RADIATION THERAPY ONCOLOGY GROUP

RTOG 0924

ANDROGEN DEPRIVATION THERAPY AND HIGH DOSE RADIOTHERAPY WITH OR WITHOUT WHOLE-PELVIC RADIOTHERAPY IN UNFAVORABLE INTERMEDIATE OR FAVORABLE HIGH RISK PROSTATE CANCER: A PHASE III RANDOMIZED TRIAL

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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.

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RADIATION THERAPY ONCOLOGY GROUP

RTOG 0924

Androgen Deprivation Therapy and High Dose Radiotherapy With or Without Whole-Pelvic Radiotherapy in Unfavorable Intermediate or Favorable High Risk Prostate Cancer: A Phase III Randomized Trial

SCHEMA

<table>
<tr><td rowspan="3">S
T
R
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F
Y</td><td>Risk Group
1. GS 7-10 + T1c-T2b + PSA < 50 ng/ml

2. GS 6 + T2c-T4 or > 50% biopsies + PSA < 50 ng/ml

3. GS 6 + T1c-T2b + PSA > 20 ng/ml</td><td rowspan="3">R
A
N
D
O
M
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Z
E</td><td>Arm 1:
Neoadjuvant androgen deprivation therapy
+ prostate & seminal vesicle RT
+ boost to prostate & proximal seminal vesicles</td></tr>
<tr><td>Type of RT Boost
1. IMRT
2. Brachytherapy (LDR using PPI or HDR)</td><td rowspan="2">Arm 2:
Neoadjuvant Androgen Deprivation Therapy
+ whole-pelvic RT
+ boost to prostate & proximal seminal vesicles</td></tr>
<tr><td>Duration of Androgen Deprivation Therapy
1. Short Term (6 months)
2. Long Term (32 months)*</td></tr>
</table>

* 32 months chosen because RTOG 9202 used 28 months and EORTC used 36 months = avg 32 months

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)
Patients who are most likely to benefit from androgen deprivation therapy and whole-pelvic radiotherapy, defined as:

a) Having a significant risk of lymph node involvement (e.g. >15%, based on the Roach formula);
b) Being in one of the following risk groups:
   - GS 7-10 + T1c-T2b (palpation) + PSA < 50 ng/ml (includes intermediate and high risk patients);
   - GS 6 + T2c-T4 (palpation) or > 50% biopsies + PSA < 50 ng/ml;
   - GS 6 + T1c-T2b (palpation) + PSA > 20 ng/ml.

Required Sample Size: **2,580 patients**

RTOG Institution #
RTOG 0924 **ELIGIBILITY CHECKLIST** (7/7/11)
Case # **(page 1 of 4)**

1 _____(Y) Does the patient have histologic proven diagnosis of adenocarcinoma of the prostate within **180** days of registration?

2 _____(Y) Is the patient at moderate to high risk for recurrence as determined by one of the following combinations?

- Gleason score 7-10 + T1c-T2b (palpation) + PSA < 50 ng/ml (this includes both intermediate and high risk patients;
- Gleason score 6 + T2c-T4 (palpation) + PSA < 50 ng/ml or Gleason score 6 + > 50% positive biopsies + PSA < 50 ng/ml;
- Gleason score 6 + T1c-T2b (palpation) + PSA > 20ng/ml

3 _____What is the Gleason score?

4 _____ What is the T-stage?

5 _____What is the PSA?

6 _____(N/Y) Are more than 50% of the core biopsies positive?

7 _____(Y) Has a history and physical examination (including a digital rectal exam) been done within **90** days prior to registration?

8 _____(Y) Are the lymph nodes negative via imaging (CT/MR of pelvis + or – abdomen) and not by nodal sampling/dissection within **90** days prior to registration or are they considered to be equivocal or questionable but ≤ 1.5 cm?

9 _____(N/Y) Was a bone scan done within **120** days prior to registration showing no evidence of bone metastases?

_____(Y) If no, was the bone scan considered to be equivocal and plain films were read as negative for metastases?

10 _____(Y) Was the baseline PSA (study entry) performed with an FDA approved assay within **12** weeks (90 days) prior to registration?

11_____(N) Was the study entry (baseline) PSA obtained during any of the following time frames?

- The 10 day period following the prostate biopsy
- After the initiation of hormonal therapy
- Within 30 days after the discontinuation of finasteride
- Within 90 days after the discontinuation of dutasteride

12 _____(Y) Is the Zubrod performance status 0 or 1?

13 _____(Y) Is the patient ≥ to 18 years old?

14 _____(Y) Was a CBC with differential done within 2 weeks (14 days) prior to registration with adequate bone marrow function as described below?

- Absolute neutrophil count (ANC) ≥ 1500 cell/mm^3
- Platelets ≥ 100,000 cells/mm^3
- Hemoglobin ≥ 8.0 g/dl

15 _____(N/Y) Was this patient diagnosed with a prior invasive (except for non-melanoma skin cancer) malignancy?

_____(Y) If yes, has the patient been considered to be disease-free for 3 or more years (1095 days)?

16 _____(Y) Is the patient able to provide study specific informed consent prior to registration?

17 _____(N) Has the patient had previous radical surgery (prostatectomy) or cryosurgery for prostate cancer?

18 _____(N) Has the patient had previous pelvic irradiation, prostate brachytherapy or bilateral orchiectomy?

19 _____(N/Y) Has the patient had previous hormonal therapy such as LHRH agonists, anti-androgens, estrogens or surgical castration?

_____(Y) If yes, did the patient begin protocol specified androgen deprivation therapy 45 days or less prior to registration?

20 _____(N) Has this patient had previous or concurrent cytotoxic chemotherapy for prostate cancer (prior chemotherapy for different cancer is allowed)?

21 _____(N) Has this patient used finasteride within 30 days prior to registration?

22 _____(N) Has this patient used dutasteride or dutasteride/tamsulosin (Jalyn) within 90 days prior to registration?

23 _____(N) Has this patient had prior radiotherapy, including brachytherapy, to the region of this study cancer that would result in overlap of radiation therapy fields?

24 _____ (N) Does this patient have any severe or active co-morbidities as defined by the following?

- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months (180 days)
- Transmural myocardial infarction within the last 6 months (180 days)
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
- Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration
- Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects or severe liver dysfunction
- Acquired immune deficiency syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.

25 _____(N) Has this patient had any prior allergic reaction to the study drug(s) involved in this protocol?

26 _____(N/Y) Will this patient be receiving brachytherapy (if no skip to Q 27)?

27 _____(Y/N/A) Is the patient sexually active and willing/able to use medically acceptable forms of contraception?

The following questions will be asked at Study Registration:
IMRT/BRACHYTHERAPY CREDENTIALING IS REQUIRED BEFORE REGISTRATION

_____ 1. Institutional person randomizing case.

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

_____(Y) 3. In the opinion of the investigator, is the patient eligible?

_____ 4. Date informed consent signed

_____ 5. Participant's Initials (First Middle Last)

_____ 6. Verifying Physician

_____ 7. Patient ID

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Ethnicity

_____ 11. Gender

_____ 12. Country of Residence

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

_____ 14. Method of Payment

_____ 15. Any care at a VA or Military Hospital?

_____ 16. Calendar Base Date (start of hormone treatment—if hormones have started prior to registration use today's date)

_____ 17. Randomization date

_____(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 urine to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 21. 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)?

_____(Y/N) 22. 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) 23. Have you obtained the patient's consent for his or her urine to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

_____(Y/N) 24. 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) 25. Did the patient agree to participate in the quality of life component?

_____ If no, provide reason:
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_____

_____26. Specify risk group:
1. Gleason score 7-10 + T1c-T2b (palpation) + PSA < 50 ng/ml (includes intermediate and high risk)
2. Gleason score 6 + T2c-T4 (palpation) or > 50% (positive) biopsies + PSA < 50 ng/ml
3. Gleason score 6 + T1c-T2b (palpation) + PSA > 20 ng/ml

_____27. Specify RT Modality for Boost
1. IMRT
2. LDR Permanent Prostate Implant (PPI) Boost
3. HDR Boost

_____28. Specify duration of ADT:
1. Short term (6 months)
2. Long term (32 months)

_____(N/Y) 29. 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 Rationale for Selected Approach and Trial Design

The term "intermediate risk" is frequently applied to prostate cancer patients whose biochemical control rates are not as favorable as low risk patients but not as poor as that of high risk patients. Usually such patients have any one of the following features: (1) Gleason's scores of 7; or (2) a serum prostate specific antigen (PSA) of 10 to 20 ng/ml; or (3) clinical T stage of T2b-T2c on digital rectal exam. However, this "intermediate risk" group encompasses a broad range of patients with heterogeneous outcomes. For example, patients with one of the adverse factors have a more favorable outcome than those with two, and those with all three do worse than those with two (Zelefsky 1998; Chism 2004; Le 2000). Furthermore, regardless of whether managed by external beam radiotherapy (EBRT), permanent prostate implant (PPI), or EBRT combined with high dose rate (HDR) brachytherapy intermediate patients with 50% or more of their biopsies positive have a prognosis comparable to high-risk patients (D'Amico 2002; Wong 2004; Rossi 2006; Kestin 2002). Recent data from the RTOG suggest that age < 70 years of age is associated with a higher rate of biochemical failure, DM, and a decreased CSS (Roach et al. unpublished data). Age less than 70 years of age was associated with a lower risk of death from other causes. However, for simplicity, our study population will not use age as a part of our selection criteria. This study will include patients who can be considered to have "unfavorable" intermediate risk prostate cancer and "favorable" high risk prostate cancer (See Eligibility, Section 3.0).

During the past decade, three strategies: (1) dose-escalation; (2) androgen deprivation therapy (ADT); and (3) whole-pelvic radiotherapy (WPRT), have independently emerged in the treatment of intermediate- and high-risk prostate cancer. No clear consensus on the optimal management of intermediate risk patients with multiple adverse features or "favorable" high-risk patients has been reached. RTOG 9413 demonstrated that patients with a risk of lymph node involvement >15% have an improvement in progression free survival (PFS) with neoadjuvant hormonal therapy combined with WPRT compared to prostate-only (PO) radiotherapy (total prostate dose in both arms of 70.2 Gy) [Roach 2003]. However, roughly half of all patients in this study had a pretreatment PSA > 20 ng/ml and roughly 70% were clinical T2c to T3. Thus, many of these patients were unfavorable intermediate or high risk and might have been better served with higher doses to their prostates and with a longer duration of ADT.

The proposed study will determine whether when higher doses of radiation is given there is a benefit to WPRT when treating unfavorable-intermediate to favorable high-risk patients. It is estimated that such patients have a risk of lymph node involvement > 15% but are not as likely to harbor occult distant metastasis as unfavorable high risk men (GS=8-10 and T3 and PSA >20) [Kattan 2003]. In addition, such patients are more likely to sustain long-term local control with high dose radiotherapy using IMRT, PPI, or boost. A subset analysis of RTOG 9413 supports the notion that patients in this type of intermediate subgroup might in fact benefit the most from WPRT (Roach 2003). Additional support for the use of whole pelvic radiotherapy can be found in retrospective data from UCSF and Stanford, Yale, University of Michigan, Italy, and Poland (as described above) [Seaward 1998; Spiotto 2007; Aizer 2009; Pan 2002; Da Pozzo 2009; Milecki 2009]. Other retrospective data question the value of NADT and WPRT when using high dose EBRT or HDR boost (Jacob 2005; Nguyen 2008).

1.2 The Relevance of RTOG 0924 to Phase III Trials Completed to Date

High doses of radiation reduce PSA failure rates (compared to lower doses) but have not been shown to improve survival rates or reduce the rate of metastasis (Mets). The lack of a benefit to date may be secondary to the presence of occult disease in regional disease not included in the radiation fields. Our current study would address this issue.

Phase III Trials including intermediate and high risk patients treated with EBRT combined with short term androgen deprivation therapy (ADT) (4 to 6 months) have demonstrated a reduction in PSA failure, the rate of distant metastasis, cause specific survival and possibly overall survival (Roach 2008; D'Amico 2004). Patients who undergo dose escalated EBRT in addition to ADT also seem to benefit (Dearnaley 2007). RTOG 0924 will build on these studies by allowing patients with "unfavorable" intermediate and "favorable" high risk disease to receive either short

term (ST) ADT or long term (LT) and dose escalated radiotherapy while testing the value of WPRT.

1.3 Principles and Supporting Data for a Phase III Trial Evaluating Whole-Pelvic Radiotherapy

1.3.1 Only patients with a significant risk of lymph node involvement can possibly benefit from WPRT.

1.3.2 Data based on extended lymph node dissections are likely to be more accurate than those based on nodal sampling or limited dissections. Based on Briganti's (2007) nomogram a patient with a T1c and 50% of cores positive and a Gleason score of 7, the PSA=10 has a ~18% of positive nodes. With a Gleason score of 8-10 it goes up to 25%. Heidenreich, et al. (2007) also concluded 20 to 25% in intermediate risk patients and 30 to 40% of high-risk patients had lymph node involvement when an extended lymph node dissection was performed. Thus, the role of WPRT needs to be defined for intermediate risk patients with multiple adverse features and "favorable" high-risk patients.

1.3.3 Retrospective data and RTOG 9413 support WPRT as a means of reducing recurrence:

- Retrospective data from UCSF suggest that patients with a risk of 15 to 35% benefit the most from WPRT (Seaward 1998).
- Retrospective data from Stanford involving the treatment of patients in the post-operative setting supports WPRT (Spiotto 2007).
- Retrospective data from Yale supports WPRT in patients with high-risk prostate cancer (Aizer 2009);
- Retrospective data from University of Michigan supports WPRT for men with a Partin Table risk of 5 to 15% (Pan 2002).
- Retrospective data from Italy demonstrated an improvement in cause specific survival (CSS) in post operative patients with positive lymph nodes treated with RT +ADT (75% WPRT) compared to ADT alone (Da Pozzo 2009).

1.3.4 RTOG 9413 demonstrated an increase in progression with hazard of 1.52 if only the prostate was irradiated in conjunction with short term neoadjuvant ADT (Roach 2003).

1.3.5 Subset analysis from RTOG 9413 suggests that the patients with the greatest benefit had a PSA< 30 and GS=7-10 or PSA >30 ng/ml and GS< 7 (Roach 2003). Thus, high-risk patients appear to benefit.

1.3.6 Higher doses of radiation to the prostate should allow the benefits to be more obvious because fewer failures will be local. With a dose of 70 Gy many of the failures may have been local even if pelvic nodes were controlled.

1.3.7 The use of IMRT should result in better results than RTOG 9413 by providing better coverage of nodes and better control (Roach 2006; Wang-Chesebro 2006) and less toxicity (Chan 2008; Chung 2009) .

1.3.8 Only an adequately powered study with patients at risk for death from prostate cancer can answer this question. In order to demonstrate a survival advantage the patients at risk must be at significant risk of death within 10 years.

1.3.9 The short term ADT arm of RTOG 9202 revealed CSS 85% at 10 years, despite a median PSA> 20 ng/ml, T2c-T3 and GS 8-10. A 40% reduction in mortality would yield a CSS of ~ 93 for an absolute difference of <10%. The same arm of RTOG 9413 was associated with a 10-year CSS of 90%. Assuming fewer deaths due to local failure the goal of a 10% reduction should be achievable (Lawton 2007).

1.4 Health-Related Quality of Life (HRQOL), Fatigue, and Quality-Adjusted Survival (QAS)

Several studies indicate a higher rate of symptomatic toxicity (mostly GI and GU) in men with prostate cancer who have received whole pelvic radiation therapy (WPRT) versus prostate-only radiation therapy (PORT). For example, in RTOG 9413, the rate of acute grade 2 or higher GI toxicity was significantly higher in patients receiving WPRT (47%) versus PORT (20%), p<0.001. Similarly, the rate of grade 2+ acute GU toxicity was also higher in patients receiving pelvic radiation (>30%) than those receiving PORT (22%), p=0.016 (Pommier 2007). These significant differences were present whether or not one compared the PORT group to the whole-pelvis group or the mini-pelvis group. Overall, the acute grade 2+ RT-related GU and GI toxicities significantly correlated with the radiation field size. Similarly, there was a significant increase in grade 2+ late GU toxicity for patients who received WPRT (15%) versus those that received PORT (5.6%), p=0.03. There was also a significant difference in late grade 2+ GI toxicity between those who received WPRT (15%) versus those that received mini-pelvis (8.5%) or PORT (7%), p=0.002. Moreover, the incidence of late grade 3+ GI toxicity in this study also

correlated with field size (4.3% were WPRT versus 0% for PORT, p=0.006). While, in general, the rates of grade 3+ toxicities are low, the rates of grade 2 toxicities are quite prominent and these symptoms (e.g. urinary frequency, dysuria, rectal pain, diarrhea, etc) can certainly affect quality of life, particularly the GI and GU domains of QOL.

Similarly, in a recent analysis comparing a consecutive sample of 277 patients with prostate cancer who received either WPRT or PORT, Aizer, et al. (2009), reported a significantly higher rate of acute GI toxicity in the patients receiving WPRT (p=0.048), as well as a trend toward an increase in acute GU toxicity in this group (p=0.09). Interestingly, they reported a higher rate of biochemical control in the patients that received WPRT (86%) versus those who received PORT (69%), p=0.002. They conclude that while WPRT may yield improvement in biochemical control, it results in a greater incidence of acute toxicity.

Not all studies, however, have shown a significant increase in toxicity from pelvic radiation to prostate-only radiation. In a randomized trial reported by Pommier, et al. (2007), comparing WPRT to PORT, they found no significant differences in acute or late digestive toxicities based upon the treatment field. However, they did note a non-significant increase in grade 2+ acute digestive toxicities on the pelvic arm (which was approximately 7% higher). They explain part of this lower rate of increased GI toxicity in this study (compared to RTOG 9413) based upon the lower pelvic volume and lower RT dose used in this study. They also found that pelvic radiation was associated with an increase in grade 2+ late GU toxicity. (43.3% versus 36.9%, p=0.17). Of note, a significant, unexpected, increase of grade 2+ urinary acute toxicities was noted in the prostate-only group, which they felt was possibly explained by the more frequent use of >2Gy per fraction in this group (versus 1.8Gy per fraction in the pelvic group).

Some have argued that the application of intensity modulated radiation therapy (IMRT) for prostate cancer has essentially prevented the development of significant toxicity from radiation. However, several studies indicate that this is not the case. In one study of >100 patients treated with IMRT to the prostate and/or seminal vesicles, grade 2 GI toxicities were observed in approximately 30% of the patients. Grade 2 acute GU toxicities were observed in 36% of the patients, in addition to 7% grade 3 GU toxicities (De Meerleer 2004).

Indeed, a recent study carefully compared the toxicity rates in patients receiving IMRT to the whole pelvis versus the prostate. In this study, all patients received IMRT to 79.2Gy with concurrent androgen deprivation with a minimum follow-up of 12 months. Thirty patients received initial whole pelvic IMRT to 45Gy in 25 fractions and 30 patients received prostate-only IMRT. Careful bladder and rectal dose volume histogram constraints were utilized. Interestingly, the rate of acute grade 2 GI toxicity was significantly increased in the pelvic radiation group at 50% versus 13% in the prostate only group (p=0.006). They concluded that whole pelvic IMRT results in clinically significant increases in GU toxicity in comparison to prostate-only IMRT (Deville 2010).

The influence of hormone therapy on toxicity rates in patients receiving radiation on prostate cancer have shown mixed findings. In a single institutional review of over 1,000 patients all treated with 3-D conformal RT, the use of long-term androgen deprivation therapy (ADT) significantly increased the risk of both GU and GI morbidity compared to patients treated with 3-D conformal RT alone (Feigenberg 2005). They found that the 5-year risk of grade 2+ GU morbidity was 8% with no ADT versus 14% with long-term ADT (p=0.02). The 5-year actuarial risk of grade 2+ GI morbidity was 17% for no ADT and 26% for long-term ADT (p=0.017). However, in a secondary analysis of several RTOG studies, Lawton, et al, found that patients treated with RT and short-term ADT had a lower probability of grade 3+ GI and GU toxicities compared with patients treated with RT alone (Lawton 2008). Of note, in RTOG 0924 patients on both arms will similarly receive at least six months of ADT.

Prior studies have demonstrated a disconnect between physician-derived toxicity scores and patient reported outcomes (PRO), such as quality of life. Indeed, there is generally an underreporting of clinically relevant symptoms based upon the toxicity scoring, as compared to the PRO information. RTOG demonstrated this “disconnect” between toxicity scores and PRO data in a lung cancer study, RTOG 9801. While there were no significant differences in the rates

of esophagitis toxicity in this randomized trial testing a radiation protector, amifostine, there were some improvements noted with amifostine based upon patient reported outcomes, such as the level of pain (Sarna 2008). In the context of prostate radiation, a similar phenomenon has been noted. Over 300 prostate cancer patients participated in the Dutch randomized trial comparing 68Gy to 78Gy (Al-Mamgani 2010). This study showed no significant differences in the rates of late GU and GI toxicity at 3 years. Yet, in both randomized arms, statistically significant decreases in QOL scores over time were seen in six scales. Moreover, the deterioration over time was only clinically relevant in the role-physical and physical-functioning scales in the patients treated in the high-dose arm. Of importance, late GU and GI toxicities showed a trend toward significant correlation with quality of life changes over time. Thus, as several studies in the past have shown an increased level of GI and GU toxicity in patients receiving whole-pelvic radiation versus prostate-only radiation, it is important to study these effects directly from the patient perspective.

There are limited data regarding quality of life studies comparing patients treated with WPRT versus PORT. In a long-term study of quality of life in men treated for prostate cancer, Hanlon, et al. (2001), reported significant differences based on field size. In particular, patients treated with pelvic radiation had significantly higher rates of self-reported rectal urgency (40% versus 22%, p=0.03), an increased use of pads for protection against bowel incontinence (10% versus 0%, p=0.01) and lower overall bowel satisfaction (72% versus 88%, p=0.03). Men treated with larger fields sizes reported more problems with getting up at night to urinate than men treated with smaller field sizes. In the words of the authors, “clearly, large field irradiation contributes to the late bowel dysfunction”. In this study, comparing WPRT to radiation focused on the prostate area, the key QOL domains expected to be affected are GI and GU, due to an increase in the dose/volume of radiation to the bowel and bladder from whole pelvic radiation. These side effects need more systematic study in clinical trials. Such studies would provide well-defined side effect profiles for better informing physicians and patients of the full consequences of WPRT and improve the awareness that they should incorporate into routine practice strategies for preventing and managing toxicities (Higano 2003). To address HRQOL, RTOG 0924 will compare the treatment arms for differences in prostate cancer HRQOL outcomes, particularly the GI and GU domains (as measured by change over time in the Expanded Prostate Cancer Index Composite [EPIC])-26 (van Andel 2003).

1.4.1 Fatigue

Fatigue has been described as the most frequent and distressing symptom related to cancer and its treatment (Bower 2005). Radiotherapy-induced fatigue is a common early side effect reported by 80% of patients during treatment (Jereczek-Fossa 2001). 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 (Lilleby 1999; Monga 1999; Monga 2005; Truong 2006). The high prevalence of this symptom in persons treated with radiotherapy, as well as its association with poor quality of life, mark it as a significant problem that requires further scientific study.

Fatigue has been found to increase significantly during the course of RT (Jereczek-Fossa 2001; Truong 2006; Beard 1997; Danjoux 2007; Prue 2006). A few reports that consider dose-volume related factors (such as small-field or conformal RT vs. whole-pelvic-field RT) support the hypothesis that higher volumes of RT may be a key factor in treatment-induced fatigue.

Danjoux, et al., (2007) prospectively evaluated fatigue in a cohort of prostate cancer patients. Patients were categorized as having conformal RT (n = 50), prostate-boost-only RT (n=33), or larger field whole pelvis plus prostate boost, RT (n=46). Fatigue severity increased more during therapy for the whole-pelvis + prostate boost group compared to either the conformal RT group or the prostate-boost-only RT group.

Beard, et al., (1997) studied fatigue in a prospective multi-institutional cohort treated with external beam irradiation techniques for prostate cancer. Twenty-five patients underwent whole pelvis RT; 60 patients underwent ‘small-field’ RT; thirty-four patients underwent conformal RT. They reported that whole pelvic fields fared significantly worse than small field or conformal RT delivery. They found trends against whole pelvic therapy in favor of conformal RT in patient reported outcomes of fatigue, energy, and vigor. The Danjoux and Beard studies suggested

that smaller fields, and resulting small treatment volumes, are related to lower levels of treatment-induced fatigue observed during a course of RT.

Well established toxicities from ADT include lean weight loss, muscle weakness, fatigue, and reduced physical activity, among others (Higano 2003; Bylow 2007). A quality of life analysis of data from a randomized trial (n = 144) found that asymptomatic men with biochemical recurrence who received ADT had significantly worse fatigue severity than those who did not (Herr 2000). Combined androgen blockade (luprolide plus flutamide) was associated with greater fatigue than luprolide alone or orchiectomy. Likewise, a study of 91 men with lymph node-positive disease who received ADT had worse fatigue at 18-month follow-up than men who did not have this treatment (van Andel 2003). Two studies demonstrated that fatigue increased from the beginning to the end of a 3-month course of neoadjuvant hormone therapy prior to radiotherapy (Stephens 2007; Stone 2000).

Only two studies could be found that addressed fatigue associated with RT and/or ADT. Voerman, et al. (2006) conducted a cross-sectional study of 238 men who completed a quality of life questionnaire after completion of prostate cancer treatment (mean time after diagnosis = 44.3 months). In the sample, 38 had been treated with RT and 112 had received RT + ADT. Men receiving ADT reported considerably worse fatigue than those who received RT alone. In another study described earlier, Truong, et al. (2006) reported fatigue scores for men undergoing RT who had received neoadjuvant ADT. Fatigue increased significantly during RT and at the end of RT. After RT completion (median = 6.5 weeks after RT), fatigue improved but remained higher than baseline.

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 worse fatigue (Monga 2005; Beard 1997; Danjoux 2007). Likewise, ADT has been associated with increased fatigue (Stephens 2007; Voerman 2006). Of note, in RTOG 0924, patients on both arms will similarly receive at least six months of ADT. Other fatigue correlates have been proposed: depression, poor sleep quality, and use of regular physical activity (Jereczek-Fossa 2001; Berger 2005; Mock 2000). Thus, we plan to address such confounding factors with brief and focused questions.

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):

1.4.1.1 *Anxiety/Depression Item in EQ-5D*

Muscle weakness question (scale of 1-5, from none to very much)

Overall Sleep Quality: Item from Pittsburgh Sleep Quality Index (Buysse 1989):

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.

	Very bad	*Fairly bad*	*Fairly good*	*Very good*
3. During the past week, how would you rate your sleep quality overall?	***0***	***1***	***2***	***3***

Usual exercise (3 items):

Participants' level of physical activity will be assessed using the Godin Leisure-Time Exercise Questionnaire (GLTEQ) [Godin 1986; Gionet 1989], 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 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 (Godin 1986; Gionet 1989).

The following questions are about your average weekly exercise. When answering the questions only count exercise that you do during free time (ignore exercise associated with your occupation and housework). Considering a typical week (7 days), how many times, on average, do you perform mild, moderate, or strenuous exercise? And when you engage in exercise, how long do you exercise, on average?

	Times Per Week **(a)**	Average Duration **(b)**
1. Mild exercise – that is, minimal effort exercise that did not make you perspire, such as easy walking, yoga, bowling, lawn bowling, shuffleboard, or golf	_____	_____ mins.
2. Moderate exercise – that is, exercise that is not exhausting and which made you perspire lightly, such as fast walking, tennis, easy bicycling, easy swimming, or popular and folk dancing	_____	_____ mins.
3. Strenuous exercise – that is, exercise that made your heart beat rapidly and made you sweat, such as running, aerobics classes, cross country skiing, vigorous swimming, or vigorous bicycling	_____	_____ mins.

1.4.2 Quality-Adjusted Survival and Failure Free Survival

In this study, the addition of prophylactic pelvic nodal radiotherapy is hypothesized to improve freedom from failure (FFF) and overall survival (OS), while having a negative impact on health related quality of life (HRQOL). As these are competing pros and cons of this strategy, it is useful to combine these factors into one equation to determine whether the potential benefits of this treatment (dose-escalated RT combined with short-term androgen deprivation), in terms of FFF and OS, outweigh the potential risks of this strategy, in terms of negatively impacting on global HRQOL, compared to RT alone. Such a quality adjusted survival (or failure free survival) analysis can be invaluable for assisting in the decisions of future patients faced with these treatment options as well as clinicians.

Quality-adjusted survival and freedom from progression can be defined by the weighted sum of different time episodes added up to a total quality-adjusted life-year or failure free survival-year [U= sum of quality (qi) of health states K times the duration (si) spent in each health state (Glasziou 1990)

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

The EQ-5D has been used across numerous disease sites (Milne 2006; Wildi 2004). The EQ-5D has been used to assess QALYs and the economic value of prostate cancer screening and treatment of pain related to prostate cancer metastasis (Essink-Bok 1998; Sandblom 2004). 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 quality-adjusted life years (QALY) to every man with prostate cancer (Sennfalt 2004).

1.4.3 Health Related Quality of Life Assessments

The following instruments will be used to assess health related quality of life (HRQOL), including fatigue and quality adjusted survival: the Expanded Prostate Cancer Index (EPIC)-26, the Patient-Reported Outcome Measurement Information System (PROMIS)-fatigue short form, and the EuroQol (EQ-5D) instrument. **These outcomes measurements will be limited to 230 consenting patients in each arm**. Of note, these are essentially the same instruments (and time points) that are being studied in the "sister" study, RTOG 0815, which is currently accruing patients. In RTOG 0815, patients with "lower" intermediate risk prostate cancer all receive high dose RT and are randomized to +/- short term hormones. Ultimately, use of essentially the same instruments and time points in both studies (RTOG 0815 and RTOG 0924) will create a huge database of relevant information related to QOL, QAS, and fatigue issues in prostate cancer patients that will facilitate a large combined analysis in the future. The outcomes instruments in this study are as follows:

1.4.3.1 *Prostate Cancer-Specific Health-Related Quality of Life: EPIC-26*

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 radiotherapy and hormonal therapy (van Andel 2003). 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 (Wei 2000).

Widespread implementation of health-related quality-of-life (HRQOL) measurement requires concise instruments. With 50 questions, the full-length Expanded Prostate Cancer Index Composite (EPIC) can be cumbersome to administer. To reduce patient burden, an abbreviated version of the EPIC (EPIC-26) was developed and validated (Szymanski 2010). The 50 questions that constitute the full-length EPIC-50 were evaluated to identify the items suitable for elimination while retaining the ability to measure the prostate cancer-specific HRQOL domains of the EPIC-50. The resulting abbreviated version (EPIC-26) was validated using question responses from 252 subjects who had undergone brachytherapy, external beam radiotherapy, or prostatectomy for prostate cancer. The EPIC-26 internal consistency was measured by Cronbach's alpha coefficient and reliability using test-retest correlation. Using the high item-scale correlations, clinically relevant content, and preservation of domain psychometrics, 26 items were retained in the EPIC-26 from the 50 questions in the full-length EPIC-50. A high correlation was observed between the EPIC-50 and EPIC-26 versions for the urinary incontinence, urinary irritation/obstruction, bowel, sexual, and vitality/hormonal domain scores (all r >/=0.96). The correlations between the different domains were low, confirming that EPIC-26 retained the ability to discern the distinct HRQOL domains. The internal consistency and test-retest reliability for EPIC-26 (Cronbach's alpha >/=0.70 and r >/=0.69, respectively for all HRQOL domains) supported its validity. EPIC-26 is a brief, valid, and reliable subjective measure of health quality among patients with prostate cancer. To reduce patient burden, this is the validated HRQOL instrument that will be used in this study.

1.4.3.2 *PROMIS-Fatigue Short Form*

The PROMIS Fatigue Scale (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).

1.4.3.3 *Quality-Adjusted Survival Analysis: EuroQol (EQ-5D)*

The EQ-5D is a patient self-administrated questionnaire that takes approximately 5 minutes to complete (Schulz 2002). 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 (Badia 1998).

The 5-item index score is transformed into a utility score between 0, "Worst health state," and 1, "Best health state." The index score or the cost-utility equation can be used in the quality adjusted survival analysis depending on the health state(s) of interest (Wu 2002). For this study we plan to report the multidimensional utilities for comparative purposes.

1.5 Correlation of Circulating Proinflammatory Cytokines to Fatigue

Plasma may be collected from patients enrolled on this protocol at baseline and during the last week of radiation treatment. The tissue specimens will be collected and processed according to the RTOG specimen processing guidelines and must be clearly labeled with the patient identification number. Specimens from participating institutions will be banked in the RTOG Biospecimen Resource for future translational analyses. Anticipated analyses for collected specimens include 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.

Alterations in the circulating levels of the proinflammatory cytokines TNF alpha, IL-1, IL-1ra, IL-6 and the marker of inflammation C-reactive protein during radiotherapy for prostate cancer predict for the likelihood of developing fatigue as measured by the PROMIS instrument.

Pro-inflammatory cytokines have been found to play a role in cancer-related fatigue (CRF) and fatigue from other chronic illnesses (Schubert 2007). The most commonly implicated cytokines are IL-1, IL-6, TNF alpha, and IFN alpha (Ryan 2007). 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 (Benzing 1999).

Because many of the therapies used to treat cancers can induce expression of these 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 radiotherapy. Ahlberg et al. (2004) evaluated 15 patients treated with pelvic radiotherapy to a dose of 46 Gy in 2 Gy fractions after hysterectomy. Fatigue was assessed with the Multidimensional Fatigue Inventory (MFI-20). Cytokine levels were assessed before starting radiotherapy, after 30 Gy, and within one week of radiotherapy. Fatigue scores were elevated at the 30 Gy and completion of radiation time points. IL-1 remained undetectable at all time points. TNF alpha and IL-6 were increased in several patients at the time points during radiotherapy and at the completion of radiotherapy. IL-6 elevated in nearly half of patients, and levels decreased through radiotherapy 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 radiation; and at long term follow up (Geinitz 2001; Geinitz 2004).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 radiotherapy; 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. Bower (2009) evaluated fatigue and cytokines in 20 men undergoing radiotherapy for prostate cancer and demonstrated that serum levels of C-reactive protein and IL-1 receptor agonist were positively associated with fatigue increases during treatment.

While several of the series that drew negative conclusions above found no increase in inflammatory cytokine levels with radiation, several series have found striking elevations. For example, Akmansu et al. (2005) found significant elevations in serum IL-6 and TNF alpha after five weeks of radiotherapy compared to pretreatment levels in 34 patients receiving radiotherapy for head and neck cancer. Greenberg et al. found significant elevations in IL-1 in the early weeks of radiotherapy for prostate cancer in 15 patients which correlated with an increase in fatigue (Greenberg 1993). 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 hormonal therapy on inflammatory markers is less well known. Small studies have shown altered cytokine expression by prostate tumors after hormonal therapy (Sugihara 1998), but levels of systemic cytokines after hormonal therapy for prostate cancer are not well described. Fatigue is a well-known complication of hormonal therapy for prostate cancer (Peters 2008). The combination of radiation and hormonal therapy for prostate cancer may result in a more persistent and prolonged fatigue compared to the series evaluating fatigue after radiation alone, with as many as 32% of patients experiencing fatigue at the completion of radiation and a substantial number experiencing fatigue as late as 6.5 weeks after completion of radiation (Stone 2000).

Correlation of inflammatory cytokines to fatigue may provide mechanistic information regarding the causes of fatigue in patients receiving radiation therapy and hormonal therapy and may provide a target for intervention in future studies. Blood collection is mandatory for patients consenting to the QOL portion of this study. 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.

1.6 Genetic Predictors of Fatigue

It will be strongly recommended that patients consent to having a blood sample sent for storage to the RTOG Biospecimen Resource. The buffy coat will be isolated from each sample and the DNA extracted. The specimens will be collected and processed according to the RTOG specimen processing guidelines. Anticipated analyses include evaluation of single nucleotide polymorphisms (SNPs) and copy number variants (CNVs) through screening DNA samples derived from case and matched control subjects using Affymetrix 6.0 microarrays. Case subjects will be patients that represent the 20% of patients in this study exhibiting the highest levels of fatigue as defined and measured by the PROMIS instrument used in this study while controls will be the 20% of patients who reported the lowest levels of fatigue as quantified using PROMIS. The goal of this study will be to identify SNPs and CNVs associated with the development of fatigue in prostate cancer patients following radiotherapy.

The hypothesis that forms the basis for this study is that SNPs and/or CNVs in certain genes are associated with the development of fatigue resulting from radiotherapy for prostate cancer. Evidence that possession of genetic variants is associated with the development of adverse effects resulting from radiotherapy comes from several studies. In one case/control study of 141 prostate cancer patients treated with radiotherapy, patients were screened for SNPs in TGFB1 (Burri in press). Those subjects who possessed either the T/T genotype at position -509, the C/C genotype at position 869 or the G/C genotype at position 915 were significantly associated with the development of a decline in erectile function compared with those who did not have these

genotypes. In addition, patients with the -509 T/T genotype had a significantly increased risk of developing late rectal bleeding compared with those who had either the C/T or C/C genotype at this position. These subjects were also genotyped for SNPs in SOD2, XRCC1, and XRCC3 (Damaraju 2006). Patients possessing the XRCC1 rs25489 G/A genotype were more likely to develop erectile dysfunction following irradiation compared to patients who had the G/G genotype. The estimated CAG haplotype frequency for XRCC1 was significantly higher in men with late rectal bleeding than in men without late rectal bleeding. In addition, patients who possessed the SOD2 rs4880 C/T genotype exhibited a significant increase in grade 2 late rectal bleeding compared to patients who had either the C/C or T/T genotype for this SNP. Furthermore, patients possessing the combination of the SOD2 rs4880 C/T genotype and XRCC3 rs861539 C/T genotype experienced a significant increase in grade 2 late rectal bleeding compared to patients without this particular genotypic arrangement. Another important study reported that possession of SNPs in the LIG4, ERCC2, and CYP2D6 was significantly associated with the development of clinical toxicity, including urinary morbidity, in patients treated with radiotherapy for prostate cancer (Dudbridge 2006).Taken together, the results of these studies provide a strong basis for the role of genetic factors in the ability to predict which prostate cancer patients will exhibit adverse radiotherapy responses.

1.7 Expression Signature to Predict Lymph Node Status

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. This study is designed as a validation of previous work showing that a 3-6 gene signature from the primary tumor is able to predict lymph node status prospectively. If validated using tissue collected as part of this study, this signature will be applied in future protocols for patient stratification for whole pelvic radiotherapy.

1.7.1 Background

A 3 gene expression signature from the primary tumor has been developed at UCSF which is strongly associated with positive lymph node status (manuscript pending). This signature will be validated using biopsy tissues collected as part of RTOG 9413. Once that is accomplished, it will be further validated as part of this study protocol.

1.7.2 Design

Biopsy blocks will be collected from institutional sites as part of the tissue collection for translational studies. Three biopsy sections will be used for manual microdissection and extraction of RNA. RNA will then be quantitated for 3 genes of interest and 3 housekeeping genes to derive a signature lymph node metastatic index. This index will be tested for associations with lymph node status.

1.7.3 Other Studies

A number of other marker signatures have been developed for prediction of outcome in high grade prostate cancers, both by RTOG investigators (Pollack et al.) and others. A standard set of these markers will be evaluated in the same biopsy samples to compare their outcome prediction with the lymph node signature already being tested.

2.0 OBJECTIVES

2.1 Primary Objective

Demonstrate that prophylactic neoadjuvant androgen deprivation therapy (NADT) and whole-pelvic radiation therapy (WPRT) will result in improvement in overall survival (OS) in patients with "unfavorable" intermediate risk or "favorable" high risk prostate cancer compared to NADT and high dose prostate and seminal vesicle (SV) radiation therapy (P + SV RT) using intensity modulated radiotherapy (IMRT) or EBRT with a high dose rate (HDR) or a permanent prostate (radioactive seed) implant (PPI) boost

2.2 Secondary Objectives

2.2.1 Demonstrate that prophylactic WPRT improves biochemical control ("Phoenix definition").
Patients not meeting these PSA criteria (Phoenix Definition) for failure who undergo salvage therapies (such as ADT, radical prostatectomy or brachytherapy, or Cryosurgery) should also be declared as failures at the time a positive biopsy is obtained or salvage therapy is administered, whichever comes first.

2.2.2 Distant metastasis (DM) free-survival, defined as imaging documented evidence of distant spread of disease;

2.2.3 Cause specific survival (CSS) will be defined as death from prostate cancer after biochemical failure followed by the development of metastatic disease followed by the development of castration resistant prostate cancer (CRPC).

2.2.4 Compare acute and late treatment adverse events between patients receiving NADT + WPRT versus NADT + P & SV RT;

2.2.5 Determine whether health related quality of life (HRQOL) as measured by the Expanded Prostate Cancer Index Composite (EPIC) significantly worsens with increasing aggressiveness of treatment (i.e. Arm 2, NADT + WPRT);

2.2.6 Determine whether more aggressive treatment (Arm 2, NADT + WPRT) is associated with a greater increase in fatigue (PROMIS Fatigue Short Form) from baseline to last week of treatment and a greater increase in circulating inflammatory markers (IL-1, IL-1ra, IL-6, TNF-alpha, and C-reactive Protein);

2.2.7 Demonstrate an incremental gain in OS and CSS with more aggressive therapy that outweighs any detriments in the primary generic domains of HRQOL (i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression); this will be reported as the Quality Adjusted Freedom From Progression Year (QAFFPY) and as the Quality Adjusted Life Year (QALY);

2.2.8 Determine whether changes in fatigue from baseline to the next three time points (week prior to radiation therapy, last week of treatment, and 3 months after treatment) are associated with changes in circulating cytokines, mood, sleep, and daily activities across the same time points.

2.2.9 Collect paraffin-embedded tissue blocks, plasma, whole blood, and urine for planned and future translational research analyses.

3.0 PATIENT SELECTION

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

3.1 Conditions for Patient Eligibility

3.1.1 Pathologically (histologically or cytologically) proven diagnosis of prostatic adenocarcinoma within 180 days of registration at moderate to high risk for recurrence as determined by one of the following combinations:

- Gleason score 7-10 + T1c-T2b (palpation) + PSA < 50 ng/ml (includes intermediate and high risk patients);
- Gleason score 6 + T2c-T4 (palpation) or > 50% (positive) biopsies + PSA < 50 ng/ml;
- Gleason score 6 + T1c-T2b (palpation) + PSA > 20 ng/ml.

3.1.2 History/physical examination (to include at a minimum digital rectal examination of the prostate and examination of the skeletal system and abdomen) within 90 days prior to registration.

3.1.3 Clinically negative lymph nodes as established by imaging (pelvic ± abdominal CT or MR), (but not by nodal sampling, or dissection) within 90 days prior to registration.

3.1.3.1 Patients with lymph nodes equivocal or questionable by imaging are eligible if the nodes are ≤ 1.5 cm.

3.1.4 No evidence of bone metastases (M0) on bone scan within 120 days prior to registration.

3.1.4.1 Equivocal bone scan findings are allowed if plain films (or CT or MRI) are negative for metastasis.

3.1.5 Baseline serum PSA value performed with an FDA-approved assay (e.g., Abbott, Hybritech) within 12 weeks (90 days) prior to registration.

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

3.1.6 Zubrod Performance Status 0-1(unless otherwise specified);

3.1.7 Age ≥ 18;

3.1.8 CBC/differential obtained within 2 weeks (14 days) prior to registration on study, with adequate bone marrow function defined as follows:

3.1.8.1 Absolute neutrophil count (ANC) ≥ 1,500 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

3.2.1 Prior invasive (except non-melanoma skin cancer) malignancy unless disease-free for a minimum of 3 years (1095 days) not in the pelvis. (For example, carcinoma in situ of the oral cavity is permissible; however, patients with prior history of bladder cancer are not allowed). Prior hematological (e.g., leukemia, lymphoma, myeloma) malignancy not allowed.

3.2.2 Previous radical surgery (prostatectomy) or cryosurgery for prostate cancer

3.2.3 Previous pelvic irradiation, prostate brachytherapy, or bilateral orchiectomy

3.2.4 Previous hormonal therapy, such as LHRH agonists (e.g., leuprolide, goserelin, buserelin, triptorelin) or LHRH antagonist (e.g. degarelix), anti-androgens (e.g., flutamide, bicalutamide, cyproterone acetate), estrogens (e.g., DES), or surgical castration (orchiectomy)

3.2.4.1 Prior pharmacologic androgen ablation for prostate cancer is allowed only if the onset of androgen ablation is ≤ 45 days prior to the date of registration.

3.2.5 Use of finasteride within 30 days prior to registration

3.2.6 Use of dutasteride or dutasteride/tamsulosin (Jalyn) within 90 days prior to registration

3.2.7 Previous or concurrent cytotoxic chemotherapy for prostate cancer; note that prior chemotherapy for a different cancer is allowable. See Section 3.2.1.

3.2.8 Prior radiotherapy, including brachytherapy, to the region of the study cancer that would result in overlap of radiation therapy fields

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 at the time of registration

3.2.9.5 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects or severe liver dysfunction

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. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.

3.2.10 Patients who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

3.2.11 Prior allergic reaction to the hormones involved in this protocol

3.2.12 Patients status post a negative lymph node dissection are not eligible

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

4.1.1 Any patient undergoing brachytherapy must have transrectal ultrasound confirmation of prostatic volume <60 cc 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.

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

4.2 Highly Recommended Evaluations/Management

4.2.1 Prior testosterone administration must have been last administered at least 90 days prior to registration.

5.0 REGISTRATION PROCEDURES

5.1 Pre-Registration Requirements for Intensity Modulated Radiation Therapy (IMRT) Treatment Approach

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 and select "Credentialing" and "Credentialing Status Inquiry".

Institutions that previously have been credentialed for one IMRT delivery technique (e.g., standard gantry mounted linear accelerator using fixed gantry angles) must repeat the credentialing process when they change to a different technology (e.g. tomotherapy or volume delivery methods such as RapidArc or VMAT).

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; 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 complete a new IMRT Facility Questionnaire (or modify their existing Facility Questionnaire on file at RTOG) and send it to RTOG for review prior to entering any cases, and set up an SFTP account for digital data submission, both of which are available on the Image-Guided Center (ITC) 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 3-D Conformal Radiation Therapy (3DCRT) Treatment Approach

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

5.2.2 The new Facility Questionnaire, or modified Facility Questionnaire on file at the RTOG if one has already been completed, (one per institution, available on the ATC website at http://atc.wustl.edu) 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 3D-CRT trials of this same disease site may enroll patients on this study without further credentialing.

5.3 Pre-Registration Requirements for Brachytherapy Treatment Approach

Only physicians who have completed the Knowledge Assessment Questionnaire available from the RPC website (http://rpc.mdanderson.org) may enter patients onto this study. Upon review and successful completion, the Radiological Physics Center 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 subsequent patients onto this study.

5.3.1 *LDR Brachytherapy Credentialing*

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

5.3.1.1 If an institution was credentialed for a previous RTOG LDR prostate brachytherapy trial,they do not have to be re-credentialed for this trial, with the exception of completing the Knowledge Assessment Form specific to this protocol, 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, the Credentialing Questionnaire, and the Reference Cases. A change in either the treatment planning computer or brachytherapy source model will require resubmission of only the Reference Cases. 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; select "brachy sources".

5.3.2 *HDR Brachytherapy Credentialing*

Only institutions that have completed the Knowledge Assessment Questionnaire, the Facility Questionnaire, and the Benchmark Cases (see RPC web site http://rpc.mdanderson.org) may enter patients onto this study. If an institution was previously credentialed for a previous RTOG HDR prostate brachytherapy trial they do not have to be re-credentialed for this trial, with the exception of completing the Knowledge Assessment Form specific to this protocol, 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. The sample clinical case with complete Implant Dosimetry Data Form and other materials are to be sent to the Radiological Physics Center (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.

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/verification of IRB/REB consent translation to RTOG Headquarters (described below)
- IRB/REB assurance number

5.4.1.1 Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved RTOG will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational/letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

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/Researchers/InternationalMembers.aspx .

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 http://www.rtog.org/LinkClick.aspx?fileticket=-BXerpBu5AQ%3d&tabid=219 (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 Logon" 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.

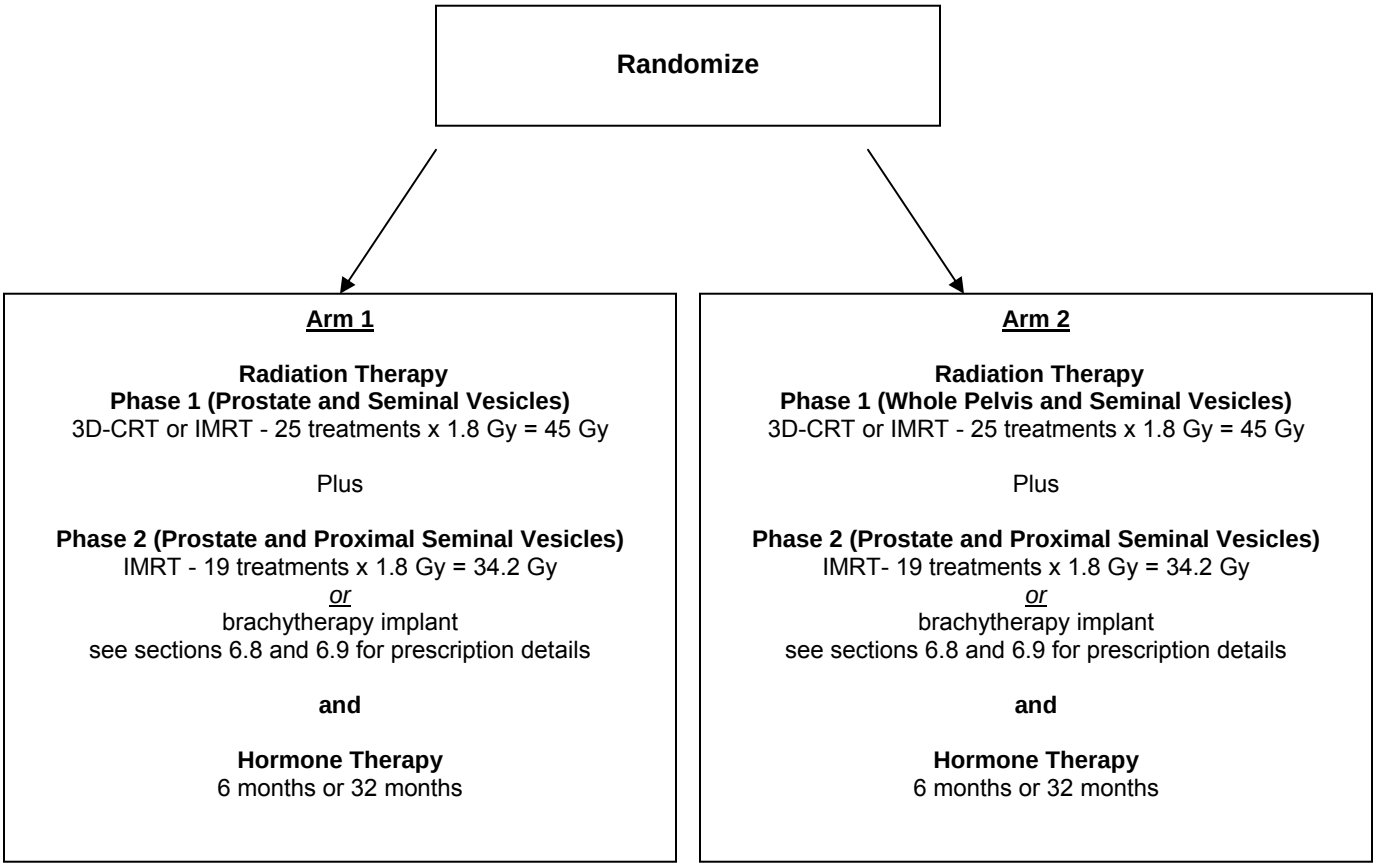
In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask for the site's user name and password. This information is required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

In both arms, radiotherapy should begin within 8 weeks (+/- 1 week) after the date of the first LHRH agonist/antagonist injection.

Note 1: As this protocol allows for treatment with EBRT exclusively 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.

When an IMRT (rather than brachytherapy) boost is used to meet the dose constraints for the composite EBRT plan (see Sections 6.4 – 6.5) that includes Phases 1 and 2, both treatment plans must be generated and summed at the beginning of the patient's treatment.



6.1 Dose Specifications

6.1.1 Arm 1 (Sequential Boost Technique – Phases 1 and 2)

6.1.1.1 *Phase 1: Treat prostate and seminal vesicles*

Acceptable Treatment Modalities
3D-CRT or IMRT

Prescribed Dose (See Table 1)
45 Gy to cover 98% of PTV

- Minimum dose within PTV – 95% of prescribed dose and for a volume that is 0.03 cc
- Maximum dose within the PTV – 107% of prescribed dose and for a volume that is 0.03 cc

Table 1: 3D-CRT and IMRT Dose Objectives for Phase 1

PTV dose (encompassing 98% of PTV)	Minimum PTV dose for a point with a volume of 0.03 cc	Maximum PTV dose to a volume of 0.03 cc of the PTV[1] (Per Protocol)	Maximum PTV dose to a volume of 0.03 cc of PTV[1] (Variation Acceptable)	Maximum PTV dose to a volume of 0.03 cc of PTV[1] (Deviation Unacceptable)
45 Gy	42.8 Gy	48.2 Gy	> 48.2 - 49.5 Gy	> 49.5 Gy

[1] The maximum dose must not be within an "Organ at risk" such as the rectum, bladder or penile bulb.

6.1.1.2 ***Phase 2****: Reduce volume to boost prostate and proximal seminal vesicles*

Acceptable Treatment Modalities
IMRT or permanent prostate implant (PPI) brachytherapy or HDR brachytherapy

Prescribed Dose (See Table 2)
34.2 Gy for IMRT to cover 98% of the PTV

- Minimum dose within PTV – 95% of prescribed dose and for a volume that is 0.03 cc
- Maximum dose within the PTV – 107% of prescribed dose and for a volume that is 0.03 cc

110 Gy for low dose rate PPI with I–125
100 Gy for low dose rate PPI with Pd-103
15 Gy in one fraction for HDR

Table 2: IMRT Dose Objectives for Prostate and Proximal Seminal Vesicle Boost

PTV dose (encompassing 98% of PTV)	Minimum PTV dose for a point with a volume of 0.03 cc	Maximum PTV dose to a volume of 0.03 cc of the PTV[1] (Per protocol)	Maximum PTV dose to a volume of 0.03 cc of PTV[1] (Variation Acceptable)	Maximum PTV dose to a volume of 0.03 cc of PTV[1] (Deviation Unacceptable)
34.2 Gy	33.4 Gy	36.6 Gy	> 36.6 – 37.6 Gy	> 37.6 Gy

[1] The maximum dose must not be within an "Organ at risk" such as the rectum, bladder, or penile bulb.

6.1.2 Arm 2 (Sequential Boost Technique)

6.1.2.1 ***Phase 1****: Whole pelvis including prostate and seminal vesicles*

Acceptable Treatment Modalities
3D-CRT or IMRT

Prescription Dose (See Table 1)
45 Gy to cover 98% of PTV

- Minimum dose within PTV – 95% of prescribed dose and for a volume that is 0.03 cc
- Maximum dose within the PTV – 107% of prescribed dose and for a volume that is 0.03 cc

6.1.2.2 ***Phase 2****: Reduce volume to boost prostate and proximal seminal vesicles*

Acceptable Treatment Modalities
IMRT or permanent prostate implant (PPI) brachytherapy or HDR brachytherapy

Prescription Dose (See Table 2)
34.2 Gy for IMRT
110 Gy for low dose rate PPI with Pd-103
100 Gy for low dose rate PPI with I–125
15 Gy in one fraction for HDR

6.2 Technical Factors

6.2.1 Either 3DCRT or IMRT may be used for phase 1 of either Arm 1 or 2. For 3DCRT treating the whole pelvis (WPRT), a minimum of 4-fields should be used and a 4 field plan is recommended. More than 4 conformal fields can be used for the Arm 1 prostate plus seminal vesicle treatments. For IMRT, no specific field arrangement is required. **For the prostate conedown boost in phase 2, IMRT must be used for patients designated for EBRT boost.**

6.2.2 RT will be delivered with megavoltage equipment at energies ≥ 6 MV. Typically, except for tomotherapy and VMAT techniques, 5 to 9 gantry angles are employed for the boost EBRT treatment.

6.2.3 Patients who receive brachytherapy as a boost component of their RT will undergo EBRT for Phase 1 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 not required to help identify the apex of the prostate. Rectal contrast is discouraged because it may distend the rectum and artificially displace the prostate in the anterior direction. IV contrast is permitted to assist in identifying the pelvic vessels. 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 the degree of fullness 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). The rectum should be kept as empty as possible; consider an enema 1-2 hours prior to simulation. 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) and normal critical structures (Section 6.4.4) will be defined in the slices in which they are visualized. The 3DCRT cases (Phase 1) must utilize "beam's eye view" representations to define final beam aperture.

6.4 Treatment Planning/Target Volumes

6.4.1 Patients treated with an IMRT boost (Phase 2) should have a composite treatment plan generated at the beginning of Phase 1 so that the final EBRT dose to critical structures is evaluated before any dose delivery has begun.

Dose for Phase 1 (CTV1/PTV1) will be 45.0 Gy at 1.8 Gy per fraction in both arms. Once Phase 1 is completed, a cone down boost to the prostate will be delivered in Phase 2 by any one of the three acceptable methods: IMRT, HDR or LDR permanent prostate implant. If an IMRT boost is planned, the prostate will receive 34.2 Gy at 1.8 Gy per fraction, for a total prostate dose of 79.2 Gy. For pelvic 3D-CRT, a 4-field technique, using opposed anterior-posterior and opposed lateral fields, is recommended. All fields should conform to the beam's-eye-view of the target. No specific field arrangement is required for IMRT, although typically 5-9 fields are used for fixed gantry treatment. Tomotherapy and VMAT are also allowed for IMRT treatment on this protocol.

6.4.2 The definition of GTV, CTV and PTV will be in accordance with the ICRU Report #50: Prescribing, Recording, and Reporting Photon Beam Therapy.

6.4.2.1 *Phase 1 Prostate and Seminal Vesicle (Arm 1)*

Gross Target Volume

Gross Target Volume (GTV1) 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.

Clinical Target Volume

The CTV1 will include the prostate and entire seminal vesicles (SV).

Planning Target Volume

The PTV1 margins should be a minimum of 0.5 cm and a maximum of 1.5 cm in all dimensions. Individual selection of a PTV margin should be based on the institutions' level of confidence in patient set-up and availability of image guidance. The maximum dose heterogeneity allowable in the PTV1 will be 7%; a variation acceptable and a deviation unacceptable are defined in the Compliance Criteria subsection (6.7.2) of the Quality Assurance section and are summarized in the table below.

6.4.2.2 *Phase 1 Pelvic Field (Arm 2)*

Clinical Target Volume (CTV1)

The CTV1 will include the prostate and entire seminal vesicles (SV), the obturator, external iliac, proximal internal iliac and common iliac nodes, using the vascular structures, up to a level corresponding to the top of L4-L5. Please refer to the pelvic nodal atlas at the RTOG Web site (Pelvic Lymph Node Volumes for Prostate Cancer Atlas; **http://www.rtog.org/atlases/PelvicLymphNodeProstateAtlas/main.html**).The presacral nodes from L5-S1 to S3 may be included if desired depending on whether the dose

constraints to the rectum are achievable (see Table 1). The CTV1 will extend superiorly from L4-L5 to 0.5 cm below the tip of the urethral contrast dye (if used) and no less than the entire prostate gland. Lateral borders will be at least 1 cm from the pelvic brim. In the lateral fields, the external and internal iliac lymph nodes below the SI joints, and the posterior extension of the seminal vesicles should be covered. The usual posterior border is approximately S2-3, but CT anatomy should take precedence. The inferior extent of the external iliac lymph nodes is at the top of the femoral heads. The inferior extent of the obturator lymph nodes is at the top of the symphysis pubis. The CTV1 will include a 7 mm margin in 3-dimensions to the contoured iliac vessels, but not extend outside of the true pelvis, into the pelvic musculature nor into adjacent identifiable organs, such as the bladder, rectum or other bowel. Extension of the CTV into adjacent bone may be carved out.

Planning Target Volume

The PTV1 margins should be a minimum of 0.5 cm and a maximum of 1.5 cm in all dimensions.

6.4.2.3 *Phase 2 Prostate and Proximal Seminal Vesicles Boost with IMRT (Arm 1 and 2)*

Gross Target Volume (GTV 2)

See Section 6.4.2.1 above for GTV1.

Clinical Target Volume (CTV2)

The CTV2 is the GTV2 plus areas considered to contain microscopic disease, delineated by the treating physician. The CTV2 includes the GTV2 (the prostate) as seen on the CT simulation scan.

Planning Target Volume (PTV2)

The PTV2 will provide a margin around the CTV2 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. Individual selection of a PTV margin should be based on the institution's level of confidence in patient set-up and the availability of image guidance. Superior and inferior margins (capping) should be 5-10 mm cm 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.

6.4.3 Normal Critical Structures

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. The normal tissues will be contoured and considered as solid organs. The bladder should be contoured from its base to the dome, and the rectum from the anus (at the level of the ischial tuberosities) for a length of 15 cm or to the rectosigmoid flexure. This generally is below the bottom of the sacroiliac joints. If IMRT is being used to treat the pelvic nodes, the potential bowel space (not just individual loops of bowel) where the small and large bowel may fall should be outlined. The borders are the abdominal wall anteriorly, pelvic sidewalls laterally (excluding the pelvic lymph node regions), superiorly to one cut above the last axial CT image on which the lymph nodes are outlined and inferiorly from the level of the top of CTV1 (outlining around the sides of the bladder near the top of the bladder to encompass the bowel that may fall into these regions). 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
PELVIC_LN	Pelvic Lymph Nodes

6.4.4 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. IMRT using inverse planning is permitted with constraints placed to adhere to critical structure dose limitations as defined below.

6.5 Critical Structures

Critical structure dose constraints shall remain consistent with those represented in prior RTOG 3DCRT/IMRT prostate protocols (see Table 3 below). Of note, the penile bulb constraint is to be regarded as a guideline, and adherence to this should not, in any way, result in compromised coverage of the dose delivery to the target volume.

Table 3: 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			

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

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/image 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/images are not required for IMRT but orthogonal verification films/images are required, just as for 3DCRT. Real-time ultrasound localization and on-line cone beam CT image guidance are important complements to conventional port films or portal imaging; however, there is some reluctance in a cooperative group setting to rely solely upon these modalities to verify patient positioning. Therefore, until more data suggests otherwise, weekly port filming/imaging is required in this study, in addition to the use of additional on-line image guidance in those centers using those modalities.

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.

6.7 Quality Assurance

6.7.1 Compliance Criteria for Cases Treated with EBRT

Cases that are treated entirely with external beam radiation therapy must meet the criteria as stated in Section 6.1.1.1, 6.1.1.2, 6.1.2.1 and 6.1.2.2 (see also Tables 1 and 2) to be scored as per protocol. That is, each case will have to meet the requirements in these sections depending on the particular arm of the study selected during randomization. Both the

Phase 1 and 2 requirements for a particular arm must be met in order to be scored as per protocol. If only one phase of treatment meets the requirement, the case will be scored with the lower score of either variation acceptable or deviation unacceptable. In addition, the critical structure dose constraints of Section 6.5 and Table 3 must be met. In this case also, the patient's treatment will be scored lower when the critical structure score is lower.

The compliance criteria for the situation where the Phase 2 boost is accomplished with brachytherapy is given in Sections 6.8 and 6.9 below (as specified by RTOG 0232).

6.7.1.1 Acceptable dose heterogeneity for external beam treatment is summarized in Tables 1 and 2. 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.

6.7.1.2 *Dose Distribution*

The ITC will display, and compare with isodose distributions for the axial and coronal planes through the planning target volume to verify correct digital submission and conversion. The submitted DVHs for the PTV will then be compared with those generated by the ITC. Per protocol scoring will be considered for those cases in which 98% of the PTV receives the prescription dose.

6.8 Dose Specifications/Technical Considerations: LDR Brachytherapy Boost

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 6.2.3. Implants will only be offered to patients with a prostate volume documented to be <60 cc by transrectal ultrasound examination, and no large TURP defects. 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 after its completion.

6.8.2 Preplanning

This will be carried out prior to the procedure or intra-operatively 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 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. The CTV is the prostate gland and entire SV (included in the initial IMRT field) while the CTV2 includes the prostate.

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), an Accredited Dosimetry Calibration Lab (ADCL) or for international participants, the national standards laboratory in their respective country, is maintained. NIST 1999 standards will be used. If sterile source assemblies or strands are used, alternatively non-stranded 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 (Nag 2000) 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

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 6.2.3. Implants will only be offered to patients with a prostate volume documented to be <60 cc by transrectal ultrasound examination and no large TURP defects. The implant may be performed during the EBRT portion of the treatment or within 2 weeks prior to its initiation or following its completion. For patients receiving HDR brachytherapy boost, RT should begin, as for other modalities, 8 weeks (+/- 1 week) following the first LHRH administration. The date of the HDR brachytherapy implant will constitute the start of RT for those patients receiving the implant 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 and single HDR fraction. Treatment will be delivered within a single 24-hour period measured from the beginning of the implant procedure.

6.9.7 Implant Dosimetry

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. If contrast material is used, it should be diluted to 10% or less to minimize CT artifact. 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, penile bulb, urethra, bladder, and rectum.

6.9.7.2 Transrectal ultrasound-based planning and treatment is acceptable. However, all implant dosimetry data must be submitted on a treatment planning CT scan (Section 6.9.7.1), and evaluation of the quality of the implant will be based on the CT using criteria defined below (Section 6.9.10)

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 CTV1 is the prostate gland and entire SV plus any visualized extracapsular extension of tumor while the CTV2 includes the prostate.

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) and 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 Compliance Criteria

A prescription dose of 15 Gy in one fraction will be delivered to the PTV. Ninety percent coverage of the PTV with the prescription dose is considered per protocol, ≥85% but <90% is considered variation acceptable, and <85% coverage is considered deviation unacceptable.

6.9.11 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 6.9.10) 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.

6.9.12 Catheter Removal

After completion of the treatment all catheters will be removed.

6.9.13 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.

6.9.13.1 *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 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.

6.9.14 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 R.T. Quality Assurance Reviews

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. These reviews will be ongoing and performed remotely. RT quality assurance reviews will be facilitated by RTOG RTQA.

6.11 Radiation Therapy Adverse Events

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

- Bowel/rectal irritation manifesting as cramping, diarrhea, urgency, proctitis, or hematochezia
- Urinary frequency, urgency, dysuria, hematuria, urinary tract infection, or incontinence
- 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 Therapy Adverse Event Reporting

See Section 7.6.

7.0 DRUG THERAPY

All eligible patients receive NADT (neoadjuvant androgen deprivation therapy) consisting of an anti-androgen combined with an LHRH (luteinizing hormone releasing hormone) agent. Use of both drugs is considered combined androgen blockade (CAB). **Protocol treatment must begin within 6 weeks after randomization.** Radiotherapy should begin at least 8 weeks (+/- 1 week) after starting LHRH agonist/antagonist injection.

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 0-7 days (can begin before, same day as, or after) of the date of the first LHRH agonist/antagonist administration and continue 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 (Kinnealey 1991; Tyrrell 1994).

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. 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 or 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. Administration will be suspended only if there is an apparent or suspected reaction to the drug. 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 or 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/Antagonist Therapy (leuprolide, goserelin, buserelin, triptorelin/degarelix)

For additional information, consult the package inserts

7.3.1 Timing: The first LHRH agonist/antagonist administration will occur together with the start of anti-androgen treatment (see Sections 7.1 and 7.2) 2 months (+/- 1 week) prior to the start of RT. The total duration of LHRH therapy will be 6 months or 32 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/antagonists 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), or subcutaneous injection (Eligard). Any duration formulation (1, 3, 4, or 6-month based on the manufacturer) is permitted to allow the duration of hormonal therapy to total 6 months or 32 months. 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 Adverse Events

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 for adverse event (AE) reporting. The CTCAE version 4 is identified and located on the CTEP web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.

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/ResearchAssociates/AdverseEventReporting.aspx) 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.

A 24-hour notification is to be made to RTOG Data Management by telephone at 215-717-2762 only when internet connectivity is disrupted. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into AdEERS by the original submitter at the site.

7.4.1 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.

7.4.2 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.

7.4.3 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 v 4, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome.

7.5 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).

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur within 30 Days of the Last Administration of the Commercially Available Agent[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- o "24-Hour; 5 Calendar Days" - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- o "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of commercially available agent /intervention and have an attribution of possible, probable, or definite require reporting as follows:

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

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

Not applicable to this study.

10.0 TISSUE/SPECIMEN SUBMISSION

Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/specimen submission or quality of life assessment. 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. **Note**: 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.

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

10.1.1.1 Anticipated analysis for collected tissue includes a validation of previous work showing that a 3-6 gene signature from the primary tumor is able to predict lymph node status prospectively. If validated using tissue collected as part of this study, this signature will be applied in future protocols for patient stratification for whole pelvic radiotherapy.

10.1.1.2 Anticipated analyses for collected plasma include 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.

10.1.1.3 Anticipated analyses for collected blood include evaluation of single nucleotide polymorphisms (SNPs) and copy number variants (CNVs) through screening DNA samples derived from case and matched control subjects using Affymetrix 6.0 microarrays. Case subjects will be patients that represent the 20% of patients in this study exhibiting the highest levels of fatigue as defined and measured by the PROMIS instrument used in this study while controls will be the 20% of patients who reported the lowest levels of fatigue as

quantified using PROMIS. The goal will be to identify SNPs and CNVs associated with the development of fatigue in prostate cancer patients following radiotherapy.

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

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 quality of life 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 (preferred) or 15 unstained slides (5 micron cut onto positive charged slides) of tumor tissue. Block or 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 slides contain 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, whole blood cells, and urine

See Appendix V for the blood and urine collection kits and instructions. Note: Kits include a label for shipping. The following materials must be provided in order for the case to be evaluable by the RTOG Biospecimen Resource: A Specimen Transmittal Form documenting the date of collection of the biospecimen; 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 for Tissue Banking/Translational Research			
Specimens taken from patient:	**Collected when:**	**Submitted as:**	**Shipped:**
Representative H&E stained slides of the primary tumor	Pre-treatment	H&E stained slide	Slide shipped ambient
A paraffin-embedded tissue block or 15 unstained slides of the primary tumor taken before initiation of treatment	Pre-treatment	Paraffin-embedded tissue block or 15 unstained slides (5 micron cut onto positively charged slides)	Block or slides shipped ambient
PLASMA: 5-10 mL of anticoagulated whole blood	Pre-treatment and last week of RT	Frozen plasma samples containing 0.5 mL per	Plasma sent frozen on dry ice via overnight carrier

in EDTA tube #1 (purple/ lavender top) and centrifuge		aliquot in 1 mL cryovials (five to ten)	
DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/ lavender top) and mix	Pre-treatment Note: If this collection is missed, the site can collect whole blood for DNA at any time point. This must be noted on the STF.	Frozen whole blood samples containing 1 ml per aliquot in 1ml cryovials (three to five)	Whole blood sent frozen on dry ice via overnight carrier
10-20 mL clean-catch urine	Pre-treatment	Two 5-10 mL urine aliquots in 2 sterile 15 ml polypropylene centrifuge tubes. Store frozen at -20° or -80°C	Urine 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

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/LinkClick.aspx?fileticket=Csxzt1v1hEk%3d&tabid=323). 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/Researchers/BiospecimenResource/BiospecimenResourceFAQs.aspx 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: See Appendix II for a summary of patient assessments.

11.2 Criteria for Discontinuation of Protocol Treatment

- Progression of disease;
- A delay in protocol treatment, as specified in Sections 6.0 and/or 7.0.

If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol.

11.3 Quality of Life Assessments

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 specified below. **Blood collection is mandatory for patients consenting to the quality of life portion of this study (see Section 10.0).**

The following instruments will be used to assess health related quality of life (HRQOL), including fatigue and quality adjusted survival: the Expanded Prostate Cancer Index (EPIC)-26, the Patient-Reported Outcome Measurement Information System (PROMIS)-fatigue short form, and the EuroQol (EQ-5D) instrument. The EPIC-26, PROMIS-fatigue short form, and EQ-5D will be collected at pretreatment (baseline), the week prior to starting RT, and 6 months, 1 year and 5 years after therapy starts. 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. In addition, in order to correlate fatigue with the cytokine changes, the PROMIS-fatigue short form (and the associated questions) also will be collected at the following time points: the last week of RT, and 3 months post RT.

11.3.1 The Expanded Prostate Cancer Index Composite (EPIC)

The 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 radiotherapy and hormonal therapy. To reduce patient burden, an abbreviated version of the EPIC (EPIC-26) was developed and validated.

11.3.2 PROMIS-Fatigue Short Form

The PROMIS Fatigue Scale 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).

11.3.3 EuroQol (EQ-5D)

The EQ-5D is a patient self-administrated questionnaire that takes approximately 5 minutes to complete. 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. The EQ-5D has been translated into most major languages, with the EuroQol Group closely monitoring the translation process; translations can be accessed at http://www.euroqol.org/.

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

Item	Due
Demographic Form **(A5)** Initial Evaluation Form **(I1)** Pathology Report **(P1)** (copy of diagnostic report)	**Within 1 week of registration**
EPIC (FA) EQ-5D (QF) PROMIS (HP) PSQI/GLTEQ form (QL)	Within 1 week of registration
EPIC (FA) EQ-5D (QF)	During the week prior to the start of RT
PROMIS (HP) PSQI/GLTEQ form (QL)	During the last week of RT, and then 3 months post RT
EPIC (FA) EQ-5D (QF) PSQI/GLTEQ form (QL) PROMIS (HP)	6 months, 1 year and 5 years post RT
Interim follow-up form (F0)	**Short term NADT:** Prior to the start of RT, 3 months post RT **Long term NADT:** Prior to the start of RT, 3 months, 6 months, 9 months, 12 months, 18 months, 24 months, 30 months, 36 months post RT
Follow-up form (F1)	**Short term NADT:** Starting at 6 months post RT, then 9 months and 12 months post RT for year 1; every 6 months for years 2-5; then annually. **Long term NADT:** Starting at 42 months post RT, then every 6 months for years 4 and 5; then annually.

12.1 Continued

Item	Due
Dosimetry Information	
Radiotherapy Form (T1) **[copy to RTOG HQ and ITC]**	Within 1 week of RT end
Complete Daily Treatment Record **(T5)[copy to RTOG HQ and ITC]** **NOTE: T5 submissions for patients receiving brachytherapy must include both the Complete Daily Treatment Record (EBRT) and either the Post-implant Dosimetry Data Form (LDR) or the Implant Dosimetry Data Form (HDR)**	Within 1 week of RT end

12.2 Summary of Dosimetry Digital Data Submission (Submit to ITC; see Section 12.2.1)

Item	Due
Preliminary Dosimetry Information (DD)	
Digital Data Submission – Treatment Plan submitted	Within 1 week of start of RT

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)**

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

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 — Within 1 week of RT end
Radiotherapy Form **(T1)**
Daily Treatment Record **(T5) [copy to HQ and ITC]**
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*

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

FOR BRACHYTHERAPY STUDIES:

12.2.1 Digital Data Submission to ITC

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

LDR Brachytherapy

Item	Due
Post-implant evaluation CT scan	3-5 weeks post implant
Post-implant structure set	
Post-implant plan **(copy to RTOG HQ)**	

Post-implant dose distribution
Post-implant dosimetry data form **(copy to RTOG HQ)**

Radiotherapy Form **(T1)** 5 weeks post implant

HDR Brachytherapy

Item	**Due**
Implant CT scan	3-5 weeks post implant
Implant structure set	
Implant plan **(copy to RTOG HQ)**	
Implant dose distribution	
Implant dosimetry data form **(copy to RTOG HQ)**	
Radiotherapy Form **(T1)**	5 weeks post implant

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

13.0 STATISTICAL CONSIDERATIONS

13.1 Primary Endpoint

13.1.1 Overall survival (OS): death due to any cause

13.2 Secondary Endpoints

13.2.1 Cause-specific survival (CSS): The event for CSS will be death due to prostate cancer;
13.2.2 Distant metastasis (DM);
13.2.3 Biochemical failure by the Phoenix definition (PSA ≥ 2 ng/ml over the nadir PSA) [Roach 2006];
13.2.4 Incidence of "acute" adverse events (based on the current version of CTCAE): The acute adverse events will be the first occurrence of worst severity of the adverse event ≤ 30 days of the completion of RT;
13.2.5 Time to "late" grade 3+ adverse events (based on the current version of CTCAE): The time of a first late grade 3+ adverse event, defined as > 30 days from the completion of RT;
13.2.6 Comparison of prostate cancer-specific health related quality of life (HRQOL) change as measured by the EPIC-26 (bowel or urinary domain);
13.2.7 Comparison of fatigue status as measured by the Patient-Reported Outcome Measurement Information System (PROMIS) fatigue domain change score (from baseline to the last week of treatment);
13.2.8 Assessment and comparison of Quality Adjusted Life Years (QALYs)
13.2.9 Collect paraffin-embedded tissue blocks, plasma, whole blood, and urine for planned and future translational research analyses.

13.3 Sample Size and Accrual

13.3.1 Sample Size

In our prior study (RTOG 9413) we showed that WPRT was associated with an improvement in progression free survival (PFS) and no statistically significant increase in grade 3 morbidity or mortality. Given our findings we believe it is appropriate to launch a Phase III Trial with the primary endpoint of OS. A patient subset of the PORT+NADT arm of 9413 with similar characteristics to Arm 1 (NADT+P&SV) of this study yielded a 10-year OS of 53%. It is hypothesized for there to be a 6.5% increase in absolute OS in the NADT+WPRT arm (Arm 2), i.e., 10-year OS of 59.5%. This corresponds to an 18% relative reduction in yearly mortality.

Assuming an exponential distribution for OS (each arm) with five planned efficacy analyses (four interim, one final), 10-year OS for Arm 1 of 53% (yearly hazard 0.0635), and 59.5% for Arm 2 (yearly hazard 0.0519), then 1,044 deaths are required to detect an 18.2% relative reduction in yearly hazard rate with 90% power, employing a one-sided log-rank test at the 0.025 level of significance. With 2,400 patients accrued over 8 years, definitive analysis would occur at approximately 14.5 years from commencement of accrual. Interim analysis efficacy testing will be based on the alpha spending approach (Lan 1983), using a boundary function suggested by Jennison and Turnbull (2000). The futility testing is based on the Freidlin and Korn method (Freidlin 2002) at a nominal significance level of 0.005. Adjustment to the final

alpha level to accommodate the efficacy rule requires a nominal increase to 1087 for the required number of events. Guarding against an ineligibility or lack-of-data rate of up to 7.5% among patients enrolled, the final targeted accrual for this study will be **2,580 patients**.

13.3.2 Accrual and Duration

The proposed trial, RTOG 0924, builds on the experience obtained in five prior RTOG trials including RTOG 9406 (dose escalation with external beam radiotherapy (EBRT), 9413 (PORT vs WPRT), 9202 (long term vs short term ADT), 0321 (EBRT + high dose rate (HDR) brachytherapy, and 0019 (EBRT and permanent prostate implant (PPI). Many of the patients treated on these trials were similar to the groups of patients proposed RTOG 0924. Based on the number of patients treated to these studies and our broader eligibility and choice of boost techniques we conservatively expect RTOG 0924 to complete accrual in approximately 9 years. Based on patient accrual in previous RTOG randomized prostate studies, it is expected that there will be no entries during the initial 6 months while institutions are obtaining IRB approval. The total duration of the study is expected to be approximately 16 years from the time the study opens to the time of the final analysis, with at least 7 years of follow-up for each patient, and an average uniform accrual rate of ~300 patients per year, or approximately 25 patients per month.

13.4 Analysis Plans

13.4.1 Analysis of the Primary Endpoint

The primary endpoint is overall survival (OS). The time to failure will be measured from the date of randomization to the date of documented death. The OS function will be estimated by the Kaplan-Meier method (1958). We want to test whether or not the OS rate in Arm 2 is higher than that of Arm 1. The null and alternative hypotheses are:

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

where, λ_1 and λ_2 are yearly death rate for Arm 1 and Arm 2, respectively. We will use the log-rank test (Mantel 1966; Kim 1990) with a nominal significance level of 0.025 (interim analysis-adjusted level 0.02) at the final analysis to test this hypothesis. In addition, the Cox (1972) proportional hazard regression model will be used to compare the treatment differences, computing both unadjusted and covariate adjusted hazard ratios with respective 95% confidence interval. The risk group (high vs. intermediate), RT modality (IMRT boost vs. HDR+PPI brachytherapy boost), age, and race (as appropriate) will be adjusted for in this latter analysis.

13.4.2 Biochemical Failure by Phoenix Definition

The biochemical failure (BF) rate by 5 years is defined as the proportion of patients with the event of BF by 5 years from randomization among all eligible patients at baseline. BF is defined by the Phoenix definition (PSA ≥2 ng/ml over the nadir PSA) [Roach 2006]. Patients who receive any salvage therapy (e.g., salvage androgen deprivation, vaccine therapy, biologic/small molecule therapy, or chemotherapy) prior to BF will be treated as failures. The salvage ADT is defined as the first administration of subsequent ADT (either LHRH agonist/antagonist 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 BF rate by 5 years will be estimated by the cause-specific hazard rate approach (Kalbfleisch and Ross, 1980; Gaynor et al, 1993).

The Z-test statistic for the difference between the two 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 two arms:

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

where and are the BF or the salvage ADT rate of Arm 1 and Arm 2, respectively, estimated by the cumulative incidence method, ri is the number of patients who are at risk and fi is the number of patients who have BF or the salvage ADT failure events (i=1,2). If H0 is rejected, then we conclude that Arm 2 is better than Arm 1. If H0 is not rejected, then we conclude that Arm 2 is not better than Arm 1.

In addition, logistic regression (Agresti 1990) will be used to compare the treatment differences in the hypothesis with and without adjustment for at least the following covariates: risk group (high vs. intermediate), RT modality (IMRT boost vs. HDR+PPI 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

CSS will be measured from the date of randomization to the date of death due to prostate cancer. DM will be measured from the date of randomization to the date of documented distant metastasis/clinical and/or radiographic appearance of disseminated disease. Both endpoints will be estimated by the cause-specific hazard rate approach (Kalbfleisch and Ross, 1980; Gaynor et al., 1993). Fine and Gray's regression (Gray 1988; Fine 1999) also will be used for both CSS and DM. Both unadjusted and adjusted hazard ratios and the respective 95% confidence interval will be computed. The stratification variables (risk group, RT modality), age, and race (as appropriate), and possibly other covariates, will be adjusted for in this analysis.

13.4.4 Comparison of the Incidence of Acute Adverse Events and Time to Late Grade 3+ Adverse Events

Adverse events will be scored according to the CTEP active version of the CTCAE. 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 (Agresti 1990) will be used to model the distribution of acute adverse events. Multiple logistic regression (Agresti 1990) 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 cause-specific hazard rate approach (Kalbfleisch and Ross, 1980; Gaynor et al., 1993) and tested using a significance level of 0.025. A Fine and Gray's regression model (Fine 1999) 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 (risk group RT modality), age, and race (as appropriate) will be considered when it is adjusted in the analysis.

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

A group sequential test with four 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 Lan-DeMets alpha-spending approach (Lan 1983) that is similar to boundaries suggested by Jennison and Turnbull (2000) [see Table 5 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 (2002). The following hypotheses are tested:

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

where λ_1 and λ_2 are the hazard rate for Arm 1 and Arm 2, respectively. If the H0 is rejected, then we conclude that the OS rate of Arm 2 will be better than Arm 1 and stop accrual if applicable.

Table 5: Schedule for the Planned Interim Analysis

Information Time	Estimated Analysis Time*	Cumulative Number of Deaths in the Two Arms	Z-value to Reject for Efficacy
0.20	5.4 years	217	≥3.322
0.40	7.6 years	435	≥2.843
0.60	9.7 years	652	≥2.535
0.80	12.0 years	870	≥2.288
1.00	14.6 years	1087	≥2.074

*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 ($\lambda_1 / \lambda_2 = 1.224$) 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.

Phase III trials are required by NCI Cooperative Group Program Guidelines to be reviewed by a Data and Safety Monitoring Committee (DSMC). This study will be reviewed by the RTOG Data Monitoring Committee (DMC) on a semi-annual basis in January and June. Based on the results of each interim analysis, the following action will be taken and the responsible statistician will recommend to the RTOG 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.

13.4.6 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.

13.4.7 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 experimental treatment and will be carried out as described in Section 13.4.5. 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 (risk group and RT modality), age, and race (as appropriate).

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

Patient accrual for the QOL measurements will be limited to 230 cases in each arm. We will have 2 co-primary QOL endpoints of EPIC-26 bowel/rectal and urinary/irritative domains, analyzed at 6 months post-RT. From the EPIC home page: http://roadrunner.cancer.med.umich.edu/epic/, for 1 domain as the primary endpoint (significance level 0.05 and 90% power), the required sample size is 86 patients (per arm). Since there will be 2 domains used, a 20% adjustment for multiplicity is employed, so that the

required sample size for 2 domains is 108 patients (per arm). A current analysis of EPIC numbers from RTOG 0415 indicated that, of 971 patients consenting to the QOL portion of the study, 886 patients (91%) completed both the bowel and urinary irritative domains at baseline. Additionally, of these 886 patients, only 464 patients (52%) completed the same domains at 6 months (this is the first time point past baseline). Using these numbers as an expectation of missing data for RTOG 0924, the projected sample size would need to be about 230 patients (per arm) to achieve 90% power. Differences in EPIC domains between NHT+RT and RT will be based on the minimally important difference (MID). In Dunn et al. (2009), the upper limit MID values were determined to be 6 points and 7 points for the bowel and urinary irritative EPIC-26 domains, respectively. These differences correspond to ½ SD (effect size 0.5).

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) [Buysse 1989] and level of physical activity as measured by the Godin Leisure-Time Exercise Questionnaire (GLTEQ) (Godin 1986; Gionet 1989). 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-26, PROMIS fatigue domain, EQ-5D) will be collected on all cases participating in this portion of the trial. Patients will complete the EPIC-26, PROMIS fatigue domain, and the EQ-5D at pretreatment (baseline), the week prior to starting RT, and 6 months, 1 year and 5 years after therapy starts. 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. In addition, in order to correlate fatigue with the cytokine changes, the PROMIS-fatigue short form (and the associated questions) also will be collected at the following time points: the last week of RT, and 3 months post RT. 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 (Verbeke 2000) will be performed to describe the change trend of the EPIC-26, 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 (risk group, comorbidity score, and RT modality).

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 GI or GU domains of the EPIC-26 instrument will be worse in Arm 2 than Arm 1 (at 6 months) 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) [Glasziou 1990].

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

where qi is the quality (the utility coefficient) of health state i, si 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 (Donaldson 2005). RTOG recognizes that all options are subject to bias and analysis with more than one method for consistency across methods is prudent.

13.4.9 Analysis for Translational Research

The feasibility of proposed translational studies will be assessed following completion of accrual and sample collection. These studies are intentionally similar in design to those included on RTOG 0815 to facilitate combined analysis. In the next few years, it is anticipated that DNA

samples from independent work already in progress will be used in genome wide association studies (GWAS) to discover SNPs associated with the development of fatigue following radiotherapy for prostate cancer. DNA samples from both 0815 and 0924 will therefore serve as a critical replication cohort to validate the SNPs that will be identified through the GWAS.

13.5 Gender and Minorities

Projected Distribution of Gender and Minorities

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	N/A	81	81
Not Hispanic or Latino	N/A	2,499	2,499
Ethnic Category: Total of all subjects	N/A	2,580	**2,580**
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	N/A	16	16
Asian	N/A	4	4
Black or African American	N/A	661	661
Native Hawaiian or other Pacific Islander	N/A	12	12
White	N/A	1887	1887
Racial Category: Total of all subjects	N/A	2,580	**2,580**

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APPENDIX I

RTOG 0924

Informed Consent Template for Cancer Treatment Trials
(English Language)

Androgen Deprivation Therapy and High Dose Radiotherapy With or Without Whole-Pelvic Radiotherapy in Unfavorable Intermediate or Favorable High Risk Prostate Cancer: A Phase III Randomized Trial

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?

The purpose of this study is to compare the effects of hormone therapy (androgen deprivation) and radiation therapy to the prostate gland and seminal vesicles with hormone therapy and radiation therapy to the whole pelvic body area on you and your prostate cancer to find out which is better.

There are 2 treatment groups in this study:
1) Patients who receive hormone therapy plus radiation therapy to the prostate gland and seminal vesicles (two small glands behind the prostate)
2) Patients who receive hormone therapy plus radiation therapy to the whole pelvis

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 2,580 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) 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)
- 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 to determine if the cancer has spread to the bones

During the study:
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 test to measure liver function

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 any 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 if treated with external beam radiation alone. 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) as a boost, the total number of daily external beam 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.

You also will receive hormone therapy for 6 months or 32 months (either 6 months total of LHRH agonist/antagonist and anti-androgen pills or 32 months of LHRH agonist and 6 months of anti-androgen pills; the duration of hormone therapy will be determined by your doctor). 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/antagonist, 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/antagonist will reduce the amount of circulating testosterone and the pill will interfere with the action of any remaining testosterone.

If you are in group 2 (often called "Arm 2"): You will receive radiation treatments to the whole pelvis once daily, 5 days a week, Monday through Friday, for a total of 25 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. If you are treated with external beam as a boost you will receive a total of 44 treatments. 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.

You also will receive hormone therapy for 6 months or 32 months (either 6 months total of LHRH agonist/antagonist and anti-androgen pills or 32 months of LHRH agonist/antagonist and 6 months of anti-androgen pills; the duration of hormone therapy will be determined by your doctor). 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/antagonist, 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/antagonist will reduce the amount of circulating testosterone and the pill will interfere with the action of any remaining testosterone.

During treatment:

- You will be seen weekly during treatment for 1) a physical exam, 2) to be examined for 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 2) to check for any side effects you may be experiencing as a result of the treatment.
- You will have a monthly blood test for blood count

When you are finished receiving therapy you will need these tests and procedures:

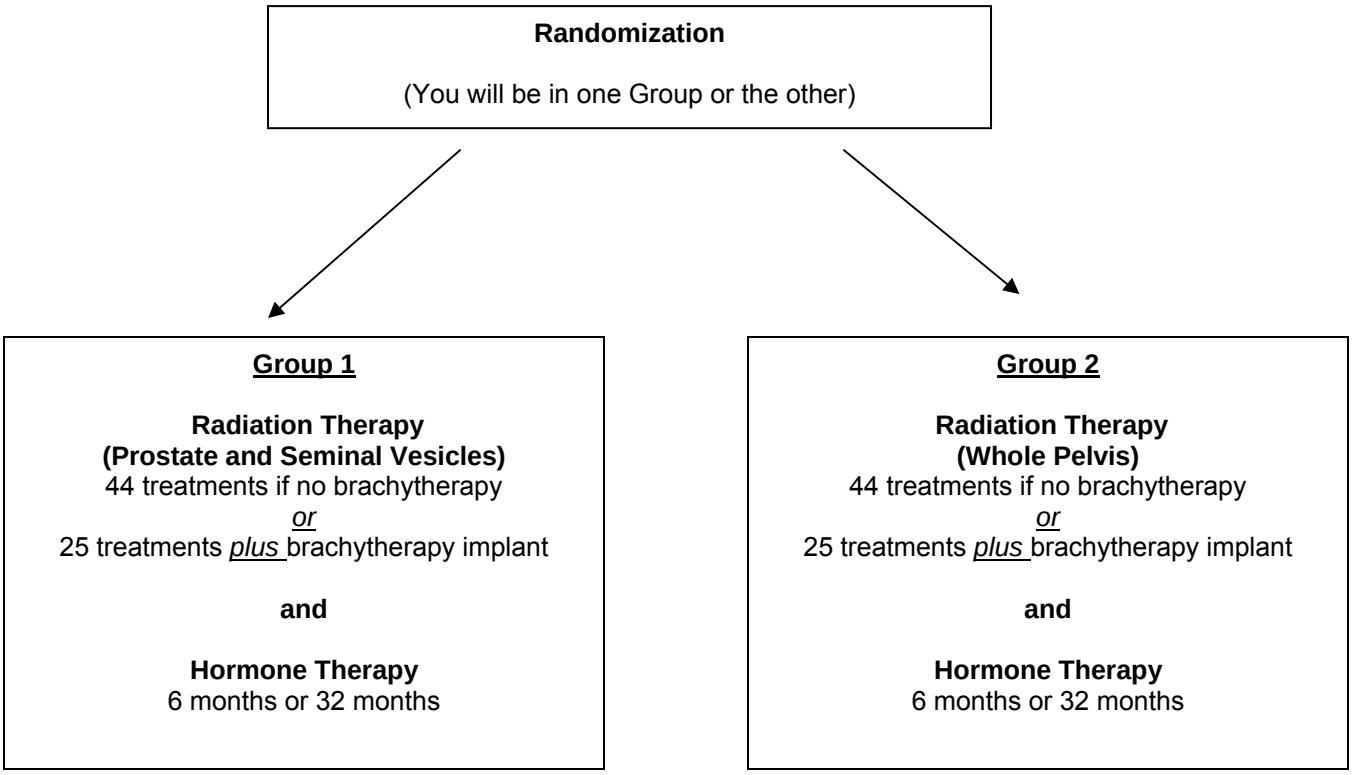
- Every 3 months for the first year, every 6 months for years 2 through 5, and then yearly after year 5:

- 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)
- You will be assessed for any side effects you may be experiencing as a result of the treatment

- Additional testing (for example, pelvic/abdominal CT or MRI scans; blood tests for blood count) 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?

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 will last 6 months or 32 months (the duration of hormone therapy will be determined by your doctor).

After you are finished receiving therapy, the study doctor will ask you to visit the office for follow-up exams every 3 months for the first year, every 6 months for years 2 through 5, and then yearly after year 5. 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 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, 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 options 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. 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
- Decrease in bone mineral density [Note: patients who receive long-term hormone therapy (32 months)] may be at higher risk for a decrease in bone mineral density]

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
- Death due to heart disease

Patients receiving treatment with LHRH agonists should undergo periodic monitoring of blood glucose and/or glycosylated hemoglobin (HbA1c) for signs of developing diabetes or worsening of blood glucose control in patients with diabetes, and also for the signs and symptoms suggestive of the development of cardiovascular disease.

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. Information from this study will help researchers learn more about the addition of whole pelvic radiation therapy to hormone 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 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 do so. You can still be a part of the main study even if you say 'no' to taking part 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 four questionnaires with questions about your symptoms (urine, bowel, and fatigue) and your sense of wellbeing (mood, sleep and daily activity) at the following times: before you begin protocol treatment; during the week prior to radiation therapy; and 6 months, 1 year, and 5 years after therapy starts. In addition, you will be asked to complete the questionnaire about your fatigue, mood, sleep and daily activity at the following times: during the last week of radiation therapy and 3 months after completing radiation therapy. It will take about 15 minutes to fill out the questionnaires. If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

If you agree to participate in the quality of life study, you will be required to have blood drawn each time you complete the questionnaires described above. Each blood draw will be about 2 tablespoons; the blood will be used to learn more about changes in your body that are related to the symptoms you may be having. A blood specimen will be collected at the same times that you complete the questionnaires. 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**

About Using Tissue, Blood, and Urine 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 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://cdp.cancer.gov/humanSpecimens/ethical_collection/patient.htm

In addition to the tumor tissue, we would like to collect some blood and urine. If you agree, you will have blood drawn before you start radiation therapy treatment 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. Urine will be collected

before you start radiation therapy treatment. This blood and urine will be kept to be used in research to learn more about cancer and other diseases.

Your tissue, blood, and urine may be helpful for research whether you do or do not have cancer. The research that may be done with your tissue, blood, and urine 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, blood, and urine 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, blood, and urine 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, blood, and urine 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, blood, and urine. Then any tissue that remains will no longer be used for research and will be returned to the institution that submitted it and any blood or urine that remains will be destroyed.

In the future, people who do research may need to know more about your health. While the 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, blood, and urine are used for genetic research (about diseases that are passed on in families). Even if your tissue, blood, and urine are used for this kind of research, the results will not be put in your health records.

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

Benefits

The benefits of research using tissue, blood, and urine 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
    - Urine ☐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
    - Urine ☐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://www.cancer.gov/cancertopics/**

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

Assessments	Pre-Treatment (may be required for eligibility)					During Treatment	Follow Up						
	Within 180 days prior to registration	Within 90 days (12 weeks) prior to registration	Within 60 days prior to registration	Within 14 days (2 wks) prior to registration	Week prior to RT	Last week of RT	3 months post RT	6 months post RT	q 3 mos for year 1	q 6 mos years 2 through 5	1 year post RT	5 years post RT	Annually after year 5
Histo/cyto eval	X												
Eligibility-related tissue collection		X											
History/physical; DRE		X											
Weekly physical						X							
Pelvic ± abdominal CT or MR		X					As clinically indicated during follow up						
Bone scan	Within 120 days												
PSA		X						X		X			X
Performance status	Pre-treatment					Weekly			X	X			X
CBC w/ diff				X		Monthly	As clinically indicated during follow up						
Transrectal ultrasound			X										
AST or ALT			X										
Tumor response evaluation; DRE						As clinically indicated			X	X			X
Adverse event evaluation						Weekly			X	X			X
QOL assess*: EPIC, PROMIS, EQ5D, PSQI/GLTEQ *(if patient consents)*	Pre-treatment				EPIC + EQ5D	PROMIS + PSQI/ GLTEQ	PROMIS + PSQI/ GLTEQ	X			X	X	
Tissue, blood*, urine *(if patient consents)*	Pre-treatment					Blood							

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, 7th Edition
DEFINITIONS OF TNM

Primary Tumor, Clinical (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

T1 Clinically inapparent tumor neither palpable nor 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 the 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 such as external sphincter, rectum, bladder, 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.

Primary Tumor, Pathologic (pT) *

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

pT3 Extraprostatic extension
- pT3a Extraprostatic extension or microscopic invasion of bladder neck**
- pT3b Seminal vesicle invasion

pT4 Invasion of rectum, levator muscles, and/or pelvic wall

*Note: There is no pathologic T1 classification
**Note: Positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease).

Regional Lymph Nodes (N)

Clinical

NX Regional lymph nodes were not assessed
N0 No regional lymph node metastasis
N1 Metastasis in regional lymph node(s)

Pathologic

pNX Regional nodes not sampled
pN0 No positive regional nodes
pN1 Metastases in regional node(s)

APPENDIX IV
AJCC STAGING SYSTEM (continued)
PROSTATE, 7th Edition
DEFINITIONS OF TNM

Distant Metastasis (M)*

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.

Histologic Grade (G)

Gleason X	Gleason score cannot be processed
Gleason ≤6	Well-differentiated (slight anaplasia])
Gleason 7	Moderately differentiated (moderate anaplasia)
Gleason 8-10	Poorly differentiated/undifferentiated (marked anaplasia)

Anatomic Stage/Prognostic Groups*

Stage I	T1a-c	N0	M0	PSA <10	Gleason ≤6
	T2a	N0	M0	PSA <10	Gleason ≤6
	T1-2a	N0	M0	PSA X	Gleason X
Stage IIA	T1a-c	N0	M0	PSA <20	Gleason 7
	T1a-c	N0	M0	PSA ≥10<20	Gleason ≤6
	T2a	N0	M0	PSA <20	Gleason ≤7
	T2b	N0	M0	PSA <20	Gleason ≤7
	T2b	N0	M0	PSA X	Gleason X
Stage IIB	T2c	N0	M0	Any PSA	Any Gleason
	T1-2	N0	M0	PSA ≥20	Any Gleason
	T1-2	N0	M0	Any PSA	Gleason ≥8
Stage III	T3a-b	N0	M0	Any PSA	Any Gleason
Stage IV	T4	N0	M0	Any PSA	Any Gleason
	Any T	N1	M0	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

*Note: When either PSA or Gleason is not available, grouping should be determined by T stage and/or either PSA or Gleason as available.

Source: Edge, SB, ed. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.

APPENDIX V
APPENDICES FOR RTOG BIOSPECIMEN COLLECTION
RTOG Blood Collection Kit Instructions
RTOG Urine Collection Kit Instructions

Shipping Instructions:

U.S. 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 kits/shipping please contact the RTOG Biospecimen Resource by e-mail: RTOG@ucsf.edu or phone: 415-476-RTOG(7864) or Fax: 415-476

This Kit is for collection, processing, storage, and shipping of plasma and whole blood:

Kit contents:

- One Purple Top EDTA tube for plasma (A)
- One Purple Top EDTA tube for Whole Blood (B)
- Twenty-five (25) 1 ml cryovials
- Biohazard bags (2) and Absorbent shipping material (2)
- 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 PLASMA AND WHOLE BLOOD:

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

- ❑ Label as many 1ml cryovials (five 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 (five 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.

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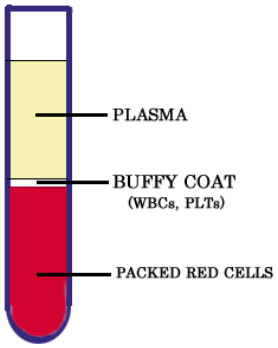

(B) Whole Blood for DNA (if requested): Purple Top EDTA tube #2

- ❑ Label as many 1ml cryovials (three 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 (three 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 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.

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- *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 V

RTOG URINE COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of urine specimens.

Kit Contents:

- One (1) Sterile Urine collection cup
- Two 7 ml disposable pipettes
- Absorbent paper towel
- Two 15 ml polypropylene centrifuge tubes
- Biohazard bags
- Parafilm for sealing outside of tubes

Preparation and Processing of Urine Specimens:

Process:

- A clean catch urine specimen will be collected. To collect the specimen, use the following instructions:
  - Males should wipe clean the head of the penis and females need to wipe between the labia with soapy water/cleansing wipes to remove any contaminants.
  - After urinating a small amount into the toilet bowl to clear the urethra of contaminants, collect a sample of urine in the collection cup.
  - After 10-25 mL urine has been collected, remove the container from the urine stream without stopping the flow of urine.
  - Finish voiding the bladder into the toilet bowl.
- Aliquot 5-10 mls of Urine into each of two 15 ml polypropylene centrifuge tubes (disposable pipets are provided in the kit). Do not fill with more than 10 mls to avoid cracking of tubes due to expansion during freezing. Replace the cap and tighten on the tubes. Make sure the cap is not cross-threaded or placed on incorrectly or leaking will occur.
- Use parafilm to seal the cap around the outside rim of the urine tube to prevent leakage.
- Discard remaining Urine and collection cup.
- Label the specimen with the RTOG study and case number, collection date and time, time point of collection, and clearly mark specimens as “urine”.
- Wrap Urine Tubes with absorbent material (paper towels) and place into biohazard bag and seal the bag. Freeze and store Urine samples in a -20°C or -80°C freezer until ready to ship.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED with RTOG study and case numbers, collection date/time, and time point collected (e.g. pretreatment, post-treatment).

Storage and Shipping:

Freezing and Storage:

- ❑ Urine specimens may be sent in batches or with other frozen biospecimens, if within 30-60 days of collection. Store at -20°C or -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 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.
- ❑ Place sealed 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.
- ❑ *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.***
- ❑ Samples received thawed will be discarded, and a notification will be sent immediately to the Principal Investigator and Clinical Research Assistant of the submitting institution. The institution should send a subsequent sample, collected as close as possible to the original planned collection date.
- ❑ **For questions regarding ordering, collection, or shipping of a Urine Collection Kit, please e-mail RTOG@ucsf.edu or call (415)476-7864 or fax (415) 476-5271.**

Shipping Address: FedEx/UPS/Courier address (For all frozen samples)
RTOG Biospecimen Resource at UCSF
1657 Scott Street, Room 223, San Francisco, CA 94115
Contact Phone: (415) 476-RTOG(7864)

APPENDIX VI

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 0924 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 0924 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 0924:

- 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 0924. 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.

DATA SUBMISSION AND RECONCILIATION

1. All case report forms (CRFs) associated with this study must be downloaded from the RTOG 0924 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 11.3)

- 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 0924 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/Antagonist Therapy (leuprolide, goserelin; buserelin, triptorelin, degarelix)

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 0924 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.