

# RADIATION THERAPY ONCOLOGY GROUP

## RTOG 0938

### A RANDOMIZED PHASE II TRIAL OF HYPOFRACTIONATED RADIOTHERAPY FOR FAVORABLE RISK PROSTATE CANCER

#### Study Chairs

<b><u>Principal Investigator/Radiation Oncology</u></b> Himu Lukka, MD McMaster University/Juravinski Cancer Centre 699 Concession Street Hamilton, Ontario Canada L6J4W5 Phone: 905-387-9495 ext.64702/ Fax: 905-575-6326 E-mail: <a href="mailto:Himu.Lukka@jcc.hhsc.ca">Himu.Lukka@jcc.hhsc.ca</a>	<b><u>Radiation Oncology</u></b> Jean-Paul Bahary, MD Centre Hospitalier de L'Universite de Montreal (CHUM) Notre-Dame Hospital – Pavillon Lachapelle (Porte: TS-3340) 1560, rue Sherbrooke Est Montreal, Quebec H2L 4M1 Phone: 514-890-8254/Fax: 514-412-7537 E-mail: <a href="mailto:jean-paul.bahary.chum@ssss.gouv.qc.ca">jean-paul.bahary.chum@ssss.gouv.qc.ca</a>
<b><u>Radiation Oncology</u></b> Colleen Lawton, MD Medical College of Wisconsin 8701 Watertown Plank Road Milwaukee, WI 53226 Phone: 414-805-4472/Fax 414-805-4369 E-mail: <a href="mailto:clawton@mcw.edu">clawton@mcw.edu</a>	<b><u>Radiation Oncology (Protons)</u></b> Jason A. Efstathiou, MD, DPhil Department of Radiation Oncology Massachusetts General Hospital 100 Blossom Street, Cox 3 Boston, MA 02114 Phone: 617-726-5866/ Fax 617-726-3603 Email: <a href="mailto:jefstathiou@partners.org">jefstathiou@partners.org</a>
<b><u>Quality of Life</u></b> Deborah Watkins Bruner, RN, PhD, FAAN Nell Hodgson Woodruff School of Nursing Emory University 1520 Clifton Road, Room 232 Atlanta, GA 30322 Phone: 404-712-9695/Fax: 404-727-8514 E-mail: <a href="mailto:deborah.w.bruner@emory.edu">deborah.w.bruner@emory.edu</a>	<b><u>Medical Physics</u></b> Rajat J. Kudchadker, PhD Department of Radiation Physics University of Texas MD Anderson Cancer Center 1515 Holcombe Boulevard, Unit 1202 Houston, TX 77030 Phone: 713-563-2538/Fax: 713-563-6949 E-mail: <a href="mailto:rkudchad@mdanderson.org">rkudchad@mdanderson.org</a>
<b><u>Urology</u></b> Lee E. Ponsky, MD Department of Urology Center Urologic Oncology and Minimally Invasive Therapies, Urology Institute University Hospitals Case Medical Center Phone: 216-844-4831/Fax: 216-844-7735 E-mail: <a href="mailto:Lee.Ponsky@UHhospitals.org">Lee.Ponsky@UHhospitals.org</a>	<b><u>Statistics</u></b> Stephanie Pugh, PhD Department of Statistics Radiation Therapy Oncology Group/ACR 1818 Market Street, Suite 1600 Philadelphia, PA 19103 Phone: 215-717-0850/Fax: 215-928-0153 E-mail: <a href="mailto:spugh@acr.org">spugh@acr.org</a>

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

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## RADIATION THERAPY ONCOLOGY GROUP

### RTOG 0938

#### A Randomized Phase II Trial of Hypofractionated Radiotherapy for Favorable Risk Prostate Cancer

#### SCHEMA

<b>S T R A T I F Y</b>	<b><u>Treatment techniques/machine</u></b>  1. All linear accelerator based treatment (excluding Cyberknife)  2. Cyberknife  3. Protons	<b>R A N D O M I Z E</b>	<b><u>Arm 1</u></b> 36.25 Gy in 5 fractions of 7.25 Gy over two and a half weeks (in 15-17 days)*
			<b><u>Arm 2</u></b> 51.6 Gy in 12 daily fractions of 4.3 Gy over two and a half weeks (in 16-18 days)*

\*For proton doses, see Section 6.1.4.

**Patient Population:** (See Section 3.0 for Eligibility) (10/22/12)

Histologically confirmed diagnosis of adenocarcinoma of the prostate within 365 days (1 year) of randomization; Gleason scores 2-6; Clinical stage T1-2a; PSA < 10 ng/mL (PSA should not be obtained within 10 days after prostate biopsy).

(7/24/13) **Required Sample Size: 240**

**ELIGIBILITY CHECKLIST** (10/22/12)  
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- \_\_\_\_(Y) 1. Does the patient have a histologically confirmed diagnosis of adenocarcinoma of the prostate within 365 days (1 year) of randomization?
- \_\_\_\_(Y) 2. Is the history/physical examination with digital rectal examination of the prostate within 60 days prior to registration?
- \_\_\_\_(Y) 3. Is there a histological evaluation of the prostate biopsy with assignment of a Gleason score to the biopsy material; Gleason scores 2-6 within 365 days (1 year) of randomization?
- \_\_\_\_(Y) 4. Is the clinical stage a T1-2a (AJCC 7<sup>th</sup> edition) within 90 days of randomization?
- \_\_\_\_(Y) 5. Is the PSA < 10 ng/mL within 60 days prior to registration? PSA should not be obtained within 10 days after prostate biopsy.
- \_\_\_\_(Y) 6. Is the Zubrod Performance Status 0-1 within 60 days prior to registration?
- \_\_\_\_(Y) 7. Has the patient provided study-specific informed consent prior to study entry?
- \_\_\_\_(Y) 8. Is the patient willing and able to complete the Expanded Prostate Cancer Index Composite (EPIC) questionnaire?
- \_\_\_\_(N) 9. Does the patient have a prior or concurrent invasive malignancy (except non-melanomatous skin cancer) or lymphomatous/hematogenous malignancy unless continually disease free for a minimum of 5 years? All patients with in situ carcinoma are eligible for this study (for example, carcinoma in situ of the oral cavity is eligible) except patients with carcinoma of the bladder (including in situ bladder cancer or superficial bladder cancer)
- \_\_\_\_(N) 10. Is there evidence of distant metastases?
- \_\_\_\_(N) 11. Is there evidence of regional lymph node involvement?
- \_\_\_\_(N) 12. Has the patient had previous radical surgery (prostatectomy), cryosurgery, or HIFU for prostate cancer?
- \_\_\_\_(N) 13. Has the patient had previous pelvic irradiation, prostate brachytherapy, or bilateral orchiectomy?
- \_\_\_\_(N) 14. Has the patient had previous hormonal therapy, such as LHRH agonists (e.g., goserelin, leuprolide) or LHRH antagonists (e.g., degarelix), anti-androgens (e.g., flutamide, bicalutamide), estrogens (e.g., DES), or surgical castration (orchiectomy)?
- \_\_\_\_(N) 15. If the patient has used finasteride within 30 days prior to registration, was the PSA obtained < 30 days after stopping finasteride?
- \_\_\_\_(N) 16. If the patient has used dutasteride within 90 days prior to registration, was the PSA obtained < 90 days after stopping dutasteride?
- \_\_\_\_(N) 17. Does the patient have a history of previous or concurrent cytotoxic chemotherapy for prostate cancer?
- \_\_\_\_(N) 18. Does the patient have severe, active co-morbidity, defined as unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months?

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- \_\_\_\_(N) 19. Has the patient had transmural myocardial infarction within the last 6 months?
- \_\_\_\_(N) 20. Does the patient have acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration?
- \_\_\_\_(N) 21. Does the patient have chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration?
- \_\_\_\_(N) 22. Does the patient have hepatic insufficiency resulting in clinical jaundice and/or coagulation defects? (Note that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol. Patients on Coumadin or other blood thinning agents are eligible for this study.)
- \_\_\_\_(N) 23. Does the patient have Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition? (Note 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.)

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**ELIGIBILITY CHECKLIST (9/29/11)**  
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**The following questions will be asked at Study Registration:**

**IMRT (for photon treatment) and IGRT CREDENTIALING IS REQUIRED BEFORE REGISTRATION.  
PROTON CREDENTIALING IS REQUIRED IF USING PROTONS.**

- \_\_\_\_\_ 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. Patient'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
- \_\_\_\_\_ 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?
- \_\_\_\_\_(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)?

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- \_\_\_\_\_(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 (Utilization of Sexual Medications/Devices and the EQ-5D)?
- \_\_\_\_\_ If no, please specify the reason from the following:
1. Patient refused due to illness
  2. Patient refused for other reason: specify \_\_\_\_\_
  3. Not approved by institutional IRB
  4. Tool not available in patient's language
  5. Other reason: specify \_\_\_\_\_
- \_\_\_\_\_(N/Y) 26. Did the patient agree to participate in VisionTree?
- \_\_\_\_\_ If no, please specify the reason from the following:
1. No computer availability
  2. Prefers not to use a computer
  3. Other reason: specify: \_\_\_\_\_
- \_\_\_\_\_ 27. Specify treatment techniques/machine:
1. All linear accelerator based treatment (excluding Cyberknife)
  2. Cyberknife
  3. Protons

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**

Prostate cancer, along with skin cancer, is among the most commonly diagnosed cancer in men (Jemal 2002). Since the introduction of prostate specific antigen (PSA) testing the majority of cases are now diagnosed with organ confined disease (Paquette 2002). Radiotherapy is a common treatment alternative and patients are commonly treated daily over a period from 7-8 weeks. Recent analyses of clinical results have suggested that PSA control is significantly affected by the dose fractionation employed (Kuban 2008; Zietman 2005). The hypothesis generally accepted is that radiation-induced death for cells is defined by the linear quadratic equation (LQE). The dose-response of tumors and normal tissues to fractionated irradiation can be described according to a ratio referred to as the alpha-beta ratio [ $\alpha/\beta$ ] (Thames 1982; Bentzen 1989; Thames 1986). Cell survival is predicted according to a formula  $S = e^{(-\alpha D - \beta D^2)}$  where  $\alpha$  and  $\beta$  represent the linear and quadratic components of the model. The alpha-beta ratio is an indication of the fractionation sensitivity of a particular cell type. The alpha-beta ratio is generally high ( $\geq 10$  Gy) for early-responding tissues (skin, mucosa and most tumors). In contrast, it is low ( $< 5$  Gy) for late-responding tissues (connective tissues and muscles).

A consensus is emerging in the literature that the  $\alpha/\beta$  ratio for prostate cancer ranges from 1 to 4 (Haustermans 1997, Brenner 1999). These values are either equal or less than the  $\alpha/\beta$  ratio for the rectal mucosa where the most significant late toxicity occurs. This lower  $\alpha/\beta$  ratio for prostate cancer than for the surrounding late-responding normal tissue creates the potential for therapeutic gain (Fowler 2003; Brenner 2002; Dale 2001; Wang 2003a; Wang 2003b; Fowler 1995). Appropriately designed schedules using large fractions could result in increases in biochemical control with no increase in late sequelae. However, using less than 5 fractions would probably not be advisable since we would potentially lose the effects of redistribution and reoxygenation of tumor cells (Kal 2003; Brenner 1998; van der Kogel 1988; Dewit 1989; Terry 1984; Dubray 1994; Gasinska 1993; Fowler 2003; Jereczek-Fossa 2002; Weiss 1999; Denham 1999; Schultheiss 1997; O'Brien 2002; Wang 1998).

In addition to the potential for significant therapeutic gain, if a hypofractionated regimen is found to produce comparable findings it would result in substantial health care cost savings and would also be more convenient for patients.

### **1.2 Hypofractionation Studies**

The idea of using hypofractionated radiotherapy for prostate cancer is not new. From 1962 to 1984, 209 patients were treated at St. Thomas Hospital in London with hypofractionation initially to a dose of 55 Gy in 12 sessions over 28 days and later to doses of 36 Gy in 6 fractions (Lloyd-Davies 1990). Even though treatment techniques were rather primitive compared to today's standards, rectal and urological toxicity were quite low.

Results from two randomized trials examining fractionation schedules for prostate cancer have since been published. The Australian trial compared 64 Gy/32 fractions (conventional schedule) to 55 Gy/20 fractions (hypofractionated schedule) in men with favorable-risk T1-2 prostate cancer (Yeoh 2006). The primary endpoint of this trial was treatment morbidity. The sample size of 220 men (110 each arm) was determined to detect a difference in the frequency of mild late radiation morbidity of 20% (40% vs. 20%) with 90% power. Efficacy was a secondary endpoint. The first 120 consecutive men are included in the interim analysis. The median follow-up was 43.5 months (range 23-62 months). Two-dimensional external beam radiation therapy (EBRT) was used in each arm; no three-dimensional conformal radiotherapy or intensity-modulated radiotherapy (3DCRT or IMRT) was used. Three- or four-field techniques were used with 6-23 MV photons. Morbidity was measured with the LENT-SOMA questionnaires. GI morbidity measured with these questionnaires emphasizes six symptoms (stool frequency, stool consistency, rectal pain, mucus discharge, urgency of defecation, and rectal bleeding). GU morbidity measures four symptoms (urinary frequency, urgency, dysuria, and hematuria). Treatment efficacy was determined clinically and biochemically. PSA nadir and three consecutive rises were examined to estimate efficacy.

Of the ten symptoms measured, only the prevalence of rectal bleeding was different between the treatment arms. The prevalence of rectal bleeding 2 years following treatment was 42% in the



hypofractionated arm (BED3 105.4 Gy) and 27% in the conventionally fractionated (BED3 106.6 Gy) arm ( $p < 0.05$ ). The prevalence of rectal bleeding is somewhat higher than expected and may be the result of the two-dimensional methods employed. If only cases with moderate to severe bleeding are considered there was no difference between the treatment arms (20% vs 14%,  $p > 0.05$ ). The authors also reported on treatment efficacy. There was no difference in the nadir PSA and the PSA levels 2 years following treatment between the treatment arms. Using the ASTRO consensus definition, the 4-year estimate of freedom from biochemical failure was 85.5% in the conventionally fractionated arm (BED10 76.8 Gy; BED1.5 149.3) and 86.2% in the hypofractionated arm (BED10 70.1 Gy; BED1.5 155.8).

Results of the other hypofractionated randomized trial came from Canada and has been published (Lukka 2005). The trial compared 66 Gy/33 fractions (Long arm) to 52.5 Gy/20 fractions (Short arm) in men with low- and intermediate-risk prostate cancer. The dose was prescribed to the isocenter and the prostate/seminal vesicle to block margin was 15 mm (could be reduced to 10 mm posteriorly at the discretion of the investigator). Treatment planning was done using diagnostic CT images, but IMRT or 6-field conformal treatment techniques were not employed. In this trial the 5-year rate of failure (biochemical or clinical) was higher in the Short arm compared to the Long arm (59.95% vs. 52.95%; HR 1.18 [0.99-1.41],  $p < 0.05$ ). At first glance this would appear to suggest that the hypofractionated regimen may be inferior compared to a conventionally fractionated regimen, but the two arms were not designed to be isoeffective. In fact, using the biologically effective dose, the Short arm is consistently less than the Long arm until the alpha-beta ratio reaches a value of  $< 1$ . The results of the Canadian trial, therefore, are not inconsistent with an alpha-beta ratio for prostate cancer of 1.5. At a median follow-up of 5.7 years there was no difference in 5-year actuarial rate of late grade 3+ GI/GU toxicity between the two arms.

### **1.3 Shorter Radiotherapy Schedules**

In recent years investigators have looked at even shorter radiotherapy schedules. In 2007 Madsen reported on 40 patients treated with fractionated stereotactic radiotherapy using 5 daily sessions of 6.7 Gy (Madsen 2007). The median follow-up was 41 months (range, 21–60 months). Acute toxicity Grade 1–2 was 48.5% (GU) and 39% (GI); 1 acute Grade 3 GU toxicity was reported. Late Grade 1–2 toxicity was 45% (GU) and 37% (GI). No late Grade 3 or higher toxicity was reported.

In 2008 Tang reported on patients with low risk disease treated with IMRT to a dose of 35 Gy. The study was a phase I/II study in which patients with T1–2b, Gleason  $\leq 6$  and prostate-specific antigen (PSA)  $\leq 10$  ng/ml prostate cancer received 35 Gy in five fractions, once a week over 29 days. Treatment was delivered with IMRT on standard linear accelerators and with daily image guidance using gold seed fiducials. The target accrual of 30 patients had been reached and all had completed treatment and at least 6 months of follow-up. Treatment was very well tolerated with no Grade 3 or 4 genitourinary toxicity, gastrointestinal toxicity, or fatigue observed (95% confidence interval 0–12%). As a group, compared with baseline, the following additional Grade 2 toxicities were observed: 13% genitourinary, 7% gastrointestinal and 10% fatigue. At 6 months all scores had returned to or improved over baseline.

More recently Stanford reported on 41 low risk patients treated with 36.25 Gy in 5 fractions using stereotactic body radiotherapy (King 2008; King 2003). The first 21 patients were treated on consecutive days but, due to higher than expected rectal toxicity treatments were modified to be given every other day (three fractions a week). With these changes no patients experienced Grade 3 or higher toxicity. Median follow up was 33 months in this study.

A multi-institution phase I/II trial of 3D conformal RT for favourable-risk prostate cancer (T1a-T2a, Gleason  $\leq 6$  and PSA  $< 10$ ) was conducted using daily localization at the Centre Hospitalier de l'université de Montréal (Menkarios 2009). RT consisted of 45 Gy in nine fractions given once a week over 57 days. Primary endpoints were feasibility and late gastrointestinal (GI) toxicity (RTOG scale), while secondary endpoints included acute GI and genitourinary (GU) toxicity, biochemical control, survival, and sexual function as assessed with the EPIC questionnaire. Between 2006 and 2008, 80 patients were treated. No treatment interruptions occurred. The median follow-up was 17 months (range, 7-34 months). Maximal acute GU toxicity Grade 2 and 3

(<3 months) was 31% and 5%, respectively (no Grade 4). Acute GI Grade 2 toxicity occurred in 14% and there were no Grade 3 or 4. Data for late toxicity up to 19 months was available for 38 patients; late Grade  $\geq 3$  toxicity was 3% (GU) and 8% (GI). Sexual function scores were stable in 37% of patients, improved in 15% and deteriorated in 48%, as compared to baseline. No patient had a PSA failure regardless of biochemical failure definition used. In summary we found that weekly hypofractionated RT consisting of 45 Gy/9 fractions is feasible, and results in an acceptable toxicity profile.

M. A. Ritter (2009) reported results of a phase I/II NIH-sponsored clinical trial carried out by 5 institutions that explored the tolerance and efficacy of increasingly hypofractionated radiation therapy for localized prostate cancer. Three increasing dose-per-fraction schedules were evaluated. These regimens were designed to maintain equivalent predicted late toxicity. Predicted tumor EQD2 doses were in excess of 82 Gy if the tumor  $\alpha/\beta$  of 1.5 Gy is assumed. Fraction size escalations were contingent upon acceptable acute and late toxicity. The three hypofractionated levels, 1, 2, and 3 were: 64.7 Gy/22 fx of 2.94 Gy, 58.08 Gy/16 fx of 3.63 Gy and 51.6 Gy/12 fx of 4.3 Gy. All patients were treated with tomotherapy or linac based IMRT with daily image guidance.

A total of 307 patients were accrued. Clinical parameters for these favorable-to-intermediate risk patients were: clinical stage T1/T2: 75%/25%; Gleason  $<7/7$ : 58%/42%; PSA  $<10/\geq 10$ : 82%/18%; median PSA: 6.2 ng/ml. Levels 1, 2, and 3 are 42, 19, and 16 months, respectively. Toxicities were acceptable: Depending on the hypofractionation level, 20-30% of patients had acute Grade 2 GU symptoms during or shortly after treatment, primarily related to alpha blocker initiation. Average international prostate symptom scores (IPSS) returned to baseline by 3 months post treatment. Four to nine percent of patients had Grade 2+ GI symptoms during treatment, declining to 2% by 2 years. Actuarial rectal bleeding at two years was 8  $\pm$  1.7%, with all cases resolving either spontaneously or after minor intervention and with similar rates among hypofractionation levels ( $p = 0.2$ ). The 5-year, nadir+2 actuarial bPFS for Level 1 was 94.7  $\pm$  2.7%, with no difference between HPFX level 1, and levels 2 and 3 at 3 years ( $p = 0.95$ ). Initial PSA, Gleason score, and T stage did not correlate with outcome ( $p = 0.63, 0.71, 0.96$ , resp.). To date, 8 patients had failed biochemically, but 3 were within the first 4 months of follow-up.

The authors conclude that toxicities were acceptable and similar across all hypofractionation levels, consistent with the  $\alpha/\beta$  of 3 assumed for late effects. Furthermore, actuarial bPFS rates at 3-5 years were high, comparable to expectations with dose escalated standard fractionation.

#### **1.4 Proposal**

Based on these preliminary results we propose a phase II randomized multicenter trial to assess quality of life outcomes, acute and late toxicity of two different hypofractionated regimens: 36.25 Gy in 5 fractions of 7.25 Gy twice a week and 51.6 Gy in 12 daily fractions of 4.3 Gy.

All patients will be treated using highly conformal dose distributions to minimize significant doses to surrounding normal tissues. IMRT and related dose painting methodologies or protons are required. Image-guided radiotherapy (IGRT; see Section 6.3.2.3.1) will be mandatory. Institution credentialing for both the radiation delivery and IGRT technique is required.

For dose delivery techniques that take more than 7 minutes (from initial beam on to last beam completion time), measures to detect and compensate for intrafraction motion are required and are detailed in the protocol. The technique for intrafraction motion correction will be documented for each institution and information relating to required table shifts will be collected.

Some RT-related side effects are deleterious and affect aspects of health-related quality of life (HRQOL) as measured by validated patient reported outcomes (PROs). Urinary, bowel, and erectile dysfunction are well-known side effects of pelvic RT (van Andel 2003). The Expanded Prostate Cancer Index (EPIC) instrument is a PRO measure of prostate cancer HRQOL that assesses a broad spectrum of bowel, urinary, sexual and hormonal symptoms. The current hypofractionated trial RTOG 0415 incorporates the EPIC instrument, providing a unique opportunity to use the EPIC score from the standard arm of the RTOG 0415 study as a useful

benchmark for the proposed study. Therefore, we propose to use the bowel and urinary domains of the EPIC instrument as a primary endpoint in this trial.

RTOG 0415 is the current RTOG hypofractionated trial that was designed as an equivalence study to determine if disease free survival (DFS) using a hypofractionated 3D-CRT/IMRT regimen (70 Gy in 28 fractions over 5.6 weeks) is no worse than DFS following conventionally fractionated 3D-CRT/IMRT (73.8 Gy in 41 fractions over 8.2 weeks) in patients treated for favorable-risk prostate cancer. RTOG 0415 is closed to accrual. The data from Arm 1 (conventional fractionation) of RTOG 0415 will be used for the trial design and to provide a benchmark of EPIC measurements. The purpose of this study is to show that the proposed hypofractionated regimens yield tolerable HRQOL as compared to conventional fractionation.

Toxicity is an important secondary endpoint of this study. Because RTOG 0415 will be in follow-up at the time this trial is expected to open, the toxicity profile of patients from this population will not be mature enough for comparison to RTOG 0938. RTOG 0126 is a Phase III trial that was designed to determine if overall survival (OS) is better in patients treated with a high-dose 3D-CRT/IMRT regimen (79.2 Gy in 44 fractions) than in patients treated with low-dose 3D-CRT/IMRT (70.2 Gy in 39 fractions). Data from a subset of favorable risk patients in the high-dose arm of RTOG 0126, which has similar patient characteristics to the eligibility criteria for this phase II study, will be used as a toxicity benchmark for RTOG 0938.

### **1.5 Identification of Genetic Markers Associated with Normal Tissue Toxicities Resulting from Radiotherapy**

A series of genome-wide association studies is being performed to identify single nucleotide polymorphisms (SNPs) and copy number variants (CNVs) associated with the development of normal tissue toxicities resulting from radiotherapy. It is anticipated that identification of these genetic markers will form the basis of an assay to predict which patients are at an altered risk for development of complications arising from cancer treatment with radiation.

We will explore promising biomarkers to date with regard to side effects from treatment. Although substantial evidence has been obtained from a series of studies suggestive of a genetic basis for clinical radiosensitivity of normal tissue, much work still remains to be accomplished in this area. The blood collected will be utilized for SNPs. Single nucleotide polymorphisms are the most common variation responsible for genetic diversity between individuals, accounting for more than 85% of the variability. Recent advances in SNP identification and analysis have made SNP genotyping an invaluable tool to examine the variations responsible for disease susceptibility and radiation responsiveness. SNP genotyping applications have recently extended into personalized health care.

We also have companion assays that will explore putative markers in pretreatment plasma, whole blood and 3-month post-treatment collection of these fluids will be tested for a number of cytokines and proteins that are thought to be predictive of long-term radiation toxicity. This may lead to identification of promising similar or new biomarkers with the goals of identifying factors predictive of outcome such that patients may be better stratified in future trials.

### **1.6 Collection of Tumor for Biomarker Studies**

Tumor biomarkers as previously published by the RTOG GU TRP group has identified a number of biomarkers that together may have value as a predictive marker. Our prior data is related to conventional fractionation. This protocol will be one of the first for a hypofractionation trial in GU.

## **2.0 OBJECTIVES**

### **2.1 Primary Objective**

To demonstrate that 1-year health-related quality of life (HRQOL) for at least one hypofractionated arm is not significantly lower than baseline as measured by the Bowel and Urinary domains of the Expanded Prostate Cancer Index Composite (EPIC) instrument.

## **2.2 Secondary Objectives**

- 2.2.1** To estimate the degree of change in HRQOL in each arm for the Sexual and Hormonal EPIC domains and the Utilization of Sexual Medications/Devices from baseline to 1-year, 2 years, and 5 years
- 2.2.2** To estimate the degree of change in global HRQOL in each arm as measured by the EQ-5D from baseline to 1-year, 2 years, and 5 years
- 2.2.3** To estimate the rate of acute and late GI and GU toxicity for each arm at 1, 2, and 5 years
- 2.2.4** To estimate PSA failure in each arm at 1, 2, and 5 years
- 2.2.5** To estimate disease free survival (DFS) in each arm at 1, 2, and 5 years
- 2.2.6** To estimate Quality Adjusted Life Years for each arm at 1, 2, and 5 years using the EQ-5D and DFS
- 2.2.7** To identify genetic markers associated with normal tissue toxicities resulting from radiotherapy
- 2.2.8** To collect tumor tissue for biomarker studies
- 2.2.9** To estimate EPIC bowel and urinary HRQOL as continuous variables

## **3.0 PATIENT SELECTION**

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

### **3.1 Conditions for Patient Eligibility (7/24/13)**

- For questions concerning eligibility, please contact RTOG Data Management (via the RTOG contact list on the RTOG website) or the Study Chair (see first page of protocol).
- 3.1.1** Histologically confirmed diagnosis of adenocarcinoma of the prostate within 365 days (1 year) of randomization
    - 3.1.1.1** Patients previously diagnosed with low risk (Gleason scores 2-6, clinical stage T1-2a, and PSA < 10) prostate cancer undergoing active surveillance who are re-biopsied and found to have low risk disease according to the protocol criteria are eligible for enrollment within 365 days (1 year) of the repeat biopsy procedure.
  - 3.1.2** History/physical examination with digital rectal examination of the prostate within 60 days prior to registration
  - 3.1.3** Histological evaluation of prostate biopsy with assignment of a Gleason score to the biopsy material; Gleason scores 2-6 within 365 days (1 year) of randomization
  - 3.1.4** Clinical stage T1-2a (AJCC 7<sup>th</sup> edition) within 90 days of randomization
  - 3.1.5** PSA < 10 ng/mL within 60 days prior to registration. PSA should not be obtained within 10 days after prostate biopsy. (Every effort should be made to obtain all serum PSA values obtained in the 1 year prior to treatment to allow for calculation of PSA kinetics.) The type of PSA assay (e.g., Abbott) should be recorded on the data forms.
  - 3.1.6** Zubrod Performance Status 0-1 within 60 days prior to registration
  - 3.1.7** Age ≥ 18
  - 3.1.8** Patient must be able to provide study-specific informed consent prior to study entry.
  - 3.1.9** Willingness and ability to complete the Expanded Prostate Cancer Index Composite (EPIC) questionnaire (**see Section 4.1.1**).

### **3.2 Conditions for Patient Ineligibility (10/22/12)**

- 3.2.1** Prior or concurrent invasive malignancy (except non-melanomatous skin cancer) or lymphomatous/hematogenous malignancy unless continually disease free for a minimum of 5 years. All patients with in situ carcinoma are eligible for this study (for example, carcinoma in situ of the oral cavity is eligible) except patients with carcinoma of the bladder (including in situ bladder cancer or superficial bladder cancer).
- 3.2.2** Evidence of distant metastases
- 3.2.3** Regional lymph node involvement
- 3.2.4** Previous radical surgery (prostatectomy), cryosurgery, or HIFU for prostate cancer
- 3.2.5** Previous pelvic irradiation, prostate brachytherapy, or bilateral orchiectomy
- 3.2.6** Previous hormonal therapy, such as LHRH agonists (e.g., goserelin, leuprolide) or LHRH antagonists (e.g., degarelix), anti-androgens (e.g., flutamide, bicalutamide), estrogens (e.g., DES), or surgical castration (orchiectomy)
- 3.2.7** Use of finasteride within 30 days prior to registration. PSA should not be obtained prior to 30 days after stopping finasteride.
- 3.2.8** Use of dutasteride within 90 days prior to registration. PSA should not be obtained prior to 90 days after stopping dutasteride.
- 3.2.9** Previous or concurrent cytotoxic chemotherapy for prostate cancer

- 3.2.10** Severe, active co-morbidity, defined as follows:
- 3.2.10.1** Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months
  - 3.2.10.2** Transmural myocardial infarction within the last 6 months
  - 3.2.10.3** Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
  - 3.2.10.4** Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration
  - 3.2.10.5** Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol. (Patients on Coumadin or other blood thinning agents are eligible for this study.)
  - 3.2.10.6** 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.

#### **4.0 PRETREATMENT EVALUATIONS/MANAGEMENT**

**NOTE:** This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility. See Appendix II for a summary of study assessments and time frames.

##### **4.1 Required Evaluations/Management**

- 4.1.1** Completion of the Expanded Prostate Cancer Index Composite (EPIC) is mandatory for all patients (per Section 3.1.9).

##### **4.2 Highly Recommended Evaluations/Management**

- 4.2.1** Visualization of the urethra at the time of CT simulation or CT scan for treatment planning or through fusion of images (e.g., MRI) with CT simulation images at that time. For patients where the maximum point dose to a point that is 0.03 cc exceeds 38.78 Gy (5 fraction arm) or exceeds 55.21 Gy (12 fraction arm), visualization of the urethra would be required.
- 4.2.2** Baseline testosterone
- 4.2.3** EPIC-Utilization of Sexual Medications/Devices Supplement (for patients who consent to this component of the study)
- 4.2.4** EQ-5D (for patients who consent to this component of the study)

##### **4.3 Optional Online Completion of Patient Reported Outcome (PRO) Assessments**

Missing data are a significant problem, particularly for PRO assessments. Unlike data for traditional endpoints, such as survival, PRO data can never be obtained retrospectively if it is not provided by the patient at the appropriate time point. This limits researchers' ability to accurately perform PRO statistical analyses and negatively impacts the clinical relevance of this effort. Typically, PRO forms are filled out in hardcopy (paper). To provide a more convenient method of completing PRO assessments, the Radiation Therapy Oncology Group (RTOG) is working with VisionTree Software, Inc., San Diego, CA. VisionTree offers patients on this study the option of completing their PRO forms online from any location that has a computer with Internet access, including the patient's home, and provides reminders to patients to complete the assessments.

VisionTree has developed a new tool, VisionTree Optimal Care (VTOC), a HIPAA-secure, user friendly, web-based software system (Gorgulho 2005; Gorgulho 2007; Pedroso 2006). The VTOC tool contains a web-based system for global patient and trial administration access, which allows improved compliance and accuracy of data collection, validation, and reporting. It is compliant with the Title 21, Code of Federal Regulations, Part 11 statistical process control system and provides a mobile solution for clinical trials. PRO data are collected with Microsoft Excel and PDF export of reports. VTOC also has mobile messaging and e-mail reminders. Surveys can be "pushed" to patients for completion at timed intervals (see <http://www.visiontree.com> for details). VisionTree has many clinical partners and clients, including ASTRO, University of California-San Francisco, Baylor College of Medicine, Duke University, Emory University, Harvard Medical School, Henry Ford Hospital, and University of Pennsylvania. ASTRO utilizes VisionTree outcomes online for maintenance of certification and for capturing quality measures. This technology would allow consenting patients on this study to fill out their PRO forms online from

any location and to receive e-mail reminders to complete assessments. E-mail reminders also can be sent to research associates (RAs) at the appropriate institutions to remind them that a PRO time point window is about to close so that a patient can be contacted to fill out PRO information on time, before it becomes “missing data”.

In a pilot RTOG study (RTOG 0828), the compliance rate of patients completing PRO assessments at 6 months significantly improved using electronic technology. Based on this pilot data, RTOG is offering VisionTree as an option in other studies, including this one. Patients who prefer to complete hardcopy PRO assessments can do so.

To complete PRO forms online, patients must have an e-mail address that they consent to use so that e-mail reminders may be sent to them. The patient’s e-mail address also will be used for password-protected access to VTOC. Patients who are interested in participating but do not yet have an e-mail address can obtain one for free from a number of sources (e.g. Yahoo!, Hotmail, or AOL). Patients will receive a login card (either printed or sent via e-mail) with which to log in using the secure, web-based VTOC portal. VTOC meets all HIPAA guidelines and is encrypted (via 128-bit SSL) for the security, privacy, and confidentiality of PRO information. It is similar to the secure login commonly used when performing online banking. The login card can then be kept and maintained by the patient.

The patient’s e-mail address only will be used by RTOG for this purpose. Patients will be sent e-mail reminders to complete PRO forms. A typical e-mail reminder would read: “Your Quality of Life forms for the study, RTOG 0938, are now due. Please go to <http://www.optimalcare.com>, use your secure login, and complete the online forms. If any questions make you feel uncomfortable, you may skip those questions and not give an answer. If you have any questions, please e-mail or call your research associate at [insert RA e-mail address] or [insert RA telephone number]. Thank you for participating in this study.” The reminders will be created by RTOG and placed into a study template that will be sent to patients at customized intervals (at the time points when PRO forms are due). The first reminder will be sent at the beginning of the “window” to complete a PRO form, with a second reminder halfway through the window period if the PRO forms are not yet completed at that time point. A maximum of 3 reminders will be sent for each of the 3 PRO time points. After a patient has completed all forms in the portal, a dialogue box will appear that says “Thank you for completing your Quality of Life forms,” and the patient will no longer receive any remaining notices for that time point. The site RA or study administrator will be informed through the VTOC “At-A-Glance” form management system when PRO forms have been completed.

If the patient declines participation in VisionTree, please document the reason in your source documentation.

See Section 11.12 for further details.

## **5.0 REGISTRATION PROCEDURES**

### **5.1 General Credentialing Procedures for All RTOG Protocols**

The first step in the credentialing process for all RTOG protocols requires the institution or investigator to complete a Facility Questionnaire. If this requirement has been met for a previous protocol, it is possible to update that information for a new protocol. In order to obtain information on previous Facility Questionnaires completed by your institution, you should contact Ms. Tammy McGlade at RTOG Headquarters ([tmcglade@acr.org](mailto:tmcglade@acr.org)). All treatment planning data for this protocol will be collected in digital format for review by the protocol PIs.

### **5.2 Technologies Accepted for Treating Patients on RTOG 0938**

Eligible patients may be treated using any of the treatment technologies listed in Sections 6.3.2.1 and 6.3.2.2 provided a center is credentialed for the treatment technique. All centers using photons to treat patients accrued to this protocol must be credentialed for IMRT. Institutions using protons must be credentialed for the use of it.

### **5.3 Pre-Registration Requirements for Image-Guided Radiotherapy (IGRT) Treatment Approach**

- 5.3.1** In order to be eligible to enroll patients for this trial and treat with photons, the center must be credentialed for both IMRT and for prostate image-guided radiotherapy (IGRT). This applies to treatment techniques typically described as IMRT as well as other systems that use inverse treatment planning techniques to paint dose to conform to irregular target volumes like the prostate. Centers treating with protons must credential for their use and for IGRT. The allowed x-ray IGRT systems are listed in Section 6.3.2.3.1. Computer assistance for image registration and calculation of patient shifts is a requirement.

In order to utilize IGRT, the institution must have met technology requirements and have provided the baseline physics information. This information is available on the Advanced Technology Consortium (ATC) web site, <http://atc.wustl.edu>. The ATC is in part comprised of RTOG RT Quality Assurance, the Image-Guided Therapy Center (ITC) at Washington University, and the Radiological Physics Center (RPC) at MD Anderson Cancer Center.

In order to become credentialed for prostate IGRT, the institution must already be credentialed for IMRT. Institutions that have not been credentialed by the RTOG to treat with IMRT MUST apply for IMRT credentialing as described below in Section 5.4. This requirement also applies for the use of other treatment systems that use inverse treatment planning to weight different treatment fields. Institutions using proton beams for patient treatment are not required to credential for IMRT. Intensity Modulated Proton Therapy (IMPT) is currently not allowed for this protocol.

**5.3.2** Image Guidance Credentialing Process

- 5.3.2.1** Each institution will be required to undergo image guidance credentialing for prostate IGRT. This will involve the review of one patient that has previously been treated using the IGRT system that will be used for protocol patients. The first step is for the institution or investigator to complete a new Facility Questionnaire (or modify their existing Facility Questionnaire on file at RTOG headquarters) and/or set up an SFTP account for digital data submission, both of which are available on the ATC web site at <http://atc.wustl.edu>.
- 5.3.2.2** Next, the institution must submit a series of daily treatment images along with a spreadsheet of IGRT data from an anonymized prostate cancer patient. See the ATC web site, <http://atc.wustl.edu>, for the spreadsheet. This series must include a minimum of 5 sequential daily pre-treatment images obtained with one of the technologies described in Section 6.3.2.3.1. These images and the spreadsheet will be reviewed by the Study Chair, Himu Lukka, MD, and the Medical Physics Co-chair, Rajat Kudchaker, PhD, prior to certification.

**5.4** Pre-Registration Requirements for Intensity Modulated Radiation Therapy (IMRT) Treatment Approach and IGRT

- 5.4.1** In order to utilize any of the dose delivery techniques allowed for 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 like volumetric modulated arc therapy [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.

**5.4.2** Credentialing When Technology (Either Treatment Modality or IGRT) has Changed From Previous Credentialing

When institutions change technology, it is necessary to repeat the credentialing process. For example, changing from gantry-mounted linear accelerator IMRT with a standard multileaf



collimator to Tomotherapy with a binary collimator requires a repeat of the credentialing process. This situation also applies to a switch to or the addition of CyberKnife™ equipment requires IMRT credentialing and the procedure described above must be completed prior to enrolling patients on this study. Fundamental changes in the techniques used for IGRT or motion management also require repeat credentialing. For example, changing from the use of EPID imaging that uses the treatment beam to an IGRT technique that used a separate kV x-ray beam requires a repeat of the IGRT credentialing process.

## **5.5 Pre-Registration Requirements for Proton Therapy Treatment Approach**

### **5.5.1 Proton Specific Requirements**

Proton facilities must be approved by the RTOG, after successfully completing a site visit by the Radiological Physics Center (RPC) and successfully transferring a proton treatment plan in digital format to the Image-Guided Therapy Center (ITC), before any patients can be entered onto this protocol. The proton approval process is specific for different treatment approaches.

**5.5.2** For proton credentialing contact the RPC at [rpc@mdanderson.org](mailto:rpc@mdanderson.org). Guidelines for the use of proton radiation therapy in NCI-sponsored clinical trials can be found on the RPC web site at <http://rpc.mdanderson.org/rpc/>.

## **5.6 Regulatory Pre-Registration Requirements (10/22/12)**

**5.6.1 U.S. and Canadian institutions** must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206). The study-related regulatory documentation also may be e-mailed to the CTSU at [CTSURegulatory@ctsu.coccg.org](mailto:CTSURegulatory@ctsu.coccg.org). This must be done 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 renewal information as appropriate.

### **5.6.1.1 Non-English Speaking Canadian and Non-North American Institutions:**

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.

## **5.6.2 Pre-Registration Requirements FOR INTERNATIONAL INSTITUTIONS**

### **5.6.2.1 *For institutions that do not have an approved LOI for this protocol:***

International sites must submit an LOI to RTOG Headquarters to receive approval to participate in this trial. For more details see link below:

<http://www.rtog.org/Researchers/InternationalMembers/LetterofIntent.aspx> .

### **5.6.2.2 *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.

## **5.7 Registration (10/22/12)**

### **5.7.1 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> 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](mailto:websupport@acr.org) or 800-227-5463 ext. 4189 or 215-574-3189. In the event that the RTOG web registration site is not accessible, participating sites can contact RTOG web support for assistance with web registration or call the RTOG Registration Desk 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 (10/22/12)**

**Protocol treatment must begin within 6 weeks after randomization. This protocol requires the use of IMRT or similar techniques that use inverse treatment planning or protons. All photon treatment techniques allowed for this protocol, whether typically classified as IMRT or not, must be credentialed using the same procedure followed for IMRT credentialing and described in Section 5.0. 3D-CRT dose delivery techniques are not allowed. An accepted IGRT technique together with radio-opaque fiducial markers or electromagnetic transponders implanted in the prostate must be used to position treatment beams. Centers must be credentialed for IMRT or protons and IGRT to enter patients on this protocol. The maximum accrual from each center will be limited to 10% of the total protocol accrual.**

**The Principal Investigator, Himu Lukka, MD, and Co-Chairs will perform a rapid review of the Treatment plan for the first 5 cases from each institution prior to the institution delivering protocol treatment. Institutions should allow 3 business days for each case to be received, processed and reviewed. If the plan must be resubmitted, it will be given a rapid review (within 3 business days).**

### **6.1 Dose Specifications**

#### **6.1.1 Total Prescribed Dose**

In Arm 1 of the study patients will receive 5 fractions of radiation; each fraction size will be 7.25 Gy. The total dose will be 36.25 Gy. The 5 treatments will be scheduled to be delivered twice a week over approximately 15-17 days. A minimum of 72 hours and a maximum of 96 hours should separate each treatment. No more than 2 fractions will be delivered per week. The total duration of treatment will be no shorter than 15 days and no longer than 17 days.

In Arm 2 of the study patients will receive 12 daily fractions of 4.3 Gy. These patients will be treated 5 days a week. The total dose will be 51.6 Gy. The total duration of treatment will be no shorter than 16 days and no longer than 18 days.

**6.1.2** Dose Coverage

For both arms, the isodose line used for the prescription dose should cover a minimum of 95% of the PTV.

**6.1.3** Minimum Dose

The minimum dose within the PTV to a point that is 0.03 cc in size must be  $\geq 95\%$  of the prescribed dose.

**6.1.4** Proton Specific Doses

Proton prescribed doses should be in terms of dose equivalent, i.e. Gy (RBE). The physical dose, which is specified below, is the dose equivalent divided by the RBE. For protons, the RBE is defined as 1.1.

$$\text{Gy} = \text{Gy (RBE)}/1.1$$

Thus the 7.25 Gy dose (5 fraction arm) which is the photon dose, should be interpreted for protons as 7.25 Gy (RBE), which converts to 6.59 Gy physical dose for protons. Similarly, the 4.3 Gy dose (12 fraction arm), which is the photon dose, should be interpreted for protons as 4.3 Gy (RBE), which converts to 3.91 Gy physical dose for protons. Throughout the document when treating with protons all doses should be interpreted as Gray (RBE). When possible for clarity, both RBE-weighted and physical dose should be specified. The dose constraints (highlighted in the tables in Section 6.6.1.6) for protons should be Gray [RBE].

In addition to the target volume delineation for protons, adjustments must be made during the treatment planning process to take into account the uncertainties along the beam direction, i.e. the range uncertainties, to ensure both distal and proximal coverage (distal and proximal margins).

**6.2** Supportive Measures

**6.2.1** Urinary

Symptomatic urinary medicines, (e.g. tamsulosin) are allowed at the discretion of the treating radiation oncologist or urologist.

**6.2.2** Bladder

Patients will be asked to have a full urinary bladder both during simulation and treatment for all techniques except where treatment time exceeds 30 minutes when patients may be treated with an empty bladder. Consistent bladder filling procedure should be used for an individual patient for simulation and for each treatment. Bladder filling may be achieved by asking patients to drink 16-24 oz of water or other fluid 2-3 hours prior to treatment and to not urinate between this time and treatment as they are able. In patients where a decision is made to treat the bladder empty (see Section 6.4.1), patients would be asked to void immediately prior to each treatment.

**6.2.3** Bowel

Patients will be advised to adhere to a low gas, low motility diet commencing one day prior to the treatment. One tablespoon of Milk of Magnesia will be taken the night before the simulation and the night before each treatment. One Fleet's enema will be administered 2-3 hours before the simulation and each treatment.

**6.3** Technical Factors [Equipment, energies]

**6.3.1** Stereotactic Targeting and Treatment

This protocol will require treatments to be performed with an image-guided technique with the use of a 3-D coordinate system defined by 3D volumetric data or orthogonal 2D images (see Section 6.3.2.3.1).

**6.3.2** Radiotherapy Delivery

**6.3.2.1** Photons

This protocol requires the use of IMRT (DMLC or SMLC) or related techniques (Tomotherapy/VMAT/Cyberknife). Related techniques include robotic dose delivery that uses inverse treatment planning techniques to determine weighting for a large number of

fields sequentially irradiating sub-regions of a target. Allowed IMRT techniques include the newer approach of VMAT moving gantry delivery. Three-dimensional coplanar or non-coplanar beam arrangements will be custom designed for each case to deliver highly conformal dose distributions. For fixed gantry angle IMRT delivery, a least 5 gantry positions should be used.

The recommended photon energies for this protocol are 6-10 MV. The use of beams with higher energy is discouraged. These energies will result in an increased neutron dose reaching the patient's total body. However, it is recognized that increasing the energy has advantages in improving dose distributions for larger patients. For this reason, beams as high as 15 MV will be allowed only when improvement of the dose distribution is evident to the treatment planner. If an institution uses mixed beam energies as part of the IMRT optimization process, using a limited number of beams with energy higher than 10 MV is allowed for the longer path lengths encountered in a particular plan for larger patients. Such beams should be mixed with beams energies that do not result in neutrons (i.e., 6-10 MV).

### 6.3.2.2

#### Protons

For proton planning two opposed lateral fields per day are required. Both fields are required to be treated daily. Dose distribution by means of passive double scattering or pencil beam (e.g., spot scanning, continuous, or uniform scanning) are acceptable when constraints are achieved. Aperture, distal, proximal margin, smearing and smoothing will be determined for each case and recorded under physicist supervision. IMPT is not allowed within this protocol.

### 6.3.2.3

#### IGRT and Electromagnetic Transponders Used for Target Localization and Field Adjustment

#### 6.3.2.3.1

Allowed x-ray IGRT techniques with or without real-time tracking: The x-ray IGRT system that can be used for this study are:

- 2D and 3D IGRT systems are allowed for this protocol
  - These systems can use either kV or MV x-rays
  - A computerized method for image registration is required for determination of the patient shift information
  - The image registration can be either manual (drag and drop images) or automatic
- Examples of 2D systems are the ExacTrac, on board imaging (OBI), electronic portal imaging device (EPID), CyberKnife real-time system, etc.
- Examples of the 3D systems are the use of helical tomo CT imaging, cone-beam CT and CT-in-the-room
- EPID imaging is allowed as long as the above conditions are met.

The use of target tracking during treatment is encouraged when this technology is available and strongly encouraged when the treatment time from initial beam-on to the end of dose delivery is longer than 7 minutes. Repeat IGRT procedures can be used to detect and correct field positions when real-time tracking is not available. Treatments that take less than 5 minutes do not require an end-of-treatment IGRT procedure. An end-of-treatment IGRT procedure should be obtained when real-time tracking is not used, and the time period from the last IGRT procedure exceeds 5 minutes.

#### 6.3.2.3.2

Use of fiducial markers: Fiducial markers placed within the prostate are required for this protocol. The size and material used for these markers must be determined based on each institution's CT-simulator and IGRT system. The markers must be visible and artifact-free on both systems. It is recommended that at least three markers are placed for each patient.

For protons, fiducial markers with daily kV imaging should be used to confirm setup and account for interfractional motion. Fiducial markers should satisfy the following requirements for prostate cancer proton therapy: (1) good radiographic visibility on kV imaging/diagnostic Xrays, (2) no or minimal distortion of delivered dose, (3) minimal artifacts on CT images used for treatment planning, and (4) no migration during treatment. A number of commercially available markers that are appropriate for protons include Visicoil (IBA) and low Z radioopaque markers.

#### 6.3.2.3.3

Dose from x-ray IGRT: Estimates of patient doses per imaging study for various imaging systems vary considerably. The doses are in the range of 1 mGy for Cyberknife's and BrainLab's ExacTrac planar kV-systems. The doses from helical MV CT scan on a tomotherapy unit were estimated to be in the range of 1 to 3 cGy for head and neck

studies, similar to doses reported for kV cone beam CT on the Elekta Synergy machine. The doses for MV cone beam CT are in the range of 10 cGy for a pelvis study to 6 cGy for a head and neck study. Thus, the doses for 3D imaging systems are in the range from 1 to 6 cGy for head and neck imaging and can contribute from 0.5 to 3% to the daily dose of 2.0 Gy. These dose estimates apply to a single imaging procedure and can be compared to the dose delivered for a single treatment fraction when IGRT imaging is performed once each day of treatment. The imaging dose typically exceeds the boundaries of the high-dose region(s) treated therapeutically, and it is sometimes necessary to repeat the procedure a number of times during, before, or after a single fraction. The imaging dose to nearby critical structures will increase when repeated IGRT procedures are performed for patients with severe set up problems (e.g., requiring frequent corrections of more than 5 mm).

The RTOG is concerned about the estimated doses given above, and is committed to limiting the imaging dose when IGRT is used in any of its protocols. This can be accomplished by minimizing the use of this technology, collimating the field down to the region of interest in the case of planar imaging, reducing the CT scan length to image only the region of interest. The imaging dose to the patient may become significant if repeated studies are done for patients with severe set up problems (e.g. requiring frequent corrections that are larger than the PTV margins). It is recommended that patients expected to have severe set up problems not be enrolled in the study. Patients who are found to have severe set up problems after commencement of treatment may have their treatment modified in the best interest of the patient. An intention to treat analysis will be conducted.

As a technique of controlling patient dose, it is recommended that a daily IGRT QA procedure be established at each institution to verify the accuracy of the imaging isocenter, coincidence of the imaging and radiation isocenter, image registration software, couch motion, etc. on a daily basis. This QA check should be performed by the therapists operating a particular treatment device and is aimed at reducing the use of repeat imaging to check that the registration software has functioned properly when a shift of patient position is carried out. Additionally, it is not recommended that an institution use a daily imaging technique that delivers greater than 10 cGy/day imaging dose to the patient. This limit dictates that repeat imaging on a particular day is held to a minimum when systems that deliver up to 10 cGy per study are used.

Adding the imaging dose to the patient's treatment dose distribution is not allowed for this protocol. This approach is taken because this dose has not traditionally been added, and many institutions using IGRT do not have a method for accurately modeling imaging dose. The exception to this rule is the technique of adding "imaging beams" to the IMRT optimization process. In this case, one or more orthogonal sets of conformal beams, having the same energy as the treatment beams, are used as input to the optimization so that the imaging dose is automatically accounted for in the final dose distribution. This method of handling the imaging dose is allowed for this protocol.

## **6.4 Set-up, Localization and Tracking (10/22/12)**

### **6.4.1 Patient Set-up**

Patients will be positioned supine in a comfortable posture. The minimum immobilization apparatus will be a pillow under the knees and the feet taped or rubber-banded together or equivalent. More complex immobilization devices are allowed, as per the discretion of the treating physician, as long as they do not interfere with the proper functioning of the image-guidance. Prone position is discouraged but allowed if tracking is used. The degree of bladder fullness should be made to duplicate what is anticipated for daily treatment, i.e., if the patient is instructed to maintain a full bladder for treatment, he should be simulated as such. Treatment bladder empty is allowed when patients are being treated with techniques exceeding 30 minutes. Consistent bladder filling procedure should be used for an individual patient for simulation and for each treatment. The degree of bladder filling for each patient entered into this study will be documented for future analysis. The use of rectal balloons will be allowed but

are not required in this protocol. The use of a rectal balloon will be documented for each patient for future analysis.

#### **6.4.2**     Localization

The acceptable IGRT techniques (see Section 6.3.2.3.1) will be utilized for initial localization, and tracking or periodic monitoring to guarantee that beam positioning is maintained throughout long treatments. The localization technique will be documented for each institution on the facility questionnaire. If an institution uses more than one treatment/localization technology, each must be described and appropriately credentialed. The initial localization and alignment is based on the center of mass of the transponders/fiducial markers. After initial localization is performed, all effort should be made to initiate the treatment delivery as quickly as possible. Significant rotations may be corrected at initial localization stage, and intra-fractional rotations will be ignored. Further adjustment during the treatment will be translational shift of the center of mass determined utilizing the IGRT (see Section 6.3.2.3.1) technique and using remote couch motion. Periodic monitoring of prostate position – minimum every 7 minutes during radiation delivery will be required for all techniques (except where tracking devices are utilized). Both where tracking devices are not employed or IGRT using non tracking devices (see the discussion of tracking in Section 6.3.2.3.1) repeat localization images will be taken at the end of each treatment. At the discretion of the radiation oncologist/physicist, monitoring of intrafraction motion may be required more frequently. The details of the doses received for daily localization are highlighted in Section 6.8. If in an individual patient the end-of-treatment images identify significant prostate movement compared to pretreatment images, monitoring of intrafraction motion more frequently would be recommended. For proton treatment repeat imaging between the treated field is recommended.

### **6.5**     **Treatment Planning** (10/22/12)

#### **6.5.1**     Simulation

##### Computed Tomography (CT)

CT will be the primary image platform for treatment planning. The simulation should be performed in the supine treatment position, with the transponders/fiducial markers/rectal balloon in place (where utilized). Axial cuts of 2.5 mm or less will be acquired throughout the pelvis and prostate from the top of the iliac crests superiorly to the perineum inferiorly..

##### Magnetic Resonance Imaging (MRI)

MRI images are not required. However, if MR scan is planned with use of Calypso system, MR should be obtained prior to the implantation of transponders.

##### Contrast

Oral, IV, urethral, and bladder contrast are allowed but not required.

#### **6.5.2**     Treatment Planning/Target Volumes

**6.5.2.1**     The definition of volumes will be in accordance with the ICRU Report #50 and ICRU Report #62: Prescribing, Recording, and Reporting Photon Beam Therapy; and ICRU Report #78: Prescribing, Recording, and Reporting Proton-Beam Therapy. It is recommended that proton facilities use the IAEA TRS 398 protocol for proton beam calibration although ICRU #59 is acceptable. The IAEA TRS -398 protocol is recommended by the ICRU #78 and is based upon a cobalt -60 dose to water calibration traceable to a national standard.

**6.5.2.2**     The Gross Tumor Volume (GTV) is defined by the physician as all known disease as defined by the planning CT and MR (when available) along with clinical information. The GTV for the purposes of this protocol is the prostate only.

**6.5.2.3**     The clinical target volume (CTV) will be the same as the GTV and will consist of the prostate without the seminal vesicles as defined by non-contrast axial CT scan.

**6.5.2.4**     The planning target volume (PTV) will be defined as the CTV plus a 3 mm margin posteriorly and 5 mm in all other dimensions. To meet dose constraints, if necessary, the ant margin can be reduced to 3 mm.

**6.5.2.5**     For proton therapy, the same PTV expansion will be used to accommodate targeting errors and intrafractional motion. Beam aperture should be designed to conform at least the 98% prescription isodose laterally to the PTV, and accommodate the dose fall-off both antero-posteriorly and cephalo-caudally in the beam's eye view. Additionally, the effect of variations in the set-up of the target with respect to tissue inhomogeneities (e.g., employing compensator smearing technique, beam-specific PTV etc.), or range uncertainties (e.g., by expanding the prescribed range and modulation, to create distal and proximal field margins)

should be addressed in the design of treatment fields for each beam direction. Review volumes called PTV-review Initial (=CTV plus a 3 mm margin posteriorly and 5 mm in all other dimensions) will be created in order to facilitate the coverage evaluation process and comparison with photon based treatment.

### **6.5.3**     Dosimetry

**6.5.3.1**     Static gantry Intensity Modulated Radiotherapy (IMRT) beam arrangements will be designed with a minimum of 5 gantry angles.

**6.5.3.2**     The use of non-coplanar beams is encouraged for photon treatments.

**6.5.3.3**     For proton planning two opposed lateral fields are required.

**6.5.3.4**     For all cases, the prescription isodose line must encompass a minimum of 95% of the PTV. For IMRT and proton treatments, the maximum dose within the PTV is 7% above the prescribed dose for a point that is 0.03 cc in size. For cyberknife treated patients the max dose allowed within the PTV is 20% above the prescribed dose for a point that is 0.03cc in size. Every effort should be made to keep the max dose within the PTV as close to the max dose for IMRT and protons treatments.

**6.5.3.5**     The prescription doses of the assigned arm of the study stated in Section 6.5.3.4 must not occur outside of the PTV. Any hotspots should be manipulated to avoid the prostate-rectal and prostate-bladder interfaces as defined by the CTV.

## **6.6**     Critical Structures (7/24/13)

### **6.6.1**     Critical Organ Dose-Volume Limits

**6.6.1.1**     **The normal tissue volume to be contoured will include bladder, rectum, bilateral femora (to the level of ischial tuberosity), seminal vesicles, penile bulb, skin, and urethra.** For patients where the maximum point dose to a point that is 0.03 cc exceeds 38.78 Gy (5 fraction arm) or exceeds 55.21Gy (12 fraction arm), visualization of the urethra is required.

**6.6.1.2**     The normal tissues will be contoured and considered as solid organs rather than contouring the bladder and rectal walls.

**6.6.1.3**     The bladder should be contoured from its base to the dome.

**6.6.1.4**     The rectum should be contoured 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.

**6.6.1.5**     The tissue within the skin and outside all other critical normal structures and PTVs are designated as unspecified tissue.

**6.6.1.6**     The following tables list maximum dose limits to a point or volume within several critical organs. These are absolute limits, and treatment delivery that does not abide by these limits will constitute a variation acceptable or deviation unacceptable protocol violation. The dose is listed as total over 5 fractions for Arm 1 and 12 fractions for Arm 2.

## 5 Fraction Arm

		Dosimetry Parameters for 5 fraction arm and with all delivery devices except CyberKnife **	Dosimetry Parameters for 5 fraction arm and treatment with CyberKnife
Organ	Volume	Dose (Gy)	Dose (Gy)
Prostate (PTV)	Maximum point dose (0.03cc)	$\leq 38.78$ Gy 107% of prescription dose *	$<43.5$ Gy 120% of prescription dose *
	Minimum dose received by 95% of PTV	$\geq 36.25$ Gy 100% of prescription dose	Same
	Minimum dose received by PTV	$\geq 34.4$ Gy 95% of prescription dose	Same
Rectum	Maximum point dose (0.03cc)	$\leq 38.06$ Gy 105% of the prescription dose	Same
	Less than 3 cc	$< 34.4$ Gy 95% of prescription dose	Same
	90% rectum	$\leq 32.625$ Gy 90% of prescription dose	Same
	80% rectum	$\leq 29$ Gy 80% of prescription dose	Same
	50% rectum	$\leq 18.125$ Gy 50% of prescription dose	Same
Bladder	Maximum point dose (0.03cc)	$\leq 38.06$ Gy 105% of prescription dose	Same
	90% Bladder	$\leq 32.625$ Gy 90% of prescription dose	Same
	50% Bladder	$\leq 18.125$ Gy 50% of prescription dose	Same
Penile bulb (recommended)	Maximum point dose	No more than 100% of prescription dose	Same
	Less than 3 cc	20 Gy 54% of prescription dose	Same
Femoral heads	Less than 10 cc cumulative (both sides)	20 Gy 54% of prescription dose	Same
Skin (recommended)	Maximum point dose	30 Gy 81% of prescription dose	Same
Urethra dose		$\leq 38.78$ Gy * 107% of prescription dose	Same

\*Visualization of the urethra would be required to confirm urethral dose is  $\leq 38.78$  Gy – 107% of prescription dose where the max point dose (0.03cc) within the PTV exceeds 38.78 Gy – 107% of prescription dose

\*\* For protons these dose constraints need to be interpreted as Gy (RBE). See Section 6.1.4.

## 12 Fraction Arm

		Dosimetry Parameters for 12 fraction arm and with all delivery devices except CyberKnife **	Dosimetry Parameters for 12 fraction arm and treatment with CyberKnife
Organ	Volume	Dose (Gy)	Dose (Gy)
Prostate (PTV)	Maximum point dose (0.03cc)	≤ 55.21 Gy 107% of prescription dose *	≤ 61.92 Gy 120% of prescription dose *
	Minimum dose received by 95% of PTV	≥ 51.6 Gy 100% of prescription dose	Same
	Minimum dose received by PTV	≥ 49.05 Gy 95% of prescription dose	Same
Rectum	Maximum point dose (0.03cc)	≤ 54.18 Gy 105% of the prescription dose	Same
	Less than 3 cc	≤ 49.05 Gy 95% of prescription dose	Same
	90% rectum	≤ 46.44 Gy 90% of prescription dose	Same
	80% rectum	≤ 41.28 Gy 80% of prescription dose	Same
	50% rectum	≤ 25.8 Gy 50% of prescription dose	Same
Bladder	Maximum point dose (0.03cc)	≤ 54.18 Gy 105% of prescription dose	Same
	90% Bladder	≤ 46.44 Gy 90% of prescription dose	Same
	50% Bladder	≤ 25.8 Gy 50% of prescription dose	Same
Penile bulb (Recommended)	Maximum point dose	No more than 100% of prescription dose	Same
	Less than 3 cc	27.86 Gy (4 Gy per fraction) 54% of prescription dose	Same
Femoral heads Skin (Recommended)	Less than 10 cc cumulative (both sides)	27.86 Gy (4 Gy per fraction) 54% of prescription dose	Same
	Maximum point dose	41.80 Gy (6 Gy per fraction) 81% of prescription dose	Same
Urethral dose		≤ 55.21 cGy 107% prescription dose	Same

\*Visualization of the urethra would be required to confirm urethral dose ≤ 55.21 Gy – 107% of prescription dose where the max point dose exceeds 55.21 Gy – 107% of prescription dose

\*\*For protons these dose constraints need to be interpreted as Gy (RBE). See Section 6.1.4.



- 6.6.1.7** For future analysis, DVH will be generated for rectal and bladder wall. The inner and outer rectal wall and the inner and outer bladder wall for this DVH will be contoured for a distance of 18mm beyond the most inferior and superior contoured prostate slice. If a rectal balloon is used, the anterior rectal wall should be extracted from the rectum wall contour with a 3mm margin concentric ring inside the rectum contour. The most inferior and most superior CT slices need to be fixed. The anterior rectal wall needs to be the same length as the rectum.

## **6.7 Image/Signal-Guidance for Target Localization**

- 6.7.1** After patient is set up on the treatment table, either the system of implanted electromagnetic transponders that do not use ionizing radiation or the 2D or 3D CT systems that use x-rays will be used to align the patient with the treatment machine geometry based on the treatment plan. The alignment result will be evaluated by the attending physician and attending physicist and be approved for treatment by attending physician. The alignment data will be recorded. A rectal balloon can be used to immobilize the prostate.
- 6.7.2** If a tracking system is used for localization of the prostate, it will be used during the treatment to track the target motion. A correction action will be performed if the target migrated more than 2 mm for more than 20 seconds in any of three orthogonal coordinates.
- 6.7.3** Cone-beam CT (CBCT) or CT on rails images may be taken prior to radiation delivery but after image-guidance with method described in either Section 6.7.2 or 6.7.3 and also taken immediately after the radiation treatment. For some special cases, CBCT or CT on rails images may be taken more frequently during the treatment per physician's clinical judgment.
- 6.7.4** The initial localizations and alignment is based on the center of mass of the transponders/fiducial markers. Significant rotations may be corrected at initial localization stage, and intra-fractional rotations will be ignored. Further adjustment during the treatment will be translational shift of the center of mass determined via IGRT technique (Section 6.3.2.3.1), using remote couch motion unless an institution has the ability to correct for rotations.
- 6.7.5** In view of intrafraction motion and to ensure the target coverage during treatment, periodic target localization will be employed every 7 minutes (except where tracking is utilized) from initial beam-on. The physicist will be on-site for image guidance and treatment.
- 6.7.6** For any image-guidance procedure, comparison with reference images or baseline data should be performed and reviewed and approved by both physician and physicist on site.
- 6.7.6.1** The comparison can be done both manually and automatically. For any image-guidance method, if any deviation is larger than 2 mm, correction should be performed.
- 6.7.6.2** All image/signal-guidance data should be recorded and saved for post treatment review and analysis. In some cases, replanning (either offline or online) based on anatomy of the day may be performed. Such request will be made by the attending physician.

## **6.8 Documentation Requirements**

- 6.8.1** RTOG Headquarters QA will facilitate the rapid review of the CTV, PTV, and designated organs at risk (critical structures), dosimetry and DVHs on, as a minimum, the first five cases submitted by each institution. After an institution has demonstrated compliance with the protocol, future cases will receive ongoing remote review.
- 6.8.2** The institution will archive treatment prescription and verification images for later review by the study chair if requested. For IMRT, at least one port film from each orthogonal film along with the digital reconstructed radiographs (DRRs) from the treatment planning program shall be acquired and kept for evaluation. Note: Images are required to be taken but not submitted.
- 6.8.3** RTOG Headquarters QA will display isodose distributions for the axial and coronal planes (or multiple axial planes as outlined in QA Guidelines) through the planning target volume to verify correct digital submission and conversion.
- 6.8.4** RTOG Headquarters QA will compare the submitted DVHs for the PTV, designated critical structures, and unspecified tissues for PI review. All DVHs will be recalculated by RTOG Headquarters staff.

## **6.9 Compliance Criteria (10/22/12)**

- 6.9.1** All linear accelerator based treatment techniques (except Cyberknife) and Proton Techniques **Cases which meet PTV criteria as stated in Section 6.6.1.6 will be scored as per protocol.** The minimum allowable dose within the PTV is >95% of the prescribed dose to a volume that is at least 0.03cc. Cases in which this small volume of at least 0.03cc receives a minimum dose

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

#### 6.9.2 Cyberknife

**Cases which meet criteria as stated in Section 6.6.1.6 will be scored as per protocol.** The minimum allowable dose within the PTV is >95% of the prescribed dose to a volume that is at least 0.03cc. Cases in which this small volume of at least 0.03cc receives a minimum dose that is <95% but >93% or a maximum dose >120% and ≤130 % of the prescribed dose will be scored as a variation acceptable. Cases in which this small volume receives less than 93% or the maximum dose exceeds 130% will be scored deviation unacceptable.

6.9.3 Acceptable dose heterogeneity will be as follows: **This maximum dose volume of the PTV must not be shared by a normal critical structure (Section 6.6.1.6).** The urethra dose should not exceed 107% of the prescription dose. In addition, the dose to the prostate rectal interface and prostate bladder interface should not exceed the dose constraint parameters highlighted in Section 6.6.1.6. The treating physician must carefully consider the tolerance dose/volume to each critical normal structure and unspecified tissue.

### 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. The first five cases enrolled from any institution will be submitted to undergo a rapid review by the study co-chair(s) prior to the start of RT to ensure protocol compliance with respect to target coverage, heterogeneity, and normal critical structure dose constraints. Once an institution has demonstrated protocol compliance, future cases will be selected randomly for review. These reviews will be ongoing throughout the study accrual period. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at ITC, whichever occurs first. The rapid review will occur and be noted for the first five cases submitted by each institution regardless of treatment (IMRT, cyberknife or protons). The cases will be reviewed by the study chair/physicists/co-chair. The proton cases will be reviewed by Drs. Efstathiou and Kudchadker. (See Section 12.2 for data submission.)

### 6.11 Radiation Therapy Adverse Events (7/24/13)

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

- Small bowel or rectal irritation manifesting as abdominal cramping, diarrhea, rectal urgency, proctitis, or hematochezia;
- Bladder complications including urinary frequency/urgency, dysuria, hematuria, urinary tract infection, and incontinence;
- Radiation dermatitis.

6.11.2 Clinical discretion may be exercised to treat side effects from radiation therapy as described in Section 9.1. Examples of typical medications used in the management of rectal side effects, such as diarrhea, include diphenoxylate or loperamide. Bladder or rectal spasms are usually treated with anticholinergic agents or tolterodine. Bladder irritation may be managed with phenazopyridine. Erectile dysfunction is often treated with medical management or mechanical devices.

#### 6.11.3 Adverse Events (AEs) and Serious Adverse Events (SAEs) Reporting Requirements

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 for AdEERS reporting of adverse events (AEs). The CTCAE version 4 is identified and located on the CTEP web site at:

[http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). All appropriate treatment areas should have access to a copy of the CTCAE version 4.

Adverse events (AEs) that meet expedited reporting criteria defined in the table(s) below will be reported via the AdEERS (Adverse Event Expedited Reporting System) application accessed via either the CTEP web site ([https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers\\_main\\$.startup](https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup)) or the RTOG web site (<http://www.rtog.org/ResearchAssociates/AdverseEventReporting.aspx>).

**Definition of an AE:** Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. February 29, 2012; <http://ctep.cancer.gov/reporting/adeers.html>]

Routine adverse event reporting guidelines are on the RTOG website (<http://www.rtog.org/ResearchAssociates/AdverseEventReporting.aspx>).

**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 experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect;
- Important medical events that do not result in death, are not life threatening, or do not 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, including a male patient's impregnation of his partner, occurring on study must be reported via AdEERS as a medically significant event.

Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table below will be reported via AdEERS. SAEs that require 24 hour AdEERS notification are defined in the expedited reporting table below. **Contact the AdEERS Help Desk if assistance is required.**

### **AdEERS REPORTING REQUIREMENTS**

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via AdEERS, the Adverse Event Expedited Reporting System, accessed via the CTEP web site, [https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers\\_main\\$.startup](https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup).

Submitting a report via AdEERS serves as notification to RTOG and satisfies RTOG requirements for expedited adverse event reporting.

AdEERS provides a radiation therapy (RT)-only pathway for events experienced involving RT only. These events must be reported via the AdEERS RT-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the RTOG Operations Office by phone, (1-800-227-5463, ext.4189)). An electronic report must be submitted immediately upon re-establishment of the Internet connection.

- AdEERS-24 Hour Notification requires that an AdEERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each AdEERS 24-hour notification must be followed by an AdEERS 5 Calendar Day Report. Serious adverse events that require 24 hour AdEERS notification are defined in the expedited reporting table below.
- Supporting source document is not mandatory. However, if the AdEERS report indicates in the *Additional Information* section that source documentation will be provided, then it is expected. If supporting source documentation accompanies an AdEERS report, include the protocol number, patient ID number, and AdEERS ticket number on each page, and fax supporting documentation the RTOG dedicated SAE FAX, 215-717-0990.

- A serious adverse event that meets expedited reporting criteria outlined in the following table but is assessed by the AdEERS System as “expedited reporting NOT required” must still be reported to fulfill RTOG safety reporting obligations. Sites must bypass the “NOT Required” assessment; the AdEERS System allows submission of all reports regardless of the results of the assessment.

**CRITERIA FOR AdEERS REPORTING REQUIREMENTS FOR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS THAT OCCUR WITHIN 30 DAYS OF THE DATE OF THE LAST PROTOCOL TREATMENT**

	<b>3</b>		<b>3</b>		<b>4 &amp; 5</b>	<b>4 &amp; 5</b>
	<b>Unexpected</b>		<b>Expected</b>		<b>Unexpected</b>	<b>Expected</b>
	<b>With Hospitalization</b>	<b>Without Hospitalization</b>	<b>With Hospitalization</b>	<b>Without Hospitalization</b>		
<b>Unrelated Unlikely</b>	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
<b>Possible Probable Definite</b>	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24 Hour: 5 Calendar Days	10 Calendar Days

**CRITERIA FOR AdEERS REPORTING REQUIREMENTS FOR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS THAT OCCUR > 30 DAYS AFTER THE DATE OF THE LAST PROTOCOL TREATMENT**

	<b>3</b>		<b>3</b>		<b>4 &amp; 5</b>	<b>4 &amp; 5</b>
	<b>Unexpected</b>		<b>Expected</b>		<b>Unexpected</b>	<b>Expected</b>
	<b>With Hospitalization</b>	<b>Without Hospitalization</b>	<b>With Hospitalization</b>	<b>Without Hospitalization</b>		
<b>Unrelated Unlikely</b>	Not required	Not required	Not required	Not Required	Not required	Not required
<b>Possible Probable Definite</b>	10 Calendar Days	Not required	Not required	Not Required	24 Hour: 5 Calendar Days	10 Calendar Days

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

**6.11.4 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)**

AML or MDS that is diagnosed as a secondary malignancy 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.

*Secondary Malignancy*

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via AdEERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

#### *Second Malignancy*

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

### **7.0 DRUG THERAPY**

Not applicable to this study

### **8.0 SURGERY**

Not applicable to this study

### **9.0 OTHER THERAPY**

#### **9.1 Permitted Supportive Therapy**

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

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

#### **9.2 Non-permitted Supportive Therapy**

Not applicable to this study

### **10.0 TISSUE/SPECIMEN SUBMISSION**

For patients who have consented to participate in the tissue/blood component of the study (See Appendix I). **Note: Patients must be offered the opportunity to participate in the correlative components of this study, such as tissue/specimen submission.** If the patient consents to participate in the tissue/specimen component of the study, the site is required to submit the patient's specimens as specified in Section 10.0 of the protocol. Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

#### **10.1 Tissue/Specimen Submission**

The RTOG Biospecimen Resource at the University of California San Francisco acquires and maintains high quality specimens from RTOG trials. Tissue from each block is preserved through careful block storage and processing. The RTOG encourages participants in protocol studies to consent to the banking of their specimens. The RTOG Biospecimen Resource provides 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 (plasma/lymphocytes), and urine will be submitted to the RTOG Biospecimen Resource (strongly recommended) for the purpose of banking and for translational research. If the patient consents, blood and urine will be collected at baseline and at 3 months post-treatment.

**10.2 Specimen Collection for Tissue Banking and Translational Research (7/24/13)**

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 (slide can be a duplicate cut stained H&E; it does not have to be the diagnostic slide)
- 10.2.2** A corresponding paraffin-embedded tissue block of the tumor (the block must match the H&E being submitted) or 10-15 five micron unstained sections cut onto positively charged slides of tumor tissue, labeled with the surgical pathology number. Block or slides must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.
- The submitted material must be from malignant tumor, not necrotic or fibrotic tissue. If the submitted material is reviewed and is not tumor, the site may be assessed a protocol violation.
- 10.2.3** A Pathology Report documenting that the submitted block or slides contains tumor. The report must include the RTOG protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.
- 10.2.4** A Specimen Transmittal Form clearly stating that tissue is being submitted for the RTOG Biospecimen Resource; if for translational research, this should be stated on the form. The form must include the RTOG protocol number and patient's case number.
- 10.2.5 Plasma and Whole Blood Collection:** For detailed, processing and shipping see Appendix V. The following materials must be provided to the RTOG Biospecimen Resource: A Specimen Transmittal Form documenting the date of collection of the biospecimen; the time point of study, the RTOG protocol number, the patient's case number, and method of storage, for example, stored at -80° C, must be included.
- 10.2.6 Storage Conditions**  
Store frozen biospecimens 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**

<b>Specimens for Tissue Banking/Translational Research</b>			
<b>Specimens taken from patient:</b>	<b>Collected when:</b>	<b>Submitted as:</b>	<b>Shipped:</b>
Representative H&E stained slides of the primary tumor	Pre-treatment	H&E stained slide Pre-treatment	Slide shipped ambient
A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or 10-15 unstained slides	Pre-treatment	Paraffin-embedded tissue block or 10-15 unstained slides	Block or slides shipped ambient
PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/lavender top) and centrifuge	Pre-treatment and at 3 months post-treatment	Frozen plasma samples containing 0.5 mL per aliquot in 1 mL cryovials (up to ten)	Plasma sent frozen on dry ice via overnight carrier
DNA: 5-10 mL of anticoagulated whole blood	Pre-treatment ( <b>Note:</b> if site missed this collection time point they may collect whole	Frozen whole blood samples containing 1 ml	Whole blood sent frozen on dry ice via overnight

in EDTA tube #2 (purple/lavender top) and mix	blood at any time point or follow-up visit) and at 3 months post-treatment	per aliquot in 1 ml cryovials (up to five)	carrier
10-20 mL clean-catch urine	Pre-treatment and at 3 months post-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**  
**2340 Sutter Street, Room S341**  
**San Francisco, CA 94143-1800**

**Courier Address (FedEx, UPS, etc.): For Frozen Specimens**  
**RTOG Biospecimen Resource**  
**University of California San Francisco**  
**2340 Sutter Street, Room S341**  
**San Francisco, CA 94115**

**Questions: 415-476-RTOG (7864)/FAX 415-476-5271; [RTOG@ucsf.edu](mailto: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 study assessments and time frames. **Note:** Details or exceptions to the study parameters are indicated in Appendix II with an asterisk (\*) and are listed in Sections 11.2 to 11.4 below.

## **11.2 Pre-Treatment Evaluation**

- 11.2.1** PSA should not be obtained for at least 10 days after prostate biopsy.
- 11.2.2** Completion of the EPIC is mandatory for all patients.
- 11.2.3** Completion of the Utilization of Sexual Medications/Devices and the EQ-5D are for patients who consent to the quality of life component of the study. **Note:** Patients must be offered the opportunity to participate in the correlative components of the study, such as quality of life assessment involving Utilization of Sexual Medication/Devices and the EQ-5D. If the patient consents to participate, sites are required to administer the Utilization of Sexual Medication/Devices and the EQ-5D prior to the start of protocol treatment.

## **11.3 Evaluation During Treatment**

- 11.3.1** Patients will be seen and evaluated at least weekly during radiation therapy with documentation of tolerance, including acute reactions.
- 11.3.2** Delay in treatment is discouraged unless the patient's medical condition or side-effects of treatment merit a delay. Delay of treatment will be at the discretion of the treating radiation oncologist.

## **11.4 Evaluation Following Treatment**

- 11.4.1** After the second year (24 months) following radiation, follow-up will continue every 6 months for years 3, 4, and 5; then annually thereafter.
- 11.4.2** Repeat EPIC (mandatory) and Utilization of Sexual Medications/Devices and EQ-5D (for patients who consent to this component of the study) assessments at the year 2 and year 5 visit.
- 11.4.3** A needle biopsy is encouraged: from the site of original tumor within the prostate and/or other site of original tumor identified by the transrectal ultrasound, as indicated for rising PSA or clinical failure (see Sections 11.6 and 11.7).
- 11.4.4** A bone scan will be performed as clinically indicated, e.g., if the patient develops a PSA recurrence with a rapid doubling time (< 6 months) or if the patient develops symptoms suggesting the presence of metastatic disease.
- 11.4.5** When documentation of disease progression is noted within 5 years, follow up will be as per protocol. When the disease progression occurs after 5 years, follow up will be at the discretion of the treating physician.

## **11.5 Criteria for Biochemical Recurrence**

- 11.5.1** Biochemical (PSA) recurrence is defined according to the proposed new Radiation Therapy Oncology Group/American Society for Therapeutic Radiology and Oncology (RTOG-ASTRO) criteria also known as the RTOG Phoenix definition: an increase of the PSA level at least 2 ng/mL greater than the minimum level reached after therapy (lowest PSA+ 2 criterion) (H. Sandler, personal communication, December 2005). All PSA levels done during a follow-up interval will be recorded on the data forms.

## **11.7 Criteria for Local Recurrence**

- 11.7.1** Clinical criteria for local recurrence are progression (increase in palpable abnormality) at any time, failure of regression of the palpable tumor by 2 years, and redevelopment of a palpable abnormality after complete disappearance of previous abnormalities. Needle biopsy is recommended. The presence of palpable disease must be recorded on the data collection forms for initial and follow-up evaluations of the patient.
- 11.7.2** Histologic criteria for local recurrence are presence of prostatic carcinoma upon biopsy and positive biopsy of the palpably normal prostate more than 2 years after the start of treatment.

## **11.8 Criteria for Nonlocal Recurrence**

- 11.8.1** Distant metastasis will be documented if clinical or bone scan evidence is demonstrated. Ultrasound evaluation of the prostate with needle biopsy as indicated by the findings is recommended at the time distant metastasis is reported.
- 11.8.2** Regional metastasis will be documented if there is radiographic evidence (CT or MRI) of lymphadenopathy and histologic confirmation.



## **11.9 Other Response Parameters**

### **11.9.1 Disease-Free Survival**

Disease-free survival will be measured from the date of randomization to the date of documentation of recurrence or until the date of death. This endpoint includes all measures of disease including physical exam, PSA, bone scans, CT/MRI, and biopsies.

### **11.9.2 Time to Local Progression**

The time to progression will be measured from the date of randomization to the date of documented local progression. Patients who have a normal exam and no evidence of having a PSA recurrence will be considered controlled locally. Patients with a residual abnormality or a PSA failure shall undergo biopsy to distinguish between local and distant failures. If their exam is normal or if they are post orchiectomy, they will be censored at the last point in time they were considered locally controlled and considered "not evaluable" for further assessment of local control.

### **11.9.3 Time to Distant and/or Regional Failure**

The time to distant or regional failure will be measured from the date of randomization to the date of documented regional nodal recurrence or distant disease relapse. Patients with evidence of biochemical failure, but a negative prostate biopsy, will be considered as distant or regional failure only.

### **11.9.4 Disease-Specific Survival**

Disease-specific survival duration will be measured from the date of randomization to the date of death due to prostate cancer. Causes of death may require review by the study chair or their designee. Death due to prostate cancer will be defined as:

#### **11.9.4.1 Primary cause of death certified as due to prostate cancer**

#### **11.9.4.2 Death in association with any of the following conditions:**

- Further clinical tumor progression occurring after initiation of "salvage" anti-tumor (e.g., (androgen suppression) therapy
- A rise (that exceeds 1.0 ng/mL) in the serum PSA level on at least two consecutive occasions that occurs during or after "salvage" androgen suppression therapy
- Disease progression in the absence of any anti-tumor therapy

#### **11.9.4.3 Death from a complication of therapy, irrespective of disease status.**

### **11.9.5 Freedom from Biochemical (PSA) Recurrence (FFBR)**

The time to PSA failure will be measured from the date of randomization to the date of a rise by 2 ng/mL or more above the nadir PSA. Nadir PSA is defined as the lowest PSA value after randomization and before the call date PSA. That is, the time of failure will be the date of the first PSA that is 2 ng/mL or more above the lowest prior post-randomization PSA value.

### **11.9.6 Overall Survival**

Survival duration will be measured from the date of randomization to the date of death from any cause. A post-mortem examination will be performed whenever possible and a copy of the final post-mortem report will be sent to RTOG Headquarters.

## **11.10 Primary Outcome Measure**

### **Prostate cancer-specific HRQOL as measured by the Expanded Prostate Index Composite (EPIC)**

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  $r \geq 0.80$  and Cronbach's  $\alpha \geq 0.82$ ) 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). 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). EPIC is a robust prostate cancer HRQOL instrument that measures a broad spectrum of symptoms; however, to decrease patient burden we will only use the domains most pertinent to this study: urinary, bowel, sexual, and hormonal. The domains were validated separately, and since each domain will be used intact, there is no threat to validity. This reduces patient burden

from 50 to 25 items. Dutch and Japanese translations of the EPIC are available, and a Spanish translation is planned but not yet available.

#### **11.11 Health Related Quality of Life (HRQOL)**

**Note:** Patients must be offered the opportunity to participate in the correlative HRQOL components of the study specified below (Utilization of Sexual Medications/Devices and the EQ-5D). If the patient consents to participate in the QOL component of the study, sites are required to administer the Utilization of Sexual Medications/Devices and the EQ-5D as specified in the Study Parameter Table in Appendix II

**11.11.1** The Utilization of Sexual Medications/Devices, developed as a companion questionnaire to the EPIC (Miller 2006), [Personal communication Dr. Martin Sanda 2/25/05] will be administered to assess utilization of medications and devices for erectile dysfunction and effectiveness of such interventions. The patient-completed Utilization of Sexual Medications/Devices will be collected to provide a context for interpreting the sexual domain score of the EPIC questionnaire.

**11.11.2** Utility as measured by the EQ-5D: The EQ-5D is a method for obtaining valuations (utilities) of HRQOL to be used as an adjustment to survival and in the cost-utility analysis. The EQ-5D instrument is intended to complement other forms of HRQOL measures, and it has been purposefully developed to generate a generic cardinal index of health, thus giving it considerable potential for future use in economic evaluation. The findings from the disease-specific QOL instruments and treatment-related side effect QOL instruments described above will help inform individual decision making. The role of the EQ-5D is to measure HRQOL at a macro level, in the same metric as it has been measured across numerous diseases, including cancer. This instrument gives us the ability to compare across and within diseases the “big picture” of what the experts who developed the EQ-5D considered the primary health states of interest to humans: mobility, self care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D will be utilized to assess an exploratory aim to evaluate the utility of the treatment arms.

The EQ-5D is a two-part self-assessment 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 including: 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 second part is a visual analogue scale (VAS) valuing current health state, measured on a 20-cm 10-point interval scale. Worst imaginable health state is scored as 0 at the bottom of the scale, and best imaginable health state is scored as 100 at the top. Both the 5-item index score and the VAS score are transformed into a utility score between 0 “Worst health state” and 1 “Best health state.” Either the index score or the VAS score can be used in the quality adjusted survival analysis depending on the health state(s) of interest (Wu 2002). For this study we will plan to report both the multidimensional and the VAS utilities for comparative purposes between standardized HRQOL and current health state. The EQ-5D has now been translated into most major languages, with the EuroQol Group closely monitoring the translation process.

#### **11.12 Optional Online Completion of PRO Assessments (7/24/13)**

**11.12.1** Patients who consent to participate in the PRO data completion have the option of completing PRO forms online from any location, including home, via VisionTree Optimal Care (VTOC). Patients without e-mail or Internet access can participate in the PRO component of the study by completing hardcopy (paper) forms. Indeed, at any time, any patient may choose to fill out their PRO form using the hardcopy form. The PRO forms completed via VTOC are identical to the hardcopy forms; this technology does not add to or change the PRO assessments in this study.

**11.12.2** If the patient wishes to complete PRO assessments online, the patient must have an e-mail address that they consent to use for this purpose. Patients’ e-mail addresses are necessary so that e-mail reminders may be sent to them to remind them to fill out PRO forms that are due. The patient’s e-mail address also will be used for password-protected access to VisionTree Optimal Care (VTOC). Patients who are interested in participating but do not yet have an e-mail address can obtain one for free from a number of sources (e.g., Yahoo!, Hotmail, or AOL).

**11.12.3** VTOC will send patients e-mail reminders to complete PRO forms. The first reminder will be sent at the beginning of the window for completion of the form, with a second reminder sent halfway through the window, if the form has not yet been completed. A maximum of 3 reminders will be sent for each of the 3 PRO assessment time points. After the patient has completed all forms, a dialogue box will appear thanking the patient for completing the PRO form(s), and the patient will no longer receive reminders for that time point.

**11.12.4** Site Research Associates (RAs) will receive training in the use of VTOC via RTOG webinars and educational sessions. The RA or study administrator will be informed via the VTOC “At a Glance” form management system when PRO forms have been completed or when the window for a particular form has closed. If the site RA receives a notice that forms have not been completed, she or he will contact the patient to remind the patient to fill out the PRO form or inquire why the forms have not been completed. The RA will complete the cover page for each form that was not completed (either via VTOC or in hardcopy) and will submit the cover page to RTOG Headquarters (see Section 12.1). All pretreatment QOL assessments (EPIC, EQ-5D, and Utilization of Sexual Medications/Devices) are to be completed at the site regardless of the patient’s consent to use VTOC. Patients who consent to use VTOC will complete all follow-up assessments using the VTOC software only.

### **11.13 Criteria for Discontinuation of Protocol Treatment**

**11.13.1** Patients who are experiencing excessive adverse events as deemed by their treating physician may be discontinued from the initiated protocol treatment. All attempts should be made to manage adverse events adequately so as to avoid this circumstance.

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

## **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** (10/22/12)

<b><u>Item</u></b>	<b><u>Due</u></b>
Demographic Form (A5)	<b>Within 2 weeks of registration</b>
Initial Evaluation Form (I1)	
Pathology Report (P1)	
EPIC (FA)	
EQ-5D (QF)	
Utilization of Sexual Medications/Devices (SA)	<b>Every 3 months for the first 2 years, every 6 months for years 3, 4, and 5, then annually after the completion of radiation therapy</b>
Follow-up Form (F1)	
EPIC (FA)	
EQ-5D (QF)	
Utilization of Sexual Medications/Devices (SA)	
PRO/QOL Forms Cover Sheets	<b>1, 2, and 5 years after the completion of radiation therapy</b>
	<b>Note:</b> PRO/QOL forms completed online will be stored on the VisionTree, Inc. web site and transferred to RTOG HQ.
	<b>Within 1 month of the PRO/QOL form being</b>

**due (Note:** Completed only if the patient did not complete a specific QOL form or if the patient completed a hardcopy of the form).

## **12.2 Summary of Dosimetry Digital Data Submission (Submit to ITC; see Section 12.2.1) [11/17/11]**

<b><u>Item</u></b>	<b><u>Due</u></b>
<b><u>Preliminary Dosimetry Information (DD)</u></b> Digital Data Submission – <u>Treatment Plan</u> submitted to ITC via SFTP account exported from treatment planning machine by Physicist Digital data submission includes the following: <ul style="list-style-type: none"><li>• CT data, critical normal structures, all GTV, CTV, and PTV contours</li><li>• Digital beam geometry for initial and boost beam sets</li><li>• Doses for sets of treated beams</li><li>• Digital DVH data for all required critical normal structures, and target volume for total dose plan</li></ul> Digital Data Submission Information Form ( <b>DDSI</b> ) – Submitted online (Form located on ATC web site, <a href="http://atc.wustl.edu/forms/DDSI/ddsi.html">http://atc.wustl.edu/forms/DDSI/ddsi.html</a> )  Hard copy isodose distributions for total dose plan  <b>NOTE: Sites must notify ITC via e-mail (<a href="mailto:itc@wustl.edu">itc@wustl.edu</a>) after digital data is submitted. The e-mail must include study and case numbers or, if the data is phantom, “dry run” or “benchmark”.</b>	<b>Within 1 week of start of RT</b>
<b><u>Final Dosimetry Information</u></b> Radiotherapy Form ( <b>T1</b> ) [copy to HQ and ITC] Daily Treatment Record ( <b>T5</b> ) [copy to HQ and ITC] Modified digital patient data as required through consultation with Image-Guided Therapy QA Center	<b>Within 1 week of RT end</b>
<b><u>IGRT Submission</u></b> IGRT data collection spreadsheet (documents set-up variances) [ <b>SG</b> ]	<b>Within 1 week of RT end</b>

### **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](mailto:itc@wustl.edu)

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

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

## **13.0 STATISTICAL CONSIDERATIONS**

### **13.1 Primary Endpoint**

Percentage of patients with greater than 5 point reduction in EPIC Bowel HRQOL measurement at 1 year compared to baseline and percentage of patients with greater than 2 point reduction in EPIC Urinary HRQOL measurement at 1 year compared to baseline for each arm

### **13.2 Secondary Endpoints**

- 13.2.2.1 Acute and late GI and GU toxicity
- 13.2.2.2 PSA failure
- 13.2.2.3 Disease free survival
- 13.2.2.4 EPIC sexual and hormonal QOL measurements
- 13.2.2.5 Identify genetic markers associated with normal tissue toxicities resulting from radiotherapy
- 13.2.2.6 Collect tumor tissue for biomarker studies
- 13.2.2.7 EPIC bowel and urinary HRQOL as continuous variables
- 13.2.2.8 EQ-5D measurements
- 13.2.2.9 Quality Adjusted Life Years using the EQ-5D

### **13.3. Patient Groups**

There are two separate and independent patient groups as defined by the Hypofractionation schedule: Arm 1 patients treated with 36.25 Gy (5 fractions of 7.25 Gy over two weeks), and Arm 2 patients treated with 51.6 Gy (12 daily fractions of 4.3 Gy over two and a half weeks).

### **13.4 Sample Size Derivation and Accrual (7/24/13)**

#### **13.4.1 Sample Size**

The primary goal of this phase II study is to determine if either hypofractionation regimen is promising enough for further investigation in a phase III study. The choice of regimen will be based on maintaining acceptable patient reported HRQOL from baseline. There will be two co-primary endpoints based on summary scores from the bowel and urinary domains of the EPIC questionnaire. Although HRQOL is collected at multiple time points, it has been decided that EPIC information collected at 1 year will be compared to baseline EPIC data to calculate the sample size and to test the primary hypothesis. In part, this is due to missing data issues with patient reported outcome data and it is more likely to have full HRQOL patient information earlier in the study (e.g., 6 months, 1 year) than later (e.g., 2 years on). The hypothesis for each arm is that the probability of the change in EPIC HRQOL scores (1-year minus baseline) is less than (or equal to) an acceptable limit. If it can be shown that either arm is tolerable in terms of patient-reported outcome (PRO) then that hypofractionated regimen will be considered for further use in a phase III study. Thus, for each arm, the hypotheses are:

$$H_0 : p \leq p_0 \text{ vs. } H_a : p > p_0$$

where  $p_0$  is the probability under the null hypothesis.

From the conventional arm of RTOG 0415, in an analysis of 108 patients (mean pretreatment score 94 with SE=9 and range 61-100), 38 patients (35%) had a change in EPIC bowel domain score (baseline to 1-year) that was worse than 5 points. For 110 patients (mean pretreatment score 88, SE=12, range 35-100), 43 (39%) had a change in EPIC urinary domain score that was worse than 2 points. Mean reduction in bowel and urinary scores have also been published in a historical series by Wei et al. (2002). The mean reduction in bowel and urinary scores observed in the RTOG 0415 analysis are in keeping with the series published by Wei. Standard radiotherapy in regimens such as used in the conventional arm of 0415 is well tolerated. Thus the HRQOL analysis from the 0415 study will be used in the sample size calculation. The percentage of patients with change in EPIC bowel domain score (baseline to 1-year) that was worse than 5 points and a change in EPIC urinary domain score that was worse than 2 points are felt to be clinically meaningful endpoints to assess for tolerability and safety. A rate for the worse-than-5 point change in bowel score of up to 35% of patients will be

considered acceptable, with a rate  $\geq 55\%$  specified as unacceptable. Similarly, a rate for the worse-than-2 point change in urinary score of up to 40% will be considered acceptable, with a rate  $\geq 60\%$  unacceptable. Using the normal approximation to the binomial distribution for  $p$ , the formula to calculate the sample size is given by:

$$n = \left[ \frac{z_{1-\alpha} \sqrt{p_0(1-p_0)} + z_{1-\beta} \sqrt{p_a(1-p_a)}}{(p_0 - p_a)} \right]^2$$

where  $p_0$  is as previously defined,  $p_a$  = the alternative probability,  $z_q = 100(q\text{th})$  percentile of the standard normal distribution. With the aforementioned design parameters, a sample size of 156 eligible patients (78 per arm) is required with 95% power and significance level 0.025 (one-sided test). The significance level 0.025 will be used for each endpoint in order to preserve an overall significance level of 0.05. Adjusting for 10% ineligibility and 25% for patient non-compliance at baseline and follow-up assessments, **the required sample size is 240 patients (120 per arm).**

#### 13.4.2 Accrual and Duration

Based on patient accrual in previous RTOG studies, the initial 6 months accrual is projected to be negligible while institutions are obtaining IRB approval. This protocol has a similar patient population to RTOG 0415 but is expected to be somewhat slower due to the credentialing procedures and lack of a standard arm. The accrual rate for that study was 25 patients per month, so 15 patients per month is the expected accrual rate for RTOG 0938. Based on this information, it is projected that the study will complete accrual in about 22 months from activation date, accounting for a 6 month start-up period of no accrual while sites obtain IRB approval and go through the credentialing process.

### 13.5 Analysis of the Primary Endpoint

The co-primary endpoints are: (1) the proportion of patients with change from baseline to the 1-year EPIC bowel domain score that exceeds 5 points; and (2) the proportion of patients change from baseline to 1-year EPIC urinary domain score that exceeds 2 points. Analysis will be done separately for each arm. The average score of each arm will be calculated, along with the standard error, based on the hypothesis

$$H_0 : p \leq p_0 \text{ vs. } H_a : p > p_0$$

The one-sample z-test for proportion with significance level of 0.025 (for each endpoint) will be used to test the hypothesis. The test is based on the following formula:

$$T.S. = \frac{\hat{p} - p_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}$$

For a given arm, if  $H_0$  is rejected for either EPIC domain, then it will be concluded that the regimen given on that arm is unacceptable in terms of PRO. However if it is not rejected for both domains, then that regimen will be considered acceptable for further use in a Phase III study. If both hypofractionated arms yield an acceptable result, then consideration may be given to using other factors, specifically, results of secondary endpoints to decide if one regimen is more acceptable than the other one.

In each arm, logistic regression will be performed, both an unadjusted and adjusted analysis. In the adjusted analysis, the variables in the regression will at least include the stratification variable, treatment modality, and, if appropriate, additional variables such as Gleason score, PSA, age and race can be included.

## 13.6 Analysis of the Secondary Endpoints

### 13.6.1 Other EPIC Domains

In addition to the bowel and urinary domains, the EPIC instrument consists of two other domains: sexual and hormonal. Information from RTOG 0415 (conventional arm) was also gathered for these domains. At baseline and 1-year, complete EPIC information was available on 103 and 104 patients for the sexual and hormonal domains, respectively. The following table summarizes the power for each domain based on the study sample size (78 eligible patients per arm) at the 0.025 significance level (one-sided test) for endpoint change in EPIC score from baseline to 1-year:

Table 1. Power Calculation for the 2 EPIC subscales sexual and hormonal

EPIC subscale	Change Score (baseline to 1-year) Cutoff	% of Patients with Change Score worse than cutoff	Alternative %	Power to detect 20% difference
Sexual	11 points	35%	55%	95%
Hormonal	3 points	38%	58%	95%

For each EPIC secondary endpoint and in each arm, a one-sample z-test will be carried out to test if an unacceptable percentage of patients have a 1-year domain score that is worse than baseline. From Table 1, both secondary domains have enough power, assuming at least 20% difference. If necessary, results from the sexual and hormonal domains can be used to supplement the bowel and urinary domain results to assess which hypofractionated arm may be more desirable. Also, for each domain, in each arm, unadjusted and adjusted logistic regression will be performed. In the adjusted analysis, variables will at least include treatment modality, and, if appropriate, will additionally include variables such as Gleason, PSA, age and race.

### 13.6.2 Acute and Late GI and GU Adverse Events (AEs)

Adverse events are evaluated by the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE). The treatment-related attribution includes definitely, probably or possibly related to treatment. An acute adverse event is defined as the first occurrence of worst severity of the adverse event  $\leq 30$  days after the completion of RT. For each arm, we will evaluate the acute radiation therapy-related adverse events. Specifically, we are interested in the percentage of acute GI and GU Grade 3+ adverse events that occur in each arm, which is considered to be similar to the high RT dose arm of RTOG 0126 in terms of RT dose. For this arm, a reported 1% of patients experienced Grade 3+ GI/GU acute toxicity, with no patient experiencing Grade 4 or 5 toxicities. If either hypofractionated arm has an acceptable percentage, then that arm will be deemed to have an acceptable adverse event profile. We will report the percentage for each arm as well as the one-sided 97.5% confidence interval. Note that the number of patients in the high dose arm of RTOG 0126 (a Phase III) trial is much greater than each arm of this Phase II study. For each arm, if the lower limit of the interval is  $>1\%$  then that arm will be further investigated for acceptability in terms of CTC toxicity

A late adverse event is defined as the first occurrence of worst severity of adverse event  $>30$  days after RT completion. Late Grade 3+ GU/GI toxicity information will be collected and reported also. Information related to the high-dose arm of RTOG 0126 is provided below in the following table:

Year	GU/GI grade 3+ Failure rate
0	0.00%
1	1.24%
2	4.60%
3	5.81%
4	6.75%
5	7.34%

Cumulative incidence will be used to estimate time to late adverse events. The cumulative incidence distribution will be monitored to observe if there is a deviation from the pattern of the one for 0126; confidence intervals will be computed at each time point.

#### **13.6.3** PSA Failure

Failure occurs when the PSA is first noted to be 2 ng/mL or more than the current nadir value ( $\text{PSA} > \text{current nadir} + 2$ ) post RT completion. PSA failure at 1, 2, and 5 years will be estimated for each hypofractionated arm by the cumulative incidence method (Gray 1988). Also, confidence intervals will be reported.

#### **13.6.4** Disease-Free Survival (DFS)

The disease-free survival duration will be measured from the date of randomization to the date of documentation of disease progression or until the date of death from any cause. DFS at 1, 2, and 5 years will be estimated for each hypofractionated arm by the Kaplan-Meier method (Kaplan 1958). Also, 95% confidence intervals will be reported.

#### **13.6.5** Analysis for Endpoints Related to HRQOL

We will use three instruments to measure HRQOL: the Expanded Prostate Cancer Index Composite (EPIC), the Utilization of Sexual Medications/Devices, and EQ-5D. Protocol eligible patients will be included in the HRQOL analysis only if they have provided baseline and at least one subsequent measurement. All HRQOL instruments (EPIC, the Utilization of Sexual Medications/Devices and EQ-5D) will be collected on all cases participating in the trial.

The EPIC, the Utilization of Sexual Medications/Devices, and EQ-5D will be collected at pretreatment (baseline) and at 1, 2, and 5 years after therapy starts. Patient self-assessment of symptoms will be performed using four primary EPIC scales: urinary, bowel, hormonal and sexual symptoms. The Utilization of Sexual Medications/Devices and EQ-5D are described in Section 11.11.

For all primary HRQOL analyses we will estimate the degree of change from baseline to 1-year. To address the non-ignorable missing data caused by censoring survival time, the data analysis will also be done with patients who have not died.

To minimize missing HRQOL data, we have included detailed instructions for collection of HRQOL and what to do if the patient misses a scheduled assessment, and RTOG provides individualized patient calendars available to Investigators and Research Associates 24/7 on the RTOG web site.

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 HRQOL 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 (Donaldson, 2005) 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 HRQOL outcome within strata based on missing data patterns



(Donaldson 2005; U.S. Department of Health and Human Services 2006). RTOG recognizes that all options are subject to bias and analysis with more than one method for consistency across methods is prudent.

The primary objective in HRQOL analysis is to estimate the change from baseline to 1-year. The response will be the change of measurement from baseline to 1-year. The one-sample t-test will be used to test the null hypothesis that response change is 0. Within each arm, to maintain the overall significance level for testing three HRQOL instruments, the Bonferroni-adjusted significance level is  $0.05/3=0.017$ . In addition to this, we will describe the distributions of HRQOL 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 trend of the EPIC and EQ5D in each arm.

To examine trade-offs between the survival time and HRQOL, we will combine them for each patient into one single measurement: QALY, which 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 Q-TWiST, the quality-adjusted time without symptoms and toxicity method.

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

where  $q_i$  is the quality (the utility coefficient) of health state  $i$ ,  $s_i$  is the duration spent in each health state, and  $k$  is the number of health states. We will use Glasziou's (1998) 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 state 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 a health state

Assumption A1 can be checked by plotting HRQOL over time according to treatment, and the t-test can be used to compare the mean HRQOL 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 HRQOL data directly.

#### **13.6.6** EPIC Bowel and Urinary as Continuous Variables

In the primary analysis, the bowel and urinary domains of the EPIC instrument are tested based on proportion of patients that exceed a certain cutoff change from baseline score. For this secondary endpoint, in each domain, the actual change score will be used as the statistic and a t-test will be used to evaluate if the change is different from 0. Confidence intervals also will be computed.

#### **13.6.7** Analysis of Rectal Balloon and Bladder Filling

In each arm, numbers permitting, an additional analysis will be conducted based on the variables rectal ballooning and bladder filling. The percent of patients with rectal balloon and without rectal balloon will be calculated, and then the percent of patients with and without a full bladder will be calculated. If applicable, analysis of endpoints will be examined within each rectal balloon and bladder filling subgroup, then compared (rectal balloon vs no rectal balloon, bladder fill vs bladder empty) to see if there is any difference in outcome. If necessary, the two-sample t-test will be used to compare between each subgroup the outcomes based on the primary and secondary QOL endpoints, i.e., the proportion of patients whose change score is worse than the cutoff point value assumed for that QOL endpoint. Also, if applicable and of interest, the endpoints acute and late toxicity, PSA failure, and DFS will be compared between subgroups.

#### **13.7** **Interim Reports to Monitor Study Progress (10/22/12)**

The RTOG Data Monitoring Committee (DMC) will monitor the trial for safety. Interim reports with descriptive statistics will be prepared twice a year until the initial paper reporting the treatment results has been accepted for publication. In general, the interim reports will contain information

about the patient accrual rate with a projected completion date for the accrual phase; data quality; compliance rate of treatment delivery with the distributions of important prognostic baseline variables; and the frequencies and severity of adverse events. The interim reports will not contain results from the treatment comparisons with respect to the primary or 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.

### **13.8 Reporting the Initial Treatment Results (10/22/12)**

The purpose of this study is to determine if either hypofractionation regimen is promising enough for further investigation in a phase III study by demonstrating that 1-year health-related quality of life (HRQOL) for at least one hypofractionated arm is not significantly lower than baseline as measured by the Bowel and Urinary domains of the EPIC instrument. The final analysis will occur after each patient has been potentially followed for at least 1 year from randomization. It will include tabulation of all cases entered and those excluded from the analyses with the reasons for such given; the distribution of the important prognostic baseline variables; and observed results with respect to the primary and secondary endpoints. Imputation for missing values will be incorporated as specified in the analysis plan. Also, where feasible, treatment comparisons with respect to all endpoints will be compared within each racial and ethnic category.

### **13.9 Gender and Minorities (7/24/13)**

#### **Projected Distribution of Gender and Minorities**

	<b>Gender</b>		
<b>Ethnic Category</b>	<b>Females</b>	<b>Males</b>	<b>Total</b>
Hispanic or Latino	N/A	7	7
Not Hispanic or Latino	N/A	233	233
<b>Ethnic Category: Total of all subjects</b>	N/A	240	<b>240</b>
	<b>Gender</b>		
<b>Racial Category</b>	<b>Females</b>	<b>Males</b>	<b>Total</b>
American Indian or Alaskan Native	N/A	0	0
Asian	N/A	1	1
Black or African American	N/A	36	36
Native Hawaiian or other Pacific Islander	N/A	1	1
White	N/A	202	202
<b>Racial Category: Total of all subjects</b>	N/A	240	<b>240</b>

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## **APPENDIX I**

### **RTOG 0938 Informed Consent Template for Cancer Treatment Trials (English Language)**

#### **A RANDOMIZED PHASE II TRIAL OF HYPOFRACTIONATED RADIOTHERAPY FOR FAVORABLE RISK PROSTATE CANCER**

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

You are being asked to take part in this study because you have prostate cancer and your doctor has recommended external beam radiation therapy.

#### **Why is this study being done?**

The purpose of this study is to compare two methods of delivering high dose radiation to the prostate to see if the effects of the treatments are similar. Both methods have been studied previously and are considered promising treatment approaches. Standard radiation therapy can involve daily treatment for several weeks, often over seven and a half or eight weeks (up to approximately 40 treatments). One of the standard treatment options for your stage and type of prostate cancer is external beam radiation therapy. More recent radiation therapy planning methods such as intensity modulated radiation therapy (IMRT) allow safer delivery of higher than standard daily doses of radiation.

IMRT enables us to give radiation treatment for prostate cancer in 5 or 12 radiation treatments. The 5 or 12 radiation treatment schedules give a higher dose of radiation per treatment over a shorter overall treatment period in comparison to standard radiation treatment. Special equipment is used to position the patient and guide focused x-ray beams toward the cancer and away from the bowel and bladder. Research so far suggests that the use of these new techniques can reduce the size of, or eventually eliminate, prostate tumors and the new techniques appear to be safe.

Currently we do not know if the 5 treatment schedule or the 12 treatment schedule gives similar results or if one works better than the other. We also do not know if the 5 or 12 radiation treatment schedules give similar results to standard radiation therapy, which is often given over the course of 39 to 41 treatments.

In this study we plan to assess the radiation side effects on bowel, bladder, and sexual function. Once this study is complete and if the side effects are found to be similar to standard radiation treatment, we plan to assess if the 5 or 12 treatment schedules control the cancer as well as the standard radiation treatment schedule.

There are a number of different approaches and timeframes used in giving these treatments for early stage prostate cancers. In this study, you will receive a total of 5 treatments twice a

week over two and half weeks (about 15 to 17 days) **OR** a total of 12 treatments five times a week over two and half weeks (about 16 to 18 days).

### **How many people will take part in the study?** (7/24/13)

About 240 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)
- A biopsy of your prostate to determine your Gleason score (a value that helps determine the stage of your prostate cancer).
- A blood test to determine your PSA (a value that helps determine the stage of your prostate cancer). About 2 teaspoons of blood will be drawn from a vein or, if you have one, a catheter. Your doctor also may check your testosterone level.
- You will be asked to complete one questionnaire: the Expanded Prostate Index Composite (EPIC). The EPIC assesses bowel, urinary, sexual, and hormone function and takes about 15 minutes to complete. Completion of the EPIC is mandatory for this study.
  - In the past, patients often have filled out quality of life questionnaires like EPIC on paper. The Radiation Therapy Oncology Group (RTOG) is working with a company, VisionTree Software, Inc., that has a web site where patients can fill out these questionnaires anywhere there is a computer with Internet access. This option is being offered as some patients may find it more convenient to fill out the forms electronically from any location, including home. When you log on to the web site, it will take you through the process of completing the questionnaires step by step. You will need an e-mail address that you agree to use for this purpose. The e-mail address is needed to identify you on the VisionTree web site and for e-mail reminders that will be sent to you when the questionnaires are due. Your e-mail address will only be used for the purpose of this study, not for mail or marketing purposes.
  - If you are interested in filling out quality of life questionnaires electronically but do not have an e-mail address, you may obtain one (quickly and for no charge at web sites such as Yahoo!, Hotmail, or AOL). You will only be sent e-mail reminders at the time that the questionnaires are due (a maximum of 3 e-mail reminders per time point).
  - Your access to the VisionTree web site is password protected and secure. You can use your e-mail address to retrieve your password if you forget it or lose your login card. You will receive a login card either by regular mail or e-mail, and it will include the information you need to log in to the VisionTree

web site the first time. You can choose to complete the questionnaires online or on paper. The choice is up to you.

***During the study ...***

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

**If you are in group 1 (often called "Arm 1"),** you will receive radiation therapy two days a week over two and a half weeks, for a total of 5 treatments.

**If you are in group 2 (often called "Arm 2"),** you will receive radiation therapy once daily, 5 days a week, Monday through Friday, for a total of 12 treatments over two and a half weeks.

After randomization, you will need the following tests and procedures. They are part of regular cancer care.

- History and physical exam, including an assessment of your ability to carry out activities of daily living (*Weekly during radiation treatment*)

You will need this assessment to see how the study treatment is affecting your body.

- Assessment of any side effects you may be experiencing from the treatment (*Weekly during radiation treatment*)

***When you are finished receiving radiation...***

You will need these tests and procedures every 3 months for the first 2 years following the start of radiation, every 6 months for years 3, 4, and 5, and then annually:

- History and physical exam, including a digital rectal exam (DRE) and an assessment of your ability to carry out activities of daily living
- A blood test to determine your PSA (a value that helps determine the stage of your prostate cancer).
- Assessment of any side effects you may be experiencing from the treatment

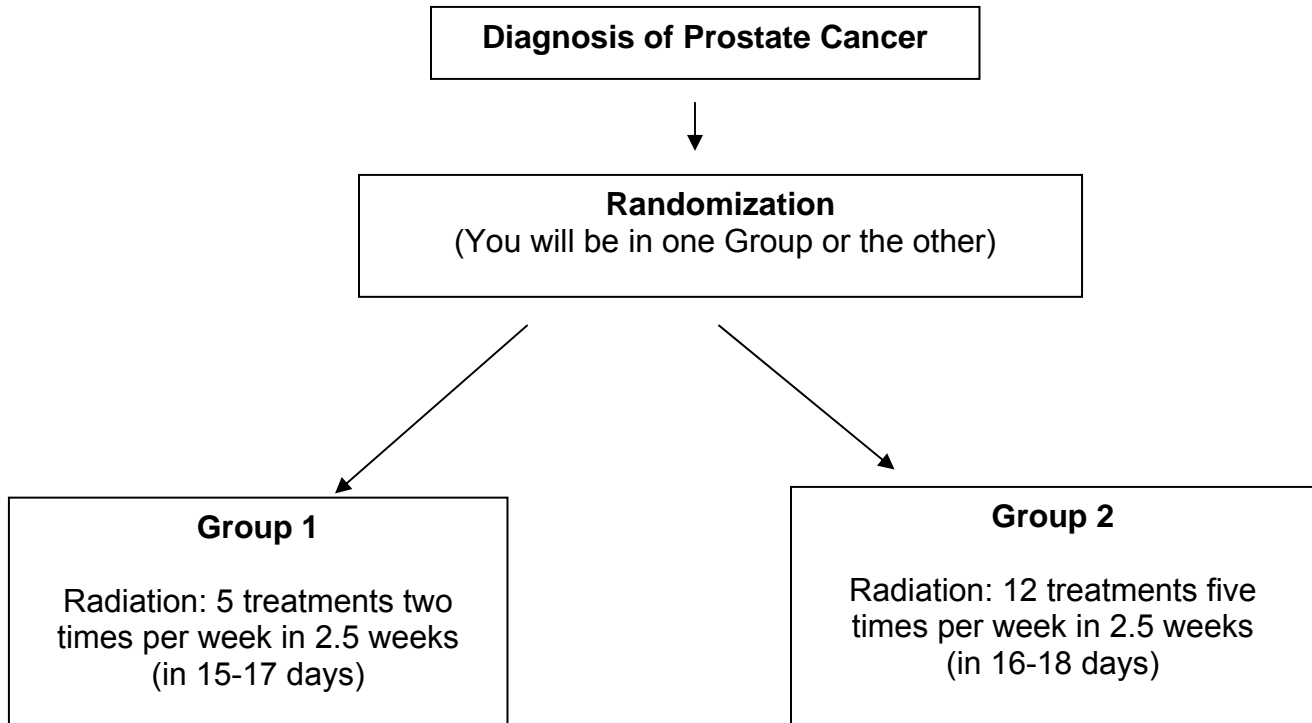
You will need these tests and procedures also:

- You will be asked to complete one questionnaire, the Expanded Prostate Index Composite (EPIC), at 12 and 24 months after radiation, and again at 5 years after radiation. The EPIC assesses bowel, urinary, sexual, and hormone function and takes about 15 minutes to complete. Completion of the EPIC is mandatory for this study.
- If your doctor suspects your cancer is growing after treatment (progression), s/he may request a needle biopsy of your prostate to check your response to treatment.



## 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 radiation treatments of either 5 treatments over two and a half weeks or 12 treatments over two and a half weeks. After you are finished receiving radiation, the study doctor will ask you to visit the office for follow-up exams every 3 months for the first 2 years following the start of radiation, then every 6 months for the years 3, 4, and 5. After that, the study doctors would like to keep track of your medical condition by seeing you for follow-up exams every year.

### 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 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. Your health care team may give you medicines to help lessen side effects. Many side effects are temporary (occur for a short period) and go away soon after you stop radiation treatment. In some cases, side effects can be serious, long lasting, or may never go away. Side effects that last a longer time or may never go away are often referred to as chronic. In addition, some of the side effects may be life threatening and, in rare instances, may cause death.

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 include those which are:**

#### **Likely**

- Tanning, redness, or darkening of skin in treatment area
- Rash, itching or peeling of skin
- Temporary hair loss in the treatment area
- Temporary fatigue, nausea or diarrhea
- Abdominal cramps
- Bladder irritation with a stinging sensation (the stinging sensation usually occurs while passing urine)
- Frequency or urgency of urination
- Rectal irritation with more frequent bowel movements
- Mild rectal bleeding that does not require treatment

#### **Less Likely**

- Urinary obstruction requiring the placement of a temporary urinary catheter
- Inability to achieve an erection (inability of the penis to become hard)
- Chronic bowel/bladder symptoms as described above under "Likely"

#### **Rare but serious**

- Injury to the bladder, urethra, bowel, or other tissues in the pelvis or abdomen. Rarely, ulcers may develop in the bladder, urethra, or bowel.
- Intestinal obstruction (this results in blockage of the bowel and may require surgery)
- Rectal bleeding that requires medication or surgery to stop the bleeding

**Reproductive risks:** You should not father a baby nor donate sperm while on this study or during the first 3 months after completion of therapy because the radiation can affect an unborn baby. It is important you understand that you and/or your partner need to use birth control while on this study. 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.

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

## **Are there benefits to taking part in the study?**

Taking part in this study may or may not make your health better. It is not known whether the higher daily doses of radiation that will be given in this study (5 treatments or 12 treatments) are equivalent. Both the 5 treatment schedule and the 12 treatment schedule of radiation delivers a higher dose of radiation to the prostate over two and a half weeks compared to the standard radiation treatment given in 39 or 41 treatments over seven and a half or eight weeks. In addition, it is not known whether either of these higher daily dose treatments (5 treatments or 12 treatments) is equivalent to the standard daily dose. We do know that the information from this study will help researchers learn more about these different doses as a treatment for prostate cancer. The main goal of this study is to obtain information on bowel, urinary, and sexual side effects of the study treatment to see if the side effects are similar to standard radiation treatments. This information could help future patients with prostate cancer.

## **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:
  - Standard radiation therapy over a seven and a half or eight week course five days a week (39-41 treatments)
  - External (three-dimensional or non–three-dimensional) radiation therapy
  - Internal radiation (seed implants or brachytherapy)
  - Three-dimensional radiation therapy or IMRT similar to the therapy described in this study
  - Surgery
  - Hormone therapy
- Taking part in another study
- Getting no treatment (with this choice, your tumor could continue to grow and your disease could spread)

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, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- VisionTree Software, Inc.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by law. This Web site will not include information that can identify you. At most, the Web site will include a summary of study results. You can search this Web site at any time.

*[Note to Informed Consent Authors: the above paragraph complies with the new FDA regulation found at 21 CFR 50.25(c) and must be included verbatim in all informed consent documents. The text in this paragraph cannot be revised.]*

*[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]*

## **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 Safety Monitoring Board will be meeting regularly to monitor safety and other data related to phase I, I/II, and II RTOG clinical trials. The Board 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).

**Please note: This section of the informed consent form is about additional research that is being done with people who are taking part in the main study. You may take part in this additional research if you want to. You can still be a part of the main study even if you say ‘no’ to 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 (10/22/12)**

We want to know your view of how your life has been affected by cancer and its treatment. This study looks at how treatment affects your quality of life, and how you are able to carry out your day-to-day activities. It also looks at the use of medications or devices that assist with maintaining your sexual health.

This information will help doctors better understand how patients feel during treatments, what effects the treatments are having, and what medications they may need to maintain a normal sex life. In the future, this information may help patients and doctors as they decide which treatments to choose based on what matters most to the patient.

You will be asked to complete two additional questionnaires (besides the EPIC questionnaire which is part of the main study) in the quality of life part of this study. The two questionnaires are the EQ-5D and the Utilization of Sexual Medications/Devices. The EQ-5D is a questionnaire used to measure your general health status. The EQ-5D has 5 questions and only takes a few minutes of your time to complete. The Utilization of Sexual Medications/Devices asks about your use of medications and devices for erectile dysfunction and how well the medicines or devices work. This information is very important in helping the study team better understand your responses related to sexual function on the main questionnaire, the EPIC. You will be asked to fill out the EQ-5D and the Utilization of Sexual Medications/Devices questionnaires at the following time points: immediately before you start radiation therapy; at 12 and 24 months following the start of your radiation treatment; and once more 5 years following the start of your radiation treatment. The EQ-5D and the Utilization of Sexual Medications/Devices take about 10 minutes for you to complete. All 3 questionnaires (the main

EPIC questionnaire, the EQ-5D, and the Utilization of Sexual Medications/Devices questionnaires) take about 25 minutes to fill out.

In the past, patients often have filled out quality of life questionnaires like EPIC on paper. The Radiation Therapy Oncology Group (RTOG) is working with a company, VisionTree Software, Inc., that has a web site where patients can fill out these questionnaires anywhere there is a computer with Internet access. This option is being offered as some patients may find it more convenient to fill out the forms electronically from any location, including home. When you log on to the web site, it will take you through the process of completing the questionnaires step by step. You will need an e-mail address that you agree to use for this purpose. The e-mail address is needed to identify you on the VisionTree web site and for e-mail reminders that will be sent to you when the questionnaires are due. Your e-mail address will only be used for the purpose of this study, not for mail or marketing purposes. If you are interested in filling out quality of life questionnaires electronically but do not have an e-mail address, you may obtain one (quickly and for no charge at web sites such as Yahoo!, Hotmail, or AOL). You will only be sent e-mail reminders at the time that the questionnaires are due (a maximum of 3 e-mail reminders per time point). Your access to the VisionTree web site is password protected and secure. You can use your e-mail address to retrieve your password if you forget it or lose your login card. You will receive a login card either by regular mail or e-mail, and it will include the information you need to log in to the VisionTree web site the first time. You can choose to complete the questionnaires online or on paper. The choice is up to you.

If any questions make you feel uncomfortable, you may skip those questions and not give an answer. You may change your mind about completing the questionnaires at any time and you may choose to discontinue answering the questionnaires altogether at any time.

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 to take part in this study, the only thing you will be asked to do is fill out the questionnaires noted above. 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 (EQ-5D and the Utilization of Sexual Medications/Devices).

YES

NO

I choose to use the VisionTree Software. I agree to fill out the Quality of Life Questionnaires (EQ-5D and the Utilization of Sexual Medications/Devices) electronically using the VisionTree web site.

YES

NO

## **Consent Form for Use of Tissue, Blood, and Urine Specimens for Research**

### **About Using Tissue, Blood, and Urine Specimens for Research**

You have had a biopsy (or surgery) to see if you have cancer. Your doctor has removed some of your 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](http://cdp.cancer.gov/humanSpecimens/ethical_collection/patient.htm).

In addition, you will have blood tests before you start treatment and at three months after the end of your treatment. We would like to keep about four teaspoons of blood for future research as well. If you agree, this blood will be kept and may be used in research to learn more about cancer and other diseases. One specific test will analyze whether your blood contains certain genes and if the side effects you had on radiation are related to these genes. We will then try to see if these genes can help us learn about why some people get worse side effects than others.

In addition, if you agree, we would like to collect about five tablespoons of urine before you start treatment and at three months after the end of treatment for future research. This urine will be kept to be used in research to learn more about cancer and other diseases. The research that may be done with your specimens are 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 specimens 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 specimens 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, or urine specimen (see choices below). Then any tissue, blood, or urine that remains will no longer be used for research and will be returned to the institution that submitted it.

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

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

Your specimens will be used only for research and will not be sold. The research done with your specimens may help to develop new treatments for cancer and other diseases in the future.

## Benefits

The benefits of research using tissue, blood, and urine specimens 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. My blood may be kept for use in research to learn about the correlation between genes and substances found in the blood and radiation side effects.
  - Blood ☐Yes ☐No
4. 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)

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** (10/22/12)

**STUDY PARAMETER TABLE**

**\*See Sections 3.0 and 4.0 (pre-study entry) and 11.2 through 11.4 (during treatment/follow up) for details and/or exceptions.**

	<b>Pre-study Entry (may be required for eligibility)</b>				<b>During Treatment</b>	<b>Follow-up (months), Every 6 months for years 3, 4 and 5, then annually</b>							
	≤60 days	≤90 days	≤180 days	≤365 days		3	6	9	12	15	18	21	24
History/physical exam including a digital rectal exam	X												
Physical exam including a digital rectal exam						X	X	X	X	X	X	X	X*
Performance status	X				X	X	X	X	X	X	X	X	X*
Prostate biopsy w/ Gleason score				X									X*
PSA	X*					X	X	X	X	X	X	X	X*
Testosterone			X										
Imaging of urethra	See Sect. 4.2.1												
Bone scan													X*
EPIC Questionnaire	X								X				X*
EPIC-Use of sexual meds/ devices (if patient consents)	X								X				X*
EQ-5D (if patient consents)	X								X				X*
Tissue, blood, urine for research (if patient consents)	Pre-treatment					blood and urine							
Adverse event evaluation	X				X	X	X	X	X	X	X	X	X*

### **APPENDIX III**

#### **ZUBROD PERFORMANCE SCALE**

- |          |                                                                                                                                                                    |
|----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>0</b> | <b>Fully active, able to carry on all predisease activities without restriction</b>                                                                                |
| <b>1</b> | <b>Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work</b> |
| <b>2</b> | <b>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours</b>                             |
| <b>3</b> | <b>Capable of only limited self-care, confined to bed or chair 50% or more of waking hours</b>                                                                     |
| <b>4</b> | <b>Completely disabled. Cannot carry on self-care. Totally confined to bed</b>                                                                                     |
| <b>5</b> | <b>Death</b>                                                                                                                                                       |

## **APPENDIX IV**

### **AJCC STAGING SYSTEM PROSTATE, 7<sup>th</sup> Edition DEFINITIONS OF TNM**

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

#### **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).

**APPENDIX IV**  
**AJCC STAGING SYSTEM (continued)**  
**PROSTATE, 7<sup>th</sup> Edition**  
**DEFINITIONS OF TNM**

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

**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)

**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  $\leq 6$  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 $\leq 6$
	T2a	N0	M0	PSA <10	Gleason $\leq 6$
	T1-2a	N0	M0	PSA X	Gleason X
Stage IIA	T1a-c	N0	M0	PSA <20	Gleason 7
	T1a-c	N0	M0	PSA $\geq 10 < 20$	Gleason $\leq 6$
	T2a	N0	M0	PSA <20	Gleason $\leq 7$
	T2b	N0	M0	PSA <20	Gleason $\leq 7$
	T2b	N0	M0	PSA X	Gleason X
Stage IIB	T2c	N0	M0	Any PSA	Any Gleason
	T1-2	N0	M0	PSA $\geq 20$	Any Gleason
	T1-2	N0	M0	Any PSA	Gleason $\geq 8$
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.

## **APPENDIX V** (11/17/11)

### **APPENDICES FOR RTOG BIOSPECIMEN COLLECTION (*as specified by the protocol*).**

#### **RTOG FFPE Specimen Plug Kit Collection RTOG Blood Collection Kit Instructions RTOG Urine Collection Kit Instructions**

#### **Shipping Instructions:**

**US Postal Service Mailing Address: For FFPE or Non-frozen Specimens Only**  
RTOG Biospecimen Resource  
University of California San Francisco  
Campus Box 1800  
2340 Sutter Street, Room S341  
San Francisco, CA 94143-1800

**Courier Address (FedEx, UPS, etc.): For Frozen or Trackable Specimens**  
RTOG Biospecimen Resource  
University of California San Francisco  
2340 Sutter Street, Room S341  
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:**
  - 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.
  - 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.
  - 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:**
  - Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified.
  - 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.
  - Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
  - 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](mailto:RTOG@ucsf.edu) or phone: 415-476-RTOG(7864) or Fax: 415-476-5271.**

## APPENDIX V

### RTOG FFPE SPECIMEN PLUG KIT INSTRUCTIONS (continued)

This Kit allows sub-sampling of an FFPE block for submission to the RTOG Biospecimen Resource. The plug kit contains a shipping tube and a punch tool.



#### **Step 1**

If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample.



#### **Step 2**

Label the punch tool with the proper specimen ID. DON'T remove specimen from the punch.

Use a separate punch tool for every specimen. Call or e-mail us if you have any questions or need additional specimen plug kits.



#### **Step 3**

Once punch tool is labeled, place in shipping tube and mail to address below. Please do not mix specimens in the same tube.

We will remove core specimen from the punch, embed in a paraffin block, and label with specimen ID.

**\*NOTE:** If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the RTOG Biospecimen Resource and we will sample a plug from the block and return the remaining block to your facility. Please indicate on the submission form the request to perform the plug procedure and return of the block.

**Ship specimen plug kit, specimen in punch tool, and all paperwork to the address below. For Questions regarding collection/shipping or to order an FFPE Specimen Plug Kit, please contact the RTOG Biospecimen Resource by e-mail: [RTOG@ucsf.edu](mailto:RTOG@ucsf.edu) or call 415-476-RTOG(7864)/Fax 415-476-5271.**

**U.S. Postal Service Mailing Address: For Non-frozen Specimens Only**

**RTOG Biospecimen Resource  
University of California San Francisco  
UCSF Box 1800  
2340 Sutter Street, Room S341  
San Francisco, CA 94143-1800**

**Courier Address (FedEx, UPS, etc.): For Frozen Specimens or Trackable shipments**

**RTOG Biospecimen Resource  
University of California San Francisco  
2340 Sutter Street, Room S341  
San Francisco, CA 94115**

## **APPENDIX V**

### **RTOG BLOOD COLLECTION KIT INSTRUCTIONS (continued)**

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

#### **Kit contents:**

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

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

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

#### **Process:**

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

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

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

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

#### **Process:**

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

**PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the STF.  
(continued on next page)**



## APPENDIX V

### RTOG BLOOD COLLECTION KIT INSTRUCTIONS (continued)

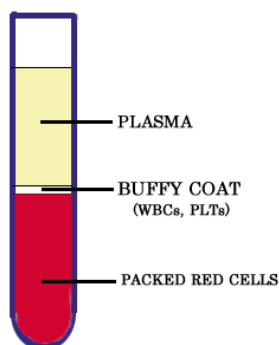
#### **(C) Whole Blood for DNA (if requested): Purple Top EDTA tube #2**

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

#### **Process:**

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

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



#### **Freezing and Storage:**

- ❑ Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.
- ❑ Store at -80°C (-70°C to -90°C) until ready to ship.
  - If a -80°C Freezer is not available,
    - Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
  - OR:**
    - Samples can be stored in plenty of dry ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only; Canada: Monday-Tuesday only).
  - OR:**
    - Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
- ❑ Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

#### **Shipping/Mailing:**

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

**(continued on next page)**

## APPENDIX V

### RTOG BLOOD COLLECTION KIT INSTRUCTIONS (continued)

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

2340 Sutter Street, Room S341

San Francisco, CA 94115

For questions, call 415-476-RTOG (7864) or e-mail: [RTOG@ucsf.edu](mailto:RTOG@ucsf.edu)

**APPENDIX V**  
**RTOG URINE COLLECTION KIT INSTRUCTIONS (continued)**

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](mailto: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  
2340 Sutter Street, Room S341, San Francisco, CA 94115  
Contact Phone: (415) 476-RTOG(7864)**