sores, hair loss, muscle aches, joint pains, visual loss, and fatigue. There is the possibility of skin irritation should paclitaxel leak from my vein into the surrounding skin. Rarely paclitaxel can cause a severe allergic reaction resulting in the development of a rash, difficulty breathing, and low blood pressure. Medication will be given prior to treatment in an effort to prevent this type of reaction. If you are treated with a high dosage or for a prolonged period, you may experience numbness of the hands and feet. Taxol can occasionally cause a slowing of the heart rhythm, or an irregular heart rhythm, but only rarely does it cause symptoms that you would notice. In addition, paclitaxel may increase the risks of radiation as listed above.

The chemotherapy combination of Emcyt, VP-16, and Taxol is potentially more toxic when used together than if used separately. There is also a very small risk of developing leukemia after taking multiple chemotherapy drugs. Your physician will be checking you closely for side effects. Side effects usually disappear after the treatment is stopped. In the meantime, your doctor may prescribe medication to keep these side effects under control.

You must use adequate birth control measures to prevent pregnancy while participating in this study. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study.

**Coumadin® (warfarin):** Coumadin® is taken by mouth in tablet form and on a schedule determined by your physician. This medication helps decrease the clotting ability of the blood so that harmful blood clots do not form. The most serious risks associated with taking Coumadin® are excessive bleeding in any tissue or organ of the body. Less frequent risks are necrosis (death of tissue) and/or gangrene (death of tissue due to lack of blood supply) of skin and other tissues. Other less frequent risks include allergic reactions, liver problems, skin problems (rash, itching, swelling), abdominal pain, cramping, gas, nausea, vomiting, diarrhea, headache, dizziness, taste disturbances, inability to tolerate cold, tiredness, and weakness, sore mouth, mouth sores, loss of appetite, loss of hair, red-orange urine, decrease in number of white blood cells in the blood that could lead to infection, “purple toes” syndrome, and persistent erection of the penis.

Your physician should know what medications you are taking, because certain medications do not react well with Coumadin®. Please do not take any new medications without discussing these with your physician.

Taking this medication will require frequent testing of your blood to monitor its effects. Your physician will determine the frequency of these tests. Your physician will also determine the dose of Coumadin® that you will take and the schedule of the doses based on the results of the blood test.

When you have your blood drawn, you may experience longer than expected bleeding at the puncture site. You may also experience some discomfort and bruising at the site of the needle insertion. Occasionally, some people experience dizziness or feel faint. In rare instances, infection may develop at the site of the needle insertion.

While taking Coumadin®, you should avoid excessive amounts of green, leafy vegetables in your diet. These foods are high in Vitamin K. Vitamin K helps your blood to clot, so excessive amounts of these foods may affect the way that the Coumadin® is working.

**COSTS (9/28/01)**

If you’re randomized to Treatment 2 (hormones and radiation plus chemotherapy), the Emcyt and VP-16 will be provided free of charge for this study. Routine blood tests and scans will be done to evaluate the effects of treatment. There may also be laboratory testing and procedures required by this study for research purposes. These additional tests may increase your medical bills although the impact will be dependent on your insurance company. If injury occurs as a result of this research, treatment will be available. The use of medication to help control side effects could result in added costs. This institution is
not financially responsible for the treatment of side effects caused by the study treatment. You will not be reimbursed for medical care other than what your insurance carrier may provide. You will not be paid for your participation in this research study.

CONTACT PERSONS
(This section must be completed)

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

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
</tr>
</thead>
</table>

For information about this study, you may contact:

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
</tr>
</thead>
</table>

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

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

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
</tr>
</thead>
</table>

ALTERNATIVES

Other treatment choices that could be considered with your condition may include the following: (1) radiation therapy; (2) chemotherapy; (3) hormones; or (4) no treatment except medications to make you feel better. With this choice, your tumor would continue to grow and your disease would spread.

These options could be given either alone or in combination with each other. If you decide to not participate in this study, radiation and hormones similar to Treatment 1 could be used off-study.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments. You should discuss your condition and the expected outcome with your doctor. Your doctor will be available to answer any questions. You are encouraged to ask your doctor any questions you have about this research study and the choices of treatment available to you. If you have any questions at all, please ask your doctor.

If your disease becomes worse, if side effects become very severe, or if developments occur that indicate the research study is not in your best interest, the treatment would be stopped. Further treatment would be discussed at that time.

BENEFITS

It is not known whether the hormones, radiation, and chemotherapy you will be given in this research study will help your condition more than the hormones and radiation without chemotherapy would. The information from this study may also help others by providing information about your type of cancer and its response to treatment. The information will be used scientifically. A possible personal benefit of this research study may be a decrease in the size of your tumor and a longer survival. None of these possible benefits is certain or guaranteed.

VOLUNTARY PARTICIPATION

You do not have to take part in this research study. You are free to withdraw or withhold your consent from taking part in this research study at any time. If you refuse to participate, there will be no penalty or loss of benefits. You may seek care from a doctor of your choice at any time. If you do not take part in this study or if you withdraw from the study, you will continue to receive care.
CONFIDENTIALITY  (9/28/01)

Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG and the Cancer Trials Support Unit). The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (FDA), the National Cancer Institute (NCI), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in this study may have access to medical records that contain your identity. However, no information by which you can be identified will be released or published.

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

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

Patient Signature (or legal Representative)   Date

TISSUE AND BLOOD TESTING  (RTOG 99-02)

I agree to the use of my tissues/other samples for research studies related to my cancer.

☐ Yes  ☐ No

Patient Signature (or legal Representative)   Date
APPENDIX II

KARNOFSKY PERFORMANCE SCALE

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

ZUBROD PERFORMANCE SCALE

0    Fully active, able to carry on all predisease activities without restriction
     (Karnofsky 90-100).
1    Restricted in physically strenuous activity but ambulatory and able to carry out
     work of a light or sedentary nature. For example, light housework, office work
     (Karnofsky 70-80).
2    Ambulatory and capable of all self-care but unable to carry out any work
     activities. Up and about more than 50% of waking hours (Karnofsky 50-60).
3    Capable of only limited self-care, confined to bed or chair 50% or more of waking
     hours (Karnofsky 30-40).
4    Completely disabled. Cannot carry on any self-care. Totally confined to bed or
     chair (Karnofsky 10-20).
DEFINITION OF TNM

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

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

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

Regional Lymph Nodes (N)
NX  Regional lymph nodes cannot be assessed
N0  No regional lymph node metastasis
N1  Metastasis in regional lymph node or nodes

Primary Tumor, Pathologic (pT)
pT2*** Organ confined
   pT2a Unilateral
   pT2b Bilateral
pT3 Extraprostatic extension
   pT3a Extraprostatic extension
   pT3b Seminal vesicle invasion
pT4 Invasion of bladder, rectum

***Note: There is no pathologic T1 classification

Distant Metastasis**** (M)
MX  Presence of distant metastasis cannot be assessed
M0  No distant metastasis
APPENDIX III (continued)

AJCC STAGING SYSTEM
PROSTATE, 5th Edition

M1 Distant metastasis
   M1a Non regional lymph node(s)
   M1b Bone(s)
   M1c Other site(s)

****Note: When more than one site of metastasis is present, the most advanced category is used.
pM1c is most advanced

Histopathologic Grade (G)
GX Grade cannot be assessed
G1 Well-differentiated (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>T1b</th>
<th>T1c</th>
<th>T1</th>
<th>T2</th>
<th>N0</th>
<th>M0</th>
<th>G1</th>
<th>G2, G3-4</th>
<th>Any G</th>
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</thead>
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<td></td>
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<tr>
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<td>N0</td>
<td>M0</td>
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<tr>
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<td>GRADE 3</td>
<td>GRADE 4</td>
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<tr>
<td>SKIN</td>
<td>None</td>
<td>Slight atrophy; Pigmentation change; Some hair loss</td>
<td>Patch atrophy; Moderate telangiectasia; Total hair loss</td>
<td>Marked atrophy; Gross telangiectasia</td>
<td>Ulceration</td>
<td>Ulceration</td>
<td></td>
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<td>SUBCUTANEOUS TISSUE</td>
<td>None</td>
<td>Slight induration (fibrosis) and loss of subcutaneous fat</td>
<td>Moderate fibrosis but asymptomatic; Slight field contracture; &lt;10% linear reduction</td>
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<td>Moderate atrophy and telangiectasia; Little mucous</td>
<td>Marked atrophy with complete dryness; Severe telangiectasia</td>
<td>Ulceration</td>
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<td>SALIVARY GLANDS</td>
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<td>Moderate dryness of mouth; Poor response on stimulation</td>
<td>Complete dryness of mouth; No response on stimulation</td>
<td>Fibrosis</td>
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<td>SPINAL CORD</td>
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<td>Mild L’Hermitte’s syndrome</td>
<td>Severe L’Hermitte’s syndrome</td>
<td>Objective neurological findings at or below cord level treated</td>
<td>Seizures or paralytic; Coma</td>
<td>Mono, para quadriplegia</td>
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<td>BRAIN</td>
<td>None</td>
<td>Mild headache; Slight lethargy</td>
<td>Moderate headache; Great lethargy</td>
<td>Severe headaches; Severe CNS dysfunction (partial loss of power or dyskinesia)</td>
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<td>Severe headaches; Severe CNS dysfunction (partial loss of power or dyskinesia)</td>
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<td></td>
<td></td>
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<tr>
<td>EYE</td>
<td>None</td>
<td>Asymptomatic cataract; Minor corneal ulceration or keratitis</td>
<td>Symptomatic cataract; Moderate corneal ulceration; Minor retinopathy or glaucoma</td>
<td>Severe keratitis; Severe retinopathy or detachment</td>
<td>Severe keratitis; Severe retinopathy or detachment</td>
<td>Severe keratitis; Severe retinopathy or detachment</td>
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<tr>
<td>LARYNX</td>
<td>None</td>
<td>Hoarseness; Slight arytenoid edema</td>
<td>Moderate arytenoid edema; Chondritis</td>
<td>Severe edema; Severe chondritis</td>
<td>Nephrosis</td>
<td>Nephrosis</td>
<td></td>
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<tr>
<td>LUNG</td>
<td>None</td>
<td>Asymptomatic or mild symptoms (dry cough); Slight radiographic appearances</td>
<td>Moderate symptomatic fibrosis or pneumonitis (severe cough); Low grade fever; Patchy radiographic appearances</td>
<td>Severe symptomatic fibrosis or pneumonitis; Dense radiographic changes</td>
<td>Severe respiratory insufficiency/continuous O2/Assisted ventilation</td>
<td>Severe respiratory insufficiency/continuous O2/Assisted ventilation</td>
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<tr>
<td>HEART</td>
<td>None</td>
<td>Asymptomatic or mild symptoms; Transient T wave inversion &amp; ST Changes; Sinus tachycardia &gt;110 (at rest)</td>
<td>Moderate angina on effort; Mild pericarditis; Normal heart size; Persistent abnormal T wave and ST changes; Low ORS</td>
<td>Severe angina; Pericardial effusion; Constrictive pericarditis; Moderate heart failure; Cardiac enlargement; EKG abnormalities</td>
<td>Tamponade/Severe heart failure/Severe constrictive pericarditis</td>
<td>Tamponade/Severe heart failure/Severe constrictive pericarditis</td>
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<tr>
<td>ESOPHAGUS</td>
<td>None</td>
<td>Mild fibrosis; Slight difficulty in swallowing solids; No pain on swallowing</td>
<td>Unable to take solid food normally; Swallowing semi-solid food; Dilation may be indicated</td>
<td>Severe fibrosis; Able to swallow only liquids; May have pain on swallowing</td>
<td>Necrosis/Perforation Fistula</td>
<td>Necrosis/Perforation Fistula</td>
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<tr>
<td>SMALL/LARGE INTESTINE</td>
<td>None</td>
<td>Mild diarrhea; Mild cramping; Bowel movement 5 times daily Slight rectal discharge or bleeding</td>
<td>Moderate diarrhea and colic; Bowel movement &gt;5 times daily; Excessive rectal mucus or intermittent bleeding</td>
<td>Obstruction or bleeding, requiring surgery</td>
<td>Necrosis/Perforation Fistula</td>
<td>Necrosis/Perforation Fistula</td>
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<tr>
<td>LIVER</td>
<td>None</td>
<td>Mild lassitude; Nausea, dyspepsia; Slighty abnormal liver function</td>
<td>Moderate symptoms; Some abnormal liver function; function tests; Serum albumin normal</td>
<td>Disabling hepatic insufficiency; Liver function tests grossly abnormal; Low albumin; Edema or ascites</td>
<td>Necrosis/Hepatic coma or encephalopathy</td>
<td>Necrosis/Hepatic coma or encephalopathy</td>
<td></td>
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<tr>
<td>KIDNEY</td>
<td>None</td>
<td>Transient albuminuria; No hypertension; Mild impairment of renal function; Urea 25-35 mg%;Creatinine 1.5-2.0 mg%; Creatinine clearance &gt; 75%</td>
<td>Persistent moderate albuminuria (2+); Mild hypertension; No related anemia; Moderate impairment of renal function; Urea &gt; 36-60 mg% Creatinine clearance (50-74%)</td>
<td>Severe albuminuria; Severe hypertension Persistent anemia (&lt; 10%); Severe renal failure; Urea &gt;60 mg% Creatinine &gt;4.0 mg% Creatinine clearance &lt; 50%</td>
<td>Malignant hypotension; Uremic coma/Urea &gt; 100%</td>
<td>Malignant hypotension; Uremic coma/Urea &gt; 100%</td>
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<tr>
<td>BLADDER</td>
<td>None</td>
<td>Slight epithelial atrophy; Minor telangiectasia (microscopic hematuria)</td>
<td>Moderate frequency; Generalized telangiectasia; Intermittent macroscopic hematuria</td>
<td>Severe frequency &amp; dysuria Severe generalized telangiectasia (often with petechiae); Frequent hematuria; Reduction in bladder capacity (&lt; 150 cc)</td>
<td>Necrosis/Contracted bladder (capacity &lt; 100 cc); Severe hemorrhagic cystitis</td>
<td>Necrosis/Contracted bladder (capacity &lt; 100 cc); Severe hemorrhagic cystitis</td>
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<tr>
<td>BONE</td>
<td>None</td>
<td>Asymptomatic; No growth retardation; Reduced bone Density</td>
<td>Moderate pain or tenderness; Growth retardation; Irregular bone sclerosis</td>
<td>Severe pain or tenderness; Complete arrest of bone growth; Dense bone sclerosis</td>
<td>Necrosis/Spontaneous fracture</td>
<td>Necrosis/Spontaneous fracture</td>
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<tr>
<td>JOINT</td>
<td>None</td>
<td>Mild joint stiffness; Slight limitation of movement</td>
<td>Moderate stiffness; Intermittent or moderate joint pain; Moderate limitation of movement</td>
<td>Severe joint stiffness; Pain with severe limitation of movement</td>
<td>Necrosis/Complete fixation</td>
<td>Necrosis/Complete fixation</td>
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APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

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

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/574-3214) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.
   a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.

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

3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).

4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.

5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

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

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.

7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.

8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (grade 5) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

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

3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.
C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

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

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

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

Commercial and Non-Investigational Agents

i. Any fatal (grade 5) or life threatening (grade 4) adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters' Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.

ii. Unknown adverse reactions (≥ grade 2) resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters' Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.

iii. All neurotoxicities (≥ grade 3) from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.

iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

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

Investigational Agents

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

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

i. Phase I Studies Utilizing Investigational Agents

- All deaths during therapy with the agent. 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.

- First occurrence of any toxicity (regardless of grade).

As above

Report by phone within 24 hours to IDB drug monitor and RTOG Headquarters.
**A written report may be required.

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

- All fatal (grade 5) and life threatening (grade 4) known adverse reactions due to investigational agent.

Report by phone to RTOG Headquarters and the Study Chairman within 24 hours
**A written report must be sent to RTOG within 10 working days with a copy to IDB. (Grade 4 myelosuppression not reported to IDB)

- All fatal (grade 5) and life threatening (grade 4) unknown adverse reactions resulting from or suspected to be related to investigational agent.

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

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

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

** See attached (if applicable to this study) NCI Adverse Drug Reaction Reporting Form
APPENDIX VI  (9/28/01, 8/22/03)

RTOG 99-02

A PHASE III PROTOCOL OF ANDROGEN SUPPRESSION (AS) AND RADIATION THERAPY (RT) VS AS AND RT FOLLOWED BY CHEMOTHERAPY WITH PACLITAXEL, ESTRAMUSTINE, AND ETOPOSIDE (TEE) FOR LOCALIZED, HIGH-RISK, PROSTATE CANCER

SHIPMENT FORM FOR STUDY AGENTS

Emcyt and VP-16 will be mailed only to institutions who have identified a single individual for receipt of shipment. Each institution must submit this form to the CTSU Regulatory Office (Fax 215-579-0206) as soon as the individual responsible for the study agent has been identified and prior to registration of the institution’s first case. Canadian Institutions must submit the Study Agent Shipment Form and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300). Allow adequate processing time (7-10 days) before calling to register the first case.

SHIP TO:

Name: ____________________________________________
Address: ____________________________________________
(No P.O. Box Numbers)
____________________________________________________
____________________________________________________
____________________________________________________
Telephone: _________________________________________
Fax#: _____________________________________________
RTOG Institution#: _________________________________
Institution Name: __________________________________
Circle one:  RTOG or CTSU
IRB Approval Date: ____________________
(attach copies of IRB approval and sample consent form)
Investigator (PI) Signature ______________________________ Date: ____________
Investigator Name  (Print) ______________________________
Investigator NCI # (Required) __________________________

Return to:
CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
FAX 215-569-0206

RTOG Headquarters Approval __________________________ Date: ____________