Official Title: Phase I and II Study of Stereotactic Body Radiation Therapy (SBRT) for Low and Intermediate Risk Prostate Cancer

NCT Number: 00547339

Document Date: 11/20/2013

Version: 15

Phase I and II Study of Stereotactic Body Radiation Therapy (SBRT) for Low and Intermediate Risk Prostate Cancer

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Protocol Version History

Version 1	7/11/2006
Version 2	9/15/2006
Version 3	2/22/2007
Version 4	7/5/2007
Version 5	7/13/2007
Version 6	11/9/2007
Version 7	1/30/2008
Version 8	07/23/2008
Version 9	08/06/2008
Version 10	12/8/2008
Version 11	9/30/09
Version 12	10/13/09
Version 13	10/8/2010
Version 14	11/04/2011
Version 15	11/20/2013

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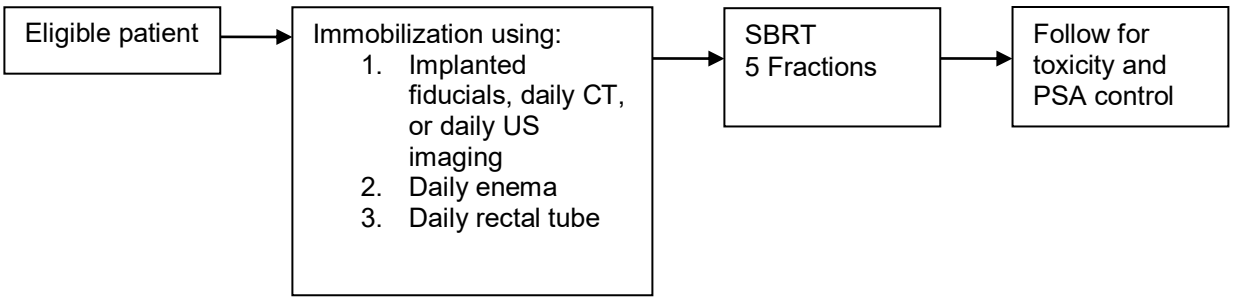
Synopsis

Schema



Number of patients = between 7-45 for phase I (depending on tolerance)
= 50 for phase II

Phase I

Patients in each dose cohort will all be treated as a single group for dose escalation. The starting dose for the dose escalation portion will be 9 Gy per fraction for 5 fractions (total dose = 45 Gy). Subsequent cohorts of patients will receive an additional 0.5 Gy per treatment (total 2.5 Gy per escalation) as follows:

No. Fractions	Dose per fraction (Gy)	Total Dose (Gy)	No. Patients
5	9	45	7-15
5	9.5	47.5	7-15
5	10	50	7-15

Minimum waiting periods will be assigned between each dose cohort to observe toxicity. The phase I portion of the study will be completed when dose limiting toxicity is reached or when a sufficiently high dose level (i.e.,10 Gy per fraction, 50 Gy total), is attained to consider the therapy likely to be efficacious.

Phase II

Additional patients will be treated at either the maximum tolerated dose (MTD) or at the 10 Gy per fraction dose level as determined from the Phase I portion of the study. The phase II study will evaluate efficacy endpoints with larger patient numbers and continue to build the toxicity profile of this regimen following the phase I study.

Eligibility

Men who satisfy all of the following conditions will be eligible for this study:

- Willing and capable to provide informed consent
- Signed study specific informed consent form.
- PSA ≤ 20 prior to hormone therapy (if given) for patients with Gleason 2-6. For those with Gleason score of 7. PSA should be less than or equal to 15 ng/ml prior to hormonal therapy (if given). Thus, risk of pelvic lymph node involvement according to Roach formula would be under 20%.
- Gleason score ≤ 7
- Appropriate staging studies identifying as AJCC stage T1a, T1b, T1c, T2a, or T2b
- No direct evidence of regional or distant metastases after appropriate staging studies

- Histologic confirmation of cancer by biopsy
- Adenocarcinoma of the prostate
- Age ≥ 18
- Zubrod Performance Status 0-2
- Up to 9 months of previous hormonal therapy is allowed (but not required)
- AUA score must be ≤ 15 (alpha blockers allowed)
- CT or Ultrasound-based volume estimation of prostate gland ≤ 60 grams
- Agreement to use effective contraceptive methods such as condom/diaphragm and spermicidal foam, intrauterine device, or prescription birth control pills.

Ineligibility

Women are not eligible for this study. Men with one or more of the following conditions also are ineligible for this study:

- Positive lymph nodes or metastatic disease from prostate cancer
- Prior invasive malignancy unless disease free for a minimum of 3 years (carcinoma *in situ* of the breast, oral cavity, or cervix, or non-melanomatous skin cancer are all permissible)
- T2c, T3, or T4 tumors
- Previous pelvic radiotherapy
- Previous surgery or chemotherapy for prostate cancer
- Previous transuretheral resection of the prostate (TURP) or cryotherapy to the prostate
- Previous hormonal therapy given for more than 9 months prior to therapy
- Concomitant antineoplastic therapy (including surgery, cryotherapy, conventionally fractionated radiotherapy, and chemotherapy) while on this protocol.
- History of Crohn's Disease or Ulcerative Colitis.
- Previous significant obstructive symptoms; AUA score must be ≤ 15 (alpha blockers allowed)
- Significant psychiatric illness
- Men of reproductive potential may not participate unless they agree to use an effective contraceptive method.
- Ultrasound or CT estimate of prostate volume > 60 grams
- Severe, active co-morbidity as defined in section 3.17.

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for Low and Intermediate Risk Prostate Cancer

ELIGIBILITY CHECKLIST

Case # _____ (page 1 of 2)

_____ (Y) 1. Prostate adenocarcinoma histologically confirmed by biopsy?

2. What is the TNM-Stage?
_____ (T1a, T1b, T1c, T2a, OR T2b)
_____ (N0)
_____ (M0)

_____ (≤ PSA) 3. What is/was the serum Prostate-Serum Antigen (PSA) prior to any hormonal therapy (if given)? (PSA ≤ 20 ng/ml for Gleason 2-6 and ≤ 15 ng/ml for Gleason 7)

_____ (≤ 7) 4. What is the Gleason score from the prostate biopsy?

_____ (N) 5. Does the patient have history of significant inflammatory colitis (e.g., Crohn's Disease or Ulcerative colitis)?

_____ (≥ 18) 6. How old is the patient (in years)?

_____ (0-2) 7. What is the patient's Zubrod performance status?

_____ (Y) 8. Has the patient agreed to use an effective method of contraception if able to have children?

_____ (Y) 9. Have the required pretreatment evaluations and staging studies been obtained?

_____ (Y/N) 10. Has the patient had prior hormonal therapy?
_____ (N) If yes, was more than 9 months of therapy given prior to study entry?

_____ (N) 11. Any prior chemotherapy or surgery for prostate cancer?

_____ (N) 12. Any prior radiotherapy to the pelvis?

_____ (N) 13. Are other concomitant cancer therapies planned including surgery, cryotherapy, chemotherapy, or conventionally fractionated radiotherapy?

_____ (N) 14. Has the patient undergone previous transurethral resection of the prostate (TURP) or cryotherapy to the prostate?

_____ (Y/N) 15. Has the patient had a previous cancer (carcinoma *in situ* of the breast, oral cavity, or cervix, or non-melanomatous skin cancer are all permissible)?

_____ (Y) If yes, has the patient been disease free for > 3 years?

_____ (Y) 16. Is the patient's AUA score ≤ 15?

_____ (N) 17. Is the patient's ultrasound or CT estimate of the prostate volume > 60 grams?

_____ (N) 18. Severe, active co-morbidity as defined in section 3.17.

_____ (Y) 19. Has the patient signed the protocol consent?

_____ (N) 20. In the past 6 months, has the patient been treated with potent immunosuppressive drugs?

Completed by_____ Date _____

1.0 INTRODUCTION

1.1 Localized Prostate Cancer

There were 232,000 new cases of prostate cancer diagnosed in the United States in 2005 and 30,000 deaths [1]. Among males, prostate carcinoma was the 2nd leading cause of cancer mortality behind lung cancer and ahead of colo-rectal cancer. The incidence of early stage prostate cancer rose dramatically in the US with the onset of widespread use of prostate-specific antigen (PSA) blood test screening. Levels have continued to increase but more slowly in men younger than 65, but have leveled off in men older than 65 since 1995. Death rates have remained level or decreasing since the mid 1990s, presumably from earlier detection with PSA screening. The main risk factors are age, ethnicity, and family history. Up to 70% of all prostate cancers are diagnosed in men greater than 65 years old which impacts therapy options as a result of competing co-morbidities. Men of African decent have the highest incidence of prostate cancer while men in North American have higher incidence than men in Asia and South America. Familial disposition may account for 5-10 percent of prostate cancers. Early detection of the disease appears to account for improvements seen in the US cause-specific mortality rate. The American Cancer Society recommends annual screening PSA testing and digital rectal examination (DRE) in all men starting at age 50 (starting at age 45 in high risk men) in order to allow diagnosis of cancer while still organ confined. With this approach, overall 5-year survival has improved from 67% in 1974 to nearly 100% in 2000; however, cancer specific survival continues to decline after five years due to the long natural history and lack of cancer control in many men.

Radiotherapy options for organ confined prostate cancer have included protracted radiation in the form of external beam delivered over 7-10 weeks of daily therapy (including 2-D, 3-D conformal, and intensity modulated radiation therapy or IMRT) [2-4] and also permanent brachytherapy seed implantation using iodine or palladium [5-7]. Treatments have also been delivered using shorter overall treatment times. These include hypofractionated external beam treatments and high dose rate (HDR) brachytherapy implants [8-11]. In addition to being more convenient for patients with fewer trips to the treatment facilities, these treatment options completed over a shorter period have unique long term effects in both tumor and normal tissues. Depending on the relative differences between tumor response and normal tissue injury, the timing in which radiotherapy is delivered may have significant impact on the therapeutic ratio (benefit/toxicity). A commonly used mathematical model used to describe these effects has been the “linear-quadratic” model proposed by Douglas and Fowler [12]. In this model, the log survival vs. dose relationship is modeled by an arithmetic power series truncated to the linear and quadratic terms. The linear coefficient in this progression is commonly called “alpha” while the quadratic coefficient is called “beta.” It has also been proposed that the linear term described by alpha corresponds to the more infrequent effect of double strand breaks within tissue DNA caused by radiation which disable the clonagenicity of the cell with little chance of repair. In turn, the beta term reflects the consequence of more than one single strand break in close enough proximity on the DNA to disable the cell. These single strand breaks occur much more frequently than double strand breaks, but they may be more readily repaired unless they happen so frequently that repair mechanisms become overwhelmed such as might occur with large dose per fraction radiation. Hence, at low dose per fraction, alpha events dominate the cellular response while at large dose per fraction, beta events become more important.

These events occur, at different rates and proportions, in both tumor and normal tissues exposed to radiation.
It has been commonplace to describe tissue response properties of various tissues toward radiation by their alpha to beta ratio. The alpha and beta values may be measured *in vitro* by exposing cell cultures to varying doses and schedules of radiation. Normal tissues, more capable of repairing radiation injury, typically have a lower alpha/beta ratio in the order of 2-3. Common cancers of the lung, cervix and head and neck are quoted to have alpha/beta ratios in the 10 range. For such tumors, exploitation of the differences between normal tissue and tumor response has led radiation oncologists to use more protracted courses of radiation using small daily doses to high total cumulative doses (so-called conventional fractionation, e.g., 2 Gy per fraction to a total dose of 70-76 Gy). Prostate cancer cell lines have been difficult to grow in tissue culture and therefore there has been less direct evidence of the alpha/beta ratio. It was generally assumed to be similar to epithelial malignancies of the gastrointestinal and bronchopulmonary tract leading to the conventional dose fractionation schedules used in clinical practice or the low dose rate implants used in permanent prostate seed brachytherapy. More recent evidence, however, has implied that the alpha/beta ratio for prostate cancer may be much lower than expected. In fact, using outcome data of patients treated with different dose fractionation schemes (in vivo), it has been suggested that the alpha/beta ratio for prostate cancer may be as low as 1.5-3 which is perhaps even lower than the surrounding normal tissues. If this were true, there would be no advantage to protracted radiotherapy schedules. This realization has led to several investigations of much shortened radiotherapy schedules. Of course, the shortest radiotherapy schedules of all have been SBRT treatment schedules which is the impetus for this protocol.

Several investigators at a variety of institutions have investigated using modestly larger dose per fraction treatment schemes as compared to conventional fractionated radiotherapy [references]. For example, in a mature prospective experience reported by Livsey and colleagues from England, 50 Gy total in 3.13 Gy fractions produced PSA control rates comparable to published reports using 70 Gy with 2 Gy fractions [13-14]. In addition, they found the treatment carried out with 3-D conformal techniques was well tolerated. That same group is carrying on the research using 3 Gy per fraction, 60 Gy total dose, and intensity modulated radiation therapy (IMRT) techniques in an effort to improve PSA control rates [11]. In the US, Kupelian and colleagues used 2.5 Gy per fraction and published mature results to 70 Gy total dose in 5.5 weeks [10]. Their patients also had good PSA control rates and acceptable rates of toxicity, especially if the volume rectum getting 70 Gy is limited to 10 cc. Similar investigations are now being planned or carried out for larger groups of patients in cooperative group trials. Altogether, these trials show that the treatment can be delivered much more quickly and conveniently using hypofractionation without compromising PSA control or toxicity so long as careful technique is respected.

1.2 Stereotactic Body Radiation Therapy (SBRT)

'Stereotactic radiosurgery' generally refers to a procedure design to treat deep-seated brain tumors or abnormalities, and is commonly performed on a specialized machine, such as the Gamma Knife. This procedure involves immobilizing the patient (cranial halo), affixing a stable 3-D coordinate system (fiducial box and head

frame), performing high resolution imaging (CT or MRI), registering the images to the coordinate system using a computer, virtually simulating delivery of very focal and conformal dose profiles of radiation with steep dose gradients toward normal tissue, and finally carrying out the treatment with sub-millimeter accuracy. Typically very high doses of radiation (15-40 Gy) are given in a single treatment with this technique. Any adjacent normal tissues that receive this dose may be significantly damaged, thus the requirement for very conformal treatments with rapid dose fall-off. An alternate strategy has been to divide total radiation dose into two or three fractions, still with fairly large dose per fraction (6-10 Gy), attempting to decrease adjacent normal tissue toxicity. These fractionated techniques are referred to as 'stereotactic radiotherapy,' and are carried out with hope that surrounding normal tissue will tolerate the treatment as a result of relatively more successful sublethal damage repair as compared to tumor.

Translation of the stereotactic radiosurgery and radiotherapy concepts to extracranial sites has not been straightforward [15-17]. With brain treatments, the skull serves as an excellent surface to rigidly couple the immobilization frame using stainless steel pins under local anesthesia. Once the skull is immobilized, targets within the skull are likewise immobilized in that there is very little movement of intracranial structures outside of fluid waves around the ventricles. Such is not the case for extracranial sites. Inherent motion, such as the heart beating, lungs expanding and emptying, and bowels churning, results in movement of potential targets. In addition, the external surface anatomy does not have structures amenable to rigid fixation to a frame. In 1994, Lax, et al, from the Karolinska Hospital in Sweden reported on the development and testing of an extracranial frame that incorporated a fiducial stereotactic coordinate system along its side panels [18]. The system used vacuum pillows to make contact with three sides of the patient (maximizing surface area of contact) and correlation of external anatomical reference points on the sternum and calf for immobilization. To decrease respiratory excursion, an abdominal press was employed forcing the patient to perform relatively more chest wall rather than diaphragmatic breathing. A formal verification of reproducibility study was carried out, and target motion was reduced to within 0.5 cm in the axial plane and 1.0 cm in the caudal/cephalad plane. With this degree of accuracy (compared to 0.05 cm target position accuracy for the Gamma Knife), stereotactic radiosurgery could not be performed; however, they did set up a program treating patients with extracranial stereotactic radiotherapy.

Stereotactic body radiation therapy (SBRT) is a new therapeutic paradigm for treating localized tumors outside of the central nervous system and involves delivering very high doses of focused radiation using unique beam arrangements and special immobilization equipment [19]. As already demonstrated in lung and liver cancers, these treatments offer hope for improved local control of cancers that may translate into gains in survival especially for smaller early stage lesions. SBRT employs daily treatment doses dramatically higher than typical for conventionally fractionated radiation therapy (CFRT). In turn, it is incorrect to assume that SBRT radiobiology is similar to historical CFRT. Indeed, a unique biology of radiation response for very large dose per fraction treatments is being appreciated both in terms of tumor control as well as normal tissue consequences translating into unique clinical outcomes. For example, local control with CFRT in early stage lung cancer is consistently reported below 50% while several series using SBRT show local control around 90% [20-21].

SBRT has been defined by the American College of Radiology (ACR) and American Society of Therapeutic Radiology and Oncology (ASTRO) to involve the use of very large dose per fraction [22]. Indeed, dose per fraction of 8 Gy minimum would obviously make SBRT very different from even the more abbreviated hypofractionation schemes described above. Typically, only 1-5 fractions are used for SBRT depending on the tolerance of adjacent or intervening normal tissues. Linear structures (like the spinal cord) and tubular structures (like the bowels) are commonly called “serially functioning tissues” akin to series electrical circuits because their function is disrupted if there is a defect anywhere along their pathways [23-24]. It has been shown that serial functioning tissues are less tolerant to SBRT than so-called “parallel functioning tissues” like the peripheral lung and liver. In response, typically more fractions are employed (e.g., five fractions rather than one) when serially functioning tissue cannot be avoided. In the case of treating prostate cancer, the rectum is an adjacent serially functioning tissue while the urethra is an intervening serially functioning tissue traversing the very center of the prostate target.

1.3 Current Protocol

Prostate cancer has several good treatment options for organ confined disease such as surgery and conventional radiation. In addition, some men with indolent disease are appropriately treated with watchful waiting. However, all of the established treatments continue to fail in a portion of patients via tumor recurrence. Furthermore, current treatments are often unpalatable for many patients because they are either too invasive or too inconvenient. It has also been shown recently that many prostate cancers may be better controlled using large dose per fraction treatments such as might be delivered by stereotactic body radiation therapy (SBRT). While large dose per fraction treatments are facilitated by new generation radiation delivery equipment, technology cannot independently overcome normal tissue consequences to tubular organs adjacent or within targets (e.g., the urethra and rectum for prostate cancer). As such, careful prospective clinical trials must be designed that appropriately bridge the information learned from laboratory testing, historical clinical experience, and the clinical experience with SBRT from other sites in order to test this new therapy for prostate cancer. This is an important problem, since localized prostate continues to recur despite current treatments and more effective, less toxic and more convenient treatments are necessary.

As the SBRT therapy is strictly local, we will select for patients with prostate cancer locally confined to the prostate gland. As such, we will select eligibility criteria sanctioned in the past by the Radiation Therapy Oncology Group to predict reasonably low risks of both extraprostatic capsular extension and seminal vesicle invasion. We will apply the Roach formula to limit eligibility to patients with under a 20% risk of pelvic lymph node involvement. Some patient eligible for this trial may have a somewhat higher risk of extraprostatic spread (e.g., T2b, Gleason 7 or PSA>10) and it will be allowed to use pre-treatment hormonal therapy in such patients at the investigator’s discretion. Hormonal therapy may also be used to shrink prostates that are massively enlarged. As the primary toxicity will likely be mucosal damage, we will avoid enrolling patients with pre-existing mucosal dysfunction (including those with previous radiation, TURP, very large prostate glands, and inflammatory bowel disease). In this way, patients will be uniformly

selected in a fashion that would identify patients likely to receive benefit from the therapy.

As the most efficacious SBRT dose for treatment of the prostate has not been prospectively identified, we will start with a careful phase I dose escalation toxicity study. Patients enrolled at each dose level will undergo routine evaluations to identify potential toxicities. Adequate waiting periods will be respected to insure dose escalation does not proceed prior to observing toxicity. When the MTD is determined or the dose reaches a significantly high level expected to be both tumoricidal and able to control PSA by the investigators, subsequently enrolled patients will be accrued into the phase II portion. In the phase II portion, further patients will be accrued to confirm toxicity data on a larger scale, and attempt to characterize whether there is enough beneficial effect in this population to warrant further clinical testing.

We will use a treatment regimen carried out in 5 total fractions. This would be a more tolerant regimen than our 3 fraction regimens published in liver and lung cancer [25-26] and may lessen the toxicity to serial functioning tissues in close approximation to the prostate (rectum and urethra). Given there will be only 5 treatments, daily enemas, rectal tubes, and even urethral catheters for simulation are all feasible undertakings that may help optimize the therapy.

It is predicted that the dose limiting toxicity from this treatment will likely relate to urethral dysfunction (e.g., ulceration, bleeding, pain, narrowing and frank stricture) and rectal damage (ulceration, bleeding, chronic inflammation, and pain). Since the radiotherapy target for radiotherapy of the prostate is the entire gland, the urethra will by definition be situated toward the center of the target thereby receiving the target margin dose at a minimum. In fact, the urethra may receive even a higher dose than the minimum target dose owing to the fact that SBRT dosimetry commonly includes a 10-30 percent higher central dose within the target. While wedges and other methods of modulation (including IMRT) may be used to steer this higher dose away from the visualized urethra, these techniques will have limited ability to protect the urethra. The prostatic urethra will likely be significantly damaged which may limit dose escalation. If it has the ability to heal by second intention as it has been shown to do after other severe insults such as transurethral resection without forming a diffuse untreatable stricture, the treatment may still be feasible. Certainly if mucosal clonagens can migrate from the bulbous urethra and bladder to “rescue” the prostatic urethra after SBRT, care will be taken to spare dose to those structures [24]. In regard to the rectum, the treatments will be carried out with a rectal tube to separate much of the circumference of the rectal wall from the prostate target. This rectal tube must be positioned appropriately above the anus and extend superiorly to above the prostate to be effective. In addition, the rectum should be evacuated of feces to avoid confounding the geometry prior to each treatment. If the dose to the rectum is tightly confined to the anterior wall next to the target, it is hoped that the ulcer likely to be produced will heal by recruitment of clonagens and blood supply from the lateral and posterior walls. Indeed, a precedent for assuming such a process exists with the reported treatment of small rectal cancers using an endorectal orthovoltage tube by Papillon and colleagues [27]. In that experience, doses as high as 150 Gy were given in as few as 4 fractions which undoubtedly resulted in ulceration at the point of treatment but still no

reported long term untoward toxicity owing to the extremely localized high dose dosimetry.

1.4 Who Would Benefit from this Treatment?

As noted above, there are several quite good but not perfect treatments for organ confined prostate cancer that have significant follow-up and published experience as well as an option for watchful waiting. Still, there are populations that might find the invasiveness of surgery and brachytherapy implants less ideal and the inconvenience of IMRT and 3-D conformal therapy impractical. General anesthesia is inappropriate for some patients due to significant co-morbid conditions. We believe a very abbreviated, non-invasive, outpatient treatment would be considered a favorable option in particular to the underserved populations of men living in more remote areas including farmers, ranchers, and those in rural communities. Furthermore, if the concept of prostate cancer having a very low alpha to beta ratio discussed previously is confirmed, this treatment using SBRT may in fact be a better option for some men with prostate cancer.

1.5 Starting Dose for the Phase I Study

There has been experience published or presented to indicate the appropriate starting dose for the phase I study. Direct evidence of tolerance by a similar treatment strategy has been presented by Madsen and colleagues from Virginia Mason University where 33.5 Gy in 5 fractions of 6.7 Gy were delivered using SBRT in men with early stage prostate cancer [28]. That dose was tolerated without grade III or higher toxicity, but had rather poor PSA control [personal communication, Berit Madsen, M.D., 5/05). Although not using SBRT techniques, Collins and colleagues used a 6 fraction regimen to 36 Gy at 6 Gy per fraction with more conventional external beam delivery techniques which again was well tolerated [29-30]. A similar but more invasive treatment approach to SBRT is the high dose rate (HDR) implant experience which gives large dose per fraction treatments on a daily basis through implanted brachytherapy catheters. Indeed the heterogeneous target dosimetry is similar in many ways to SBRT. While HDR has mostly been used as a boost treatment after conventional external beam treatment, there is institutional data from Martinez and colleagues using HDR as monotherapy. That group at the William Beaumont Hospital used a 4 fraction regimen of 9.5 Gy to a total dose of 38 Gy and published an acceptable toxicity profile in treated patients [31-32]. Grills, et al. reported an update of these results of HDR monotherapy for the management of 65 patients with T1a-T2b, and total Gleason Score 7 or less. The preliminary biochemical PSA control rate was 98% at 3 years and it was similar to their experience with standard ^{103}Pd low dose rate brachytherapy [40]. In a similar experience using HDR, Yashioka and colleagues from Japan used higher total doses up to 48-50 Gy in 6 Gy fractions as monotherapy for localized prostate cancer without untoward toxicity [33-34]. Considering all of these experiences as basis for dose selection, we will use a starting dose of 9 Gy per fraction and deliver a total of 5 fractions to a total dose of 45 Gy. Subsequent dose levels will require a modest dose per fraction escalation of 0.5 Gy (e.g., 9 Gy to 9.5 Gy to 10 Gy per fraction, etc). We hope to reach as high of biologically potent dose as possible without exceeding tolerance (i.e., a 2 Gy equivalent dose of at least 100 Gy) that would be delivered in around 2 weeks rather than 10-12 weeks as would be required with conventional fractionation.

2.0 OBJECTIVES

2.1 In phase I, to the primary objective is to escalate the dose of stereotactic radiotherapy to a tumorcidal dose without exceeding the maximum tolerated dose in patients with organ confined prostate cancer.

2.2 In phase I, a secondary objective is to determine the dose-limiting toxicity (if the maximum tolerated dose is reached).

2.3 In phase II, the primary objective is to determine the late severe grade 3-5 GU and GI toxicity from 270-540 days (i.e., 9-18 months) from the start of the protocol treatment. It is graded based on CTCAE v3.0.

2.4 In phase II, secondary objectives will be to determine the 2 year biochemical (PSA) control (freedom from PSA failure), disease free and overall survival, local control, freedom from distant metastases, and the incidence of high grade adverse events of any type from the therapy in the treated patients in order to determine if the therapy is promising enough for further clinical investigation.

3.0 PATIENT SELECTION

3.1 All patients must be willing and capable to provide informed consent to participate in the protocol.

3.2 Eligible patients must have appropriate staging studies identifying them as AJCC stage T1 (a, b, or c) or T2 (a and b only) adenocarcinoma of the prostate gland. The patient should not have direct evidence of regional or distant metastases after appropriate staging studies. Histologic confirmation of cancer will be required by biopsy.

3.3 The patient's Zubrod performance status must be 0-2

3.4 The Gleason score should be less than or equal to 7

3.5 The serum PSA should be less than or equal to 20 ng/ml prior to starting hormonal therapy (if given) for patients with Gleason score 2-6. For patients with Gleason score of 7, PSA should be less than or equal to 15 ng/ml prior to starting hormonal therapy (if given). As such, the risk of pelvic lymph node involvement according to the Roach formula would be under 20%.

3.6 Eligible patients should not have had previous pelvic radiotherapy or have had chemotherapy or surgery for prostate cancer. Hormonal therapy given for up to 9 months prior to SBRT is allowed as a neoadjuvant therapy or to downsize the prostate gland.

3.7 There must be no plans for the patient to receive other concomitant or post treatment adjuvant antineoplastic therapy while on this protocol including surgery, cryotherapy, conventionally fractionated radiotherapy, hormonal therapy, or chemotherapy given as part of the treatment of prostate cancer.

3.8 Patients should not have undergone previous transurethral resection of the prostate (TURP) or cryotherapy to the prostate.

3.9 Patients must be past their 18th birthday at time of registration.

3.10 Patients with history of inflammatory colitis (including Crohn's Disease and Ulcerative colitis) are not eligible.

3.11 Patients may have used prior hormonal therapy, but it should be limited to no more than 9 months or therapy prior to enrollment.

3.12 Patients should not have significant urinary obstructive symptoms; AUA score must be ≤ 15 (alpha blockers allowed).

3.13 The ultrasound or CT based volume estimation of the patient's prostate gland should not be greater than 60 grams.

3.14 Patients should not have a history of significant psychiatric illness.

3.15 Men of reproductive potential may not participate unless they agreed that they or their partner use an effective contraceptive method such as condom/diaphragm and spermacidal foam, intrauterine device (IUD), or prescription birth control pills.

3.16 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years (e.g., carcinoma *in situ* of the breast, oral cavity, or cervix are all permissible).

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

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

3.17.2 Transmural myocardial infarction within the last 6 months.

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

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

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

3.17.6 Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.

3.17.7 History of treatment with potent immunosuppressive drugs for such conditions as post organ transplant, severe rheumatoid arthritis, etc. within the past 6 months.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

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

4.1 Required Evaluations/Management

4.1.1 History and physical examination to include digital rectal examination of the prostate, determination of AUA score, and completion of EPIC prostate quality of life questionnaire.
4.1.2 Zubrod performance status (Appendix II).
4.1.3 Lymph node evaluation performed within 90 days prior to registration by either CT or MRI (lymph node dissection is acceptable but not required).
4.1.4 Prostate Specific Antigen (PSA) prior to treatment (prior to hormonal therapy, if given).
4.1.5 See Section 11.1; note that failure to perform one or more of these tests may result in assessment of a protocol violation.

4.2 Highly Recommended Evaluations/Management
Cystoscopy, if advised by the urologist, may be performed to check for urethral damage including strictures, bladder pathology, or a large median prostate lobe. Anosocopic exam with initial and follow up exams.

5.0 REGISTRATION PROCEDURES

5.1.1 *Preregistration Requirements for diagnostic pathology review*
There are no requirements for central review of pathology used for initial diagnosis.
5.1.2 *Pre-Registration Requirements for SBRT Treatment Approach*
In order to utilize SBRT in this protocol, the institution must have met technology requirements and have provided a description of techniques, methods, training, and experience showing competency to the study PIs.
5.2 *Registration*
5.2.1 Fax Registration
Prior to registration, participating investigators and institutions should review the eligibility checklist and confirm eligibility. Patients can be registered only after eligibility criteria are met. To register a patient, the site should fax the Enrollment Form to the Project Manager (fax #: 214-648-5923). A unique, participant ID number will then be assigned.
5.3 *Accreditation*
5.3.1 Institutional Processes
Prior to treating patients on protocol, the institution's specific methods for immobilization (e.g., frame vs. frameless), targeting, dose construction, daily verification of accuracy, ongoing assessment of accuracy and Quality Assurance policies must be described to and approved by the study PI and other approved institutional PIs. The primary purpose of accreditation will be to insure that dose is delivered to the targets and avoiding normal tissues according to protocol criteria. This accreditation may be assessed by written documentation, conference calls, or direct observation via site visits. Additional data may be required of institutions to verify that techniques are performing as intended.

6.0 RADIATION THERAPY

6.1 Dose Specifications
6.1.1 *Stereotactic Targeting and Treatment*
The term "stereotactic" for the purposes of this protocol implies the targeting, planning, and directing of therapy using beams of radiation along any trajectory in 3-D space guided by one or several fiducials of known 3-D coordinates. This differs from conventional radiation therapy in which therapy is directed toward skin marks or bony landmarks and assumed to correlate to the actual tumor target based on a historical simulation. It should be understood that Stereotactic Body

Radiation Therapy (SBRT) has become a treatment that is well beyond just stereotactic targeting. Indeed SBRT is mostly about ablative range dose per fraction, accounting properly for errors including motion, careful construction of dosimetry that compacts high dose into the tumor and not normal tissues, and extra careful treatment conduct. This protocol will require treatments to be conducted with the use of a fixed 3-D coordinate system defined by fiducials. The coordinate system defined by the fiducials should be directly related to the radiation producing device (e.g., couch and gantry) in a reproducible and secure fashion. Capability should exist to define the position of targets within the patient according to this same 3-D coordinate system. As such, the patient is set up for each treatment with the intention of directing the radiation toward an isocenter or target according to the known 3-D coordinates as determined in the process of treatment planning. The nature of the fiducials themselves may include radio-opaque markers or rods placed at known locations in a frame or fixed structure adjacent to the patient as well as use of the tumor itself as a fiducial (e.g. acquiring tomographic views of the tumor simultaneously with the treatment). Metallic "seeds" or markers placed within the tumor will be allowed so long as they are not prone to migration movement.

6.1.2 *Dose Fractionation*

Patients will receive 5 fractions of radiation. A minimum of 36 hours and a maximum of 8 days should separate each treatment. No more than 3 fractions will be delivered per week (7 consecutive days). Total dose will depend on the phase of the study (see schema).

6.1.3 *Premedications*

Unless contraindicated, it is recommended that all patients receive corticosteroid premedication (e.g. Decadron 4 mg p.o. in a single dose, or equivalent) 15-60 minutes prior to each of the five treatments for the intended purpose of modulating immediate acute inflammatory effects. It is strongly recommended that all patients be treated prophylactically with drugs intended to avoid urinary retention associated with SBRT. This class of drugs include alpha blockers (e.g., tamsulosin aka Flomax, doxazosin aka Cardura, terazosin aka Hytrin, etc) and 5-alpha reductase inhibitors (e.g., finasteride aka Proscar, dutasteride aka Avodart, etc), or drugs with similar intended effect. It is recommended to start the therapy at least one day prior o the first SBRT treatment and continue for 3 months post finishing all SBRT therapy. The drugs should be taken at standard doses for obstructive indications, and contraindications to these drugs should be respected. Analgesic premedication, such as Tylenol 650 mg 30 minutes prior to therapy and as needed every 6 hours, to avoid general discomfort during long treatment durations also is recommended when appropriate.

6.1.4 *Supportive medicines*

Consider Tamsulosin (e.g., Flomax) during treatment period to reduce urinary symptoms. Consider using 5-alpha reductase inhibitor like Finasteride (e.g. Proscar) to relieve potential obstructive issues. For both drugs, standard doses will be utilized as needed unless contraindicated. Also consider 1 tablespoon of Milk of Magnesia, taken the night before simulation/treatment (*Note: Inform patient that this will cause diarrhea*). Fleet's enema should be taken 2 hrs~~,~~ before simulation/treatment. An antibiotic (Bactrim or similar) may be prescribed to alleviate UTI if necessary. This should be taken at standard doses as needed.

6.2 Technical Factors

6.2.1 *Physical Factors*

Only photon (x-ray) beams produced by linear accelerators, betatrons, or microtron accelerators with photon energies 6-21 MV will be allowed. Cobalt-60 and charged particle beams (including electrons, protons, and heavier ions) are not allowed.

6.2.1 *Dose Verification at Treatment*

Personal dosimeter measurements (e.g. diode, TLD, etc.) may be obtained for surface dose verification for accessible beams as per institutional preference. This information is not required by the protocol.

6.3 Localization, Simulation, and Immobilization

6.3.1 *Patient Positioning*

Patients will be positioned supine in a stable position capable of allowing accurate reproducibility of the target position from treatment to treatment. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments. A variety of immobilization systems may be utilized including stereotactic frames that surround the patient on three sides and large rigid pillows (conforming to patients external contours) with reference to the stereotactic coordinate system (see Section 6.1). All positioning systems must be validated and accredited by the Study Committee (Principal Investigator and Institutional PIs) prior to enrolling or treating patients on this trial. Patient immobilization must be reliable enough to insure that the Gross Tumor Volume (GTV) does not deviate beyond the confines of the Planning Treatment Volume (PTV) as defined in Section 6.4 with any significant probability (i.e., < 5%).

6.3.2 *Inhibition of Effects of Internal Organ Motion*

Special considerations must be made to account for the effect of internal organ motion (i.e., breathing, etc.) on target positioning and reproducibility. In some cases, the intrafractional tumor motion is small and no special maneuvers are required to achieve motion limits as defined in section 6.4 (this may be true for many cases of prostate cancer). Treating in the prone position will accentuate internal organ motion problems related to breathing and should be avoided unless special measures are taken to account for this motion. When accounting for intrafractional motion, acceptable maneuvers including reliable abdominal compression, accelerator beam gating with the respiratory cycle, and active breath-holding techniques. Internal organ inhibition maneuvers must be reliable enough to insure that the Gross Tumor Volume (GTV) does not deviate beyond the confines of the Planning Treatment Volume (PTV) as defined in Section 6.4 with any significant probability (i.e., < 5%). Assessment of this motion will be left to the institution and may included identifying the position of radio-opaque seeds implanted into the prostate prior to each treatment. This type of interfractional motion analysis with correction is only required by protocol just prior to each separate treatment. Intrafraction assessment during the course of each treatment (dynamic and adaptive maneuvers) is allowed and encouraged especially if treatment times are long.

6.3.3 *Localization and treatment maneuvers*

A more direct method of localization of the prostate gland than conventional treatment (i.e., one that uses skin and boney landmarks solely as a surrogate to the prostate position) must be used in this protocol. Acceptable methods would include daily ultrasound or placing a radio-opaque seed or marker that can be visualized and triangulated using dual imaging or markers that emit a signal that can me used to detect position electronically all placed prior to simulation and planning. Also, it would be acceptable to perform computed tomography such as axial, spiral or conebeam CT prior to each treatment in the treatment position to

identify the tumor target directly. Image quality should be good enough to identify the prostate borders.

In addition to the identification of the prostate in the preceding paragraph, the rectum should also be identified and reliably repositioned with a large (e.g., around 60 cc) rectal tube. Prior to positioning at least 30 minutes and no more than 2 hours before each treatment, patients should undergo an effective bowel evacuation. Typically, this will involve 1-2 fleet's enemas. This maneuver is to clear the rectum of stool and significant gas accumulation. Just prior to relocalization and treatment, a rectal tube filled with air should be introduced into the rectum to both visualize the rectum and separate the anterior and posterior walls. The rectal balloon and implementation plan must be approved by the PI prior to use.

Isocenter port localization films (anterior/posterior and lateral) should be obtained at each treatment on the treatment unit (or patients should undergo a tomographic imaging study utilizing the linear accelerator couch, if available) immediately before treatment to ensure proper alignment of the geometric center (i.e., isocenter) of the simulated fields. Verification CT scans and portal films may be taken at the discretion of the participating institution, but are not required for protocol participation.

6.4 Treatment Planning/Target Volumes

6.4.1 *Image Acquisition*

Computed Tomography (CT) will be the primary image platform for targeting and treatment planning. The planning CT scans must allow simultaneous view of the patient anatomy and fiducial system for stereotactic targeting. Treatment planning images should be performed in the treatment position using all aids/maneuvers described above including urethral tube, bladder contrast, urethrogram, and rectal balloon after bowel evacuation with enemas. The treatment planning scans must use a small caliber radio-opaque urethral catheter to allow visualization of the prostatic urethra as it will be a high dose spillage avoidance structure for treatment planning as indicated in section 6.4.2 below. Axial acquisitions with gantry 0 degrees will be required with spacing ≤ 3.0 mm between scans. Images will be transferred to the treatment planning computers via direct lines, disc, or tape.

Image fusion with other imaging modalities such as MRI that might be useful in delineating the target and normal tissues is encouraged.

The entire prostate without the seminal vesicles will constitute the CTV target for this protocol. It is not required to identify a GTV within the prostate, but if institutions have special techniques to identify the gross tumor, such as MRI with high tesla strength, it is encouraged to collect the contours. CTV target volume (entire prostate gland) will be outlined by an appropriately trained physician. The target will generally be drawn using CT soft tissue windows. An additional 0.3-0.5 cm in the axial plane and 0.5-1.0 cm in the longitudinal plane (cranio-caudal) will be added to the GTV to constitute the planning treatment volume (PTV) depending on the institution's accuracy and treating physician's preference.

6.4.2 *Dosimetry*

Three-dimensional coplanar or non-coplanar 3-D beam, arc rotation, or Intensity Modulated Radiotherapy (IMRT) beam arrangements will be custom designed for each case to deliver highly conformal prescription dose distributions. Non-

opposing, non-coplanar beams are preferable. Typically, 10-15 beams of radiation will be used with roughly equal weighting. Generally, more beams are used for larger lesion sizes. When static beams are used, a minimum of 10 non-opposing beams should be used. For arc rotation techniques, a minimum of 300 degrees (cumulative for all beams) should be utilized. For this protocol, the isocenter is defined as the common point of gantry and couch rotation for the treatment unit. Field aperture size and shape should correspond nearly identically to the projection of the PTV along a beam's eye view (i.e. no additional "margin" for dose build up at the edges of the blocks or MLC jaws beyond the PTV). As such, prescription lines covering the PTV will typically be the 60-90% line (rather than 95-100%); however, higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue. The isocenter in stereotactic coordinates will be determined from system fiducials (or directly from the tumor) and translated to the treatment record.

The treatment dose plan will be made up of multiple static beams or arcs as described above. The plan should be normalized to a defined point corresponding closely to the center of mass of the PTV (COM_{PTV}). Typically, this point will be the isocenter of the beam rotation; however, it is not a protocol requirement for this point to be the isocenter. Regardless, the point identified as COM_{PTV} must have defined stereotactic coordinates and receive 100% of the normalized dose. Because the beam apertures coincide nearly directly with the edge of the PTV (little or no added margin), the external border of the PTV will be covered by a lower isodose surface than usually used in conventional radiotherapy planning, typically around 80% but ranging from 60-90%. The prescription dose in five fractions will be delivered to the margin of the PTV and fulfill the requirements below. As such, a "hot spot" will exist within the PTV centrally at the COM_{PTV} with a magnitude of the prescription dose times the reciprocal of the chosen prescription isodose line (i.e., 60-90%).

For purposes of dose planning and calculation of monitor units for actual treatment, all tissues within the body should be modeled in the planning system as to their electron density. Proper heterogeneity correction algorithms should be approved by the PI.

Successful treatment planning will require accomplishment of all of the following criteria:

1) Normalization
   The treatment plan should be normalized such that 100% corresponds to the center of mass of the PTV (COM_{PTV}). This point will typically also correspond (but is not required to correspond) to the isocenter of the treatment beams.
2) Prescription Isodose Surface Coverage
   The prescription isodose surface will be chosen such that 95% of the target volume (PTV) is conformally covered by the prescription isodose surface and 99% of the target volume (PTV) receives a minimum of 90% of the prescription dose.
3) Target Dose Heterogeneity
   The prescription isodose surface selected in number 2 (above) must be ≥ 60% of the dose at the center of mass of the PTV (COM_{PTV}) and ≤ 90% of the dose at the center of mass of the PTV (COM_{PTV}). The COM_{PTV} corresponds to the normalization point (100%) of the plan as noted in 1) above.

4) High Dose Spillage

a) *Location*

Any dose greater than 105% of the prescription dose should occur primarily within the PTV itself and not within the normal tissues outside of the PTV. Therefore, the cumulative volume of all tissue outside of the PTV receiving a dose greater than 105% of prescription dose should be no more than 15% of the PTV volume. *However, if possible, attempts should be made to avoid higher than the prescription isodose to the prostatic urethra within the prostate.* Ideally, these hot spots will be manipulated to occur within the peripheral zones of the prostate. IMRT and other techniques will be encouraged to accomplish this goal.

b) *Volume*

Conformality of PTV coverage will be judged such that the ratio of the volume of the prescription isodose meeting criteria 1) through 4) to the volume of the PTV is ideally less than 1.3.

5) Respect all critical organ dose-volume limits listed in Section 6.5.1 below.

6) Urethral "hot spot" avoidance. It is recommended that efforts be made by the use of compensation or intensity modulation to avoid excessive dose to the urethra. The prostatic urethra should be identified as an avoidance structure such that dose beyond the prescription dose ideally does not fall on this structure. As an example, if the treatment dose covering the PTV corresponds to the 80% isodose line for a given patient, hot spots of 20% higher dose will exist within the prostate. The intensity modulation techniques should be employed to distribute these hot spots away from the prostatic urethra and more into the peripheral zones of the prostate. Part of the rationale for daily image guidance on this protocol is to carry out this intention of avoiding a "hot spot" to the urethra in practice during treatment as depicted on the treatment plan.

6.5 Critical Structures

6.5.1 *Critical Organ Dose-Volume Limits*

The following table lists maximum dose limits to a point or volume within several critical organs. These are absolute limits, and treatment delivery that exceeds these limits will constitute a major protocol violation (See Section 5.7). The dose is listed as total over 5 fractions and per fraction.

These limits were formulated with the approval of the study committee using known tolerance data, radiobiological conversion models, norms used in current practice at academic centers. Participating centers are encouraged to observe prudent treatment planning principles in avoiding unnecessary radiation exposure to critical normal structures irrespective of these limits.

In order to verify each of these limits, the organs must be contoured such that appropriate dose volume histograms can be generated. Instruction for the contouring of these organs will follow below.

Organ	Volume	Dose (cGy)
Spinal Cord	Maximum point dose	22 Gy (4.4 Gy per fraction)
	Less than 8 cc	20 Gy (4 Gy per fraction)

Cauda Equina	Maximum point dose	27.5 Gy (5.5 Gy per fraction)
	Less than 10 cc	25 Gy (5 Gy per fraction)
Sacral Plexus	Maximum point dose	30 Gy (6 Gy per fraction)
	Less than 10 cc	27.5 Gy (5.5 Gy per fraction)
Peri-prostatic Anterior rectal wall	Maximum point dose	No more than 105% of the prescription dose
Peri-prostatic Lateral rectal walls	Maximum point dose	No more than 100% of the prescription dose
	Less than 3 cc cumulative (both sides)	No more than 90% of the prescription dose
Peri-prostatic Posterior rectal wall and anus	Maximum point dose	No more than 45% of the prescription dose
Rectum superior to prostate	Maximum point dose	30 Gy (6 Gy per fraction)
	Less than 10 cc	25 Gy (5 Gy per fraction)
Small intestine	Maximum point dose	29 Gy (5.8 Gy per fraction)
	Less than 10 cc	19.5 Gy (3.9 Gy per fraction)
Prostatic urethra	Maximum point dose	No more than 105% of prescription dose
Bladder	Maximum point dose	No more than 105% of prescription dose
	Less than 10 cc	18.3 Gy (3.65 Gy per fraction)
Penile bulb	Maximum point dose	No more than 100% of prescription dose
	Less than 3 cc	30 Gy (6 Gy per fraction)
Femoral heads	Less than 10 cc cumulative (both sides)	30 Gy (6 Gy per fraction)
Skin within fold (e.g., the gluteal fold)	Maximum point dose	20 Gy (4 Gy per fraction)
Skin not within fold	Maximum point dose	27.3 Gy (5.45 Gy per fraction)
Seminal Vesicles	No dose constraint	Collect dose statistics for documentation only

6.5.2 *Contouring of Normal Tissue Structures*

6.5.2.1 Spinal Cord

The spinal cord will be contoured as one structure based on the bony limits of the spinal canal. The spinal cord should be contoured anywhere it is visualized in the treatment plan (typically superior to L2).

6.5.2.2 Cauda Equina

The cauda equina will be contoured as one structure based on the bony limits of the spinal canal. The cauda equina should be contoured starting superiorly at the bottom of the spinal cord (typically around L2 and terminal at the inferior extent of the thecal sac (typically at S3).

6.5.2.3 Sacral Plexus

The left and right sacral plexus will be contoured collectively as one structure. The location of the sacral plexus will be approximated by contouring the space defined medially by the sacral foramina from S1-S3 including contouring within the sacral foramina, posteriorly along the limits of the true pelvis, laterally to 2-3

cm lateral to the sacral foramina, and anteriorly about 3-5 mm from the posterior limits of the countour.

6.5.2.4 Peri-prostatic Rectal wall

The circumference of the rectum adjacent to the prostate will be divided into 4 equal quadrants (anterior, left lateral, right lateral, and posterior). Assigning 0 degrees at the most anterior aspect of the rectum at the mid sagittal plane, the dividing lines between each quadrant will occur at 45, 135, 225, and 315 degrees. The right and left lateral walls will be combined into a single structure. Only the rectal wall will be included in these contours, not the contents of the lumen. Patients will be treated with a rectal balloon filling the lumen which should therefore not be included in the contours.

6.5.2.4.1 *Anterior Peri-prostatic Rectal Wall*

Starting inferiorly just above the anal sphincter, the anterior quadrant of the rectal wall (from 315 to 45 degrees) should be contoured (absent the lumen) up to 1 cm above the superior extent of the prostate.

6.5.2.4.2 *Lateral Peri-prostatic Rectal Wall*

Starting inferiorly just above the anal sphincter, the lateral quadrant of the rectal wall (from 45 to 135 degrees and also from 225 to 315 degrees) should be contoured (absent the lumen) up to 1 cm above the superior extent of the prostate. These two structures should be combined as a single structure for purposes of dose volume analyses.

6.5.2.4.3 *Posterior Peri-prostatic Rectal Wall*

Starting inferiorly just above the anal sphincter, the posterior quadrant of the rectal wall (from 135 to 225 degrees) should be contoured (absent the lumen) up to 1 cm above the superior extent of the prostate.

6.5.2.5 Rectum Superior to Prostate

Starting inferiorly at the superior extent of the Peri-prostatic Rectal Wall described above, the entire wall and lumen of the rectum should be contoured up to the level of the sacral promontory.

6.5.2.6 Small Intestine

The small intestines should be contoured as a conglomerate of all bowel loops within each CT cut starting at the first appearance of small intestine in the pelvis and extending superiorly up to the level of the sacral promontory within each cut.

6.5.2.7 Prostatic Urethra

The prostatic urethra will be identified by the urethral catheter plus 1-2 mm of tissue radially into the prostate. The inferior aspect of the prostatic urethra coincides with the apex of the prostate (urethrograms may be helpful in identifying the apex). The superior aspect of the prostatic urethra coincides with the base of the prostate at the bladder inlet.

6.5.2.8 Bladder

The bladder should be contoured in its entirety absent its contents. As such, only the wall of the bladder is included in the dose volume analysis. The bladder wall may be approximated by contouring the outer outline of the entire bladder and subtracting this volume from the same volume minus 0.5 cm in all directions (to define the inner surface of the bladder).

6.5.2.9 Penile Bulb

The penile bulb will be contoured starting superiorly at the inferior aspect of the pelvic diaphragm (urethral sphincter) and extending inferiorly and anteriorly up to 3 cm.

6.5.2.10 Femoral heads

The femoral heads will be contoured bilaterally as one structure.

6.5.2.11 Skin

The skin will constitute the external contour minus 5 mm. The skin within folds, especially in the gluteal folds as the skin surfaces make contact, will be contoured as a separate structure.

6.5.2.12 Seminal vesicles

The seminal vesicles should be contoured right and left as one structure. There is no protocol dose constraint for these structures, but they will be contoured to collect dose deposition data.

6.5.2.13 Anus

Anus will be contoured as one structure starting just inferior to rectum.

6.6 Documentation Requirements

6.6.1 In general, treatment interruptions should be avoided by preventative medical measures and nutritional, psychological, and emotional counseling. Treatment breaks, including indications, must be clearly documented on the treatment record.

6.7 Compliance Criteria

6.7.1 *Accreditation Compliance*

All criteria listed in Section 5 must be completed to the satisfaction of the study committee in order to be accredited. Upon completion of the criteria, a letter will be sent to institutions' PIs informing them of accreditation for the study. No institution will be allowed to enroll patients without accreditation.

6.7.2 *Dosimetry Compliance*

Section 6 describes appropriate conduct for treatment planning dosimetry. Criteria for both major and minor deviations are provided in the table in Section 6.4. In addition to the criteria in section 6.4, the table in Section 6.5 lists dose volume limits for specific organs and structures. Exceeding these limits by more than 2.5% constitutes a minor protocol violation. Exceeding these limits by more than 5% constitutes a major protocol violation.

6.7.3 *Treatment Delivery Compliance*

Set-up films will be compared to digitally reconstructed radiographs from the same beam's eye view. Deviations of less than 0.5 cm will be considered compliant. Deviations from 0.5-0.75 cm will be considered minor protocol deviations. Deviations greater than those listed as minor will be considered major protocol deviations.

6.8 R.T. Quality Assurance Reviews

Dr. Timmerman, along with a medical physicist, will perform an RT Quality Assurance Review after complete data for the first 20 cases enrolled has been received at the University of Texas Southwestern. They will perform the next review after complete data for the next and subsequent 20 cases enrolled has been received at the University of Texas Southwestern. 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, whichever occurs first.

6.9 Radiation Adverse Events

6.9.1 *Gastro-intestinal*

Monitored treatment related toxicity associated with gastrointestinal function will include colitis, dehydration, diarrhea, enteritis, fistula, nausea, vomiting, obstruction, proctitis, fecal incontinence, stricture/stenosis, hemorrhage, and

ulcer. The consequences of gastro-intestinal toxicity should all be graded according to the Common Terminology Criteria For Adverse Events (CTCAE).

6.9.2 *Renal/Genitourinary/Sexual/Reproductive*

Monitored treatment related toxicity associated with renal and genito-urinary function will include cystitis, fistula, urinary incontinence, urinary obstruction, stricture/stenosis, hemorrhage, and urinary retention. Monitored treatment related toxicity associated with sexual and reproductive function will include erectile dysfunction and ejaculatory dysfunction. The consequences of renal/genitourinary/sexual and reproductive toxicity should all be graded according to the Common Terminology Criteria For Adverse Events (CTCAE). In addition, patients will fill out the AUA scoring sheets reflecting basic urinary function at regular intervals according to the study calendar in Appendix VI.

6.9.3 *Neurology*

Monitored treatment related toxicity associated with neurology function will include myelitis, motor and sensory neuropathy, plexopathy, and pain. The consequences of neurology toxicity should all be graded according to the Common Terminology Criteria For Adverse Events (CTCAE).

6.9.4 *Constitutional Symptoms*

Monitored treatment related toxicity associated with constitutional function will include fatigue, fever, and weight loss. The consequences of constitutional toxicity should all be graded according to the Common Terminology Criteria For Adverse Events (CTCAE).

6.9.5 *Skin*

Monitored treatment related toxicity associated with skin function will include fibrosis, rash (desquamation), ulceration, and telangiectasia. The consequences of skin toxicity should all be graded according to the Common Terminology Criteria For Adverse Events (CTCAE).

6.9.6 *Quality of Life and Other Toxicities*

Other treatment related toxicity attributed to the therapy will be captured, recorded and the consequences of should all be graded according to the Common Terminology Criteria For Adverse Events (CTCAE). Quality of life after prostate cancer treatment will be assess using the Expanded Prostate Cancer Index Composite (EPIC) formalism [41]. Validation and description of this scale can be found at the website: http://roadrunner.cancer.med.umich.edu/epic/epicmain.html

6.10 Serious Adverse Event Reporting

6.10.1 ERGO

Electronic Research Grant Organizer (ERGO) constitutes a mechanism for reporting serious adverse events to the UTSW IRB for reporting purposes.

Any adverse event equivalent to CTCAE V.3 grade 3, 4, or 5 or which precipitates hospitalization or prolongs an existing hospitalization must be reported regardless of designation (expected or unexpected) along with the attribution. This includes all deaths that occur within 30 days after the patient was discontinued from the study regardless of attribution AND any events that occur beyond 30 days and are considered probably related to treatment.

Participating sub-sites must file an SAE report (the CRF plus information describing the event, the grade, and the attribution) within 48 hours of the investigator's awareness of the occurrence of the event.

Attribution of an event can be categorized as:

- Not Related
- Possibly Related
- Likely Related

Adverse events (below grade 3) do not need to be submitted immediately. Rather, they should be documented in the Adverse Events CRF along with a brief description of the event, grade, and attribution).

All SAE reports should be made via FAX transmission to:

Department of Radiation Oncology
Clinical Research Office
The University of Texas Southwestern Medical Center
Attention: Jean Wu, Project Manager
FAX #: 214-648-5923

7.0 DRUG THERAPY

Not applicable to this trial.

8.0 OTHER THERAPY

8.1 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.

8.1.1 Obstructive flow medicines (alpha blockers) 5 alpha reductase inhibitors)
8.1.2 Antiemetics
8.1.3 Anticoagulants
8.1.4 Antidiarrheals
8.1.5 Analgesics
8.1.6 Hematopoietic Growth Factors
8.1.7 Herbal products
8.1.8 Nutritional supplementation

9.0 SPECIMEN SUBMISSION

9.1 Specimen Investigational Nature

Initially serum will be collected in order to build proteomic profiles of treatment response, however, with time there may be other analytical methodologies that are not yet devised. Blood cells will be processed and RNA and DNA collected. Ultimately, gene expression and genotyping will be performed and correlated with treatment outcome or normal tissue response.

9.2 Specimen Collection for Translational Research

Serum will be collected and frozen for subsequent analysis for patients who choose to participate

9.3 Whole blood will be drawn [20 ml per collection timepoint: 10 ml from red top and 10 ml from lavender top tubes] using standard procedure in order to collect lymphocytes as well as plasma serum. Blood will be processed using standard procedure immediately after it is collected and then stored at -70 to -80 degrees C. The samples will be kept indefinitely or until exhausted.

9.3.1 Collection Timepoints

1. Within 1 week prior to the first treatment (baseline)
2. Immediately after the first treatment
3. Immediately before the second treatment (approximately 48-72 hours after the first treatment)
4. Immediately after the fifth treatment
5. 6 months after completing the fifth treatment

9.3.2 A Pathology Report from the pretreatment core biopsy describing the original tumor specimen is required. 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.

9.3.3 For serum collection, the following materials must be provided: the date of collection of the serum, timepoint of blood collection, type of sample, the protocol number, and the patient's study specific study-ID number.

9.3.4 Submit materials for Translational Research to:

Michael Story, Ph.D.
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd, Dallas, Texas 75390
(214) 648-5557
Michael.Story@utsouthwestern.edu

9.4 Confidentiality/Storage

9.4.1 Upon receipt, the specimen is labeled with the protocol number and the patient's assigned study-identification number only. The 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.

9.4.2 Specimens for translational research will be stored for an indefinite period of time (or until exhausted) and may be used 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.

9.4.3 Specimen will be stored at the UT Southwestern Medical Center Division of Molecular Radiation Biology laboratories (NC 7.206) and the UT Southwestern Tissue Repository.

10.0 PATIENT ASSESSMENTS

10.1 Study Parameters: See Appendix II.

10.2 Follow-up Schedule

10.2.1 Initial follow-up visit at 1.5 months from the end of treatment.

10.2.2 After initial follow-up visit, follow-up will be done at 3, 6, 9, and 12 months post therapy.

10.2.3 Then every six months until three years post treatment.

10.2.4 Then annually for years 3-10.

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

10.3 Criteria for Toxicity

10.3.1 All acute and late adverse events from protocol radiation therapy will be reported and scored for severity using the NCI Common Terminology Criteria for Adverse

Events (CTCAE) version 3.0. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov).

Please note that this study will not be using separate toxicity scales for acute and late radiation adverse events.

10.4 Measurement of Response

10.4.1 Although not required, it is encouraged that prostate tumor dimensions in centimeters or grams be recorded on the data collection forms for the follow up evaluations. PSA levels should be obtained per study calendar.

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

10.4.2.1 No Evidence of Disease (NED): No clinical evidence of disease on digital rectal examination and no PSA failure.

10.4.2.2 Equivocal Disease (ED): This rating will be assigned under the following circumstances:

1) If abnormalities are present on the prostate digital rectal examination but are thought to be abnormal due to treatment and felt not to represent tumor.
2) If clinical evidence of residual tumor is present but this has regressed from a previous examination (initial registration).
3) PSA 2.1 - 4 ng/mL. Rebiopsy is required, before starting hormone therapy, in any patient with PSA failure but with negative bone scan and CT scans. If the biopsy is negative, then they will be scored as NED.

10.4.2.3 Progressive Disease (PD): Progressive disease will be declared if one or more of the following criteria are met:

1) Clinical evidence in the prostate gland of disease progression or recurrence.
2) Clinical or radiographic evidence of tumor recurrence within the pelvic lymphatics or soft tissue beneath the bifurcation of the common iliac arteries,
3) Clinical or radiographic evidence of hematogenous (osseous, hepatic, etc.) and/or extrapelvic lymphatic of soft tissue relapse.

10.5 Other Response Parameters

10.5.1 Disease-Free Interval: The disease-free interval will be measured from the date of accession to the date of documentation of progression or until the date of death (from other causes).

10.5.2 Time to Biochemical Failure: The RTOG-ASTRO definition (also known as the Phoenix definition) of PSA failure will be used. Thus, when the PSA rises by more than 2 ng/ml above the lowest level (nadir) achieved after treatment, biochemical failure has occurred and the date of the failure is recorded at the time the nadir plus 2 ng/ml level is reached.

10.5.3 Time to Local Progression: The time to progression will be measured from the date of study entry to the date of documented local progression as determined by clinical exam.

10.5.4 Time to Distant Failure: The time to distant failure will be measured from the date of study entry 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 failure only.

10.5.5 Overall Survival: The survival time will be measured from the date of accession to the date of death. All patients will be followed for survival. Every effort should be made to document the cause of death.

10.5.6 Disease-Specific Survival Disease-specific survival will be measured from the date of study entry to the date of death due to prostate cancer. The following will be considered as failure events in assessing disease specific survival:

Death certified as due to prostatic cancer.

Death from other causes with active malignancy (clinical or biochemical progression).

Death due to complications of treatment, irrespective of the status of malignancy.

Death from other causes with previously documented relapse (either clinical or biochemical) but inactive at the time of death will not be considered in disease-specific survival, but will be analyzed separately.

10.5.7 Responsibilities of the Medical Monitor:

The medical monitor is required to review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the medical monitor must comment on the outcomes of the event or problem and in case of a serious adverse event or death, comment on the relationship to participation in the study. The medical monitor must also indicate whether he/she concurs with the details of the report provided by the principal investigator. Reports for events determined by either the investigator or medical monitor to be possibly or definitely related to participation and reports of events resulting in death must be promptly forwarded to the USAMRMC ORP HRPO.

11.0 DATA COLLECTION

Data should be submitted to:

Department of Radiation Oncology
Clinical Research Office
The University of Texas Southwestern Medical Center
Attention: Jean Wu, Project Manager
5801 Forest Park Road
Dallas, Texas 75390-9183
FAX #: 214-648-5923

Patients will be identified only by initials (first middle last) and a unique study ID number assigned to each study participant; 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. Participating sub-sites must remove or black-out identifiers from source documentation that is sent to UTSW.

11.1 Summary of Data Submission

Item	Due
Demographics	Within 2 weeks of study entry
Eligibility and Entry Characteristics including baseline H&P and PSA	Within 2 weeks of study entry
Pathology Report	Within 2 weeks of study entry
AUA and EPIC baseline forms	Within 2 weeks of study entry
SBRT dosimetry information	Within 1 week after completion of SBRT
Follow-up H&P data including PSA	After last SBRT treatment, post SBRT follow-up at 1.5, 3, 6, 9, 12 months, then every 6 months to 3 years; then annually for years 3-10

AUA and EPIC post treatment forms	After last SBRT treatment, post SBRT follow-up at 1.5, 3, 12, and 18 months
Adverse Event assessment	After each SBRT treatment, then post SBRT follow-up at 1.5, 3, 6, 9, and 12 months, then every 6 months to 3 years; then annually for years 3-10

13.0 STATISTICAL CONSIDERATIONS

13.1 Phase I Study Endpoints

13.1.1 *Primary Endpoint*

The primary endpoint of the phase I portion is to either reach the maximum tolerated dose (MTD) or a dose of 50 Gy total (whichever comes first) by escalating the dose of SBRT toward the tumorcidal dose of 50 Gy total. Patients will be treated in cohorts of seven to fifteen,.. Toxicity will be graded using the NCI Common Toxicity Criteria for Adverse Events (CTCAE) v. 3.0. A dose- limiting toxicity (DLT) is any treatment-related grade 3, 4, or 5 toxicity in the following categories (specific conditions listed in section 6.9): gastrointestinal, renal, genito-urinary, sexual- reproductive, or neurological. A DLT will also include any treatment-related grade 4 or 5 toxicity related in the following categories (specific conditions listed in section 6.9): constitutional symptoms. In addition, any other grade 4 or 5 toxicity attributed to the therapy constitutes DLT. All reported DLTs will be verified by study chair, data monitoring committee, and independent review before final determination that a DLT has in fact occurred. Doses will be escalated an additional 0.5 Gy per treatment for 5 treatments (total 2.5 Gy per increment). The phase I portion of the study will be completed when either of the following events occur: 1) the MTD for a cohort is reached or 2) when the highest protocol dose level is treated and tolerated (10 Gy per fraction, total 50 Gy) where we consider the therapy likely to be tumorcidal per determination of the investigators.

13.1.2 *Phase I Dose Escalation*

The phase I study is designed to end if the rate of DLTs within 90 days from the start of treatment is 33% or higher. For each dose level cohorts, a total of seven to fifteen patients will be enrolled. If zero out of the first seven with 90 day follow-up, two or fewer out of the first nine with 90 day follow-up, three or fewer out of the first twelve with 90 day follow-up, or four or fewer out of the first fifteen of patients with 90 day follow-up experience a DLT as defined above, then the dose will escalate to the next dose level. If three or more of the first nine patients, four or more of the first twelve, or five or more of the first fifteen patients experience a DLT, then the MTD will be considered to have been exceeded. The MTD will be defined as the immediately previous lower dose level tolerated. The probability that at least two of nine patients will experience a DLT when the true rate of acute DLTs is 33% is 0.80; that is, the probability of making the correct decision if the true DLT rate is at least 33% is 0.80.

The sample size of the phase I component of this study will not exceed 45 patients.

13.1.3 *Phase I Waiting Periods*

Dose escalation on the phase I portion of this study should not occur until a sufficient waiting period has occurred after patients have been treated. A period of 90 days must pass in order to assess toxicity. If 90 days have transpired without DLT in each

of the first seven (7) patients enrolled to a specific dose level, then dose escalation to the next level may proceed. Patients will continue to be enrolled to each dose level (up to a maximum of 15 patients) with ongoing assessment of those reaching 90 day follow-up so long as either criteria for defining the MTD (section 13.1.2) or criteria for further dose escalation is not reached. If fifteen patients are enrolled to a given dose level yet criteria for adequate follow-up are not reached in a representative sample of patients (section 13.1.2), further enrollment to the protocol will be suspended until adequate follow-up is reached.

13.2 Phase II Study Endpoints

Patients will be treated at either the MTD or highest dose from the phase I study.

13.2.1 *Primary Endpoint*

Late severe GU and GI toxicity is defined as grade 3-5 GU and GI toxicity occurring between 270-540 days (i.e., 9-18 months) from the start of the protocol treatment. It is graded based on CTCAE v3.0. Grade 3-5 GU or GI toxicity that originally occurred prior to 270 days from start of protocol treatment will only be considered late severe GU or GI toxicity if it persists at a severity grade of 3-5 based on CTCAE v3.0 after 270 days.

13.2.2 *Secondary Endpoints*

- Acute severe GU and GI toxicity is defined as grade 3-5 toxicity occurring prior to 270 days from the start of protocol treatment. It is graded based on CTCAE v3.0.
- Non GU and GI toxicity.
- Biochemical failure RTOG-ASTRO definition (also known as Phoenix definition) - Thus, when the PSA rises by more than 2 ng/ml above the lowest level (nadir) achieved after treatment,, biochemical failure has occurred and the date of the failure is recorded at the time the nadir plus 2 ng/ml level is reached.
- Overall survival
- Disease-specific survival
- Clinical progression including local/regional and distant relapse

13.3 Sample Size

13.3.1 *Overview*: The primary goal of this study is to estimate the rate of late grade 3-5 genitourinary and gastrointestinal toxicity following treatment with stereotactic body radiation therapy. For purposes of this phase II study, late toxicity will be defined as toxicity occurring 270-540 days (i.e., 9-18 months) from the start of radiotherapy. It is graded based on CTCAE v 3.0.

13.3.2 *Sample Size Derivation*: The phase II component of this study is designed to test whether late GU/GI toxicity at 270-540 days from the start of treatment following the protocol treatment is above 10%. The sample size is determined so that the probability of rejecting the treatment because of excessive late toxicity is 90% if the true late toxicity rate is 23% or higher. Assuming an exponential distribution for time from the end of the acute period *(270 days from the start of protocol treatment)* to the occurrence of late toxicity, the hazard rate for the expected 10% toxicity rate and the unacceptable 23% toxicity rate is 0.006/month and 0.015/month, respectively. Following the asymptotic property of the observed hazard and using Z-test for the logarithm of the hazard ratio [35-36], we require 12 cases with severe late GU/GI toxicity. Thus, 47 patients are required to be accrued within three to four years and be followed for 270 days after the acute period (i.e., a total of 540 days) to have a statistical power of 90% with a one-sided significance level of 0.05. Considering 5% ineligible cases and lack-of-data cases, the sample size of the phase II component of this study is 50 patients. Patients treated in phase I at the dose level ultimately used in phase II will be included in the phase II analysis as part of the 50 patient trial.

The sample size of the phase II component of this study will not exceed <u>50</u> patients.

13.4 Patient Accrual and Study Duration

13.4.1 It is expected that it will take approximately three to five years to complete the study. The analysis for late toxicity will be carried out after each patient has had at least 270 days (i.e., 9 months) of follow-up from the end of the acute period, a total of 540 days (i.e., 18 months) of follow-up. For the secondary endpoint of biochemical failure, an additional 18 months of follow-up are needed to estimate the 3-year failure rate. Study-related data will be stored for 5 years after termination of the study when accrual is no longer taking place and all patients have discontinued follow-up procedures. Blood drawn for translation research will be kept indefinitely or until exhausted.

13.5 Analysis Plan

Interim Reports: Interim reports will be prepared every six months until the results of the study are published. In general, the interim reports will contain information about patient accrual rate with projected completion dates of the trial, status of QA review and compliance rate of treatment per protocol, and the frequencies and severity of toxicity.

13.5.2 *The Analysis of Severe Late GU/GI Toxicity*: This analysis will be carried out when each patient has had at least 270 days (i.e., 9 months) of follow-up after the end of the acute period, a total of 540 days (i.e., 18 months) of follow-up. The time to the occurrence of severe late GU/GI toxicity is defined as the time interval from start of protocol treatment to the date of onset of grade 3-5 GU/GI toxicity. The time analysis for recording severe late GU/GI toxicity for this protocol will be limited to 540 days from start of protocol therapy. If no such toxicity is observed before the time of the analysis, the patient will be censored at the time of the analysis. The hazard rate will be estimated by the life table approach with a time span of 18 months. The one-sided Z-test will be used to test the significance of the difference between the logarithm of the observed hazard rate and the logarithm of the hypothesized hazard rate of 0.006/month with variance equal to the reciprocal of the number of cases with late toxicity observed. Because of the lead time of 9 months for the acute period, the 18-month late toxicity will be estimated by the 9-month toxicity rate using the cumulative incidence approach [37] to the defined time to severe late GU/GI toxicity.

13.5.3 *Estimation of Secondary Endpoints Related to the Efficacy*: Cumulative incidence approach [37] will be used to estimate the failure rate for biochemical, disease-specific, local-regional and distant failures. Kaplan-Meier method [38] will used to estimate the overall survival rate.

13.6 Gender and Minorities

<u>Projected Minority Inclusion</u>

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	NA	14	14
Not Hispanic or Latino	NA	83	83
Ethnic Category: Total of all subjects*	NA	**97**	**97**
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	NA	2	2
Asian	NA	6	6
Black or African American	NA	16	16
Native Hawaiian or other Pacific Islander	NA	2	2

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
White	NA	57	57
Racial Category: Total of all subjects*	NA	97	**97**

NA = Not Applicable

14.0 DATA SAFETY MONITORING PLAN

14.1 Data Safety Monitoring Committee and Institutional IRB reporting

A data safety monitoring committee including radiation oncologists not participating in this trial will be formed to review toxicity endpoints and efficacy data. In the phase I component, the data safety monitoring committee will review and verify all reported DLTs. In particular, this committee will scrutinize the grading of adverse events and the attribution to therapy previously assigned by the investigators. This panel will have access to basic patient information so as to have the ability to critically review toxicity events. This study will use this committee to perform ongoing safety assessment at regular defined intervals defined in the statistics section of this protocol. Unexpected toxicities occurring between defined interim analyses points will be reported to the treating center's IRB and also to the University of Texas Southwestern IRB.

14.2 Early Stopping for Toxicity

In phase I, stopping for toxicity will be related to dose limiting toxicity as described in the statistical section. Early stopping of the phase II portion of this protocol will be based on unacceptable toxicity, defined as grade 3 - 5 toxicity related to the following organ systems: gastrointestinal, renal, genitor-urinary, sexual, reproductive, neurological, blood, bone marrow, or constitutional symptoms OR any other grade 4 or 5 toxicity attributed to the therapy occurring in 30% or more of treated patients. If a single patient has more than one unacceptable toxicity, they will only be counted as one unacceptable toxicity for this analysis.

Three interim analyses of toxicity are planned after 25% (12 patients), 50% (24 patients), and 75% (36 patients) of the total number of evaluable patients to be accrued in phase II. These interim analyses will be done after patients have finished their toxicity assessment periods for each group (i.e., 90 days of post therapy follow-up).

The following early stopping rules reject the null hypothesis that the toxicity rate is less than or equal to 10% in favor of the alternative hypothesis that the toxicity rate is at least 30% with an overall Type I error rate of no more than 0.05[5]:

6 or more cases of unacceptable toxicities out of the first 12 evaluable patients, or
7 or more cases of unacceptable toxicities out of the first 24 evaluable patients, or
8 or more cases of unacceptable toxicities out of the first 36 evaluable patients.

The final analysis will test the same null hypothesis using the rejection rule of 10 or more patients with unacceptable toxicities out of the total sample of 47 evaluable patients. This will insure an overall significance level of 0.05 for the final conclusion. If more than 47 of the 50 accrued patients are evaluable, then the first 47 evaluable patients will be used for this analysis.

If the number of unacceptable toxicities observed demonstrate via the monitoring rules above that the treatment-related unacceptable toxicity rate is 30% or more, consideration

will be initiated for stopping the study. In this case, the study chair, study PIs, and statistician will review the toxicity data along with the Data Safety Monitoring Committee and make appropriate recommendations about continuing the study. Additionally, the treatment-related unacceptable toxicity rate will continued to be monitored during the five year follow-up period. If the unacceptable toxicity rate exceeds 30% at any time during the five year follow-up period, the study chair, study PIs, and statistician will review the toxicity data along with the Data Safety Monitoring Committee and make appropriate recommendations about reporting the information.

14.3 Reporting Requirements and Responsibilities of the Organizing PI to the USAMRMC, ORP, and HRPO:

The protocol will be conducted in accordance with the protocol submitted to and approved by the USAMRMC ORP HRPO and will not be initiated until written notification of approval of the research project is issued by the USAMRMC ORP HRPO.

Accurate and complete study records will be maintained and made available to representatives of the U.S. Army Medical Research and Materiel Command as a part of their responsibility to protect human subjects in research. Research records will be stored in a confidential manner so as to protect the confidentiality of subject information.

All unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and subject deaths related to participation in the study should be promptly reported by phone (301-619-2165), by email (hsrrb@det.amedd.army.mil), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-ZB-PH, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

Any deviation to the protocol that may have an effect on the safety or rights of the subject or the integrity of the study must be reported to the USAMRMC ORP HRPO as soon as the deviation is identified.

Major modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the USAMRMC ORP HRPO for approval prior to implementation. All other amendments will be submitted with the continuing review report to the USAMRMC ORP HRPO for acceptance.

A copy of the approved continuing review report and the local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available. A copy of the approved final study report and local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available.

The knowledge of any pending compliance inspection/visit by the FDA, OHRP, or other government agency concerning clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters or actions taken by any Regulatory Agencies including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements will be reported immediately to USAMRMC ORP HRPO.

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APPENDIX I
STUDY PARAMETER TABLE

	Pre-Treatment			During Treatment	Follow-Up (months after therapy)											
	Within 180 days of study entry	Within 90 days of study entry	Within 30 days of study entry	With each treatment	1.5	3	6	9	12	18	24	30	36	42	48	54
Prostate Biopsy with Gleason Score for Diagnosis	X[e]															
PSA			X[a]		X	X	X	X	X	X	X	X	X	X	X	X
History/physical			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight			X		X	X	X	X	X	X	X	X	X	X	X	X
Performance Status			X		X	X	X	X	X	X	X	X	X	X	X	X
CT or MRI of pelvis		X		X[b]												
AUA Symptom index			X		X	X			X	X						
EPIC Questionnaire			X		X	X			X	X						
BUN, creatinine, CBC, & platelets		X[c]														
Blood Draw for Translational Research			X[f]	X[g]			X									
Informed consent			X													
Tumor response evaluation			X		X	X	X	X	X	X	X	X	X	X	X	X
Bone scan[D]																
Adverse event evaluation				X	X	X	X	X	X	X	X	X	X	X	X	X

[a]Baseline PSA should be recorded as pre-hormonal level if taking hormones even if >30 days prior to entry.
[b]CT or MRI prior to each treatment may include conebeam CT, orthogonal imaging of seeds or daily ultrasound localization is acceptable alternative to daily CT or MRI.
[c]For reference but not eligibility
[d]At time of PSA failure or suspected progression
[e]Repeat prostate biopsy for patients with biopsy >180 days from study entry is not required unless the PSA taken at within 30 days of study entry is greater than the PSA taken at the time of biopsy by more than 5 ng/ml.
[f]1 week prior to first treatment
[g]Immediately after first treatment, immediately before second treatment, immediately after fifth treatment.

APPENDIX II

ZUBROD PERFORMANCE SCALE

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

KARNOFSKY PERFORMANCE SCALE

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

APPENDIX III

AJCC STAGING SYSTEM
PROSTATE, 6th Edition

DEFINITION OF TNM

Primary Tumor, Clinical (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

T1 Clinically inapparent tumor neither palpable or visible by imaging
- T1a Tumor incidental histologic finding in 5% or less of tissue resected
- T1b Tumor incidental histologic finding in more than 5% of tissue resected
- T1c Tumor identified by needle biopsy (e.g., because of elevated PSA)\

T2 Tumor confined with prostate*
- T2a Tumor involves one-half of one lobe or less
- T2b Tumor involves more than one-half of one lobe but not both lobes
- T2c Tumor involves both lobes

T3 Tumor extends through prostate capsule**
- T3a Extracapsular extension (unilateral or bilateral)
- T3b Tumor involves the seminal vesicle(s)

T4 Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles and/or pelvic wall.

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

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

Regional Lymph Nodes (N)

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

Primary Tumor, Pathologic (pT)

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

pT3 Extraprostatic extension
- pT3a Extraprostatic extension**
- pT3b Seminal vesicle invasion
- pT4 Invasion of bladder, rectum

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

AJCC STAGING SYSTEM
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Distant Metastasis (M)*

MX	Presence of distant metastasis cannot be assessed (not evaluated by any modality)	
M0	No distant metastasis	
M1	Distant metastasis	
	M1a	Nonregional lymph node(s)
	M1b	Bone(s)
	M1c	Other site(s) with or without bone disease

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

Histopathologic Grade (G)

GX	Grade cannot be assessed
G1	Well-differentiated (slight anaplasia [Gleason 2-4])
G2	Moderately differentiated (moderate anaplasia [Gleason 5-6])
G3-4	Poorly undifferentiated or undifferentiated (marked anaplasia [Gleason 7-10])

Stage Grouping

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

APPENDIX V

GLEASON CLASSIFICATION

Histologic patterns of adenocarcinoma of the prostate

Pattern	Margins Tumor Areas	Gland Pattern	Gland Size	Gland Distribution	Stromal Invasion
1	Well defined	Single, separate, round	Medium	Closely packed	Minimal, expansile
2	Less definite	Single, separate rounded but more variable	Medium	Spaced up to one gland diameter, average	Mild, in larger stromal planes
3	Poorly defined	Single, separate more irregular	Small, medium, or large	Spaced more than one gland diameter, rarely packed	Moderate, in larger or smaller stromal planes
or 3	Poorly defined	Rounded masses of cribriform or papillary epithelium	Medium or large	Rounded masses with smooth sharp edges	Expansile masses
4	Ragged, infiltrating	Fused glandular masses or "hypernephroid"	Small	Fused in ragged masses	Marked, through smaller planes
5	Ragged, infiltrating	Almost absent, few tiny glands or signet ring	Small	Ragged anaplastic masses of epithelium	Severe between stromal fibers or destructive
or 5	Poorly defined	Few small lumina in rounded masses of solid epithelium central necrosis	Small	Rounded masses and cords with smooth sharp edges	Expansile masses

The Gleason Classification is a system of histologic grading based on over-all pattern of tumor growth at relatively low-magnification *(40 to 100x)*. Five patterns of growth are recognized and numbered in order of increasing malignancy. Because of histologic variation in the tumor, two patterns are recorded for each case, a primary or predominate pattern and a secondary or lesser pattern.

The Gleason Score is the sum of the primary and secondary pattern, If only one pattern is present, the primary
and secondary pattern receive the same designation.

(Primary = 2, Secondary = 1, Gleason = 3)
(Primary = 2. Secondary = 2, Gleason = 4)

1. Gleason, D.F. et al: Prediction of prognosis for prostatic carcinoma by combined histologic grading and clinical staging. J Urol 111:58, 1974.

APPENDIX VI

ON-STUDY AUA SYMPTOM SCORE (PQ)

PATIENT NAME _____ CASE # _____

INSTITUTION NAME _____ TOTAL SCORE _____

PLEASE FILL OUT THIS SHORT QUESTIONNAIRE TO HELP US FIND OUT MORE ABOUT ANY URINARY PROBLEMS YOU MIGHT HAVE. CIRCLE A NUMBER IN EACH COLUMN THAT BEST DESCRIBES YOUR SITUATION. YOU MUST ANSWER ALL QUESTIONS.

	Not at all	**Less than one time in five**	**Less than half the time**	**About half the time**	**More than Half the time**	**Almost always**
1. Over the past month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	**0**	**1**	**2**	**3**	**4**	**5**
2. Over the past month or so, how often have you had to urinate again, less than two hours after you finished urinating?	**0**	**1**	**2**	**3**	**4**	**5**
3. Over the past month or so, how often have you found you stopped and started again several times when you urinated?	**0**	**1**	**2**	**3**	**4**	**5**
4. How often do you find it difficult to postpone urination?	**0**	**1**	**2**	**3**	**4**	**5**
5. Over the past month or so, how often have you had a weak urinary stream?	**0**	**1**	**2**	**3**	**4**	**5**
6. Over the past month or so, how often have you had to push or strain to begin urination?	**0**	**1**	**2**	**3**	**4**	**5**
	Not at all	**Once every 8 hours**	**Once every 4 hours**	**Once every 3 hours**	**Once every 2 hours**	**At least once every hour**
7. Over the past month or so, how often did you most typically get up at night to urinate?	**0**	**1**	**2**	**3**	**4**	**5**

Total per column _____ _____ _____ _____ _____

_____ _____

Patient Signature Date This Form was Completed

APPENDIX VII

EXPANDED PROSTATE CANCER INDEX COMPOSITE (EPIC)

Quality of life after prostate cancer treatment will be assessed using the Expanded Prostate Cancer Index Composite (EPIC) formalism [41]. Validation and description of this scale can be found at the website: http://roadrunner.cancer.med.umich.edu/epic/epicmain.html

The actual forms used for this assessment can also be downloaded on a PDF file from this website. We will use the standard form for this protocol.

Appendix VIII

Risks to Subjects

Procedure	Risks	Measures to Minimize Risks
History and physical exam (H&P), digital rectal exam (DRE), PSA test at study entry and 1.5, 3, 6, 9, and 12 months post-treatment, then every 6 months for 5 years; annually for years 5-10)	Discovery of previously unknown condition/progression of prostate cancer	Will be performed by MD and/or nurse practitioner with oncology experience.
Blood draws (at all study timepoints)	Discomfort, bleeding, bruising, dizziness, fainting, infection	Blood will be drawn by an experienced phlebotomist.
Zubrod Performance status evaluation; AUA Questionnaire – to measure urinary symptoms; EPIC Questionnaire – to assess quality of life after prostate cancer treatment	Discomfort, psychological stress of answering personal questions	Subjects informed that they may refuse to answer, take a break, or discontinue participation at any time
Metallic marker implantation into prostate (once prior to treatment)	Discomfort, bleeding, bruising, dizziness, fainting, infection	An experienced professional will perform this procedure.
Self-administered Fleet's enema (1 or 2 prior to screening visit and each treatment)	Discomfort	Detailed instructions will be provided.

Insertion of urethral catheter (at treatment planning)	Very likely: Pain or discomfort during insertion; Less likely, but serious: Bleeding from the urethra or bladder, urethral irritation with urge to urinate frequently, urinary tract infection	Every effort will be made to minimize discomfort. Antibiotics will be prescribed as necessary. The urethra may be numbed with local anesthesia, and the thinnest catheter possible will be used.
Insertion of rectal balloon (at treatment planning and prior to each treatment)	Very likely: Pain or discomfort during insertion; Less likely, but serious: Bleeding from the rectum, rectal irritation with urge for frequent bowel movements	Performed by an experienced physician, nurse, or technician.
Stereotactic body radiation therapy (5 treatments)	<u>Dermatologic</u>: Very likely: Skin redness or tanning, rash, itching, peeling, temporary hair loss in treatment area	Referral to a dermatologist if necessary.
	<u>Gastrointestinal.</u> Very likely: Nausea, diarrhea, abdominal cramps, rectal irritation with frequent urge to have a bowel movement, bowel movements with mucus; Less likely: Incontinence; Less likely but serious: Injury to bowel, rectal bleeding, intestinal obstruction	Premedication with corticosteroid suggested; insertion of rectal balloon
	<u>Genitourinary.</u> Very likely: Bladder irritation with frequent urge to urinate, burning on urination, injury to urethra slowly causing a narrowing (may need surgical correction); Less likely: Incontinence; Less likely but serious: Injury to bladder, urethra or other tissues in pelvis or abdomen; urinary obstruction	Recommended premedication with corticosteroid, alpha blocker, 5 alpha reductase inhibitor; imaging guidance prior to each treatment suggested; care taken to minimize dose to bulbous urethra and bladder; wedges or other modulation methods to steer higher dose away from prostatic urethra
	<u>Sexual/Reproductive.</u> Very likely: Impotence (may be irreversible); Less likely: Ejaculatory dysfunction (may be irreversible), sterility	Restriction of dose on penile bulb.
	<u>Teratogenic</u>: possible harm to an unborn child	Use of contraception required for participation; need for immediate

		reporting of causing a pregnancy stressed
	<u>Constitutional</u>: Very likely: fatigue	Participants will be educated and asked to inform study personnel if encounter symptoms.
	General discomfort from lengthy (60 – 90 minutes) procedure	Premedication with analgesic recommended.
FAX transmittal of case report forms (CRFs) to primary site	Loss of privacy	Sensitive patient information will be blacked-out. CRFs will only be identified by subject initials and unique, study identification number before fax transmittal.
Unforeseen risks	E.g., unpredictable interaction between SBRT and concomitant medications	Strong encouragement to report any difficulties and keep researchers aware of any change in medications