RADIATION THERAPY ONCOLOGY GROUP

RTOG 0815

A PHASE III PROSPECTIVE RANDOMIZED TRIAL OF DOSE-ESCALATED RADIOTHERAPY WITH OR WITHOUT SHORT-TERM ANDROGEN DEPRIVATION THERAPY FOR PATIENTS WITH INTERMEDIATE-RISK PROSTATE CANCER

Study Chairs

Principal Investigator/Radiation Oncology Alvaro A. Martinez, MD, FACR William Beaumont Hospital Department of Radiation Oncology 3601 W. Thirteen Mile Road Royal Oak, MI 48009 Phone: 248-551-7058/Fax: 248-551-0089 E-mail: amartinez@beaumont.edu	External Beam Radiotherapy Co-Chair Daniel J. Krauss, MD William Beaumont Hospital Department of Radiation Oncology 3601 W. Thirteen Mile Road Royal Oak, MI 48009 Phone: 248-551-3576/Fax: 248-551-0089 E-mail: dkrauss@beaumont.edu
High Dose Rate Brachytherapy Co-Chair I-Chow Hsu, MD UCSF, Department of Radiation Oncology 1600 Divisadero St. Suite H1031 San Francisco, CA 94143-1708 Phone: 415-353-7175/Fax: 415-353-9883 E-mail: ihsu@radonc.ucsf.edu	Low Dose Rate Brachytherapy Co-Chair Gerard Morton, MD Toronto-Sunnybrook Regional Cancer Center Department of Radiation Oncology 2075 Bayview Ave. Toronto, ON M4N 3M5 CANADA Phone: 416-480-6165/Fax: 416-217-1338 E-Mail: gerard.morton@sunnybrook.ca
Medical Physics Co-Chair Di Yan, PhD William Beaumont Hospital 3601 W. Thirteen Mile Road Royal Oak, MI 48009 Phone: 248-551-6589/Fax: 248-551-3784 E-mail: dyan@beaumont.edu	Outcomes/Utility Co-Chair Deborah Watkins Bruner, PhD, RN, FAAN University of Pennsylvania, School of Nursing Claire M. Fagin Hall, Room 330 418 Curie Boulevard Philadelphia, PA 19104-4217 Phone: 215-746-2356/Fax 215-573-7507 E-mail: wbruner@nursing.upenn.edu
Quality of Life Co-Chair Benjamin Movsas, MD Henry Ford Health System 2799 W. Grand Boulevard Detroit, MI 48202 Phone: 313-916-5188/Fax 313-916-3235 E-mail: bmovsas1@hfhs.org	Fatigue Co-Chair Mohamed Elshaikh, MD Henry Ford Health System Department of Radiation Oncology 2799 W. Grand Boulevard Detroit, MI 48202 Phone: 313-916-3779/Fax: 313-916- 3235 E-mail: MELSHAI1@hfhs.org

(Study Chairs continued on next page)

RTOG 0815 Study Chairs (continued)

Translational Research Co-Chair	Senior Statistician
Deborah Citrin, MD Radiation Oncology Branch National Cancer Institute 10 CRC, B2-3500 10 Center Drive Bethesda, MD 20892 Phone: 301-496-5457/Fax: 301-480-5439 E-mail: citrind@mail.nih.gov	Daniel Hunt, PhD Radiation Therapy Oncology Group/ACR 1818 Market Street, Suite 1600 Philadelphia, PA 19103 215-940-8825/FAX: 215-928-0153 E-mail: dhunt@acr.org

Activation Date: September 14, 2009
Version Date: December 10, 2010
Includes Amendments 1-2
Update Date: January 11, 2011
(Broadcast: January 11, 2011)

Document History

	Version/Update Date	Broadcast Date
Update	January 11, 2011	January 11, 2011
Amendment 2	December 10, 2010	January 11, 2011
Amendment 1	August 17, 2010	January 11, 2011
Update	September 17, 2009	September 17, 2009
Update	September 14, 2009	September 14, 2009
Activation	September 14, 2009	September 14, 2009

RTOG Headquarters
1-800-227-5463, ext. 4189

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Institutions not aligned with 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 https://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 unless otherwise directed by the protocol. Do not send study data or case report forms to the CTSU Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by RTOG. Please send query responses and delinquent data to 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 IAM account contact information current. This will ensure timely communication between the clinical site and the RTOG data center.

INDEX

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0815

A Phase III Prospective Randomized Trial of Dose-Escalated Radiotherapy With or Without Short-Term Androgen Deprivation Therapy for Patients With Intermediate-Risk Prostate Cancer

SCHEMA

STRATIFY		RANDOMIZE	
	Number of Risk Factors*		**Arm 1**
	1. One risk factor		Dose-escalated RT alone
	2. Two or 3 risk factors		
	Comorbidity Status 1. ACE-27** grade ≥ 2 2. ACE-27 grade < 2		
	RT Modality		**Arm 2**
	1. Dose-escalated EBRT		Dose-escalated RT combined with short-term (6 months) androgen blockade (LHRH agonist + antiandrogen)
	2. EBRT + LDR brachytherapy boost		
	3. EBRT + HDR brachytherapy boost		

Intermediate risk factors: Gleason Score 7; PSA >10 but ≤20; T-Stage T2b-T2c. Patients with all three intermediate risk factors and ≥ 50% of their sampled biopsy cores involved will not be eligible for this study. Note: The percentage of biopsy cores involved will only be considered with respect to eligibility for those patients with all 3 of the above risk factors (i.e., patients with one or two of the above risk factors are eligible irrespective of the percentage of biopsy cores involved).***

****The "untreated malignancy" section of the ACE-27 form is to be disregarded with respect to the patient's newly diagnosed, untreated prostate cancer.***

*****Patients with Gleason score ≥ 8, PSA > 20, or clinical stage > T2c are ineligible for this study.***

See pre-registration requirements in Section 5.0.

Note: To be used on this protocol, low-dose rate brachytherapy sources must be listed on the joint RPC/AAPM source registry at http://rpc.mdanderson.org/rpc. Select "Brachy Sources/Source Registry".

Note: As this protocol allows for treatment with exclusively EBRT or EBRT + brachytherapy (at the discretion of the treating physician), this must be specified at the time of study enrollment. Should a patient who was originally intended to receive brachytherapy be found, post-enrollment, to be a poor brachytherapy candidate based on transrectal ultrasound examination, he will no longer be eligible for participation in this study. **Therefore, it is strongly recommended to obtain ultrasound assessment of prospective brachytherapy patients before enrollment on this study.**

Patient Population: (See Section 3.0 for Eligibility) [12/10/10]
Clinically localized, lymph node negative adenocarcinoma of the prostate diagnosed within 6 months* prior to registration at intermediate risk for recurrence as determined by harboring one or more of the following intermediate-risk features: Gleason Score 7; PSA >10 but ≤20; Clinical Stage T2b-T2c.

*Patients previously diagnosed with low risk (Gleason score < 6, clinical stage < T2a, and PSA < 10) prostate cancer undergoing active surveillance who are re-biopsied and found to have intermediate risk disease according to the protocol criteria are eligible for enrollment within 6 months of the repeat biopsy procedure

Required Sample Size: **1520**

RTOG Institution #
RTOG 0815 **ELIGIBILITY CHECKLIST** (12/10/10)
Case # **(page 1 of 4)**

1. _____ (Y) Is there pathologic (histological) proven diagnosis of intermediate risk prostatic adenocarcinoma within 6 months prior to registration?
2. _____ (Y) Is the patient's prostate cancer considered at intermediate risk for recurrence by presenting with one or more of the following:
    ____ (N/Y) Gleason Score 7
    ____ (N/Y) PSA > 10 but ≤ 20
    ____ (N/Y) T-Stage: T2b-T2c
3. _____ (Y/NA) Does the patient have clinically negative (N0) lymph nodes as defined by pelvic +/- abdominal CT or MRI, nodal sampling, or dissection within 60 days prior to registration?
4. _____ (Y/N/NA) Is there no evidence of bone metastases (M0) on a bone scan performed 60 days prior to registration?
5. _____ (Y) Has the patient had a history/physical examination within 60 days of registration to include the following:
    - digital rectal examination of the prostate
    - formal comorbidity assessment via the ACE-27
6. _____ (Y) Is Zubrod Performance Status 0-1?
7. _____ (Y) Is the patient ≥ 18 years old?
8. _____ (Y) Has the baseline serum PSA value been performed with an FDA-approved assay (e.g., Abbott, Hybritech) within 60 days prior to registration?
9. _____ (Y/NA) For patients undergoing brachytherapy, has the CBC/differential been obtained within 60 days prior to registration with adequate bone marrow function defined as follows:
    - Absolute neutrophil count (ANC) ≥ 1,800 cells/mm^3
    - Platelets ≥ 100,000 cells/mm^3
    - Hemoglobin (HGB) ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve HGB ≥ 8.0 g/dl is acceptable)?
10. _____ (N) Does the patient have any of the following risk factors:
    - Gleason Score ≥ 8
    - PSA > 20
    - T-Stage: ≥T3?
11. _____ (N/NA) If the patient has three intermediate risk factors, are ≥50% of the number of biopsy cores positive for cancer?
12. _____ (N) Does the patient have prior history of invasive (carcinoma in situ is allowed) malignancy (except non-melanomatous skin cancer) or hematological (e.g., leukemia, lymphoma, myeloma) malignancy unless disease free for a minimum of 5 years?

(Continued on the next page)

13. _____ (N) Has the patient had prior radical surgery (prostatectomy), high-intensity focused ultrasound (HIFU), or cryosurgery for prostate cancer?
14. _____ (N) Has the patient received prior hormonal therapy, such as LHRH agonists (e.g. goserelin, leuprolide), antiandrogens (e.g., flutamide, bicalutamide), estrogens (e.g., DES), or bilateral orchiectomy?
15. _____ (N) Has the patient used finasteride within 30 days prior to registration?
16. _____ (N) Has the patient used dutasteride within 90 days prior to registration?
17. _____ (N) Has the patient received prior or concurrent cytotoxic chemotherapy for prostate cancer (prior chemotherapy for a different cancer is permitted)?
18. _____ (N) Has the patient received prior radiotherapy, including brachytherapy, to the region of the study cancer that would result in overlap of radiation therapy fields?
19. _____ (N) Is there prior history of a TURP for patients receiving brachytherapy?
20. _____ (N) Does the patient have any of the following conditions:
    - Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months
    - Transmural myocardial infarction within the last 6 months
    - Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
    - Chronic Obstructive Pulmonary Disease (COPD) exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days of registration
    - Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects
    - AIDS (based on current CDC definition)
21. _____ (N) Is the patient sexually active with a woman of childbearing potential and not willing/able to use medically acceptable forms of contraception (e.g., surgical, barrier, medicinal)?

The following questions will be asked at Study Registration:

IMRT/BRACHYTHERAPY CREDENTIALING IS REQUIRED BEFORE 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?

_____ 4. Date the patient provided study-specific consent prior to study entry

_____ 5. Patient's Initials (First Middle Last) [May 2003; If no middle initial, use hyphen]

_____ 6. Verifying Physician

_____ 7. Patient's ID Number

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)

_____ 11. Gender

_____ 12. Patient's Country of Residence

_____ 13. Zip Code (U.S. Residents)

_____ 14. Method of Payment

_____ 15. Will any component of the patient's care be given at a military or VA facility?

_____ 16. Calendar Base Date (Date Radiotherapy Began)

_____ 17. Registration/randomization date: This date will be populated automatically.

_____(Y/N) 18. Have you obtained the patient's consent for his or her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 19. Have you obtained the patient's consent for his or her blood to be kept for use in research to learn about, prevent, treat, or cure cancer? **Note**: Blood collection is mandatory for patients consenting to the QOL portion of this study.

_____(Y/N) 20. Have you obtained the patient's consent for his or her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

(Continued on the next page)

_____(Y/N) 21. Have you obtained the patient's consent for his or her blood to be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease)? **Note:** Blood collection is mandatory for patients consenting to the QOL portion of this study.

_____(Y/N) 22. Have you obtained the patient's consent to allow someone from this institution to contact him or her in the future to take part in more research?

_____(N/Y) 23. Did the patient agree to participate in the quality of life component?

_____ If no, please specify the reason from the following:
1. Patient refused due to illness
2. Patient refused for other reason: specify _____
3. Not approved by institutional IRB
4. Tool not available in patient's language
5. Other reason: specify_____

_____ 24. Number of risk factors:
1. One risk factor
2. Two or 3 risk factors

_____ 25. Comorbidity status:
1. ACE-27 ≥grade 2
2. ACE-27 <grade 2

_____ 26. RT modality:
1. Dose-escalated EBRT
2. EBRT + LDR brachytherapy boost
3. EBRT + HDR brachytherapy boost

_____(N/Y) 27. Specify use of IMRT.

The Eligibility Checklist must be completed in its entirety prior to web registration. 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

1.1 Background and Rationale (12/10/10)

Androgen-deprivation therapy (ADT) is a well-recognized treatment for prostate cancer[1,2] and has been shown, as an adjunct to radiotherapy (RT), in multiple prospective randomized trials, to improve clinical outcomes including biochemical, local, and distant disease control as well as disease-free and overall survival.[3-9] The majority of studies in which these benefits have been demonstrated included patients with high-risk, locally advanced, or, in some cases, node-positive disease. The most significant findings produced by these clinical trials for high-risk patients are as follows: (1) patients in this population receiving ADT have improved outcomes over those not receiving ADT, and (2) long-term (2-3 years) ADT is superior to short-term (4 months) ADT.

The mechanism of benefit of ADT in these patients remains unclear, but several potential explanations exist. First, although ADT is not regarded as a curative modality by itself, it may have the potential to eradicate subclinical, microscopic distant disease. Second, there may exist a synergistic relationship between RT and concurrent administration of ADT such that the response of local-regional disease, particularly that in the pelvic lymph nodes that typically receive significantly lower doses than those received by the prostate, is enhanced.[10] Finally, the benefits of ADT in these patients may simply be a manifestation of compensating for what, in a percentage of patients, would be suboptimal definitive local therapy in the form of "standard-dose" (65-70 Gy) RT.

This current RTOG phase III, prospective, randomized trial is designed primarily to define the magnitude of benefit for adding ADT to dose-escalated RT specifically in the treatment of intermediate-risk prostate cancer. The study will allow this to be accomplished on several levels. For purposes of eligibility for this particular study, 3 intermediate-risk features have been identified: T2b-T2c disease, PSA >10 but ≤20, and Gleason score of 7. One or more of these risk features associated with a newly diagnosed prostate cancer connotes clinicopathologic eligibility for this study. Patients with all 3 of these risk factors who additionally present with ≥ 50% of their sampled biopsy cores positive are believed to be at high risk for systemic progression and are excluded from this study.

This study population represents a heterogeneous group, albeit all intermediate-risk by conventional criteria, and bias will be minimized by stratifying patients according to whether they harbor a single vs. multiple intermediate risk factors. While it is acknowledged that potential sources of bias (e.g., Gleason 7, 3+4 vs 4+3[11-14]) are not directly accounted for, this schema is the most optimal and practical method for potentially identifying which patients from this heterogeneous group stand to benefit from the addition of short-term ADT. In addition, by stratifying according to the multiple forms of dose escalation permitted on this study (external beam radiotherapy [EBRT], low dose rate [LDR] brachytherapy boost, and high dose rate [HDR] brachytherapy boost), it is hoped that differences in terms of the interaction of ADT with various radiotherapeutic techniques may be better understood. That is, is the lack of benefit with ADT suggested in prior brachytherapy series[15-17] a patient selection, biologic, or technical phenomenon? Is it simply a dose escalation phenomenon? By allowing both dose-escalated EBRT and brachytherapy in this study and stratifying patients accordingly, a greater understanding of this interplay should be elicited. Finally, a stratification variable will be added to account for patients' pre-existing comorbidity. The Adult Comorbidity Evaluation 27 (ACE-27)[18-20] will be used to describe any such conditions at levels of none, minimal, moderate, or severe with corresponding grades of 0,1,2,3, or 4, respectively, at the time of study entry. Prior prospective data have suggested minimal or no benefit to the addition of ADT to RT for patients with greater than moderate comorbidity on this scale (grade ≥ 2).[21]

The role of ADT in the intermediate-risk population is not well defined, with ADT administration based largely on old practice patterns, physician bias, and extrapolation of data from studies examining patients with different disease characteristics treated with older radiotherapy modalities and lower total doses. No prospective, randomized data exist examining the use of ADT exclusively in an intermediate-risk prostate cancer setting. Likewise, there are no prospective, randomized data to define the role of ADT in the setting of dose-escalated RT for any patient population. The data yielded by this prospective, randomized clinical trial should result in a better understanding of the benefits of ADT in the intermediate risk patient population treated

with a range of contemporary radiotherapeutic options. This will allow for physicians to make more informed, objective decisions regarding the use of ADT in this patient population and spare the morbidity of such therapy to patient subgroups in which a benefit is not observed.

Several prospective series have now shown clear benefits in terms of biochemical, local, and distant disease control comparing "dose-escalated" to "standard-dose" RT, illustrating the point that RT techniques used in earlier randomized studies demonstrating the benefits of ADT in these patients were suboptimal by current practice standards. A randomized dose-escalation study from M.D. Anderson has demonstrated, at 8 years of follow-up, improvements in biochemical and clinical disease progression (including distant metastases) for patients treated to an isocenter dose of 78 Gy vs 70 Gy.[22] Massachusetts General Hospital has published a randomized trial that has demonstrated the benefits of delivering doses of 79.2 Gy vs 70.2 Gy while using proton beam therapy as a boost,[23] and a randomized trial from the Netherlands has demonstrated an improvement in freedom from failure for patients receiving 78 Gy vs 68 Gy.[24] Prospective, nonrandomized dose-escalation data from Memorial Sloan Kettering Cancer Center has suggested similar benefits in biochemical and clinical control and, despite the fact that this study was not randomized, suggests an advantage in terms of reduction in the risk of distant failure irrespective of whether or not short-term androgen deprivation therapy was used.[25] These advantages conferred by dose escalation have been a result of more sophisticated imaging and treatment planning techniques that have resulted in the ability to not only increase dose delivery to the prostate, but also to enhance bladder and rectal sparing with a concomitant reduction in the risks of acute and chronic toxicity.[26]

While the benefits of dose escalation are becoming better defined in the setting of EBRT, this has been a relatively recent phenomenon that has yet to be significantly evaluated in the setting of concurrent or adjuvant ADT. Dose escalation, however, has been implemented for a longer period of time using brachytherapy techniques. It is therefore the brachytherapy series that provide the longest available follow-up with respect to the use of ADT in the setting of dose escalation. These series have provided, to this point, only retrospective experiences, but multiple large reviews from different institutions have suggested an equivocal or, in some cases, detrimental effect from the use of adjuvant ADT with brachytherapy (either HDR or LDR).[15-17]

Nonetheless, concurrent long-term ADT with RT remains standard treatment for patients with high-risk disease, and, more recently, published results of a prospective study that included intermediate-risk patients suggest a possible benefit to short-term ADT for this patient subgroup.[7] That is, do patients with organ-confined prostate cancer harboring moderately aggressive features such as a Gleason score of 7 or a pretreatment PSA value of 10-20 ng/mL stand to benefit from the addition of ADT to definitive RT? The trial by D'Amico et al. focused on the role of short-term (6-month) ADT in conjunction with EBRT and suggested benefits in terms of biochemical control, cause-specific survival, and even overall survival. Once again, however, ADT was not administered in the setting of dose-escalated RT, and the trial included both intermediate- and high-risk patients, thereby leaving many questions unanswered with respect to the use of ADT in the setting of intermediate-risk prostate cancer.

The result of the integration of the above data into clinical practice is a situation in which there have evolved two distinct practice "standards" for patients with intermediate risk prostate cancer treated primarily with radiotherapy, and those standards are the two randomization arms of this study. There is currently evidence supporting treatment with either approach, but the fact remains that ADT remains untested in the setting of dose-escalated RT. The question of whether or not the potential implications of ADT with respect to quality of life and potential exacerbation of medical comorbidities are outweighed by increased cure rates of prostate cancer will remain unanswered until this issue is addressed in prospective, randomized fashion.

1.2 The Influence of Short-Term Androgen Deprivation Therapy on Health-Related Quality of Life (HRQOL), Fatigue, and Quality-Adjusted Survival (QAS) in Patients With Intermediate-Risk Prostate Cancer Receiving Dose-Escalated Radiotherapy

1.2.1 Health-Related Quality of Life (HRQOL)

Some of the side effects associated with RT and ADT negatively affect HRQOL, and others may contribute to increased risks for serious health concerns. Urinary, bowel, and erectile dysfunction are well-known side effects of pelvic RT. Sexual side effects are the most well recognized adverse effects from ADT and include loss of libido, erectile dysfunction, and hot

flashes. Loss of libido is distressing to many men, and they may not pursue treatments for erectile dysfunction that they may have otherwise pursued after radical prostatectomy or RT. The incidence of hot flashes, which may not abate over the course of ADT, is close to 80%. Physiologic effects, including gynecomastia, changes in body composition (weight gain, reduced muscle mass, increase in body fat), and changes in lipids, are less commonly recognized as side effects of ADT. These effects may lead to an exacerbation of potentially more serious conditions, such as hypertension, diabetes, and coronary artery disease.[27] Loss of bone mineral density, anemia, and hair changes also may occur. Additionally, both the diagnosis of prostate cancer and the hormonal therapy can cause psychological distress. These side effects need more systematic study in clinical trials. Such studies would provide well-defined side effect profiles for better informing physicians of the far-reaching consequences of ADT and improve the awareness that they should incorporate into routine practice strategies for preventing and managing toxicities.[28]

ADT has been shown to have a negative impact on health-related quality of life (HRQOL) in patients with asymptomatic lymph node positive prostatic carcinoma. One study showed significantly worse sexual, emotional, and physical function, with more hot flashes and worse overall HRQOL (using the Functional Assessment of Cancer Therapy-General [FACT-G] scale) in those patients, compared with patients receiving no therapy.[29] To address HRQOL, RTOG 0815 will compare the treatment arms for differences in prostate cancer HRQOL outcomes (as measured by change over time in the Expanded Prostate Cancer Index Composite [EPIC]) in a subset of patients in each treatment arm. The EPIC is a prostate cancer HRQOL instrument that measures a broad spectrum of urinary, bowel, sexual, and hormonal symptoms related to RT and ADT.[29]

1.2.2 Fatigue

Fatigue has been described as the most frequent and distressing symptom related to cancer and its treatment.[30] RT-associated fatigue is a common early side effect reported by 80% of patients during treatment.[31] There is evidence that cancer-related fatigue (CRF) has profound effects on ability to function in usual roles and activities and can linger for months or years after treatment completion.[32-35] The high prevalence of this symptom in persons treated with RT, as well as its association with poor quality of life, mark it as a significant problem that requires further scientific study.

The etiology of fatigue, its correlates, and prevalence in the context of prostate cancer treatment are poorly understood. Past research suggests that irradiation of larger volumes was associated with more fatigue.[34,36,37] Likewise, ADT has been associated with increased fatigue.[38,39] Only a few studies have examined predictors or correlates of fatigue. In a sample of 28 men receiving EBRT and ADT, Truong[35] found that age, Gleason score, PSA, T-stage, ADT duration, and RT dose and fraction did not predict severity of fatigue at the completion of treatment. In contrast, other investigators[37] found that post-treatment fatigue was associated with baseline fatigue, role limitations, treatment type, and treatment location. Other fatigue correlates have been proposed: depression, poor sleep quality, and lack of regular physical activity.[31,40,41] Thus, we plan to address such confounding factors with brief and focused questions. Of importance, no studies have compared the severity and correlates of fatigue in men receiving RT ± ADT. Also many of the previous studies were secondary analyses or had small subject samples.

Because fatigue is a major problem associated with both RT and ADT, it would be informative to examine this common symptom in the context of a large clinical trial. The large sample would allow for the examination of predictors (demographic and treatment) of fatigue severity as well as the effect of fatigue on quality of life. Secondary hypotheses are that higher fatigue severity will be associated with poorer overall quality of life and that higher baseline fatigue, poorer performance status, and older age will predict higher fatigue severity during, at the end of, and following treatment.

In order to minimize the potential impact of various confounding factors on fatigue, a secondary endpoint of this study, the following key information regarding potential confounds will also be collected at the time of the PROMIS-fatigue short form (using limited questions to minimize patient burden):

- Anxiety/depression item in EQ5D
- Muscle weakness question (scale of 1-5, from none to very much)
- Overall Sleep Quality: Item from Pittsburgh Sleep Quality Index:[42]
- Level of physical activity (per GLTEQ)

Sleep quality will be measured by 1 item (Q3) of the Pittsburgh Sleep Quality Index (PSQI), a self-rated questionnaire which measures sleep quality and disturbances over a 1-week or 1-month time period.[42] The sum of the 19 items yields a global score which has been demonstrated to discriminate good and poor sleepers; also, it has good internal consistency (Cronbach's alpha=0.83), stability (test-retest reliability=.85, *P*<.001) and discriminant validity. It has been used in patients with cancer and demonstrated sleep problems as expected. [42]

Participants' level of physical activity will be assessed using the Godin Leisure-Time Exercise Questionnaire (GLTEQ),[43,44] which measures time spent per week in each of light, moderate, and vigorous activities. A score can be computed for each level of exercise. A total score is computed by summing the three levels weighted by their respective metabolic (MET) equivalents of 3, 5, and 9. The GLTEQ has good test-retest reliability and has shown convergent validity with both objective and other self-report measures of physical activity.[43,44]

1.2.3 Quality-Adjusted Survival and Failure Free Survival

In this study, the addition of short term ADT is hypothesized to improve overall survival (OS), while having a negative impact on HRQOL. As these are potentially competing advantages and disadvantages of ADT, it is useful to combine these factors into one equation, quality-adjusted life year (QALY). QALYs will be used to determine whether the potential benefits of the ADT, in terms of OS, outweigh the potential disadvantages of this strategy, in terms of a negative effect on HRQOL, compared to the RT only arm. Such a quality adjusted survival (or failure free survival) analysis can be invaluable to future patients faced with these treatment options.

Quality-adjusted survival and freedom from progression can be defined by the weighted sum of different time episodes added up to a total QALY or failure free survival-year [U= sum of quality (q_i) of health states K times the duration (s_i) spent in each health state.[45]

$$\mathbf{U} = \sum_{\mathbf{i=1}}^{\mathbf{K}} \mathbf{q_i s_i}$$

The EQ-5D has been used across numerous disease sites. For example, the EQ-5D mean score for 95 patients with NSCLC (93% male, mean age 62 years) was 0.58 (SD 0.32) [on a scale of "0" death or worst possible health to "1" best possible health].[46] The EQ-5D has been used to assess QALYs and the economic value of prostate cancer screening,[47] and treatment of pain related to prostate cancer metastasis.[48] Further, the EQ-5D was used in a recent study to estimate the economic value of the welfare loss due to prostate cancer pain by estimating the extent to which pain affects HRQOL among patients with prostate cancer. Health status and economic outcomes were modeled among a well-defined population of 200,000 Swedish prostate cancer patients. Health utility ratings (using the EQ-5D) were obtained from a subset of 1,156 of the prostate cancer patients. A descriptive model showed that optimal treatment that would reduce pain to zero during the whole episode of disease would add on average 0.85 QALYs to every man with prostate cancer.[49]

1.3 Correlation of Circulating Proinflammatory Cytokines to Fatigue in Patients Undergoing Radiotherapy for Prostate Cancer (12/10/10)

As described above, fatigue is a major problem for patients treated with RT and ADT. A better understanding of biologic events correlated with fatigue in patients receiving RT and ADT may provide insight into the mechanisms of fatigue in these patients and as a result may provide possible avenues for intervention. Pro-inflammatory cytokines have been found to play a role in cancer-related fatigue (CRF) and fatigue from other chronic illnesses.[50] In this study, we will test the hypothesis that alterations in the circulating levels of the proinflammatory cytokines such as TNF alpha, IL-1, IL-1ra, IL-6 and the marker of inflammation C-reactive protein during RT for prostate cancer predict the likelihood of developing fatigue as measured by the PROMIS instrument.

Pro-inflammatory cytokines have been studied as possible markers of CRF. The most commonly implicated cytokines are IL-1, IL-6, TNF alpha, and IFN alpha.[51] The mechanism by which these cytokines may cause fatigue or be correlated with fatigue is complex; however, IL-1, IL-6, and TNF alpha are known to stimulate the hypothalamic pituitary axis, which is also implicated in CRF. TNF alpha also plays a role in modulating central neurotransmission, another potential central mechanism of CRF.[52]

Because many of the therapies used to treat cancers can induce expression of pro-inflammatory cytokines, it is possible that the cytokine release caused by these therapies also correlate with the occurrence of CRF. Several small studies have addressed the issue of cytokine levels and their correlation with fatigue in patients receiving RT. Ahlberg et al. evaluated 15 patients treated with pelvic RT to a dose of 46 Gy in 2 Gy fractions after hysterectomy.[53] Fatigue was assessed with the Multidimensional Fatigue Inventory (MFI-20). Cytokine levels were assessed before starting RT, after 30 Gy, and within one week of RT. Fatigue scores were elevated at 30 Gy and at completion of RT. IL-1 remained undetectable at all time points. TNF alpha and IL-6 were increased in several patients at the time points during and at the completion of RT. IL-6 elevated in nearly half of patients, and levels decreased through RT in the remainder with a resultant negative correlation between serum IL-6 and fatigue in this small population. Unfortunately this is a small series of patients in whom surgical therapy was the primary therapy, which is known to alter cytokine levels such as IL-6, CRP, and TNF alpha postoperatively.

Geitnez et al. evaluated cytokine levels in 41 breast cancer patients that had undergone breast conserving therapy. Patients rated fatigue with the Fatigue Assessment Questionnaire and a visual analog scale of fatigue intensity before, during, and 2 months after RT; and at long term follow up.[54,55] Serum IL-1 beta, IL-6, and TNF alpha were also measured at these time points. Fatigue was elevated on the visual analogue scale during RT; however, no change was noted on the Fatigue Assessment Questionnaire. IL-1beta, IL-6, and TNF alpha did not change during therapy and did not correlate with fatigue.

While several of the series that drew negative conclusions above found no increase in inflammatory cytokine levels with RT, several series have found striking elevations. For example, Akmansu et al. found significant elevations in serum IL-6 and TNF alpha after five weeks of RT compared to pretreatment levels in 34 patients receiving RT for head and neck cancer.[56] Greenberg et al. found significant elevations in IL-1 in the early weeks of RT for prostate cancer in 15 patients which correlated with an increase in fatigue.[57] Fatigue was assessed daily on a visual analogue scale. Patients were screened for depression during this study to rule out depression as a confounding factor.

In contrast, the effect of ADT on inflammatory markers is less well known. Small studies have shown altered cytokine expression by prostate tumors after ADT,[58] but levels of systemic cytokines after hormonal therapy for prostate cancer are not well described. Fatigue is a well-known complication of ADT for prostate cancer.[59] The combination of RT and ADT for prostate cancer may result in a more persistent and prolonged fatigue compared to the series evaluating fatigue after RT alone, with as many as 32% of patients experiencing fatigue at the completion of RT and a substantial number experiencing fatigue as late as 6.5 weeks after completion of RT.[35] Correlation of inflammatory cytokines to fatigue may provide mechanistic information regarding the causes of fatigue in these patients and may provide a target for intervention in future studies.

Blood collection is mandatory for patients consenting to the QOL portion of this study and optional for other participants. It will be strongly recommended that patients consent to having a tissue block sent for storage to the RTOG Biospecimen Resource. Paraffin-embedded tissue blocks of diagnostic prostate biopsies will be obtained from participating institutions and banked in the RTOG Biospecimen Resource for future translational analyses. Plasma and whole blood may be collected from patients enrolled on this protocol before and during protocol therapy and banked for future translational research analyses. Specifically, plasma will be collected at baseline and during the last week of RT treatments. Whole blood will be collected at baseline only. The tissue specimens will be collected and processed according to the RTOG specimen processing guidelines and must be clearly labeled with the patient's case number. Anticipated analyses include correlation of whole genome single nucleotide polymorphisms to incidence and severity of

toxicity from therapy, and evaluation of circulating markers that may correlate to patient reported outcomes. An example of one anticipated analysis is the evaluation of plasma cytokines for correlation to fatigue as measured by the PROMIS instrument in patients enrolled on this trial. Examples of cytokines that may be tested include CRP, TNF alpha, IL-1, IL-1ra, and IL-6.

2.0 OBJECTIVES

2.1 Primary

To demonstrate an overall survival (OS) advantage for the addition of short-term (6 months) ADT to dose-escalated RT for patients with intermediate-risk prostate cancer. The events for OS will be defined as death due to any cause.

2.2 Secondary (12/10/10)

2.2.1 Determine whether the addition of ADT to dose-escalated RT improves clinical failures (local recurrence, regional recurrence, or distant metastasis), biochemical failure by the "nadir + 2" (Phoenix) definition[60], freedom from failure (the first occurrence of clinical failure or biochemical failure by the Phoenix definition), rate of salvage ADT, and prostate cancer-specific mortality without resulting in increased non-prostate cancer-specific mortality over dose-escalated RT alone

2.2.2 Estimate the magnitude of benefit of ADT with respect to OS for patients treated with different RT modalities (i.e., EBRT alone vs. LDR brachytherapy boost vs. HDR brachytherapy boost)

2.2.3 Compare acute and late treatment adverse events for patients receiving vs. not receiving ADT and correlate this with the presence or absence of pre-existing comorbidity as documented by the Adult Comorbidity Evaluation 27 (ACE-27) assessment.[18-20]

2.2.4 Determine whether HRQOL as measured by the EPIC significantly worsens as a function of treatment assignment (i.e., ADT + RT compared to RT alone)

2.2.5 Demonstrate that the addition of ADT to dose-escalated RT is associated with higher fatigue severity than dose-escalated RT alone by the Patient-Reported Outcome Measurement Information System (PROMIS) fatigue domain

2.2.6 Demonstrate an incremental gain in OS with more aggressive therapy that outweighs the detriments in the primary generic domains of HRQOL (i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), reported as QALY.

2.2.7 Determine whether the PROMIS score change is correlated with plasma cytokine change

2.2.8 Collect paraffin-embedded tissue blocks, plasma, and whole blood for future translational research analyses

3.0 PATIENT SELECTION

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED

3.1 Conditions for Patient Eligibility (12/10/10)

3.1.1 Pathologically (histologically) proven diagnosis of prostatic adenocarcinoma, at intermediate risk for recurrence, within 6 months prior to registration as determined by having one or more of the following intermediate-risk features: Gleason Score 7; PSA >10 but ≤20; Clinical Stage T2b-T2c.

3.1.1.1 Patients previously diagnosed with low risk (Gleason score < 6, clinical stage < T2a, and PSA < 10) prostate cancer undergoing active surveillance who are re-biopsied and found to have intermediate risk disease according to the protocol criteria are eligible for enrollment within 6 months of the repeat biopsy procedure.

3.1.2 Clinically negative lymph nodes as established by imaging (pelvic +/- abdominal CT or MRI), nodal sampling, or dissection within 60 days prior to registration, except as noted immediately below:

3.1.2.1 Patients with a single intermediate risk factor only do not require abdominopelvic imaging, but these studies may be obtained at the discretion of the treating physician. Patients with 2 or 3 risk factors are required to undergo pelvic +/- abdominal CT or MRI.

3.1.2.2 Patients with lymph nodes equivocal or questionable by imaging are eligible without biopsy if the nodes are ≤1.5 cm; any node larger than this on imaging will require negative biopsy for eligibility.

3.1.3 No evidence of bone metastases (M0) on bone scan within 60 days prior to registration.

3.1.3.1 Bone scan is not required for patients enrolled with a single intermediate risk factor only, but this scan may be obtained at the discretion of the treating physician. Patients with 2 or 3 risk factors will require a negative bone scan for eligibility.

3.1.3.2 Equivocal bone scan findings are allowed if plain film x-rays are negative for metastasis.

3.1.4 History/physical examination (to include, at a minimum, digital rectal examination of the prostate and examination of the skeletal system and abdomen, and formal comorbidity assessment via the ACE-27 instrument) within 60 days prior to registration. Note: The ACE-27 is posted on the RTOG website, next to the protocol. Institutions may access a web-based Comorbidity Calculator at http://oto2.wustl.edu/clinepi/comorbid.html.

3.1.5 Zubrod Performance Status 0-1

3.1.6 Age ≥ 18

3.1.7 Baseline serum PSA value performed with an FDA-approved assay (e.g., Abbott, Hybritech) within 60 days prior to registration

3.1.7.1 Study entry PSA must not be obtained during the following time frames: (1) 10-day period following prostate biopsy; (2) following initiation of ADT; (3) within 30 days after discontinuation of finasteride; or (4) within 90 days after discontinuation of dutasteride.

3.1.8 For patients undergoing brachytherapy only: CBC/differential obtained within 60 days prior to registration, with adequate bone marrow function defined as follows:

3.1.8.1 Absolute neutrophil count (ANC) ≥ 1,800 cells/mm^3

3.1.8.2 Platelets ≥ 100,000 cells/mm^3

3.1.8.3 Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.)

3.1.9 Patient must be able to provide study-specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility (12/10/10)

3.2.1 Patients with Gleason Score ≥ 8; PSA > 20; *OR* Clinical Stage ≥ T3 are ineligible for this trial.

3.2.1.1 Should findings of extracapsular extension or seminal vesicle invasion be noted on prostate MRI, this study, if used, will not render patients ineligible for accrual to this protocol. Primary tumor staging for eligibility purposes is to be based on palpable or core biopsy evidence only with respect to extracapsular extension or seminal vesicle involvement.

3.2.2 Patients with all three intermediate risk factors who also have ≥ 50% of the number of their biopsy cores positive for cancer are ineligible for this trial.

3.2.3 Prior invasive malignancy (except non-melanomatous skin cancer) or hematological (e.g., leukemia, lymphoma, myeloma) malignancy unless disease free for a minimum of 5 years (prior diagnoses of carcinoma in situ are permitted)

3.2.4 Prior radical surgery (prostatectomy), high-intensity focused ultrasound (HIFU) or cryosurgery for prostate cancer

3.2.5 Prior hormonal therapy, such as LHRH agonists (e.g., goserelin, leuprolide), antiandrogens (e.g., flutamide, bicalutamide), estrogens (e.g., DES), or bilateral orchiectomy

3.2.6 Use of finasteride within 30 days prior to registration

3.2.7 Use of dutasteride within 90 days prior to registration

3.2.8 Prior or concurrent cytotoxic chemotherapy for prostate cancer; prior chemotherapy for a different cancer is permitted.

3.2.9 Prior RT, including brachytherapy, to the region of the study cancer that would result in overlap of RT fields

3.2.8.1 Any patient undergoing brachytherapy must have transrectal ultrasound confirmation of prostate volume <60 cc, AUA score ≤15 within 60 days of registration, and no history of prior transurethral resection of the prostate (TURP); prior TURP is permitted for patients who receive EBRT only)

3.2.9 Severe, active co-morbidity, defined as follows:

3.2.9.1 Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months

3.2.9.2 Transmural myocardial infarction within the last 6 months

3.2.9.3 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration

3.2.9.4 Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days before registration

3.2.9.5 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol.

3.2.9.6 Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. While the treatment

employed in this study is not significantly immunosuppressive, it is felt that a diagnosis of AIDS associated with prostate cancer is likely to impact this study's primary endpoint of overall survival. Patients who are HIV seropositive but do not meet criteria for diagnosis of AIDS are eligible for study participation.

3.2.10 Men who are sexually active with a woman of child-bearing potential and not willing/able to use medically acceptable forms of contraception (e.g., surgical, barrier, medicinal) during protocol treatment and during the first 3 months after cessation of protocol treatment; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

Note: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management (12/10/10)

4.1.1 AST or ALT <2 x the upper limit of normal within 60 days prior to registration

4.1.2 Alkaline phosphatase within 60 days prior to registration

4.1.3 Serum total testosterone within 60 days prior to registration

4.1.4 Any patient undergoing brachytherapy must have transrectal ultrasound confirmation of prostatic volume <60 cc and American Urologic Association (AUA) symptom index composite score ≤15 within 60 days of registration. This may be performed before or after study enrollment. If a patient is thought to be a poor brachytherapy candidate based on anatomy at the time of ultrasound, he may still participate in the study but must receive EBRT only per protocol guidelines. If a patient is deemed an inadequate brachytherapy candidate after he has already been enrolled on the protocol, he will no longer be eligible for study participation.

5.0 REGISTRATION PROCEDURES

Institutions that have been previously credentialed for prostate 3DCRT or IMRT on prior RTOG protocols and that have successfully irradiated a phantom and been approved by the RPC need not perform additional credentialing for RTOG 0815. However, respective institutions may only administer treatment for which they have been previously credentialed (i.e., an institution credentialed for 3DCRT only may not administer IMRT on this study without completing the IMRT credentialing process). Credentialing requirements for IMRT and 3DCRT are specified in Sections 5.1 and 5.2 below.

5.1 Pre-Registration Requirements for IMRT Treatment Approach (12/10/10)

5.1.1 In order to utilize IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements or determining if they already have been met are available on the Radiological Physics Center (RPC) web site. Visit http://rpc.mdanderson.org/rpc and select "Credentialing" and "Credentialing Status Inquiry".

An IMRT phantom study with the RPC must be successfully completed (if the institution has not previously met this IMRT credentialing requirement). Instructions for requesting and irradiating the phantom are available on the RPC web site at http://rpc.mdanderson.org/rpc/; select "Credentialing" and "RTOG". Upon review and successful completion of the phantom irradiation, the RPC will notify both the registering institution and RTOG Headquarters that the institution has completed this requirement. Subsequently, RTOG Headquarters will notify the institution that the site can enroll patients on the study.

5.1.2 The institution or investigator must either modify their existing Facility Questionnaire on file at RTOG or complete a new IMRT Facility Questionnaire, and submit it to RTOG for review prior to entering any cases, and set up an SFTP account for digital data submission. The Facility Questionnaire and SFTP account are available from the Image-Guided Therapy Center (ITC) via the ATC web site at http://atc.wustl.edu. Upon review and successful completion of the "Dry-Run" QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution has successfully completed this requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study.

5.2 Pre-Registration Requirements for 3DCRT Treatment Approach (12/10/10)

5.2.1 Only institutions that have met the technology requirements and that have provided the baseline physics information that are described in 3DCRT Quality Assurance Guidelines may enter patients onto this study.

5.2.2 The new Facility Questionnaire (one per institution, available on the ATC website at http://atc.wustl.edu) or a modification to your existing Facility Questionnaire on file is to be sent to RTOG for review prior to entering any cases. Upon review and successful completion of a "Dry-Run" QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution has successfully completed this requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study. Institutions that have previously enrolled patients on 3DCRT trials of this same disease site may enroll patients on this study without further credentialing.

5.3 Pre-Registration Requirements for Brachytherapy Treatment Approach

Note: To be used on this protocol, low-dose rate brachytherapy sources must be listed on the joint RPC/AAPM source registry at http://rpc.mdanderson.org/rpc. Select "Brachy Sources/Source Registry".

5.3.1 Institutions must be pre-credentialed by the Radiological Physics Center (RPC) prior to registering any cases to this study. The credentialing materials may be found on the RPC website at http://rpc.mdanderson.org under the "Credentialing" tab.

5.3.1.1 If an institution was credentialed for a previous RTOG prostate brachytherapy trial (98-05, P-0019, 0232, or 0526), they do not have to be re-credentialed for RTOG 0815 if the radiation oncologist and physicist are the same as on the approved credentialing request, and the institution is using the same seed model and planning system as on the approved credentialing request. A change of physician will require submission of the Knowledge Assessment Form and Clinical Test Case. A change in physicist will require submission of the Knowledge Assessment Form and the Reference Cases. A change in either the treatment planning computer or brachytherapy source model will require resubmission of only the Reference Cases.

5.3.2 *LDR Brachytherapy Credentialing*

In order to use brachytherapy on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements, or determining if they have already been met, are available at the RPC web site, http://rpc.mdanderson.org/rpc/ by selecting "Credentialing" and "RTOG".

5.3.3 *HDR Brachytherapy Credentialing*

Only institutions that have completed the Knowledge Assessment Questionnaire, the Facility Inventory, and the Benchmark Cases, as described in the RTOG HDR Prostate Implant Quality Assurance Guidelines (see RPC web site http://rpc.mdanderson.org/rpc) may enter patients onto this study. The sample clinical case with complete post implant data form and other materials are to be sent to the RPC. Upon review and successful completion, the RPC will notify both the registering institution and RTOG Headquarters that the institution has successfully completed this requirement. The RTOG RT Quality Assurance Department will then notify the institution that all requirements have been met and the institution is eligible to enter subsequent patients onto this study. Institutions previously credentialed for RTOG 0321 do not have to be re-credentialed for RTOG 0815.

The first five cases from any newly-credentialed institution will be reviewed by the study co-chair for each respective RT modality to ensure protocol compliance with respect to target coverage, heterogeneity, and normal critical structure dose constraints. Once an institution has demonstrated protocol compliance, future cases will be selected randomly for review.

5.4 Regulatory Pre-Registration Requirements

5.4.1 **U.S. and Canadian institutions** must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206), along with the completed CTSU-IRB/REB Certification Form, http://www.rtog.org/pdf_file2.html?pdf_document=CTSU-IRBCertifForm.pdf, prior to registration of the institution's first case:

- IRB/REB approval letter;
- IRB/REB approved consent (English and native language versions*)

  ***Note**: Institutions must provide certification of consent translation to RTOG Headquarters

- IRB/REB assurance number

5.4.2 *Pre-Registration Requirements FOR CANADIAN INSTITUTIONS*

5.4.2.1 Prior to clinical trial commencement, Canadian institutions must complete and fax to the CTSU Regulatory Office (215-569-0206) Health Canada's Therapeutic Products Directorates' Clinical Trial Site Information Form, Qualified Investigator Undertaking Form, and Research Ethics Board Attestation Form.

5.4.3 *Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS*

5.4.3.1 **For institutions that do not have an approved LOI for this protocol:**
International sites must receive written approval of submitted LOI forms from RTOG Headquarters prior to submitting documents to their local ethics committee for approval. See http://www.rtog.org/pdf_forms.html?members/forms=Intl_LOI_Form.doc

5.4.3.2 **For institutions that have an approved LOI for this protocol:**
All requirements indicated in your LOI Approval Notification must be fulfilled prior to enrolling patients to this study.

5.5 Registration

5.5.1 Online Registration

Patients can be registered only after eligibility criteria are met.

Each individual user must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:

- The investigator and research staff must have completed Human Subjects Training and been issued a certificate (Training is available via http://phrp.nihtraining.com/users/login.php).
- A representative from the institution must complete the Password Authorization Form at www.rtog.org/members/webreg.html (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site (http://www.rtog.org), going to "Data Center Login" and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient's record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study's database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

Institutions can contact RTOG web support for assistance with web registration: websupport@acr.org or 800-227-5463 ext. 4189 or 215-574-3189.

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask for the site's user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.

6.0 RADIATION THERAPY

Protocol treatment must begin within 4 weeks after randomization (administration of either RT alone [Arm 1] or RT + ADT [Arm 2]). Patients randomized to receive short-term ADT should begin RT 8 weeks after the first LHRH agonist injection.

Note: As this protocol allows for treatment with exclusively EBRT or EBRT + brachytherapy (at the discretion of the treating physician) this must be specified at the time of study enrollment. Should a patient who was originally intended to receive brachytherapy be found, post-enrollment, to be a poor brachytherapy candidate based on transrectal ultrasound examination, he will no longer be eligible for participation in this study. Therefore, it is strongly recommended to obtain ultrasound assessment of prospective brachytherapy patients before enrollment on this study.

6.1 Dose Specifications: 3D Conformal Radiotherapy (3DCRT) or IMRT (12/10/10)

6.1.1 Dose will be normalized such that exactly 98% of the PTV receives the prescription dose and will be scored as per protocol. The maximum allowable dose within the PTV is 107% of the prescribed dose to a volume that is at least 0.03 cc. The minimum allowable dose within the PTV is >95% of the prescribed dose to a volume that is at least 0.03cc.

6.1.2 Patients treated entirely via EBRT shall receive prescription doses to the PTV (with the above constraints) of 79.2 Gy delivered in 1.8 Gy fractions. All attempts should be made to deliver the PTV dose with the above heterogeneity constraints with adherence to the critical structure parameters listed below in Table 1. The PTV prescription dose may be reduced by as many as two fractions (total prescription dose of 75.6 or 77.4 Gy) at the discretion of the treating radiation oncologist only if felt that critical structure dose constraints cannot be met for that particular case at a prescription dose of 79.2 Gy. See Section 6.5 below for specifics regarding when to implement a dose reduction. The final prescription dose will be reported specifically to the study coordinator and recorded on a patient-by-patient basis.

Table 1. Critical Structure Dose Constraints

Normal organ limit†	No more than 15% volume receives dose that exceeds	No more than 25% volume receives dose that exceeds	No more than 35% volume receives dose that exceeds	No more than 50% volume receives dose that exceeds
Bladder Constraint	80 Gy	75 Gy	70 Gy	65 Gy
Rectum Constraint	75 Gy	70 Gy	65 Gy	60 Gy
Penile Bulb	Mean dose less than or equal to 52.5 Gy (See Section 6.5)			

†Normal organ limit refers to the volume of that organ that should not exceed the dose limit.

6.2 Technical Factors

6.2.1 RT will be delivered with megavoltage equipment at energies ≥6 MV.

6.2.2 Patients who receive brachytherapy as a component of their RT will undergo EBRT implementing either 3DCRT or IMRT as described. The prostate and seminal vesicles will be treated to a dose of 45 Gy in 1.8 Gy fractions prescribed to a PTV dose as above.

6.3 EBRT Localization, Simulation, and Immobilization

Simulation will be CT-based in all cases. The use of urethral contrast at the time of simulation is recommended but not required. Patients will be positioned supine on a flat tabletop with a customized thermoplastic immobilization cast or a molded foam cradle for stabilization and setup reproducibility. The degree of bladder fullness should be made to duplicate that which is anticipated for daily treatment, i.e., if the patient is instructed to maintain a full bladder for treatment, he should be simulated as such (especially for cases in which image guidance or adaptive treatments are not implemented). CT images should be acquired at a slice thickness of ≤3 mm from the top of the iliac crests superiorly to the perineum inferiorly. Target volumes (Section 6.4.1) and normal critical structures (Section 6.4.1.5) will be defined in the slices in which they are visualized. The 3DCRT cases must utilize “beam’s eye view” representations to define final beam aperture.

6.4 Treatment Planning/Target Volumes

6.4.1 The definition of volumes will be in accordance with the ICRU Report #50: Prescribing, Recording, and Reporting Photon Beam Therapy.

6.4.1.1 The Gross Tumor Volume (GTV) is defined by the physician as all known disease as defined by the planning CT, urethrogram, and clinical information. If a urethrogram is used, the GTV will encompass a volume inferiorly 5 mm superior to the tip of the dye and no less than the entire prostate. Prostate dimensions should be defined as visualized on CT scan.

6.4.1.2 The Clinical Target Volume (CTV) is the GTV plus areas considered to contain microscopic disease, delineated by the treating physician, and is defined as follows:
CTV is the GTV (prostate) plus areas at risk for microscopic disease extension plus the proximal bilateral seminal vesicles. Only the proximal 1.0 cm of seminal vesicle tissue adjacent to the prostate shall be included in the clinical target volume.[61] This 1.0 cm of seminal vesicles refers to both radial (in plane) and superior (out of plane) extent. If both prostate and seminal vesicle are visualized in the same CT slice, this seminal vesicle tissue will contribute to the 1.0 cm of tissue.

6.4.1.3 The Planning Target Volume (PTV) will provide a margin around the CTV to compensate for the variability of treatment set up and internal organ motion. A range of 5-10 mm around the CTV is required to define each respective PTV. Superior and inferior margins (capping) should be 5-10 mm depending on the thickness and spacing of the planning CT scan. Careful consideration should be made when defining the 5-10 mm margin in 3 dimensions.

6.4.1.4 The ICRU Reference Points are to be located in the central part of the PTV and, secondly, on or near the central axis of the beams. Typically these points should be located on the beam axes or at the intersection of the beam axes.

6.4.1.5 Normal Critical Structures to be defined on the treatment planning CT scan will include the following: bladder, rectum (from its origin at the rectosigmoid flexure superiorly or the bottom of the SI joints, whichever is more inferior to the inferior-most extent of the ischial tuberosities), bilateral femora (to the level of ischial tuberosity), penile bulb, and skin. Any small bowel within the primary beam aperture should be defined as well. All structures will be contoured in their entirety as solid organs. See the ITC web site (**http://atc.wustl.edu**) to view examples of target and normal tissue contours.

The following table summarizes the naming of targets and critical structures for submission of data to the ITC.

Standard Name	***Description***
GTV	Gross Target Volume
CTV	Clinical Target Volume
PTV	Planning Target Volume
BLADDER	Bladder
FEMUR_LT	Left Femoral Head
FEMUR_RT	Right Femoral Head
PENILE_BULB	Penile Bulb
RECTUM	Rectum
SKIN	External Patient Contour
SEM_VES	Seminal Vesicles

6.4.1.6 The PTV forms the entire target as described. No extension of fields to specifically treat regional lymph nodes is permitted. 3D conformal beams will be shaped to include the entire PTV and minimize dose to surrounding critical structures as described. Intensity modulated radiotherapy (IMRT) using inverse planning is permitted with constraints placed to adhere to critical structure dose limitations as defined above.

6.5 Critical Structures (12/10/10)

Critical structure dose constraints shall remain consistent with those represented in prior RTOG 3DCRT/IMRT prostate protocols (see Table 1 above). While every effort should be made to deliver prescription doses to the PTV as specified while adhering to these constraints, it is

recognized that certain anatomical factors may prevent this. As mentioned in Section 6.1, a prescription dose reduction to a level of 77.4 Gy or 75.6 Gy is permitted if constraints cannot be met at a prescription dose of 79.2 Gy. For purposes of compliance, up to a 5% absolute increase in the volume of critical structure receiving greater than the specified dose will be considered "variation acceptable," e.g. up to 20% of the rectum may receive a dose of > 75.6 Gy without a protocol deviation. Any increase in critical structure volume greater than 5% receiving more than the specified dose will be considered a "deviation unacceptable." It is at this point that a dose reduction to 77.4 Gy or 75.6 Gy should be implemented. The prescription dose should be the maximum deliverable up to 79.2 Gy while respecting the critical normal structure constraints. Of note, the penile bulb constraint is to be regarded as a guideline, and adherence to this should not, in any way, result in a reduction of the prescription dose or compromised dose coverage of the target volume.

6.6 Treatment Verification

6.6.1 First day port films or portal images of each field along with orthogonal isocenter verification films (or images) must be obtained. If modifications are made in field shaping or design, a port film of each modified field along with orthogonal isocenter verification films (or images) is required on the first day's treatment of that field. Thereafter, weekly verification films or images of orthogonal isocenter views (anterior to posterior and lateral projection) are required.

For **IMRT** the intensity profiles of each beam must be independently verified and compared to the planned field intensity. Portal films are not required for IMRT but orthogonal verification films are required, just as for 3DCRT. These images are to be archived by the institution for later review if requested by the study chair.

6.6.2 Daily on-line target localization (kV or MV imaging with fiducials, trans-abdominal ultrasound, or other) or off-line adaptive approaches to account for interfraction organ motion and setup variability are permitted on this study but not required. The use of image guidance or daily target localization including the specific type implemented must be documented by the treating physician and submitted to RTOG headquarters using the appropriate sections of the Facility Questionnaire.

6.6.3 Management of Radiation Dose to the Patient from Daily Localization

According to the literature, the estimates of patient dose per imaging study for various imaging systems vary considerably. The doses are in the range of 0.1 cGy BrainLab's ExacTrac planar kV-systems and can be considered negligible compared with doses from MV portal imaging and kV and MV CT. The doses from helical MV CT scans on a Tomotherapy unit are estimated to be in range from 1 to 3 cGy, similar to doses reported for kV cone beam CT on Elekta Synergy machine. The doses for MV cone beam CT vary from 1 cGy to 10 cGy depending on the field size. Thus, the doses for 3D imaging systems used one time each day are in the range of 0.1 to 10 cGy and can contribute from 0.06 to 6% to a daily dose of 1.8 Gy. As a technique of controlling patient dose, it is recommended that a QA procedure be established at each institution to verify the accuracy of the image registration software on a daily basis. This QA check should be performed by the therapists operating a particular treatment device and is aimed at reducing the use of repeat imaging to check that the registration software has functioned properly when a shift of patient position is carried out. Additionally, it is not recommended that an institution use a daily imaging technique that delivery greater than 3 cGy/dy to the patient. This limit dictates that repeat imaging on a particular day is held to a minimum when systems that deliver up to 3 cGy per study are used.

6.7 Quality Assurance

6.7.1 Documentation Requirements

The institution will archive treatment prescription and verification images for later review by the study chair if requested. At least one port film or pretreatment alignment film per field along with the digital reconstructed radiographs (DRRs) from the treatment planning program or, alternatively, a simulation verification radiograph shall be acquired and kept for evaluation if requested except where geometrically impractical.

6.7.2 Compliance Criteria

Cases which meet criteria as stated in Section 6.1.1 will be scored as per protocol. The minimum allowable dose within the PTV is >95% of the prescribed dose to a volume that is at least 0.03cc. Cases in which this small volume of at least 0.03cc receives a minimum dose that

is <95% but >93% or a maximum dose that is >107% and <110% of the prescribed dose will be scored as a variation acceptable. Cases in which such a small volume receives less than 93% or >110% of the prescribed dose will be scored as a deviation unacceptable.

6.7.2.1 Acceptable dose heterogeneity will be as follows: **This maximum dose volume of the PTV must not be shared by a normal critical structure. (Section 6.4.1.5).** The maximum point dose to normal critical structures outside the PTV including the unspecified tissue should not exceed the prescription dose. The treating physician must carefully consider the tolerance dose/volume to each critical normal structure and unspecified tissue.

6.8 Dose Specifications/Technical Considerations: LDR Brachytherapy Boost (12/10/10)

Note: As this protocol allows for treatment with exclusively EBRT or EBRT + brachytherapy (at the discretion of the treating physician) this must be specified at the time of study enrollment. Should a patient who was originally intended to receive brachytherapy be found, post-enrollment, to be a poor brachytherapy candidate based on transrectal ultrasound examination, he will no longer be eligible for participation in this study. Therefore, it is strongly recommended to obtain ultrasound assessment of prospective brachytherapy patients before enrollment on this study.

6.8.1 LDR, permanent seed, brachytherapy boost is permitted at the discretion of the treating radiation oncologist in conjunction with EBRT as described in Section 6.2.2. Implants will only be offered to patients with a prostate volume documented to be <60 cc by transrectal ultrasound examination, an AUA score ≤15, and no prior history of TURP (Section 3.2.8.1). The implant may be performed under either general or spinal anesthesia and will be performed following the EBRT portion of treatment no more than 2 weeks following its completion.

6.8.2 Preplanning

This will be carried out prior to the procedure or intraoperatively via transrectal ultrasound examination. The prostate will be defined from base to apex in the axial plane at 5 mm slice intervals. The treatment length and prostate volume will be recorded. The CTV will consist of the prostate only. The PTV may be the same as the CTV or a 2-3 mm margin may be added anteriorly and laterally and up to 5 mm craniocaudally at the discretion of the treating physician.

6.8.3 Isotope Selection

Iodine-125 or Palladium-103 seeds may be used. The sources will be received and inventoried in accordance with state and federal regulations. If nonsterile loose sources or cartridges are used, at least 10% of the sources will be assayed in such a manner that direct traceability to either the National Institute of Standards and Technology (NIST) or an Accredited Dosimetry Calibration Lab (ADCL) is maintained. NIST 1999 standards will be used. If sterile source assemblies or strands are used, alternatively nonstranded loose seeds equal to 5% of the total, or five seeds, whichever is fewer, may be ordered and assayed. Agreement of the average measured source strength shall agree with that indicated in the vendor's calibration certificate to within 5%. No measured source strengths should fall outside 10% of that indicated in the vendor's calibration certificate.

6.8.3.1 For I-125, the allowable source strength for each seed is 0.277 U to .650 U (NIST 99 or later). For Pd-103 sources, this range is 1.29 U to 2.61 U (NIST 99 or later).

6.8.3.2 The vendor's stated source strength shall be used in all dosimetry calculations. Calculations will be performed in accordance with NIST 1999 calibration standards, the point source formalism described in the report generated by AAPM Task Group 43 and subsequent published AAPM Subcommittee Reports. The AAPM's recommendations for Pd-103 dose specifications and prescription are being followed.

6.8.4 Prescription Doses

The prescription dose for permanent seed interstitial boost will be **110 Gy for I-125 and 100 Gy for Pd-103**. Doses will be prescribed as minimal peripheral dose to the PTV.

6.8.5 Postimplant Imaging

A pelvic x-ray with seed count verification will be obtained immediately postimplant. If the seed count does not match the number of seeds implanted, PA and lateral chest x-rays will be obtained to rule out pulmonary seed migration. CT scan for postimplant dosimetric analysis will be obtained following implant completion. Use of a Foley catheter for this test is encouraged for accurate urethral dosimetry but not required. This may be obtained immediately postoperative on the day of the implant if desired but no later than 5 weeks postimplant. The use of intravesical contrast is encouraged. CT slices should be acquired at ≤3 mm thickness and

should encompass the pelvis from, at minimum, the bottom of the sacroiliac joints superiorly to 2 cm caudal to the prostatic apex.

6.8.5.1 Structures defined will include the prostate, bladder, and rectum. The rectum will be defined from the bottom of the sacroiliac joints to the ischial tuberosity and will extend to the outer surface of the visualized rectal wall. The postimplant, CT-defined prostate will be defined as the "evaluated target volume" (ETV) and will form the basis for dosimetric analysis.

6.8.6 Dosimetry

Postimplant evaluation will be performed on equipment capable of providing structural and volume-based dosimetric assessment on both the target and critical structures. Volume acquisition will be based on contiguous axial CT slices as described above. Both target volume and critical structures will be contoured on each applicable axial slice. Isodose line displays and dose-volume histograms for all structures will be generated.

6.8.6.1 The calculation grid should be set no larger than (2 mm x 2 mm x axial slice width).

6.8.6.2 The planning system shall be capable of transmitting data via DICOM RT to the ITC electronically.

6.8.6.3 Guidelines established by the American Brachytherapy Society[62] are to be followed. DVH-based analysis must be used in the postplan evaluation. The following values shall be reported. Vn is the percentage of the ETV that received at least n% of the prescription dose. Dm is the minimum dose received by m% of the ETV.

6.8.6.4 Target coverage will be documented in terms of V100, V90, V80, D90.

6.8.6.5 Dose uniformity will be expressed in terms of V150.

6.8.6.6 The rectum will be defined from the bottom of the SI joints to the ischial tuberosity. The maximum rectal dose as well as the volume and percentage of rectum receiving >100% of the prescription dose will be recorded.

6.8.7 Compliance Criteria

6.8.7.1 Per protocol: D90 for the ETV is greater than 90% of the prescription dose but less than 130% of the prescription dose.

6.8.7.2 Variation acceptable: D90 for the ETV is greater than 80% of the prescription dose, but less than 90% of the prescription dose, or greater than 130% of the prescription dose.

6.8.7.3 Deviation unacceptable: D90 for the ETV is less than 80% of the prescription dose.

6.8.8 Dosimetric Data to be Submitted to the ITC

6.8.8.1 Copies of preimplant TRUS images with CTV and PTV annotated

6.8.8.2 A copy of the implant record generated during the procedure

6.8.8.3 A copy of the image taken after the procedure and a copy of the image or scout taken during the post implant CT

6.8.8.4 A copy of the postimplant CT scan, ETV and bladder and rectum delineation and dosimetry calculations (must be submitted electronically)

6.8.8.5 A copy of the postimplant dosimetry report that contains the information required in Section 6.8.6 above.

6.8.9 Quality Assurance

Individual case review will be performed by Dr. Morton, the LDR brachytherapy study co-chair overseeing this subgroup of patients enrolled on this protocol, as specified below in Section 6.10.

6.9 Dose Specifications/Technical Considerations: HDR Brachytherapy Boost (12/10/10)

Note: As this protocol allows for treatment with exclusively EBRT or EBRT + brachytherapy (at the discretion of the treating physician) this must be specified at the time of study enrollment. Should a patient who was originally intended to receive brachytherapy be found, post-enrollment, to be a poor brachytherapy candidate based on transrectal ultrasound examination, he will no longer be eligible for participation in this study. Therefore, it is strongly recommended to obtain ultrasound assessment of prospective brachytherapy patients before enrollment on this study.

6.9.1 HDR brachytherapy boost is permitted at the discretion of the treating radiation oncologist in conjunction with EBRT as described in Section 6.2.2. Implants will only be offered to patients with a prostate volume documented to be <60 cc by transrectal ultrasound examination, AUA symptom index $\leq$15, and no prior history of TURP (Section 3.2.8.1). The implant may be performed during the EBRT portion of the treatment or within 1 week prior to its initiation or following its completion. For patients receiving HDR brachytherapy boost who are randomized to Arm 2, RT should begin, as for other modalities, 8 weeks following the first LHRH administration.

The date of HDR brachytherapy implant will constitute the start of RT for those patients receiving implants prior to EBRT.

6.9.2 All implants will be performed under transrectal ultrasound guidance. Epidural, spinal, or general anesthesia may be used. Epidural analgesia may be used for interfraction pain control.

6.9.3 At least 14 treatment catheters should be used to ensure adequate target coverage with acceptable dose heterogeneity.

6.9.4 Fiducial markers identifying the prostatic base and apex should be placed at the time of the implant procedure unless previously placed for guidance of EBRT.

6.9.5 The use of intraoperative cystoscopy is encouraged to ensure the absence of treatment catheters within the urethra or bladder. The cystoscope should be retroflexed within the bladder for visualization of the bladder neck. Light pressure on the treatment catheters should result in mucosal tenting confirming adequate coverage at the prostatic base.

6.9.6 All patients will be treated with a single implant. Two treatment fractions will be delivered prior to its removal. A minimum interval of 6 hours will be allotted between fractions and must be delivered within a single 24-hour period.

6.9.7 Implant Dosimetry (CT or Ultrasound-Based)

6.9.7.1 The treatment planning CT scan must be performed with the patient in the supine position with the Foley catheter in place. Metallic obturators or non-CT compatible dummy ribbons must be removed prior to the CT scan. The scan must include all of the CTV with at least 9 mm superior and inferior margin, and the scan must include the tips of all the implanted catheters. The scan thickness must be ≤0.3 cm and the slices must be contiguous. The brachytherapy target volume (Section 6.9.8) and normal critical structures (Section 6.9.9) must be outlined on all CT slices including the prostate, seminal vesicles, urethra, bladder, and rectum.

6.9.7.2 Real-time, transrectal ultrasound-based planning is acceptable. The prostate must be defined from base to apex in axial slices with a maximum slice thickness of 5 mm. A Foley catheter must be in place for definition of the urethra.

6.9.7.3 Dwell times in positions located outside of the PTV should be turned down or off to minimize normal tissue irradiated. A dwell time optimization program based on implant geometry or an inverse planning algorithm may be used. Manual optimization is also accepted.

6.9.8 The CTV is the prostate gland plus any visualized tumor. The PTV is equivalent to the CTV.

6.9.9 Critical structures to be defined using CT planning include the bladder, rectum, urethra, and penile bulb within the volume of interest defined in Section 6.9.7.1. The outermost extent of the bladder/rectal wall will define those structures. The urethra is defined by the outer surface of the Foley catheter.

6.9.9.1 The volume of bladder and rectum receiving 75% of the prescription dose must be kept to less than 1 cc (V75 <1 cc) and the volume of urethra receiving 125% of the prescription dose must be kept to less than 1 cc (V125 <1 cc). Urethral V150 should be 0%. If the dose to normal critical structures cannot be kept below the specified level, we recommend readjusting the implant or repeating the implant procedure until a more optimal implant is obtained.

6.9.10 Ultrasound-Based Planning

For ultrasound-based planning, the urethra will be defined by the Foley catheter in slices extending from the base to the prostate apex. The anterior rectal wall must be defined along the length of the prostate.

6.9.10.1 Attempts should be made to limit the volume of urethra receiving ≥115% of the prescription dose to ≤5%. Up to 10% will be considered variation acceptable. Dose to > 1 cc of the anterior rectal wall should not exceed 75% of the prescription dose.

6.9.11 Compliance Criteria

A prescription dose of 21 Gy will be delivered to the PTV in two equal fractions of 10.5 Gy. Ninety-five percent coverage of the PTV with the prescription dose is considered per protocol, ≥90% but <95% is considered variation acceptable, and <90% coverage is considered deviation unacceptable. The first fraction of 10.5 Gy will be delivered as soon as possible following completion of the implant procedure and treatment planning. Both fractions must be delivered within a single 24-hour period and separated by a minimum of 6 hours. Overnight hospital stay is permitted between fractions if necessary.

6.9.12 Catheter Position Verification

Visual inspection of the catheters prior to delivery of each treatment is required. Fluoroscopy or CT may be also used to verify the position of the catheters in relation to the Foley catheter

balloon and fiducial markers. The physician may adjust the catheters if catheter displacement is identified prior to the treatment. If the catheters cannot be satisfactorily repositioned and the PTV (Section 6.9.11) and normal critical structure (Section 6.9.9.1) DVH parameters are not met with a new plan, then the treatment should be postponed until a satisfactory implant is done. If the planning process is repeated, then a second set of data should be submitted.

6.9.13 Catheter Removal

After completion of the treatment all catheters will be removed.

6.9.14 Data Submission

All data will be digitally submitted to ITC and include CT data, normal critical structures, all PTV contours, and digital DVH data for all normal critical structures, and the PTV for dose plan.

6.9.14.1 *Contours and Isodose Distributions*

For **CT-planned cases** contours of the PTV and normal critical structures with at least 9 mm in the cephalad and caudal directions must be submitted digitally to ITC. Electronic data transmission will be used after the institution has successfully completed a practice run with the ITC. Institutions previously credentialed for previous prostate brachytherapy protocols need not complete a practice run. For **ultrasound-planned cases**, at least 3 axial slices with the above overlying isodose curves will be submitted. These must include the base plane, apex, and widest axial dimension.

6.9.15 Quality Assurance

Individual case review will be overseen by Dr. Hsu, the HDR brachytherapy study co-chair overseeing this subgroup of patients enrolled on this protocol, as specified in Section 6.10.

6.10 Radiation Quality Assurance Reviews (12/10/10)

The study co-chairs for the respective RT modalities offered in this trial will oversee quality assurance reviews for patients treated in those respective fashions. RT quality assurance reviews will be ongoing and performed remotely. RT quality assurance reviews will be facilitated by RTOG RTQA.

6.11 Radiation Adverse Events

6.11.1 All patients will be seen weekly by their treating radiation oncologist while undergoing therapy. Any observations with respect to the following symptoms/side effects will be recorded:

6.11.1.1 Bowel/rectal irritation manifesting as cramping, diarrhea, urgency, proctitis, or hematochezia

6.11.1.2 Urinary frequency, urgency, dysuria, hematuria, urinary tract infection, or incontinence

6.11.1.3 Radiation dermatitis

6.11.2 Clinical discretion may be used in managing radiotherapy-related side effects. Diarrhea/rectal frequency/urgency may be managed with diphenoxylate or loperamide. Bladder irritation may be mitigated with phenazopyridine. Urinary frequency/urgency can be managed with anticholinergic agents or alpha-blockers such as tamsulosin. Erectile dysfunction can be managed with phosphodiesterase (PDE) inhibitors such as sildenafil.

6.12 Radiation Adverse Event Reporting

See Section 7.5 for additional Adverse Events information and 7.6 for Adverse Event Reporting Guidelines.

7.0 DRUG THERAPY

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.

Patients randomized to receive short-term androgen deprivation therapy must begin this treatment within 4 weeks after randomization. Androgen deprivation therapy will consist of "total androgen blockade" consisting of both LHRH agonist and anti-androgen (either Casodex or Eulexin) for a total duration of 6 months.

7.1 Anti-Androgen Therapy: Casodex (Bicalutamide)

For further information, consult the package insert.

7.1.1 Timing: Oral anti-androgen therapy will begin within (before, same day as, or after) 10 days of the date of the first administration of LHRH agonist for patients randomized to Arm 2 and continued for a total duration of 6 months. The total duration of administered anti-androgen therapy must be documented and submitted to RTOG headquarters.

7.1.2 Description: 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, (+,-). Bicalutamide is a racemic mixture with the antiandrogen activity residing exclusively in the (-) or R-enantiomer. Bicalutamide has a long half-life compatible with once-daily dosing. Bicalutamide is well tolerated and has good response rates in phase II trials.[63,64]

7.1.3 Supply: Commercially available.

7.1.4 Storage: Bicalutamide should be stored in a dry place at room temperature between 68°-77°F.

7.1.5 Administration: Bicalutamide is administered orally at a dose of one 50 mg tablet per day. Bicalutamide will begin within (before, same day as, or after) 10 days of the date of the first LHRH agonist administration, and continue for a total duration of 6 months (i.e. the total duration of planned androgen deprivation). Administration will be suspended only if there is an apparent or suspected reaction to the drug. During RT interruptions, bicalutamide will be continued. Any treatment interruptions or failure of the patient to comply with the prescribed medication schedule must be documented and reported to RTOG headquarters.

7.1.6 Toxicity: Consult the package insert for comprehensive toxicity information. In animal experiments, birth defects (abnormal genitalia, hypospadias) were found in male offspring from female animals dosed with bicalutamide during pregnancy. Although offspring from male animals dosed with bicalutamide did not show any birth defects, patients enrolled in this trial are advised not to cause pregnancy nor donate sperm while receiving protocol therapy or during the first 3 months after cessation of therapy. The use of barrier contraceptives is advised. The most frequent adverse events reported among subjects receiving bicalutamide therapy are breast tenderness, breast swelling, and hot flashes. When bicalutamide 50 mg was given in combination with an LHRH analog, the LHRH analog 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%). Other side effects include impotence and loss of libido, fatigue, and rarely, photosensitivity and diarrhea.

7.1.7 Dose Modifications: AST and ALT will be measured pretreatment and then monthly during antiandrogen therapy. If the AST or ALT rises to ≥ 2x the institutional upper limit of normal, bicalutamide must be discontinued. Elevated AST/ALT values to < 2x the institutional upper limit of normal are subject to dose modifications or discontinuation of anti-androgen at the discretion of the treating physician.

7.2 Anti-Androgen Therapy: Eulexin (Flutamide)

For further information, consult the package insert.

7.2.1 Timing: See Section 7.1.1.

7.2.2 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 nonsteroidal antiandrogen that is metabolized into a hydroxylated derivative, which effectively competes with the hydrotestosterone for androgen receptor sites.

7.2.3 Supply: Commercially available.

7.2.4 Storage: Flutamide should be stored at temperatures ranging from 20-30°C (68-86°F) and protected from excessive moisture.

7.2.5 Administration: Flutamide is administered orally at a dose of 250 mg (two 125-mg capsules) three times a day for a total daily dose of 750 mg. Flutamide will begin within (before, same day as, or after) 10 days of with the date of the first LHRH agonist administration (and continue for a total duration of 6 months. Administration will be suspended only if there is an apparent or suspected reaction to the drug (See Section 7.1.5). During RT interruptions, flutamide will be continued. Any treatment interruptions or failure of the patient to comply with the prescribed medication schedule must be documented and reported to RTOG headquarters.

7.2.6 Toxicity: Consult the package insert for comprehensive toxicity information. The reported side effects of treatment include diarrhea and anemia. A high percentage of patients treated with flutamide alone developed gynecomastia within 2 to 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. Other side effects include impotence and loss of libido, fatigue, and rarely, photosensitivity.

7.2.7 Dose Modifications: If gastrointestinal disturbances (cramps, diarrhea) occur prior to initiation of radiotherapy, flutamide will be withheld until the side effects subside; the drug will then be reintroduced at a dose of 250 mg/day and increased (at 3-day intervals) to 500 mg/day and 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 prostate irradiation, the toxicity will be ascribed to flutamide and the drug will be permanently discontinued. AST and ALT will be measured pretreatment, then monthly during oral antiandrogen therapy. If AST or ALT increase ≥ 2x the institutional upper limit of normal, flutamide must be discontinued. Elevated AST/ALT values to < 2x the institutional upper limit of normal are subject to dose modifications or discontinuation of anti-androgen at the discretion of the treating physician.

7.3 LHRH Agonist Therapy (leuprolide, goserelin, buserelin, triptorelin)

For additional information, consult the package inserts.

7.3.1 Timing: For patients randomized to ADT (Arm 2), the first LHRH administration will occur together with the start of anti-androgen treatment (see Sections 7.1.5 or 7.2.5) 8 weeks prior to the start of RT. The total duration of LHRH therapy will be 6 months. The total administered duration as well as the specific agent used must be documented and submitted to RTOG headquarters.

7.3.2 Description: LHRH agonists are long-acting analogs of the native LHRH peptide and are effective at reducing serum testosterone. Analogs approved by the FDA (or by Health Canada for Canadian institutions) can be used in this study.

7.3.3 Supply: Commercially available. (Note: Buserelin is not commercially available in the United States. It is commercially available for use in Canada and other countries.)

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

7.3.5 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.

7.3.6 Toxicity: Consult the package insert for comprehensive toxicity information. Class-related toxicity is generally a manifestation of the mechanism of action and related to low testosterone levels. In the majority of patients testosterone levels increase above normal in 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 gastrointestinal 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. Other side effects include impotence and loss of libido, weight gain, depression, dizziness, loss of bone density, anemia, increased thirst and urination, unusual taste in the mouth, skin redness or hives, pain at injection site, and muscle mass and strength loss, hair changes, penile length and testicular volume loss, increased cholesterol, hypertension, diabetes exacerbation, emotional lability, nausea, vomiting, and rarely, allergic generalized rash and difficulty breathing.

7.4 Modality Review

All records of ADT administration for patients randomized to Arm 2 should be submitted to RTOG headquarters. Protocol compliance will be assessed at the RTOG semi-annual meetings by the study chair/co-chairs. The recommended ADT duration is six months and will be measured from the day of initial LHRH agonist injection until the final day of activity (e.g. 90-day depot injection preparations given on day 1 and 91 equal 6 months of ADT). Likewise, submitted records of anti-androgen therapy should reflect their total duration of administration, which should mirror the duration of LHRH agonist treatment. The review process is contingent on timely submission of hormone therapy treatment data as specified in Section 12.1. The scoring mechanism is: Per Protocol/Acceptable Variation, Not Per Protocol, and Not Evaluable. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

7.5 Adverse Events (8/17/10) (12/10/10)

Beginning October 1, 2010, this study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for grading of all adverse events. A copy of the CTCAE version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). The CTEP home page also can be accessed from the RTOG web page at http://www.rtog.org/regulatory/regs.html. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. **All AE reporting on the study case report forms will continue to use CTCAE version 3.0.**

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

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

In order to ensure consistent data capture, serious adverse events reported on AdEERS reports also must be reported on an RTOG case report form (CRF). In addition, sites must submit CRFs in a timely manner after AdEERS submissions.

7.5.1 Adverse Events (AEs)

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. January 2005; http://ctep.cancer.gov/reporting/adeers.html]

The following guidelines for reporting adverse events (AEs) apply to **all** NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported on the AE section of the appropriate case report form (see Section 12.1). **Note: AEs indicated in the AdEERS Expedited Reporting Requirements in text and/or table in Section 7.6 also must be reported via AdEERS.**

NOTE: If the event is a Serious Adverse Event (SAE) [see next section], further reporting will be required. Reporting AEs only fulfills Data Management reporting requirements.

7.5.2 Serious Adverse Events (SAEs) — All SAEs that fit any one of the criteria in the SAE definition below must be reported via AdEERS. Contact the AdEERS Help Desk if assistance is required.

Certain SAEs as outlined below will require the use of the 24 Hour AdEERS Notification:

- **Phase II & III Studies: All unexpected potentially related SAEs**
- **Phase I Studies: All unexpected hospitalizations and all grade 4 and 5 SAEs regardless of relationship**

Definition of an SAE: Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Any pregnancy occurring on study must be reported via AdEERS as a medically significant event.

Pharmaceutically supported studies will require additional reporting over and above that which is required by CTEP.

SAEs (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable, or definite) should be reported via AdEERS.

All supporting source documentation indicated as being provided in the Additional Information Section of the AdEERS Report must be properly labeled with the study/case numbers and the date of the event and must be faxed to the RTOG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTOG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTOG trial. The RTOG Case Number without any leading zeros should be used as the Patient ID when reporting via AdEERS. Non-RTOG intergroup study and case numbers must also be included, when applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient's case number as the patient ID when reporting via AdEERS.

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

7.5.3 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the AdEERS system within 30 days of AML/MDS diagnosis. If you are reporting in CTCAE version 4, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment-related secondary malignancy.

7.6 AdEERS Expedited Reporting Requirements

CTEP defines expedited AE reporting requirements for phase 2 and 3 trials as described in the table below. **Important:** All AEs reported via AdEERS also must be reported on the AE section of the appropriate case report form (see Section 12.1).

Phase 2 and 3 Trials Utilizing a Commercially Available Agent: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days[1] of the Last Dose of the Investigational Agent (Bicalutamide, Flutamide, LHRH Agonists) in this Study

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with a commercially available agent require reporting as follows:**

AdEERS 24-hour notification followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 unexpected events

AdEERS 10 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

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

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

March 2005

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

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with a commercially available agent.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing a Commercially Available Agent:

None

8.0 SURGERY

Not applicable to this study

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

9.1.1 Diarrhea/rectal frequency/urgency may be managed with diphenoxylate or loperamide. Bladder irritation may be mitigated with phenazopyridine. Urinary frequency/urgency can be managed with anticholinergic agents or alpha-blockers such as tamsulosin. Erectile dysfunction can be managed with phosphodiesterase (PDE) inhibitors such as sildenafil.

10.0 TISSUE/SPECIMEN SUBMISSION

Note: Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/specimen submission. If the patient consents to participate in the tissue/specimen component of the study, the site is required to submit the patient's specimens as specified in Section 10.0 of the protocol. Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

10.1 Tissue/Specimen Submission

The RTOG Biospecimen Resource at the University of California San Francisco acquires and maintains high quality specimens from RTOG trials. Tissue from each block is preserved through careful block storage and processing. The RTOG encourages participants in protocol studies to consent to the banking of their tissue. The RTOG Biospecimen Resource provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions. The RTOG Biospecimen Resource also collects tissue for Central Review of pathology. Central Review of tissue can be for eligibility and/or analysis.

In this study, tissue will be submitted to the RTOG Biospecimen Resource for the purpose of tissue banking (recommended) and translational research (recommended).

10.2 Specimen Collection for Tissue Banking and Translational Research (Recommended) (12/10/10)

For patients who have consented to participate in the tissue/blood component of the study (See Appendix I). Note: Blood collection is mandatory for patients consenting to the QOL portion of this study and optional for other participants.

The following must be provided in order for the case to be evaluable for the Biospecimen Resource:

10.2.1 One H&E stained slide

10.2.2 A paraffin-embedded tissue block of the tumor core biopsy, or at least ten 5 micron unstained sections on "plus" slides labeled with the surgical pathology number. Block or unstained slides must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.

10.2.3 A Pathology Report documenting that the submitted block or unstained slides contain(s) tumor. The report must include the RTOG protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

10.2.4 A Specimen Transmittal Form clearly stating that tissue is being submitted for the RTOG Biospecimen Resource; if for translational research, this should be stated on the form. The form must include the RTOG protocol number and patient's case number.

10.2.5 Plasma and whole blood cells

See Appendix V for the blood collection kit and instructions. **Note**: Kit includes a label for shipping. The following must be provided in order for the case to be evaluable by the Biospecimen Resource: A Specimen Transmittal Form documenting the date of collection of the plasma and whole blood; the RTOG protocol number, the patient's case number, time point of study, and method of storage, for example, stored at -80° C, must be included.

10.2.6 Storage Conditions

Store frozen specimens at -80° C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:

- Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:

- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:

- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

10.2.7 Specimen Collection Summary

Specimens taken from patient:	Specimens collected when:	Submitted as:	Shipped:
Representative H&E stained slides of the primary tumor	Pretreatment	H&E stained slide	Slide shipped ambient
A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or at least 10 unstained 5 micron sections on "plus" slides	Pretreatment	Paraffin-embedded tissue block or unstained slides	Block or unstained slides shipped ambient
PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1	Pretreatment, during the last week of RT	Frozen plasma samples containing 0.5 mL per aliquot in 1 mL cryovials	Plasma sent frozen on dry ice via overnight carrier

(purple/lavender top) and centrifuge		(up to ten)	
DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) and mix	Pretreatment	Frozen whole blood samples containing 1 ml per aliquot in 1ml cryovials (up to five)	Whole blood sent frozen on dry ice via overnight carrier

10.2.8 Submit materials for Tissue Banking and Translational Research as follows:

U.S. Postal Service Mailing Address: For Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
1657 Scott Street, Room 223
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu

10.3 Reimbursement (12/10/10)

RTOG will reimburse institutions for submission of protocol specified biospecimen materials sent to the Biospecimen Resource at the University of California San Francisco and other protocol-specified collection repositories/laboratories. After confirmation from the RTOG Biospecimen Resource or other designated repository/laboratory that appropriate materials have been received, RTOG Clinical Trials Administration will authorize payment according to the schedule posted with the Reimbursement and Case Credit Schedule found on the RTOG web site (http://www.rtog.org/pdf_document/RTOG_STUDY_LIST.pdf). Biospecimen payments will be processed quarterly and will appear on the institution's summary report with the institution's regular case reimbursement.

10.4 Confidentiality/Storage

(See the RTOG Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/biospecimen/tissuefaq.html for further details.)

10.4.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient's case number only. The RTOG Biospecimen Resource database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.4.2 Specimens for tissue banking will be stored for an indefinite period of time. Specimens for the translational research component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (12/10/10)

See Appendix II for assessments and timeframes. See Sections 11.1.1 to 11.1.6 for details and/or exceptions to Appendix II.

11.1.1 The pelvic +/- abdominal CT or MRI is required for patients with >1 risk factor (Section 3.1.1) and as described in Sections 3.1.2.1 and 3.1.2.2.

11.1.2 Transrectal ultrasound is a one-time test that is required only for patients receiving LDR or HDR brachytherapy boost as a component of their treatment. This should ideally be performed prior to study enrollment as the RT modality (EBRT alone, EBRT + HDR, EBRT + LDR) must be

specified at the time of enrollment. In the event that transrectal ultrasound is performed post-enrollment and results in a change in the RT modality being administered, the patient will no longer be eligible for participation in this study. (See last paragraph of Section 11.3)

11.1.3 The CBC/differential is required only for patients who will receive either LDR or HDR brachytherapy boost (must be known at the time of registration).

11.1.4 See Section 3.1.7 for special circumstances regarding PSA. Also, PSA will be obtained prior to each follow-up visit.

11.1.5 Serum testosterone need only be obtained from patients randomized to receive ADT (Arm 2) at the time of study entry (baseline prior to starting ADT), at the start of RT (8 weeks following 1st LHRH agonist administration)—may be performed in conjunction with timing of AST/ALT/alkaline phosphatase—and every 6 months until rising to baseline levels or for 3 years (whichever is sooner).

11.1.6 Patients receiving anti-androgen therapy (Arm 2) will need monthly liver function testing (AST, ALT, alkaline phosphatase) for the duration of that treatment.

11.2 Measurement of Response

11.2.1 Overall survival is the primary study endpoint and the event date of overall survival will be the date of death due to any cause.

11.2.2 Biochemical failure is defined as the documented rise of 2 ng/ml above its post-treatment nadir value.

11.2.3 Local recurrence is defined as the documented local recurrence as follows: Patients with clinical (palpable) suspicion of local recurrence following treatment completion should undergo biopsy for pathologic confirmation of local recurrence. Once pathologic confirmation is obtained, the event date will be the date at which the palpable progression was first identified. In the event of biochemical failure (nadir + 2 ng/ml), metastatic workup including, at minimum, chest x-ray, bone scan, and abdominopelvic CT should be obtained to exclude the possibility of distant failure. If negative, prostate biopsy should be performed. If positive, biochemical failure will be considered the local recurrence event.

11.2.4 Regional recurrence is defined as the documented progression in pelvic lymph nodes. If discovered on CT of the pelvis prompted by a biochemical failure, then the event date will be the date of documented biochemical failure.

11.2.5 Distant failure is defined as the documented metastatic disease by any method. If diagnosed on diagnostic imaging prompted by biochemical failure, then the event date will be the date of biochemical progression.

11.2.6 Freedom from failure is defined as the first event of biochemical failure, local recurrence, regional recurrence, or distant metastasis, as described above.

11.2.7 Prostate cancer specific mortality is defined as a death due to prostate cancer or a complication from treatment

11.2.8 Non-prostate cancer specific mortality is defined as a death without evidence of prostate cancer or a complication from treatment.

11.2.9 Rate of salvage ADT administration is defined as the first administration of subsequent ADT (either LHRH agonist or anti-androgen) is given.

11.3 Criteria for Discontinuation of Protocol Treatment

Patients who are experiencing excessive adverse events as deemed by their treating physician may be discontinued from the initiated protocol treatment. All attempts should be made to manage adverse events adequately so as to avoid this circumstance. As specified in Sections 7.1 and 7.2, anti-androgen therapy will be withheld if AST/ALT values are elevated to ≥ 2x the institutional upper limit of normal.

Study analysis will be based on “intent to treat.” If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol.

11.4 Health-Related Quality of Life (HRQOL)

Note: Patients must be offered the opportunity to participate in the correlative components of the study, such as quality of life assessment. If the patient consents to participate in the quality of life component of the study, the site is required to administer the QOL assessments as specified in Section 11.0 of the protocol. Sites are not permitted to delete the quality of life component from the protocol or from the

sample consent. **Blood collection is <u>mandatory</u> for patients consenting to the QOL portion of this study.**

11.4.1 <u>Prostate Cancer-Specific Health-Related Quality of Life: EPIC</u>

The Expanded Prostate Cancer Index Composite (EPIC) is a prostate cancer health-related quality of life (HRQOL) patient self-administered instrument that measures a broad spectrum of urinary, bowel, sexual, and hormonal symptoms related to RT and ADT.[29] Instrument development was based on advice from an expert panel and prostate cancer patients, which led to expanding the 20-item University of California-Los Angeles Prostate Cancer Index (UCLA-PCI) to the 50-item EPIC. Summary and subscale scores were derived by content and factor analyses. Test-retest reliability and internal consistency were high for EPIC urinary, bowel, sexual, and hormonal domain summary scores (each r ≥0.80 and Cronbach's alpha ≥0.82) and for most domain-specific subscales. Correlations between function and bother subscales within domains were high (r >0.60). Correlations between different primary domains were consistently lower, indicating that these domains assess distinct HRQOL components. EPIC domains had weak to modest correlations with the Medical Outcomes Study 12-item Short-Form Health Survey (SF-12), indicating rationale for their concurrent use. Moderate agreement was observed between EPIC domains relevant to the Functional Assessment of Cancer Therapy Prostate module (FACT-P) and the American Urological Association Symptom Index (AUA-SI), providing criterion validity without excessive overlap.[65]

EPIC is a robust prostate cancer HRQOL instrument that measures a broad spectrum of symptoms; however, to decrease patient burden we will only use the domains most pertinent to this study: urinary, bowel, sexual, and hormonal. The domains were validated separately, and since each domain will be used intact, there is no threat to validity. Dutch and Japanese translations of the EPIC are available, and a Spanish translation is planned but not yet available.

11.4.2 <u>Patient-Reported Outcome Measurement Information System (PROMIS)-Fatigue Short Form</u>

The PROMIS fatigue measure (7 items) was developed by the Patient-Reported Outcome Measurement Information System (PROMIS), part of the NIH Roadmap Initiative, focused on developing a publicly available resource of standardized, accurate, and efficient PRO measures of symptoms, distress, and functioning. Two content domains of fatigue, experience and impact, were identified by a panel of experts. An item pool of 58 fatigue experience and 54 fatigue impact items were developed. The psychometric properties of these items were evaluated in a sample of 450 individuals from the general US population using classical test theory indices, monotonicity, and scalability. The expert panel selected the 10 best items in each domain. These 20 items were presented to a panel of clinical experts. Only one item was dropped because of redundancy. A preliminary fatigue short-form measure of 7 items was created using items selected for consistency in the response scale, broad coverage across the fatigue continuum (i.e., high to low), and good precision of measurement (discrimination function).

11.4.3 <u>Quality-Adjusted Survival Analysis: EuroQol (EQ-5D)</u>

The EQ-5D is a patient self-administrated questionnaire that takes approximately 5 minutes to complete.[66] The first part consists of 5 items covering 5 dimensions including: mobility, self care, usual activities, pain/discomfort, and anxiety/depression. Each dimension can be graded on 3 levels: 1-no problems, 2-moderate problems, and 3-extreme problems. Health states are defined by the combination of the leveled responses to the 5 dimensions, generating 243 (3^5) health states to which unconsciousness and death are added.[67]

The 5-item index score is transformed into a utility score between 0, “Worst health state,” and 1, “Best health state.” The index score can be used in a quality adjusted survival analysis depending on the health state(s) of interest.[68] For this study we plan to report the multidimensional utilities for comparative purposes. The EQ-5D has now been translated into most major languages, with the EuroQol Group closely monitoring the translation process; translations can be accessed at www.euroqol.org.

11.4.4 <u>Pittsburgh Sleep Quality Index (PSQI)</u>

Sleep quality will be measured by 1 item (Q3) of the Pittsburgh Sleep Quality Index (PSQI), a self-rated questionnaire which measures sleep quality and disturbances.[42] The Pittsburgh Sleep Quality Index (PSQI) was developed to discriminate between good and poor sleepers. The PSQI has good internal consistency (Cronbach’s alpha=0.83), stability (test-retest

reliability=.85, P<.001) and discriminant validity. It has been used in patients with cancer and demonstrated sleep problems as expected.[42]

11.4.5 Godin Leisure-Time Exercise Questionnaire (GLTEQ)

Participants' level of physical activity will be assessed using the Godin Leisure-Time Exercise Questionnaire (GLTEQ),[43,44] which measures time spent per week in each of light, moderate, and vigorous activities. A score can be computed for each level of exercise. A total score is computed by summing the three levels weighted by their respective metabolic (MET) equivalents of 3, 5, and 9. The GLTEQ has good test-retest reliability and has shown convergent validity with both objective and other self-report measures of physical activity.[43,44]

12.0 DATA COLLECTION

Data should be submitted to:

RTOG Headquarters*
1818 Market Street, Suite 1600
Philadelphia, PA 19103

***If a data form is available for web entry, it must be submitted electronically.**

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission (12/10/10)

Item	Due
Demographic Form **(A5)** Initial Evaluation Form **(I1)** Pathology Report **(P1)** Pathology Material **(P2)**	**Within 2 weeks of study entry**
EPIC **(FA)** PROMIS **(HP)** EQ-5D **(QF)** PSQI/GLTEQ Form **(QL)**	
Post Treatment Evaluation Form **(F0)**	**ARM 2 only: At the start of RT and 3 months post RT**
Follow-up Form **(F1)**	**ARM 1: At 3 months, 6 months, 9 months, and 12 months after completion of RT, then every 6 months for 4 years, then annually** **ARM 2: At 6 months, 9 months, and 12 months after completion of RT, then every 6 months for 4 years, then annually**
EPIC **(FA)** PROMIS **(HP)** EQ-5D **(QF)** PSQI/GLTEQ Form **(QL)**	**During the last week of RT and at 6 months, 1 year and 5 years after completion of RT**
Autopsy Report **(D3)**	**At the time of death (if available)**

12.2 Summary of Dosimetry Digital Data Submission (Submit to ITC; see Section 12.2.2) [12/10/10]

Item	Due
Preliminary Dosimetry Information (DD)	

Digital Data Submission – Treatment Plan submitted to ITC via SFTP account exported from treatment planning machine by Physicist Digital data submission includes the following: • CT data, critical normal structures, all GTV, CTV, and PTV contours • Digital beam geometry for initial and boost beam sets • Doses for initial and boost sets of concurrently treated beams • Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan **(DV)**	**Within 1 week of start of RT**
Digital Data Submission Information Form **(DDSI)** – Submitted online (Form located on ATC web site, http://atc.wustl.edu/forms/DDSI/ddsi.html)	
Hard copy isodose distributions for total dose plan **(T6)**	
NOTE: Sites must notify ITC via e-mail (itc@wustl.edu) after digital data is submitted. The e-mail must include study and case numbers or, if the data is phantom, "dry run" or "benchmark".	
Final Dosimetry Information Radiotherapy Form **(T1)** [for EBRT ALONE] **[copy to HQ and ITC]**	**Within 1 week of RT end**
Daily Treatment Record **(T5) [copy to HQ and ITC]** **NOTE: A second T5 must be submitted for patients opting for brachytherapy boost** Modified digital patient data as required through consultation with Image-Guided Therapy QA Center	

NOTE: ALL SIMULATION AND PORTAL FILMS AND/OR DIGITAL FILM IMAGES WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.

12.2.1 **Digital Data Submission to ITC**

The following forms are to be submitted to ITC via http://atc.wustl.edu/.

Item	Due
Post-implant evaluation CT scan	**3-5 weeks post implant**
Post-implant structure set	
Post-implant plan	
Post-implant dose distribution	
Radiotherapy Form **(T1) [**for EBRT WITH BRACHYTHERAPY]	**5 weeks post implant**

NOTE: Copies of simulation and port films/images will be submitted to RTOG Headquarters ONLY if specifically requested.

12.2.2 *Digital Data Submission to ITC*

Digital data submission may be accomplished using media or the Internet.

For network submission: The SFTP account assigned to the submitting institution by the ITC shall be used, and e-mail identifying the data set(s) being submitted shall be sent to:

itc@wustl.edu

For media submission: Please contact the ITC about acceptable media types and formats. Hardcopies accompanying digital data should be sent by mail or Federal Express and should be addressed to:

Image-Guided Therapy Center (ITC)
ATTN: Roxana Haynes
4511 Forest Park, Suite 200
St. Louis, MO 63108
314-747-5415
FAX 314-747-5423

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints (12/10/10)

13.1.1 Primary Endpoint

Overall survival (OS): The failure event for OS will be death due to any cause (See Section 11.2.1).

13.1.2 Secondary Endpoints

13.1.2.1 Biochemical failure by the Phoenix (nadir + 2) defintion[60] (See Section 11.2.2)
13.1.2.2 Local recurrence (See Section 11.2.3)
13.1.2.3 Regional recurrence (See Section 11.2.4)
13.1.2.4 Distant metastasis (See Section 11.2.5)
13.1.2.5 Freedom from failure (FFF) (See Section 11.2.6)
13.1.2.6 Prostate cancer-specific mortality (See Section 11.2.7)
13.1.2.7 Non-prostate cancer-specific mortality (See Section 11.2.8)
13.1.2.8 Rate of salvage ADT (See Section 11.2.9)
13.1.2.9 Rates of OS for patients treated with the 3 different RT modalities in each arm
13.1.2.10 Incidence of "acute" adverse events (based on CTCAE, v. 3.0): The acute adverse events will be the first occurrence of worst severity of the adverse event ≤30 days of the completion of RT.
13.1.2.11 Time to "late" grade 3+ adverse events (based on CTCAE, v. 3.0): The time of a first late grade 3+ adverse event, defined as >30 days from the completion of RT.
13.1.2.12 Comparison of prostate cancer-specific health related quality of life (HRQOL) change as measured by the EPIC (urinary, bowel, sexual, and hormonal domain)
13.1.2.13 Comparison of fatigue status as measured by the Patient-Reported Outcome Measurement Information System (PROMIS) fatigue domain
13.1.2.14 Assessment and comparison of Quality Adjusted Life Years (QALYs)
13.1.2.15 Correlation between the fatigue PROMIS score change and plasma cytokine change
13.1.2.16 Collect paraffin-embedded tissue blocks, plasma and whole blood for future translational research analyses

13.2 Sample Size

The sample size calculation addresses the specific primary hypothesis that the OS rate at 5 years in Arm 2 will be better than in Arm 1. Assume an exponential survival distribution for each arm and define λ_1 is the hazard rate for Arm 1 and λ_2 is the hazard rate for Arm 2. (H_A: $\lambda_1 > \lambda_2$).

$$H_0: \lambda_1 \leq \lambda_2 \text{ vs. } H_A: \lambda_1 > \lambda_2$$

Based on the prior results from multiple dose-escalation trials in which patients were treated without androgen deprivation, we project that the rate of 5-year OS of Arm 1 is 90% (a yearly hazard rate of 0.0211). The study is designed to show an absolute improvement of 3.3% in the 5-year overall survival rate (i.e., a 5-year overall survival rate of 93.3%), which translates to a yearly hazard rate of 0.0139 in Arm 2. An exponential distribution for overall survival distribution was assumed for each arm. Three interim analyses and a final analysis are planned for early stopping for the efficacy and futility. The efficacy testing is based on the power family of test[69] with Δ=0 and the futility testing is based on the Freidlin and Korn[70] method at a nominal significance level of 0.005. Two hundred twenty deaths are required to detect a 34% relative reduction in the yearly death rate with 85% statistical power using a one-sided log-rank test at the 0.025 significance level. After adjusting the sample size for these interim analyses, the sample size per arm for the

hypotheses is 684. Guarding against an ineligibility or lack-of-data rate of up to 10%, **the final targeted accrual for this study will be 1520 patients.**

13.3 Accrual and Duration (12/10/10)

The proposed trial, RTOG 0815, builds on the experience obtained in RTOG 0126. RTOG 0126 involved a similar group of patients treated with dose-escalated radiotherapy and accrued 1431 patients over 6 years at an average rate of 20 cases per month. We are estimating an average of 20 cases per month in the new trial. We expect RTOG 0815 to complete accrual in 6.3 years. Based on patient accrual in previous RTOG randomized prostate studies, there will be relatively few entries during the initial 6 months while institutions are obtaining IRB approval. The total duration of the study is expected to be 11.3 years from the time the first patient is entered to the final analysis under the null hypothesis, the hazard rate of Arm 2 will not be better than that of Arm 1, and a uniform accrual rate of 20 patients per month.

The RTOG Data Monitoring Committee (DMC) will begin evaluating patient accrual semiannually following the anticipated quiet period. In accordance with CTEP policies for slowly accruing trials, if the average monthly accrual rate for the trial in the fifth and sixth quarters after study activation (i.e., in months 13-18) is less than 20% of the rate projected in the paragraph above (i.e., less than 4 patients per month), the study will close to further accrual. If the average monthly accrual rate is greater than 20% but less than 50% of projected (i.e., fewer than 10 patients per month), the trial will be placed on probation for 6 months. If the average monthly accrual rate at the end of the probationary period is less than 50% of projected, the study will close to future accrual. The participation of non-RTOG institutions through CTSU is expected to follow a similar pattern as seen in RTOG.

13.4 Analysis Plan (12/10/10)

13.4.1 Analysis of the Primary Endpoint

The primary endpoint is overall survival (OS). The time to failure for overall survival will be measured from the date of randomization to the date of documented death due to any cause. The overall survival function will be estimated by the Kaplan-Meier method.[71] We want to test whether or not the overall survival rate in Arm 2 is higher than that of Arm 1. The null and alternative hypotheses are:

$$H_0: \lambda_1 \leq \lambda_2 \text{ vs. } H_A: \lambda_1 > \lambda_2$$

where, λ_1 and λ_2 are yearly death rate for Arm 1 and Arm 2, respectively. We will use the log-rank test[72,73] with a significance level of 0.025 at the final analysis to test this hypothesis. In addition, the Cox proportional hazard regression model[74] will be used to compare the treatment differences. Both adjusted and unadjusted hazard ratios and the respective 95% confidence interval will be computed. The number of risk factors (1 vs. 2 or 3), comorbidity status (ACE-27 grade ≥ 2 vs, < 2), and RT modality (EBRT vs. EBRT+LDR brachytherapy boost vs. EBRT+HDR brachytherapy boost), age, and race (as appropriate) will be adjusted for in this analysis.

13.4.2 Biochemical Failure by Phoenix Definition and Freedom From Failure

The freedom from failure (FFF) rate by 5 years is defined as the proportion of patients without events of FFF failure by 5 years from randomization among all eligible patients at baseline. The failure events for FFF will be the first occurrence of clinical failure (local recurrence, regional recurrence, or distant metastasis), biochemical failure by the Phoenix definition (PSA ≥2 ng/ml over the nadir PSA).[60] Patients who are event free with less than 5 years of follow-up, die due to any cause, or who receive any salvage therapy (e.g., salvage androgen deprivation, vaccine therapy, biologic/small molecule therapy, or chemotherapy) will be censored. The biochemical failure (BF) rate by 5 years is defined in a similar way; the proportion of patients with biochemical failure by 5 years (PSA ≥2 ng/ml over the nadir PSA)[60] from randomization among all eligible patients at baseline. The salvage ADT is defined as the first administration of subsequent ADT (either LHRH agonist or anti-androgen). The rate of salvage ADT is defined as the proportion of patients who have salvage ADT by 5 years among all eligible patients at baseline. The endpoint FFF rate by 5 years will be estimated by the Kaplan-Meier method[71] and the BF rate by 5 years will be estimated by cumulative incidence method.[75]

The Z-test statistic for the difference between the 2 rates with the standard errors estimated by Greenwood's method will be used, with a significance level of 0.025. The following test statistics (T.S.) will be used for testing between the 2 arms:

$$T.S. = \frac{(1-\hat{p}_1)-(1-\hat{p}_2)}{\sqrt{\hat{p}_1^2\sum_{i=1}^{n_1}\frac{f_i}{r_i(r_i-f_i)}+\hat{p}_2^2\sum_{j=1}^{n_2}\frac{f_j}{r_j(r_j-f_j)}}} = \frac{\hat{p}_2-\hat{p}_1}{\sqrt{\hat{p}_1^2\sum_{i=1}^{n_1}\frac{f_i}{r_i(r_i-f_i)}+\hat{p}_2^2\sum_{j=1}^{n_2}\frac{f_j}{r_j(r_j-f_j)}}} \quad (1)$$

where $\hat{p}_1$ and $\hat{p}_2$ are the FFF, BF, or the salvage ADT rate of Arm 1 and Arm 2, respectively, estimated by the Kaplan-Meier method or cumulative incidence method, r_i is the number of patients who are at risk and f_i is the number of patients who have FFF, BF, or the salvage ADT failure events (i=1,2). If H_0 is rejected, then we conclude that Arm 2 is better than Arm 1. If H_0 is not rejected, then we conclude that Arm 2 is not better than Arm 1.

In addition, logistic regression[76] will be used to compare the treatment differences in the hypothesis with and without adjustment for at least the following covariates; the number of risk factors (1 vs. 2 or 3), comorbidity status (ACE-27 grade ≥ 2 vs, < 2), and RT modality (EBRT vs. EBRT+LDR brachytherapy boost vs. EBRT+HDR brachytherapy boost), age, and race (as appropriate). Odds ratios and the respective 95% confidence intervals will be computed.

13.4.3 Time to Failure of Secondary Survival Endpoints

The time to failure for secondary endpoints (local recurrence, regional recurrence, distant metastasis, prostate cancer-specific mortality, non-prostate cancer specific mortality) will be measured from the date of randomization to the date of the event of interest. The failure events for the secondary endpoints are defined as follows—local recurrence: biopsy-proven failure within the prostate/seminal vesicles; distant metastasis: clinical and/or radiographic appearance of disseminated disease; prostate cancer-specific mortality: death due to prostate cancer; non-prostate cancer-specific mortality: death in a patient with disease clinically controlled.

The treatment effect on these failures may impact the observable measures of outcomes (local recurrence, regional recurrence, distant metastasis, prostate cancer-specific mortality, non-prostate cancer-specific mortality) and other competing risks may dilute the sensitivity. We will use the cause-specific hazard rate[77,78] (the instantaneous rate of cause-specific mortality in the presence of competing failure types as a function of time) approach to consider the competing events. Freidlin and Korn[70] showed that the cause-specific hazard rate approach is better than other approaches, for example, the cumulative incidence method,[75] in most cases. The log-rank test on the times to the specific type of failure, which considers the presence of competing events, will be used to test whether the survival rates of these secondary endpoints in one arm are higher than that of the other arm for each hypothesis at a significance level of 0.025. In this approach, patients who experience other failure first are censored. In addition, Fine and Gray's regression[79] will be used for these secondary survival outcomes. Both unadjusted and adjusted hazard ratios and the respective 95% confidence interval will be computed. At least the treatment arm, the stratification variables (the number of risk factors, comorbidity status, and RT modality), age, and race (as appropriate) will be adjusted for in this analysis.

13.4.4 Estimation of Rates of OS of Patients Treated with the Different RT Modalities

Three different RT modalities are allowed for this trial: EBRT, EBRT+LDR brachytherapy boost, and EBRT+HDR brachytherapy boost. The rate of OS for patients treated with an RT modality among three modalities is defined as the proportion of patients who are treated with an RT modality and alive at 5 years from the randomization among all eligible patients treated with the RT modality at baseline. This rate will be estimated in each arm separately.

13.4.5 Comparison of the Incidence of Acute Adverse Events and Time to Late Grade 3+ Adverse Events and Correlation with Pre-Existing Comorbidity with Adverse Events

Adverse events are scored according to CTCAE, v. 3.0. An acute adverse event will be defined as the first occurrence of worst severity of the adverse event occurring less than or equal to 30 days after the completion of RT. Univariate logistic regression[76] will be used to model the distribution of acute adverse events. Multiple logistic regression[76] will be used to model the

distribution of acute adverse events adjusted for covariates. Both unadjusted and adjusted odds ratios and the respective 95% confidence interval will be computed and tested using a one-sided Chi-Square test statistic with the significance level of 0.025. Late grade 3+ adverse events will be defined as grade 3+ adverse events occurring more than 30 days after the completion of RT. The time to late grade 3+ adverse events will be measured from the time protocol treatment started to the time of the worst late grade 3+ adverse event. If no such late adverse event is observed until the time of the analysis, the patient will be censored at the time of the analysis. Death without late adverse event will be considered as the competing risk for late adverse events and the distribution of time to late grade 3+ adverse events will be estimated using the cumulative incidence method[75] and tested using a one-sided Gray's test statistic[75] with the significance level of 0.025. A Fine and Gray's regression model[79] will be used to compare the treatment differences of time to late adverse event with and without adjusting for other covariates. Both unadjusted and adjusted hazard ratios and the respective 95% confidence interval will be computed. At least the treatment arm, the stratification variables (the number of risk factors and RT modality), age, and race (as appropriate) will be considered when it is adjusted in the analysis.

The correlation of acute adverse events and the ACE-27 grade (≤ 2 vs. 2) will be calculated by Chi-square test statistics at the significance level of 0.05. The acute toxicity will be considered in two ways: 1) absent or present or 2) ≥ grade 3 or < grade 3. The correlation of late adverse events (≥ grade 3 vs. < grade 3) and the ACE-27 grade (≤ 2 vs. 2) will be calculated by Chi-square test statistics at the significance level of 0.05.

13.4.6 Analysis for Endpoints Related to Quality of Life (QOL)

Patient accrual for the QOL measurements will be limited to 200 cases in each arm.
Quality of life will be assessed via the following instruments: the Expanded Prostate Cancer Index (EPIC), the Patient-Reported Outcome Measurement Information System (PROMIS) fatigue domain, and the EuroQol (EQ-5D).

Information regarding potential confounds will also be collected in a short form (QL) using limited questions to minimize patient burden. This information can be used to evaluate the potential impact of these confounding factors on fatigue. Patient responses to the following will be collected in the QL form: muscle weakness (one item), overall sleep quality as measured by one item from the Pittsburgh Sleep Quality Index (PSQI),[42] and level of physical activity as measured by the Godin Leisure-Time Exercise Questionnaire (GLTEQ).[43,44] Anxiety/depression is also a potential confound with fatigue and patient responses to the anxiety/depression item in the EQ-5D can be used.

Protocol-eligible patients will be included in the QOL analysis only if they agree to participate in the QOL portion of this study. All the QOL instruments (EPIC, PROMIS fatigue domain, EQ-5D) will be collected on all cases participating in this portion of the trial. Patients will complete the EPIC, PROMIS fatigue domain, and the EQ-5D at pretreatment (baseline), week 3 of RT, at the last week of RT, and at 6 months, 1 year, and 5 years after the end of RT. At the same time points, the QL form (i.e., one item from the PSQI, 3 items from the GLTEQ, and one question regarding general muscle weakness) will be collected. To minimize missing QOL data, we have included detailed instructions for collection of QOL and what to do if the patient misses a scheduled assessment, and RTOG provides individualized patient calendars available to Investigators and Research Associates 24/7 on the RTOG web site.

We will describe the distributions of QOL data collection patterns over all collection points in each treatment arm. Longitudinal data analysis, specifically the general linear mixed-effect model[80] will be performed to describe the change trend of the EPIC, PROMIS fatigue domain, and the EQ-5D across the 2 treatments. The primary objective in HRQOL analysis is to determine the QOL differences. The response will be the change of measurement from baseline for each measurement. The model will include the baseline and stratification variables (the number of risk factors, comorbidity score, and RT modality).

Patient self-assessment of symptoms will be performed using 4 primary EPIC domains: urinary, bowel, sexual, and hormonal symptoms. The PROMIS fatigue domain consists of 7 questions to quantify the fatigue continuum (i.e., high to low), and good precision of measurement

(discrimination function). Each question has a 5-point Likert scale (1-never, 2-rarely, 3-sometimes, 4-often, 5-always). The EQ-5D is a 2-part self-assessment questionnaire and only the first part will be used. This consists of 5 items covering 5 dimensions (mobility, self care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is measured by a 3-point Likert scale (1-no problems, 2-moderate problems, and 3-extreme problems). There are 243 (=3^5) health states. We will transform the 5-item index score into a utility score between 0 (worst health state) and 1 (best health state) for comparative purposes. We hypothesize that the measurements from the EPIC will be worse in Arm 2 than Arm 1 because of the aggressiveness of treatment. We also hypothesize that measurements from the PROMIS fatigue domain will be higher in Arm 2 than in Arm 1.

To address the non-ignorable missing data caused by censoring survival time, the data analysis also will include patients who have not died. To examine trade-offs between survival time and QOL, we will combine them for each patient into a single measurement: Quality Adjusted Life Year (QALY). If (and only if) the primary endpoint hypothesis is substantiated, we will conduct a cost-utility analysis. The cost-utility analysis will not be done until after the primary endpoint results are published. QALY is defined by the weighted sum of different time episodes added up to a total quality-adjusted survival time. These health state-based methods of quality-adjusted survival analysis are known as the quality-adjusted time without symptoms and toxicity method (Q-TwiST).[45]

$$\text{Q-TwiST} = \sum_{i=1}^{k} q_i \, s_i$$

where q_i is the quality (the utility coefficient) of health state i, s_i is the duration spent in each health state, and k is the number of health states. We will use Glasziou's multiple health-state (Q-TwiST) models to use the repeated measures of EQ-5D. Because Glasziou's method incorporates longitudinal QOL data into an analysis of quality-adjusted survival, the health-stated model must be constructed on the following assumptions:

A1) QOL is independent from treatment.
A2) A health state is independent from previous states.
A3) Proportionality of quality-adjusted duration and duration of the actual state of health

Assumption A1 can be checked by plotting QOL over time according to treatment, and the *t* test can be used to compare the mean QOL scores of each treatment arm. Assumption A2 can be checked by comparing the QOL for patient groups in a given health state where the groups are defined by duration of previous health state experience using a regression model. Suitable checks for assumption A3 at minimum would be a simple plot. If data does not support these assumptions, we will use a method which uses the longitudinal QOL data directly. Cost-utility will be analyzed at 2 time points: at 1 year and 5 years posttherapy. We will use the 5-item utility score in EQ-5D for the cost-utility analysis. We will use the Z-test to test the hypothesis that the cost-utility in the 2 treatment arms is the same with a significance level of 0.05 and a 2-sided test.

To inspect the missing data mechanism, we will use at least a graphical method. A missing completely at random (MCAR) mechanism exists when missing values are randomly distributed across all observations. A missing at random (MAR) mechanism exists when values are not randomly distributed across all observations, rather than one or more sub-samples. If the cause of missing data is MCAR, listwise deletion (complete case analysis) will be done. If the MAR assumption is supported by the data, then an imputation method such as multiple imputation will be applied to impute missing data. If the MAR assumption is not supported by the data, then adjusting for covariates (such as the baseline QOL score) might reduce the conditional association between outcomes and missing values. If missing data patterns look similar when stratified by such covariate(s), then an analysis that adjusts for such covariate(s) will be conducted and an imputation method such as multiple imputation will be applied. If approximate conditional independence cannot be obtained with any set of covariates, then MNAR (missing not at random) must be addressed by an explicit model for the missing data mechanism and then an imputation method such as multiple imputation will be applied. All results from the imputed analysis using the multiple imputation will be compared to the

complete case analysis results to assess any potential biases. We will conduct a sensitivity analysis using various assumptions on the missing data to determine what impact missing data and imputation methods have on the study conclusions. Imputation methods when prescribed by validated instrument developers will be employed first. Additional methods or methods used when none are described for a given instrument may include linear mixed-effects models to obtain separate estimates for the QOL outcome within strata based on missing data patterns.[81,82] RTOG recognizes that all options are subject to bias and analysis with more than one method for consistency across methods is prudent.

13.4.7 Correlation Between the Fatigue PROMIS Score Change and Plasma Cytokine Change

Four hundred patients participating in the QOL portion of this trial will be used for this analysis. The analysis will be done in each arm separately to test the prognostic vales of biomarkers. At least the following plasma cytokines will be evaluated: CRP, TNF alpha, IL-1, IL-1ra, and IL-6. The highest fatigue is typically reported and plasma cytokine levels are known to be altered in the third to fourth week of radiation therapy (RT). Therefore, the evaluation time point will be 3 weeks after the start of RT. The fatigue PROMIS score change for each item will be calculated by subtracting the fatigue PROMIS score at 3 weeks following the start of RT from the baseline score. Similarly, the cytokine change will be calculated by subtracting the plasma cytokines measurement at 3 weeks following the start of RT from the baseline measurement. The fatigue PROMIS score change ranges from -4 to 4 (1-5 for each item). This will be categorized in a meaningful group at the time of analysis. The measure of each cytokine change will be a continuous variable. At the least, an Analysis of Variance (ANOVA) will be conducted to see if there is a correlation between the fatigue PROMIS score change and plasma cytokine change. Additional methods, such as linear mixed-effects, will be used. Additional time points will be tested in a similar way**.**

13.4.8 Collect paraffin-embedded tissue blocks, plasma, and whole blood for future translational research analyses

The feasibility of proposed translational studies will be assessed following completion of accrual and sample collection. At the time of data maturity of this study, we will propose specific details of the markers to be investigated. We will address the assays that will be used and a list of specific correlative aims with appropriate statistical considerations.

13.4.9 Group Sequential Testing for Early Termination and Reporting of Efficacy and Futility

A group sequential test with 3 planned interim analyses and a final analysis will be performed. The interim analysis will be carried out when the cumulative deaths are met. At each planned interim analysis, the p-value from the log-rank test statistic assessing treatment efficacy and futility with respect to the primary endpoint, OS, will be compared to the nominal significance level. The efficacy testing is based on the power family of test[69] with Δ=0 (see Table 2 for nominal significance level for efficacy testing) and for the futility testing boundary we will use a less aggressive boundary, Rule C (at a nominal significance level of 0.005) in Freidlin and Korn.[70] The following hypotheses are tested:

$$H_0: \lambda_1 \leq \lambda_2 \text{ vs. } H_A: \lambda_1 > \lambda_2$$

where λ_1 and λ_2 are the hazard rate for Arm 1 and Arm 2, respectively. If the H_0 is rejected, then we conclude that the OS rate of Arm 2 will be better than Arm 1 and stop accrual if applicable.

Table 2: Schedule for the Planned Interim Analysis

Information Time	Estimated Analysis Time*	Cumulative Number of Deaths in the Two Arms	Nominal Significance Level for Efficacy (Z-value)
0.25	4.7 years	55	0.0001 (4.049)
0.50	6.8 years	109	0.0018 (2.863)
0.75	8.9 years	163	0.015 (2.338)
1.00	11.1 years	218	0.025 (2.024)

*Time to the interim analysis from the first patient entry without considering ineligibility or lack-of-data rate and under the null hypothesis

For futility testing, the alternative hypotheses, H_A ($\lambda_1 = \lambda_2 + 0.0072$) will be tested at 0.005 level (the futility nominal significance level). If the computed p-value is less than 0.005 then we will

consider stopping the trial in favor of the H_0 and conclude that the overall survival rate of Arm 1 will be better than Arm 2. Otherwise, we will continue the trial.

Based on the results of each interim analysis, the following action will be taken and the responsible statistician will recommend to the RTOG Data Monitoring Committee (DMC) that the randomization be discontinued, if applicable, and the study be considered for early publication. Before making such a recommendation, the accrual rate, treatment compliance, safety of the treatments, and the importance of the study are taken into consideration along with the p-value. The RTOG DMC will then make a recommendation about the trial to the RTOG Group Chair.

13.4.10 Interim Report to Monitor the Study Progress

Interim reports with descriptive statistics will be prepared twice per year until the initial paper reporting the treatment results has been submitted. In general, the interim reports will contain information about the patient accrual rate with a projected completion date for the accrual phase, compliance rate of treatment delivery with the distributions of important prognostic baseline variables, and the frequencies and severity of the adverse event by treatment arm. The interim reports will not contain the results of the treatment comparisons with respect to the primary endpoint and secondary endpoints.

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13.4.11 Reporting the Initial Treatment Analysis

The analysis reporting the treatment results will be carried out after the criteria for early stopping/reporting are met. Five interim analyses and one final analysis will be performed for efficacy and futility of the addition of ADT and will be carried out as described in Section 13.4.9. It will include tabulation of all cases entered and those excluded from the analyses; the distribution of the important prognostic baseline variables; safety treatments; treatment compliance; and observed results with respect to the primary and secondary endpoints will be shown. All eligible patients randomized will be included in the comparison and will be grouped by assigned treatment in the analysis (intent-to-treat analysis). In addition, exploratory analyses of treatment comparisons of the primary and secondary survival endpoints will be tested using the Cox or Fine and Gray's proportional hazard model that includes treatment arms, the stratification factors (the number of risk factors and RT modality), age, and race (as appropriate).

13.5 Gender and Minorities

In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, participation rates of men will be examined in the interim analyses. Based on the accrual statistics from RTOG 94-08, we project that 81% of the men in the study will be White, 15% will be Black or African American, 3% will be Hispanic, 0.5% will be Asian, 0.3% will be Pacific Islander and 0.2% will be American Indian or Alaskan Native. The following table lists the projected accrual by race/ethnicity.

Projected Distribution of Gender and Minorities

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	N/A	46	46
Not Hispanic or Latino	N/A	1474	1474
Ethnic Category: Total of all subjects	N/A	1520	1520
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	N/A	49	49
Asian	N/A	7	7
Black or African American	N/A	228	228

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Native Hawaiian or other Pacific Islander	N/A	5	5
White	N/A	1231	1231
Racial Category: Total of all subjects	N/A	1520	1520

13.5.1 In the setting of prostate cancer, African American ethnicity has been associated with both increased incidence and inferior clinical outcomes. The etiology of this phenomenon remains unclear. As such, no specific differences in outcome are hypothesized based on race/ethnicity in this study. Data will be collected and available for retrospective outcomes analysis at the time of study conclusion.

REFERENCES

1. Labrie F, Cusan L, Gomez JL, et al. Down-staging of early stage prostate cancer before radical prostatectomy:
 the first randomized trial of neoadjuvant combination therapy with flutamide and a luteinizing hormone-releasing hormone agonist. *J Urol*. 1994;44(6):29-37.
2. Vaillancourt L, Tetu B, Fradet, Y, et al. Effect of neoadjuvant endocrine therapy (combined androgen blockade) on normal prostate and prostatic carcinoma: a randomized study. *Am J Surg Pathol*. 1996;20(1):86-93.
3. Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomized trial. *Lancet*. 2002;360(9327):103-108.
4. Hanks GE, Pajak TF, Porter A, et al. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: the Radiation Therapy Oncology Group Protocol 92-02. *J Clin Oncol*. 2003;22(2):3972-8.
5. Pilepich MV, Winter K, John MJ, et al. Phase III Radiation Therapy Oncology Group (RTOG) trial 86-10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate. *Int J Radiat Oncol Biol Phys*. 2001;50(5):1243-52.
6. Pilepich MV, Winter K, Lawton CA, et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma – long-term results of phase III RTOG 85-31. *Int J Radiat Oncol Biol Phys*. 2005;61(5):1285-90.
7. D'Amico AV, Manola J, Loffredo M, et al. 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. *JAMA*. 2004;292(7):821-827.
8. Denham JW, Steigler A, Lamb DS, et al. Short-term androgen deprivation and radiotherapy for locally advanced prostate cancer: results from the Trans-Tasman Radiation Oncology Group 96.01 randomised controlled trial. *Lancet Oncol*. 2005;6(11):841-850.
9. Laverdiere J, Abdenour N, Diaz de Bedoya L, et al. The efficacy and sequencing of a short course of androgen suppression on freedom from biochemical failure when administered with radiation therapy for T2-T3 prostate cancer. *J Urol*. 2004;171:1137-1140.
10. Lawton CA, Desilvio M, Roach M, et al. An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions. *Int J Radiat Oncol Biol Phys*. 2007;69(3):646-655.
11. Kang DE, Fitzsimmons NJ, Presti JC, et al. Risk stratification of men with Gleason score 7-10 tumors by primary and secondary Gleason score: results from the SEARCH database. *J Urol*. 2007;70(2):277-282.
12. Partin AW, Mangold LA, Lamm DM, et al. Contemporary update of prostate cancer staging nomograms (Partin tables) for the new millennium. *J Urol*. 2001;58:843-848.
13. Rasiah KK, Stricker PD, Haynes AM, et al. Prognostic significance of Gleason pattern in patients with Gleason score 7 prostate carcinoma. *Cancer*. 2003;98:2560-2565.
14. Makarov DV, Sanderson H, Parton AW, et al. Gleason score 7 prostate cancer on needle biopsy: is the prognostic difference in Gleason scores 4+3 and 3+4 independent of the number of involved cores? *J Urol*. 2002;167:2440-2442.
15. Merrick GS, Butler WM, Wallner KE, et al. Androgen deprivation therapy does not impact cause-specific or overall survival after permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys*. 2006;65(3):669-677.
16. Beyer DC, McKeough T, Thomas T. Impact of short course hormonal therapy on overall and cancer specific survival after permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys*. 2005;61(5):1299-1305.
17. Martinez AA, Demanes DJ, Galalae R, et al. Lack of benefit from a short course of androgen deprivation for unfavorable prostate cancer patients treated with an accelerated hypofractionated regime. *Int J Radiat Oncol Biol Phys*. 2005;62(5):1322-1331.
18. Johnston AS, Piccirillo JF, Creech C, et al. Validation of a comorbidity education program. *J Registry Mgt.* 2001;28:125-31.
19. Piccirillo JF, Costas I, Claybour P, et al. The measurement of comorbidity by cancer registries. *J Registry Mgt.* 2003;30:8-14.
20. Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel EL Jr. Prognostic importance of comorbidity in a hospital-based cancer registry. *JAMA.* 2004;291(20):2441-2447.

21. D'Amico AV, Chen M, Renshaw AA, et al. Androgen suppression and radiation vs. radiation alone for prostate cancer: a randomized trial. *JAMA.* 2008;299(3):289-295.
22. Kuban DA, Tucker SL, Dong L, et al. Long-term results of the M.D. Anderson randomized dose escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2008;70(1):67-74.
23. Zietman AL, DeSilvio ML, Slater JD, et al. Comparison of conventional-dose vs. high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA*. 2005;294(10):1233-1239.
24. Peeters S, Heemsbergen WD, Koper P, et al. Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. *J Clin Oncol*. 2006;24(13):1990-1996.
25. Zelefsky MJ, Yamada Y, Fuks Z, et al. Long-term results of conformal radiotherapy for prostate cancer: impact of dose escalation on biochemical tumor control and distant metastases-free survival outcomes. *Int J Radiat Oncol Biol Phys*. 2008;Feb 13 [Epub ahead of print].
26. Michalski JM, Purdy JA, Winter K, et al. Preliminary report of toxicity following 3D radiation therapy on 3DOG/RTOG 94-06. *Int J Radiat Oncol Biol Phys*. 2000;46(2):391-402.
27. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol.* 24: 4448-4456, 2006.
28. Higano CS. Side effects of androgen deprivation therapy: Monitoring and minimizing toxicity. *Urology.* 61:32-38, 2003.
29. van Andel G, Kurth KH. The impact of androgen deprivation therapy on health related quality of life in asymptomatic men with lymph node positive prostate cancer. *Eur Urol.* 44:209-214, 2003.
30. Bower, J.E. and J.E. Bower, Prevalence and causes of fatigue after cancer treatment: the next generation of research.[comment]. *Journal of Clinical Oncology*, 2005. 23(33): p. 8280-2.
31. Jereczek-Fossa, B.A., H.R. Marsiglia, and R. Orecchia, Radiotherapy-related fatigue: how to assess and how to treat the symptom. A commentary. Tumori, 2001. 87(3): p. 147-51.
32. Lilleby, W., et al., Long-term morbidity and quality of life in patients with localized prostate cancer undergoing definitive radiotherapy or radical prostatectomy. *International Journal of Radiation Oncology, Biology, Physics*, 1999. 43(4): p. 735-43.
33 Monga, U., et al., Prospective study of fatigue in localized prostate cancer patients undergoing radiotherapy. *Radiation Oncology Investigations*, 1999. 7(3): p. 178-85.
34. Monga, U., et al., Longitudinal study of quality of life in patients with localized prostate cancer undergoing radiotherapy. *Journal of Rehabilitation Research & Development*, 2005. 42(3): p. 391-9.
35. Truong, P.T., et al., Prospective evaluation of the prevalence and severity of fatigue in patients with prostate cancer undergoing radical external beam radiotherapy and neoadjuvant hormone therapy. *Canadian Journal of Urology*, 2006. 13(3): p. 3139-46.
36. Beard, C.J., et al., Complications after treatment with external-beam irradiation in early-stage prostate cancer patients: a prospective multiinstitutional outcomes study. *Journal of Clinical Oncology*, 1997. 15(1): p. 223-9.
37. Danjoux, C., et al., Prospective evaluation of fatigue during a course of curative radiotherapy for localised prostate cancer. *Supportive Care in Cancer*, 2007. 15(10): p. 1169-76.
38. Stephens, R.J., et al., The quality of life of men with locally advanced prostate cancer during neoadjuvant hormone therapy: data from the Medical Research Council RT01 trial (ISRCTN 47772397). *BJU International*, 2007. 99(2): p. 301-10.
39. Voerman, B., et al., Health-related quality of life in Dutch men with prostate cancer. *Journal of Psychosocial Oncology*, 2006. 24(2): p. 49-64.
40. Berger, A.M., et al., Sleep wake disturbances in people with cancer and their caregivers: state of the science. *Oncology Nursing Forum Online*, 2005. 32(6): p. E98-126.
41. Mock, V., et al., NCCN Practice Guidelines for Cancer-Related Fatigue. *Oncology* (Williston Park), 2000. 14(11A): p. 151-61.
42. Buysse, D.J., et al., The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Research*, 1989. 28(2): p. 193-213.
43. Godin, G., J. Jobin, and J. Bouillon, Assessment of leisure time exercise behavior by self-report: a concurrent validity study. *Canadian Journal of Public Health Revue Canadienne de Sante Publique*, 1986. 77(5): p. 359-62.
44. Gionet, N.J. and G. Godin, Self-reported exercise behavior of employees: a validity study. *Journal of Occupational Medicine*, 1989. 31(12): p. 969-73.
45. Glasziou PP, Simes RJ, Gelber RD. Quality adjusted survival analysis. *Stat Med.* 9:1259-1276, 1990.
46. Trippoli S, Vaiani M, Lucioni C, et al. Quality of life and utility in patients with non-small cell lung cancer. Quality-of-life Study Group of the Master 2 Project in Pharmacoeconomics. *Pharmacoeconomics*. 19:855-

863, 2001.
47. Essink-Bot ML, de Koning HJ, Nijs HG, et al. Short-term effects of population-based screening for prostate cancer on health-related quality of life. *J Natl Cancer Inst.* 90:925-931, 1998.
48. Sandblom G, Carlsson P, Sennfalt K, et al. A population-based study of pain and quality of life during the year before death in men with prostate cancer. *Br J Cancer*. 90:1163-1168, 2004.
49. Sennfalt K, Carlsson P, Sandblom G, et al. The estimated economic value of the welfare loss due to prostate cancer pain in a defined population. *Acta Oncol.* 43:290-296, 2004.
50. Schubert, C., S. Hong, et al. (2007). "The association between fatigue and inflammatory marker levels in cancer patients: A quantitative review." *Brain, Behavior, and Immunity* 21(4): 413-427.
51. Ryan, J. L., J. K. Carroll, et al. (2007). "Mechanisms of Cancer-Related Fatigue." *Oncologist* 12(suppl_1): 22-34.
52. Benzing, T., R. Brandes, et al. (1999). "Upregulation of RGS7 may contribute to tumor necrosis factor-induced changes in central nervous function." *Nat Med* 5(8): 913-8.
53. Ahlberg, K., T. Ekman, et al. (2004). "Levels of fatigue compared to levels of cytokines and hemoglobin during pelvic radiotherapy: a pilot study." *Biol Res Nurs* 5(3): 203-10.
54. Geinitz, H., F. B. Zimmermann, et al. (2001). "Fatigue, serum cytokine levels, and blood cell counts during radiotherapy of patients with breast cancer." *Int J Radiat Oncol Biol Phys* 51(3): 691-8.
55. Geinitz, H., F. B. Zimmermann, et al. (2004). "Fatigue in patients with adjuvant radiation therapy for breast cancer: long-term follow-up." *J Cancer Res Clin Oncol* 130(6): 327-33.
56. Akmansu, M., D. Unsal, et al. (2005). "Influence of locoregional radiation treatment on tumor necrosis factor-alpha and interleukin-6 in the serum of patients with head and neck cancer." *Cytokine* 31(1): 41-5.
57. Greenberg, D. B., J. L. Gray, et al. (1993). "Treatment-related fatigue and serum interleukin-1 levels in patients during external beam irradiation for prostate cancer." *J Pain Symptom Manage* 8(4): 196-200.
58. Sugihara, A., O. Maeda, et al. (1998). "Expression of cytokines enhancing the osteoclast activity, and parathyroid hormone-related protein in prostatic cancers before and after endocrine therapy: an immunohistochemical study." *Oncol Rep* 5(6): 1389-94.
59. Stone, P., J. Hardy, et al. (2000). "Fatigue in patients with prostate cancer receiving hormone therapy." *Eur J Cancer* 36(9): 1134-41.
60. Roach M, 3rd, Hanks G, Thames H, Jr., et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: Recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys. 65:965-974, 2006.
61. Kestin LL, Goldstein NS, Vicini FA, et al. Treatment of prostate cancer with radiotherapy: should the entire seminal vesicles be included in the clinical target volume? *Int J Rad Oncol Biol Phys*. 2002;54(3):686-697.
62. Nag S, Bice W, DeWyngaert K, Prestidge B, et al. The American Brachytherapy Society recommendations for permanent prostate Brachytherapy post-implant dosimetric analysis. *Int J Radiat Oncol Biol Phys*. 2000;1:221-230.
63. Kinnealey, GT, and Furr, BJ. Use of the nonsteroidal anti-androgen Casodex in advanced prostatic carcinoma. *Urol Clin North Am.* 18(1):99-110, 1991.
64. Tyrrell, CJ. Tolerability and quality of life aspects with the anti-androgen Casodex (ICI 176,334) as monotherapy for prostate cancer. International Casodex Investigators. *Eur Urol.* 26 Suppl 1:15-9, 1994.
65. Wei JT, Dunn RL, Litwin MS, et al. Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. *Urology*. 56:899-905, 2000.
66. Schulz MW, Chen J, Woo HH, et al. A comparison of techniques for eliciting patient preferences in patients with benign prostatic hyperplasia. *J Urol.* 168:155-159, 2002.
67. Badia X, Herdman M, Kind P. The influence of ill-health experience on the valuation of health. *Pharmacoeconomics*. 13:687-696, 1998.
68. Wu AW, Jacobson KL, Frick KD, et al. Validity and responsiveness of the euroqol as a measure of health related quality of life in people enrolled in an AIDS clinical trial. *Qual Life Res.* 11:273-282, 2002.
69. Pampallona S, Tsiatsis AA (1994). Group sequential designs for one and two sided hypothesis testing with provision for early stopping in favour of the null hypothesis. *Journal of Statistical Planning and Inference*; 42:19-35.
70. Freidlin B, Korn EL. Testing treatment effects in the presence of competing risks. Stat Med. 24:1703-1712, 2005.
71. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 53:447-457, 1958.
72. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Canc Chemo Rep.* 50:163-170, 1966.

73. Kim K, Tsiatis AA. Study duration for clinical trials with survival response and early stopping rule. *Biometrics*. 46:81-92, 1990.
74. Cox DR. Regression models and life tables. *J Royal Statistics Soc.* 34:187-220, 1972.
75 Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Annual Statistics*. 16:1141-1143, 1988.
76. Agresti A. Categorical Data Analysis. New York: Wiley; 1990.
77. Kalbfleisch JD, Ross LP. The statistical analysis of failure time data. New York: John Wiley & Sons; 1980.
78. Gaynor JJ, Feuer EJ, Tan CC, et al. On the use of cause-specific failure and conditional failure probabilities: examples from clinical oncology data. *JASA*. 88:400-403, 1993.
79. Fine J, Gray RJ: A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 94:496-509, 1999.
80. Verbeke G, Molenberghs G. Linear mixed models for longitudinal data. New York: Springer-Verlag, Inc.; 2000.
81. Donaldson GW, Moinpour CM. Learning to live with missing quality-of-life data in advanced-stage disease trials. *J Clin Oncol.* 23:7380-7384, 2005.
82. Guidance for industry patient-reported outcome measures: Use in medical product development to support labeling claims: U.S. Department of Health and Human Services and Food and Drug Administration. pp. http://www.qolpro.org/ (accessed Aug. 1, 2006).

APPENDIX I

RTOG 0815

Informed Consent Template for Cancer Treatment Trials
(English Language)

A Phase III Prospective Randomized Trial of Dose-Escalated Radiotherapy With or Without Short-Term Androgen Deprivation Therapy for Patients With Intermediate-Risk Prostate Cancer

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have prostate cancer.

Why is this study being done? (12/10/10)

The purpose of this study is to compare the effects of dose-escalated radiation therapy with or without hormone therapy on your prostate cancer. Prior studies have suggested possible advantages to the administration of hormonal therapy with radiation. However, those studies were performed with radiation techniques that do not match those commonly used in clinical practice today (that is, dose-escalated radiotherapy). Therefore, we will be testing to see if similar benefits for hormonal therapy are seen when used with current radiation therapy techniques.

In current clinical practice, either radiation therapy alone (called Arm 1 or Group 1 in this study) or radiation therapy combined with hormone therapy (called Arm 2 or Group 2 in this study) would be considered an acceptable standard treatment for patients with a newly diagnosed intermediate risk prostate cancer. The researchers conducting this study are testing the hypothesis that the side effects of hormonal therapy are outweighed by an advantage in prostate cancer cure rates for patients receiving that treatment.

There are 2 treatment groups in this study:
1) Patients who receive radiation therapy only
2) Patients who receive radiation therapy plus hormone therapy

If you agree to participate in this study, you will receive one of these 2 treatments.

How many people will take part in the study?

About 1520 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests, or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- History and physical exam, including a digital rectal exam (DRE), an assessment of your ability to carry out activities of daily living (which will include questions such as whether you are able to feed, bathe, and dress yourself), and an assessment of other health conditions you may have (comorbidity).
- Blood tests to determine your PSA (prostate-specific antigen) and for blood count. The PSA value is a number that helps determine the aggressiveness of your prostate cancer.

- A CT (Computed Tomography) scan or MRI (Magnetic Resonance Imaging) of your pelvis and abdomen to determine if there is any evidence of cancer spread to the pelvic lymph nodes. A CT scan is a study using x-rays to look at one part of your body. An MRI is imaging using a strong magnetic field to look at one part of your body.
- A bone scan (for some patients, if applicable) to determine if the cancer has spread to the bones

During the study … (12/10/10) (1/11/11)

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- Transrectal ultrasound assessment of the prostate (brachytherapy patients only)
- Blood tests to measure testosterone and liver function
- An assessment of urinary symptoms and function (brachytherapy patients only)

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your study doctor can choose the group you will be in. You will have an equal chance of being placed in either group.

If you are in group 1 (often called "Arm 1"): You will receive radiation treatments to the prostate gland and seminal vesicles once daily, 5 days a week, Monday through Friday, for a total of 44 treatments. Each radiation treatment will take approximately 20 minutes but may be specific to the center in which you are being treated. If you choose to receive brachytherapy (permanent or temporary radiation seed implant), the total number of daily treatment sessions will be 25. The logistics of the brachytherapy implant procedure (if you have chosen to undergo this type of treatment) should be thoroughly reviewed by your treating physician.

If you are in group 2 (often called "Arm 2"): You will receive radiation treatments to the prostate gland and seminal vesicles as specified under group 1 above.

You also will receive hormone therapy for 6 months. The hormone therapy will begin 2 months before the start of the radiation treatments. There are two parts to the hormone therapy. You will take injections of a luteinizing hormone releasing hormone (LHRH) agonist, either under the skin or in the muscle (typically every 1 to 3 months), and you will take a pill, either flutamide three times per day or bicalutamide once per day. The injected LHRH agonist will reduce the amount of circulating testosterone and the pill will interfere with the action of any remaining testosterone.

During Radiation Therapy or Radiation Plus Hormone Therapy:

- You will be seen weekly during radiation treatment to check for any side effects you may be experiencing as a result of the treatment.
- During the third week and the last week of radiation treatment, your ability to carry out activities of daily living (which will include questions such as whether you are able to feed, bathe, and dress yourself) will be assessed.
- If you are receiving brachytherapy: Blood test for blood count during the first and fifth weeks of treatment
- If you are receiving hormone therapy: Blood test to measure testosterone; monthly blood tests for liver function

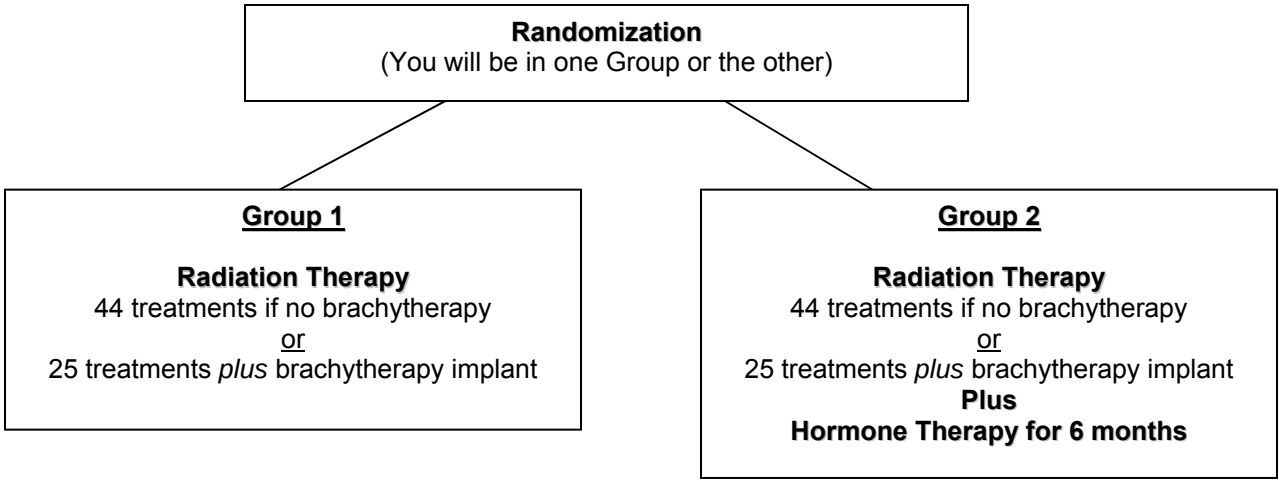
When you are finished receiving radiation therapy or radiation plus hormone therapy, you will need these tests and procedures:

- PSA measurement will be obtained at 6-8 weeks after finishing radiation treatment and prior to each follow-up visit.
- A physical assessment, including a digital rectal exam (DRE) and an assessment of your ability to carry out activities of daily living (which will include questions such as whether you are able to feed, bathe, and dress yourself) at 3 (group 1 only), 6, 9, and 12 months after finishing radiation treatment, every 6 months for 4 years, and yearly thereafter.

- If you receive hormone therapy: Testosterone levels will be checked every six months for three years or until they return to normal levels.
- Additional testing may be ordered as deemed clinically appropriate by your treating physician.

Study Plan

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.



How long will I be in the study? (12/10/10)

You will receive 44 radiation treatments over approximately 2 months. If you choose to receive the brachytherapy implant, you will receive 25 daily treatments plus the implant procedure over a timeframe of approximately 6 weeks. Hormone therapy, if given, will last 6 months. After you are finished receiving therapy, the study doctor will ask you to visit the office for follow-up exams at 3 (group 1 only), 6, 9, and 12 months after finishing radiation treatment, every 6 months for 4 years, and yearly thereafter. The study doctors would like to keep track of your medical condition by seeing you every year for your lifetime.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the radiation and hormone therapy (if given) can be evaluated by him/her. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, researchers don't know all the side effects that may happen. Side effects may be mild or very serious. These side effects may be related either to the radiotherapy, hormonal therapy (if randomized to receive it), or both. There are several radiotherapy options allowed on this study in the form of external beam radiation, low dose rate brachytherapy, and high dose rate brachytherapy. Each of these may be associated with subtle differences in their side effect profiles. ***The type of radiotherapy you receive on this study is a choice to be made between you and your physician.*** Your health care team may give you medicines to help lessen

side effects. Many side effects go away soon after you stop radiation or hormone therapy (if given). In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the *radiation therapy* include those which are:
Likely

- Increased urinary frequency or urgency
- Burning or discomfort/straining with urination
- Increased frequency of bowel movements or change in stool consistency
- Increased straining/discomfort with bowel movements
- Mild fatigue

Less Likely

- Rectal bleeding (usually mild)
- Chronic bowel/bladder symptoms as described above
- Temporary blockage of urination requiring use of a catheter
- Erectile dysfunction

For patients undergoing brachytherapy, risks associated with aspects of an invasive procedure such as those associated with anesthesia, infection, and bleeding must be considered and discussed with your treating physician. If permanent seed brachytherapy is used, there is a possibility of loss or migration of seeds leading to areas of under- or overdosage in certain parts of the prostate or elsewhere. Rectal or bladder complications may occur if these organs are affected because of seed misplacement.

Rare, But Serious

- Permanent rectal or bladder injury requiring surgery for treatment

Risks and side effects related to the *hormone therapy* include those which are:
Likely

- Hot flashes
- Erectile dysfunction
- Loss of libido
- Mild fatigue
- Breast tenderness or mild enlargement
- Diarrhea

Less Likely

- Headaches
- Bone/joint pain
- Liver toxicity (detected on a blood test) requiring reduced dose or stopping treatment
- Severe fatigue
- Skin rash/hives
- Swelling
- Decrease in bone mineral density
- There may be increased risk of rectal or bladder side effects as a result of the interaction between the hormone therapy and the external beam radiation therapy.

Rare, But Serious

- Severe allergic reaction
- Increased long-term risk of cardiovascular disease
- Increased long-term risk of developing diabetes

Reproductive risks: You should not father a baby nor donate sperm while on this study or during the first 3 months after the completion of therapy because the radiation and drugs in this study can affect an unborn baby. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some

methods might not be approved for use in this study. Some of the drugs and radiation used in this study may make you unable to have children in the future.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. It is not known how much of a benefit combining hormone therapy with radiation therapy will have for your type of prostate cancer compared to the usual treatment. We do know that the information from this study will help researchers learn more about the combination of hormone therapy plus radiation therapy as a treatment for prostate cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting treatment or care for your cancer without being in a study; this could include the following options, either alone or in combination with each other:
  - o Radiation therapy (external beam radiation therapy and/or brachytherapy)
  - o Radiation therapy plus hormone therapy
  - o Hormone therapy
  - o Surgery
- Taking part in another study
- Getting no treatment

Talk to your study doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

Data are housed at RTOG Headquarters in a password-protected database. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The Radiation Therapy Oncology Group (RTOG)
- The National Cancer Institute (NCI) and other government agencies involved in keeping research safe for people, like the Central Institutional Review Board (CIRB) and the Food and Drug Administration (FDA)
- The Cancer Trials Support Unit (CTSU), an organization sponsored by the NCI to provide greater access to cancer trials

What are the costs of taking part in this study?

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the study doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

A Data Monitoring Committee (DMC) will be regularly meeting to monitor safety and other data related to this study. The Committee members may receive confidential patient information, but they will not receive your name or other information that would allow them to identify you by name.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). *[*Only applies to sites using the CIRB.]*

Please note: This section of the informed consent form is about additional research that is being done with people who are taking part in the main study. You may take part in this additional research if you want to. You can still be a part of the main study even if you say 'no' to participating in this additional research.

You can say "yes" or "no" to each of the following studies. Below, please mark your choice for each study.

Quality of Life Study

We want to know your view of how your life has been affected by cancer and its treatment. This "quality of life" study looks at how you are feeling physically and emotionally during your cancer treatment. It also looks at how you are able to carry out your day-to-day activities.
This information will help doctors better understand how patients feel during treatments and what effects the medicines are having. In the future, this information may help patients and doctors as they decide which medicines to use to treat cancer.

You will be asked to complete 4 questionnaires at the following times: before treatment begins, during the last week of radiation therapy (with or without hormone therapy), and at 6 months, 1 year, and 5 years after the end of radiation therapy. It takes about 15 minutes to fill out each questionnaire. If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

In addition, if you agree to participate in this part of the study, you will have blood drawn before you start radiation therapy treatment (with or without hormone therapy) and during the last week of radiation therapy treatment. We would like to keep about 2 tablespoons of blood at each of these times for future research. If you agree, this blood will be kept to be used in research to learn more about cancer and other diseases.

If you decide to take part in this study, you will be asked to fill out the questionnaires and have blood drawn. You may change your mind about completing the questionnaires and having blood drawn at any time.

Just like in the main study, we will do our best to make sure that your personal information will be kept private.

Please circle your answer.

I choose to take part in the Quality of Life Study. I agree to fill out the Quality of Life Questionnaires and have blood drawn.

YES **NO**

Use of Tissue and Blood for Research

About Using Tissue and Blood for Research

You are going to have a biopsy (or surgery) to see if you have cancer. Your doctor will remove some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue that is left over from your surgery for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research. This information sheet is available to all at the following web site: http://www.rtog.org/tissue%20for%20research_patient.pdf

In addition, if you agree, you will have blood drawn before you start radiation therapy treatment (with or without hormone therapy) and during the last week of radiation therapy treatment. We would like to keep about 2 tablespoons of blood at each of these times for future research. This blood will be kept to be used in research to learn more about cancer and other diseases.

Your tissue and/or blood may be helpful for research. The research that may be done is not designed specifically to help you. It might help people who have cancer and other diseases in the future. Reports about research done with your tissue and/or blood will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over tissue and/or blood for future research is up to you. No matter what you decide to do, it will not affect your care or your participation in the main part of the study.

If you decide now that your tissue and/or blood can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue and/or blood. Then any tissue and/or blood that remain will no longer be used for research and will be returned to the institution that submitted it.

In the future, people who do research may need to know more about your health. While the study doctor/institution may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue and/or blood are used for genetic research (about diseases that are passed on in families). Even if your tissue and/or blood are used for this kind of research, the results will not be put in your health records.

Your tissue and/or blood will be used only for research and will not be sold. The research done with your tissue and/or blood may help to develop new treatments for cancer in the future.

Benefits

The benefits of research using tissue and blood include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at _____ [IRB's phone number].

No matter what you decide to do, it will not affect your care.

1. My specimens may be kept for use in research to learn about, prevent, or treat cancer, as follows:
   - Tissue ☐Yes ☐ No
   - Blood ☐Yes ☐ No

2. My specimens may be kept for use in research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease), as follows:
   - Tissue ☐Yes ☐ No
   - Blood ☐Yes ☐ No

3. Someone may contact me in the future to ask me to take part in more research.
   ☐Yes ☐ No

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or **TTY: 1-800-332-8615**

You may also visit the NCI Web site at http://cancer.gov/

- **For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/**
- **For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/**

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* **pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.**

Participant _____

Date _____

APPENDIX II: STUDY PARAMETER TABLE *(See Section 11.1 for details and/or exceptions.)* [12/10/10]

	Pre-Treament (may be required for eligibility		**During Treatment**					**Follow-Up**			
	≤ 6 months prior to registration	≤ 60 days prior to registration	Weekly during RT	Weeks 1 and 5 of RT	Week 3 of RT; last week of RT	Monthly (Arm 2 only)	6-8 weeks post RT	**ARM 1** 3, 6, 9, and 12 months post RT	**ARM 2** 6, 9, and 12 months post RT	Every 6 months for 4 years	Annually
Elig-related tissue collection	X										
History/physical		X									
CT or MRI abd/pelvis & bone scan		X									
Transrectal ultrasound		For brachy patients only									
Performance status		X			X			X	X	X	X
AUA		For brachy patients only									
PSA		X					X				
CBC w/ diff & ANC		For brachy patients only		X							
AST, ALT, alk phosphatase		X				X					
Serum testosterone		X		See 11.1.5				See 11.1.5			
Tumor response eval: physical, DRE, PSA								X	X	X	X

(continued on next page)

APPENDIX II: STUDY PARAMETER TABLE *(See Section 11.1 for details and/or exceptions.)* [12/10/10]
(continued)

	Pre-Treatment (may be required for eligibility)		**During Treatment**				**Follow Up**				
	≤ 6 months prior to registration	≤ 60 days prior to registration	Weekly during RT	Weeks 1 and 5 of RT	Week 3 of RT; last week of RT	Monthly (Arm 2 only)	**ARM 1** 3, 6, 9, and 12 months post RT	**ARM 2** 6, 9, and 12 months post RT	6 mos, 1 yr, 5 yrs post RT	Every 6 months for 4 years	Annually
QOL Assess. (if patient consents): EPIC, PROMIS, EQ-5D, PSQI/ GLTEQ		Within 2 weeks after registration			Last week of RT				X		
Tissue for banking (if patient consents)		X									
Blood for banking (if patient consents)*		X			Last week of RT						
AE evaluation			X				X	X		X	X

***Blood collection is mandatory for patients consenting to the QOL portion of the study.**

APPENDIX III

ZUBROD PERFORMANCE SCALE

0	**Fully active, able to carry on all predisease activities without restriction**
1	**Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work**
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**
3	**Capable of only limited self-care, confined to bed or chair 50% or more of waking hours**
4	**Completely disabled. Cannot carry on self-care. Totally confined to bed**
5	**Death**

APPENDIX IV

AJCC STAGING SYSTEM
PROSTATE, 6th Edition
DEFINITION OF TNM

Primary Tumor, Clinical (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

T1 Clinically inapparent tumor neither 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-half of one lobe or less
- T2b Tumor involves more than one-half of one lobe but not both lobes
- T2c 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 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 classified not 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(s)

(continued on next page)

APPENDIX IV (continued)
AJCC STAGING SYSTEM
PROSTATE, 6th Edition

Primary Tumor, Pathologic (pT)

pT2* Organ confined
- pT2a Unilateral, involving one-half of one lobe or less
- pT2b Unilateral, involving more than one-half of one lobe but not both lobes
- pT2c Bilateral disease

pT3 Extraprostatic extension
- pT3a Extraprostatic extension**
- pT3b Seminal vesicle invasion

pT4 Invasion of bladder, rectum

*Note: There is no pathologic T1 classification

**Note: Positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease).

Distant Metastasis (M)*

MX Presence of distant metastasis cannot be assessed (not evaluated by any modality)

M0 No distant metastasis

M1 Distant metastasis
- M1a Nonregional lymph node(s)
- M1b Bone(s)
- M1c Other site(s) with or without bone disease

*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 [Gleason 2-4])

G2 Moderately differentiated (moderate anaplasia [Gleason 5-6])

G3-4 Poorly undifferentiated or undifferentiated (marked anaplasia [Gleason 7-10])

(continued on next page)

APPENDIX IV (continued)
AJCC STAGING SYSTEM
PROSTATE, 6th Edition

Stage Grouping

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

APPENDIX V (12/10/10)

APPENDIX FOR RTOG BIOSPECIMEN COLLECTION: BLOOD COLLECTION KIT INSTRUCTIONS

Shipping Instructions:

US Postal Service Mailing Address: For FFPE or Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
1657 Scott Street, Room 223
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen or Trackable Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

- ❑ Include all RTOG paperwork in pocket of biohazard bag.
- ❑ Check that the Specimen Transmittal Form (STF) has the consent boxes checked off.
- ❑ Check that all samples are labeled with the RTOG study and case number, and include date of collection as well as collection time point (e.g., pretreatment, post-treatment).

- ❑ **FFPE Specimens:**
  - o Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of the container. If you can hear the slides shaking it is likely that they will break during shipping.
  - o FFPE Blocks can be wrapped with paper towel, or placed in a cardboard box with padding. Do not wrap blocks with bubble wrap. Place padding in top of container so that if you shake the container the blocks are not shaking. If you can hear the slides shaking it is likely that they will break during shipping.
  - o Slides, Blocks, or Plugs can be shipped ambient or with a cold pack either by United States Postal Service (USPS) to the USPS address (94143) or by Courier to the Street Address (94115). **Do NOT ship on Dry Ice**.

- ❑ **Frozen Specimens:**
  - o Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified.
  - o Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs). There should be plenty of dry ice under and above the specimens. If the volume of specimens is greater than the volume of dry ice then ship in a larger Styrofoam box, or two separate boxes. Any Styrofoam box can be used, as long as it is big enough.
  - o Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
  - o Send frozen specimens via overnight courier to the address above. Specimens should only be shipped Monday through Wednesday (Monday-Tuesday for Canada) to prevent thawing due to delivery delays. Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen at -80° C until ready to ship.

- ❑ **For Questions regarding collection/shipping please contact the RTOG Biospecimen Resource by e-mail: RTOG@ucsf.edu or phone: 415-476-RTOG(7864) or Fax: 415-476-5271.**

(continued on next page)

APPENDIX V (12/10/10)

RTOG BLOOD COLLECTION KIT INSTRUCTIONS (continued)

This Kit is for collection, processing, storage, and shipping of serum, plasma, or whole blood *(as specified by the protocol)*:

Kit contents:

- One Red Top tube for serum (A)
- One Purple Top EDTA tube for plasma (B)
- One Purple Top EDTA tube for Whole Blood (C)
- Twenty-five (25) 1 ml cryovials
- Biohazard bags (3) and Absorbent shipping material (3)
- Styrofoam container (inner) and Cardboard shipping (outer) box
- UN1845 DRY Ice Sticker and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal Form (STF) and Kit Instructions

PREPARATION AND PROCESSING OF SERUM, PLASMA AND WHOLE BLOOD:

(A) Serum (if requested): Red Top Tube

- ❑ Label as many 1ml cryovials (up to 10) as necessary for the serum collected. Label them with the RTOG study and case number, collection date, time, and time point, and clearly mark cryovials "serum".

Process:

1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the STF.
3. Aliquot 0.5 ml serum into as many cryovials as are necessary for the serum collected (up to 10) labeled with RTOG study and case numbers, collection date/time, protocol time-point collected (e.g. pretreatment, post-treatment), and clearly mark specimen as "serum".
4. Place cryovials into biohazard bag and immediately freeze at -70 to -90° C, and store frozen until ready to ship. See below for storage conditions.
5. Store serum at -70 to -90° C until ready to ship on dry ice. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the STF.

(B) Plasma (If requested): Purple Top EDTA tube #1

- ❑ Label as many 1ml cryovials (up to 10) as necessary for the plasma collected. Label them with the RTOG study and case number, collection date, time, and time point, and clearly mark cryovials "plasma".

Process:

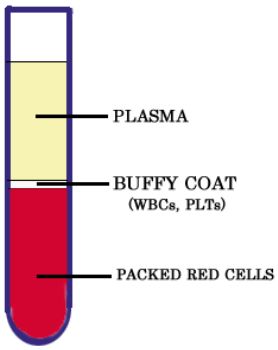
1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the STF..
3. If the interval between specimen collection and processing is anticipated to be more than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot 0.5 ml plasma into as many cryovials as are necessary for the plasma collected (up to 10) labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as "plasma". Avoid pipetting up the buffy coat layer.
5. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C.
6. Store frozen plasma until ready to ship on dry ice.
7. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the STF.

(continued on next page)

APPENDIX V

RTOG BLOOD COLLECTION KIT INSTRUCTIONS (continued)



(C) Whole Blood for DNA (if requested): Purple Top EDTA tube #2

- ❑ Label as many 1ml cryovials (up to 5) as necessary for the whole blood collected..Label them with the RTOG study and case number, collection date/time, and time point, and clearly mark cryovials "blood".

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot 1.0 ml blood into as many cryovials as are necessary for the blood collected (up to 5) labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as "blood".
3. Place cryovials into biohazard bag and freeze immediately at -70 to -80° Celsius.
4. Store blood samples frozen until ready to ship on dry ice.
5. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on STF.

Freezing and Storage:

- ☐ Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.
- ❑ Store at –80°C (-70°C to -90°C) until ready to ship.
  If a -80°C Freezer is not available,
  - Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

  OR:
  - Samples can be stored in plenty of dry ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only; Canada: Monday-Tuesday only).

  OR:
  - Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
- ❑ Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

Shipping/Mailing:

- ❑ Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- ❑ Include all RTOG paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.
- ❑ Wrap frozen specimens of same type (i.e., all serum together, plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.

(continued on next page)

APPENDIX V

RTOG BLOOD COLLECTION KIT INSTRUCTIONS (continued)

- *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice.* ***Add padding to avoid the dry ice from breaking the tubes.***
- **For questions regarding collection, shipping or to order a Blood Collection Kit, please e-mail RTOG@ucsf.edu or call (415)476-7864.**

Shipping Address:

Courier Address (FedEx, UPS, etc.): For all Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115
For questions, call 415-476-RTOG (7864) or e-mail: RTOG@ucsf.edu

APPENDIX VI (1/11/11)

CANCER TRIALS SUPPORT UNIT (CTSU) LOGISTICS ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206	CTSU Patient Registration Voice Mail – 1-888-462-3009 Fax – 1-888-691-8039 Hours: 9:00 AM – 5:30 PM Eastern Time, Monday – Friday (excluding holidays) [Registrations received after 5:00 PM ET will be handled the next business day. For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301-704-2376 between 9:00 am and 5:30 pm.]	RTOG Headquarters 1818 Market Street, Suite 1600 Philadelphia, PA 19103 Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
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 https://members.ctsu.org**		

PARTICIPATION PROCEDURES

REGISTRATION/RANDOMIZATION

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 and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site at http://members.ctsu.org

All forms and documents associated with this study can be downloaded from the RTOG 0815 Web page on the CTSU registered member Web site (https://members.ctsu.org). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS.

Requirements for RTOG 0815 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet
- CTSU RT Facilities Inventory Form

  NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Radiological Physics Center (RPC) monitoring program. For sites enrolling through the CTSU an RT Facilities Inventory From must be on file with CTSU. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility.

Pre-study requirements for patient enrollment on RTOG 0815:

- Patient must meet all inclusion criteria, and no exclusion criteria should apply
- Patient has signed and dated all applicable consents and authorization forms
- All baseline laboratory tests and prestudy evaluations performed
- Institutions previously credentialed for prostate 3DCRT or IMRT on prior RTOG protocols and that have successfully completed a phantom and been approved by RPC need not perform additional credentialing for RTOG 0815. Institutions may only administer treatment for which they have been previously credentialed. Those institutions which have never been credentialed must meet the technology guidelines and provide baseline physics information as described in protocol sections 5.1 and 5.2. Institutions wishing to treat patients with Brachytherapy must also meet the credentialing requirements for the Brachytherapy treatment approach as described in protocol section 5.3.

CTSU Procedures for Patient Enrollment

1. Contact the CTSU Patient Registration Office by calling 1-888-462-3009 between 9:00 a.m. and 5:30 p.m. Eastern Time, Mon-Fri. Leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, e.g. within one hour, call the registrar cell phone at 1-301-704-2376.

2. Complete the following forms:

- CTSU Patient Enrollment Transmittal Form
- Eligibility Checklist

3. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 5:30 p.m., Mon-Fri, Eastern Time (excluding holidays); however, please be aware that registrations received after 5:00 p.m. will be processed the next day. The CTSU registrar will check the investigator and site information to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and will follow-up with the site to resolve any discrepancies.

4. Once investigator eligibility is confirmed and enrollment documents are reviewed for compliance, the CTSU registrar will access the RTOG's on-line registration system, to obtain assignment of a treatment arm and assignment of a unique patient ID (to be used on all future forms and correspondence). The CTSU registrar will confirm registration by fax.

Patients randomized to receive short-term androgen deprivation therapy must begin this treatment within 4 weeks after randomization.

DATA SUBMISSION AND RECONCILIATION

1. All case report forms (CRFs) associated with this study must be downloaded from the RTOG 0815 Web page located on the CTSU registered member Web site (https://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 directly to the RTOG unless an alternate location is specified in the protocol. Do not send study data to the CTSU.

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

SPECIAL MATERIALS OR SUBSTUDIES

1. Specimen collection for correlatives (Protocol section 10.0)

- Collect, prepare, and submit specimens as outlined in the protocol
- Do not send specimens, supporting clinical reports, or transmittals to the CTSU

NOTE: Blood Collection is **mandatory** for patients consenting to the QOL portion of this study. All other specimen collections are optional but highly recommended and sites are reminded that all patients **must** be offered the opportunity to participate in the correlative components of this study. Sites are **not** permitted to delete the tissue/specimen or QOL components from the protocol or from the sample consent.

2. Quality of Life Substudies (Protocol section 11.4)

- Submit completed forms as outlined in the protocol

SERIOUS ADVERSE EVENT (AE) REPORTING (Section 7.5)

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 (https://members.ctsu.org) or by selecting Adverse Event Reporting Forms from the document center drop down list on the RTOG 0815 page.

3. Do not send adverse event reports to the CTSU.

4. Secondary AML/MDS/ALL reporting: Reporting of cases of secondary AML/MDS/ALL is to be performed using AdEERS.

DRUG PROCUREMENT (Section 7.0)

Commercial agents: Casodex (Bicalutamide); Eulexin (Flutamide); LHRH Agonist Therapy (leuprolide, goserelin; buserelin, triptorelin)

1. Information on drug formulation, procurement, storage and accountability, administration, and potential toxicities are outlined in Section 7.0 of the protocol.

2. You may navigate to the drug forms by selecting Pharmacy Forms from the document center tree on the RTOG 0815 Web page.

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 can be found in the CTMB Monitoring Guidelines and are available for download from the CTEP web page http://ctep.cancer.gov/monitoring/guidelines.html.

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 System–Web (CDS-Web) Monitoring

This study will be monitored by the Clinical Data System (CDS-Web). The sponsoring Group fulfills this reporting obligation by transmitting the CDS data collected from the study-specific case report forms, via the Web to the NCI Center for Biometrics (NCICB). Cumulative CDS data are submitted quarterly.