Official Title: Phase II Study of Stereotactic Ablative Radiotherapy (SABR) for Low/Intermediate Risk Prostate Cancer with Injectable Rectal Spacer

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UT SOUTHWESTERN
Harold C. Simmons Cancer Center

Phase II Study of Stereotactic Ablative Radiotherapy (SABR) for Low/Intermediate Risk Prostate Cancer with Injectable Rectal Spacer
STU 092013-013

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Amendment/Version # 9

PROTOCOL NUMBER: STU 092013-013
PROTOCOL TITLE: Phase II Study of Stereotactic Ablative Radiotherapy (SABR) for Low/Intermediate Risk Prostate Cancer with Injectable Rectal Spacer

Principal Investigator (PI) Name: Dr. Michael Folkert

PI Signature: _____

Date:_____

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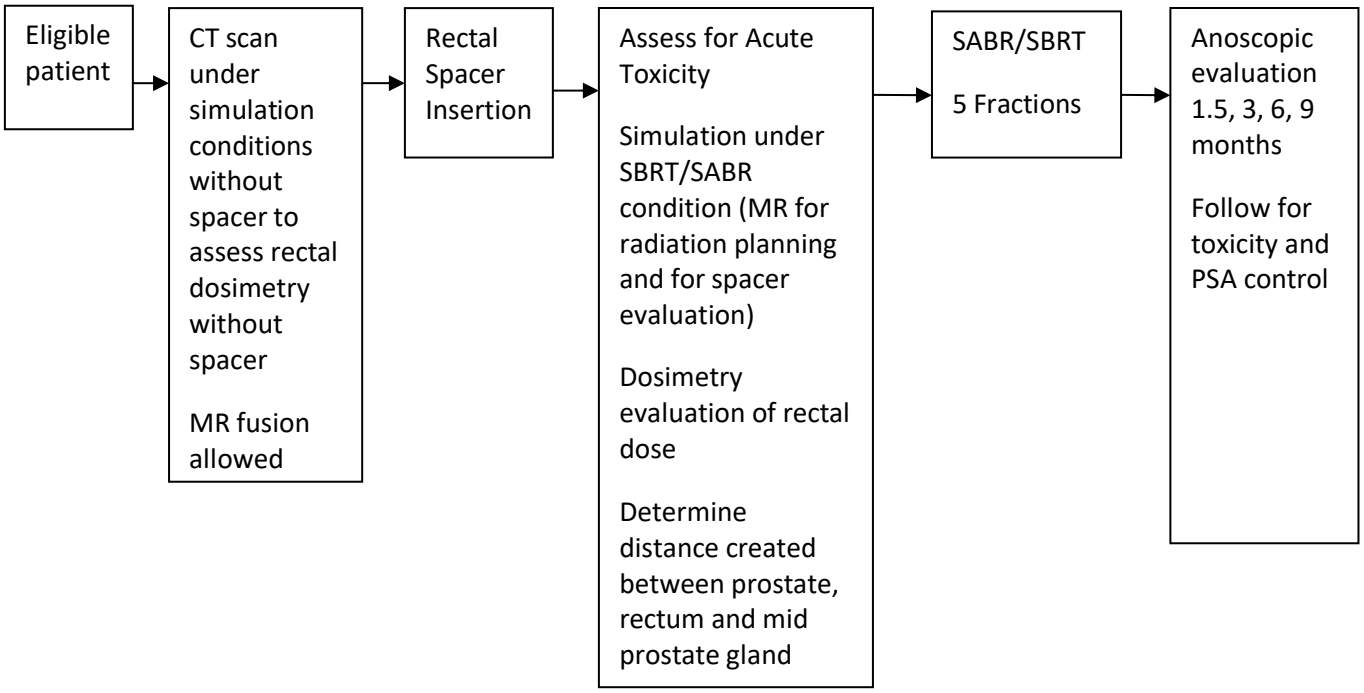
LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DOT	Disease Oriented Team
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IHC	Immunohistochemistry
IND	Investigational New Drug
IV (or iv)	Intravenously
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
pCR	Pathologic Complete Response
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
p.o.	peros/by mouth/orally
PR	Partial Response
RCB	Residual Cancer Burden
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SCCC	Simmons Comprehensive Cancer Center
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
WBC	White Blood Cells

STUDY SCHEMA



Number of patients = 45 patients

PHASE II STUDY

Patients will be treated with 5 fractions of SABR/SBRT according to protocol guidelines. We have selected 9 Gy per fraction for 5 fractions (total dose = 45) based on our phase I/II study experience without the rectal spacer.

No. Fractions	Dose per fraction (Gy)	Total Dose (Gy)	No. Patients
5	9	45	45

The phase II study will be completed when enrollment is completed and minimum follow-up is reached, or if unexpected excess toxicity is noted.

STUDY SUMMARY

Title	Phase II Study of Stereotactic Ablative Radiotherapy (SABR) for Low/Intermediate Risk Prostate Cancer with Injectable Rectal Spacer
Short Title	SABR with Injectable Rectal Spacer for Low/Intermediate Risk Prostate Cancer
Protocol Number	STU 092013-013
Phase	Phase 2
Methodology	Single arm, open label
Study Duration	Minimum 3 years; Voluntary 10 years at Investigator's discretion
Study Center(s)	Multi-center
Objectives	To reduce rectal toxicity due to SABR
Number of Subjects	45
Diagnosis and Main Inclusion Criteria	Low/Intermediate risk prostate cancer
Study Product(s), Dose, Route, Regimen	Placement of rectal spacer followed by Stereotactic Ablative Radiotherapy (SABR): 5 fractions (9 Gy per fraction) for a total of 45 Gy
Duration of Administration	2-3 weeks
Reference therapy	SABR

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Localized Prostate Cancer

There is estimated to be 238,590 new cases of prostate cancer diagnosed in the United States in 2013 and 29,720 deaths [1] . Among males, prostate carcinoma was the 2nd leading cause of cancer mortality behind lung cancer. About 60% of prostate cancer are diagnosed in men age 65 or older which impacts therapy options as a result of competing co-morbidities. With introduction of PSA screening, majority of prostate cancer is diagnosed in organ confined disease [2].

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) [3-5] and also permanent brachytherapy seed implantation using iodine or palladium [6-8]. Treatments have also been delivered using shorter overall treatment times. These include hypofractionated external beam treatments and high dose rate (HDR) brachytherapy implants [9-12]. In addition, studies using extreme hypofractionated approach including stereotactic body radiation therapy (SBRT)/Stereotactic Ablative Radiotherapy (SABR) have emerged, including the phase I/II study completed here at UT Southwestern [13, 14]. 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[15]. 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.

The alpha beta notion described above has led to many hypofractionated studies using modestly larger doses per fraction. Randomized studies have been published, including the Australian trial comparing 64 Gy in 32 fractions versus 55 Gy in 20 fractions in men with favorable risk prostate cancer[16]. Biochemical outcomes were not different, and toxicity was similar, except for increased rectal bleeding in the hypofractionated arm. Another study compared 66 Gy in 33 fractions versus 52.5 Gy in 20 fractions[17]. While the outcome seem to favor the longer fractionation, the study was not adequately designed to address this question as the biologically effective dose of the hypofractionated arm was less than the conventional fractionation arm. 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[18]. Their patients had good PSA control rates and acceptable rates of toxicity, especially if the volume rectum getting 70 Gy is limited to 10 cc. Altogether, these trials show that the treatment can be delivered much more quickly and conveniently using equivalent effective doses with hypofractionation without compromising PSA control or significant toxicity so long as careful technique and normal tissue dose tolerance is respected. Furthermore, investigation of hypofractionated strategies for the high risk patients is under investigation. For example, a randomized phase III study using hypofractionated strategy in high risk prostate cancer patients has been reported where 62 Gy/20 fractions was superior to standard 80 Gy/40 fractions[19]. Interestingly, 62 Gy in 20 fractions converts to roughly 48.1 Gy in 5 fractions[20].

1.2 Study Agent(s) Background and Associated Known Toxicities

1.2.1 Stereotactic Body Radiation Therapy (SBRT)/Stereotactic Ablative Radiotherapy (SABR)

'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 [21-23]. 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 [23]. 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)/ Stereotactic ablative radiotherapy (SABR) 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 [24]. 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. SABR employs daily treatment doses dramatically higher than typical for conventionally fractionated radiation therapy (CFRT). In turn, it is incorrect to assume that SABR 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 SABR show local control around 90% [25, 26].

SABR 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 [27]. Indeed, dose per fraction of 8 Gy minimum would obviously make SABR very different from even the more abbreviated hypofractionation schemes described above. Typically, only 1-5 fractions are used for SABR 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 [28, 29]. It has been shown that serial functioning tissues are less tolerant to SABR 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 Other Agents

Rectal spacers

Our rectal toxicity data analysis suggests that rectal toxicity will likely be circumvented if we are able to respect dose tolerances as defined in our analysis. This has also been the case in world of conventional fractionation radiation therapy, where determination of rectal dose constraints (specifically, limiting volume of rectum receiving 70 Gy in 2 Gy/daily fraction dose) by Pollack's group has provided a means of dose escalating radiation treatments without increasing rectal toxicity[32].

When using such high dose per fraction, as is the case in SABR, three strategies for improve rectal dose can be considered. One strategy is to de-escalate the total dose significantly (6-6.5 Gy/fraction). While this lower dose may prove to be effective for treatment of localized prostate cancer, and would certainly reduce toxicity, as has been the case with other institution's experience[14], the follow up data from these institutions remain short, and if the alpha beta ratio hypothesis proves to be inaccurate, then we may be subjecting patients to suboptimal therapy. Furthermore, such lower doses are likely to be less effective in patients with more aggressive, high risk prostate cancer. Dose escalation has proved to be important in high risk prostate cancer even using conventional fractionation strategies, and suggestion of importance of considering hypofractionation for high risk prostate cancer was demonstrated in phase III randomized study from Italy[19], suggesting that dose de-escalation strategies would limit our ability to treat higher risk prostate cancer patients with SABR.

Second strategy is to continue to explore radioprotectors to try to reduce toxicity. However, a suitable radioprotector drug, particularly when using SABR treatment has not yet been discovered. Third strategy is to consider methods to reduce dose to the rectum via physical or dosimetric means. In the case of conventionally fractionated treatments, sophisticated treatment planning using intensity modulated radiation therapy or 3D conformal therapy has allowed rectal dose parameters to be respected to a point of acceptable rectal toxicity risks. However, in the case of SABR, avoidance of such high doses with sophisticated treatment planning using our parameters, though feasible in most cases, may remain significantly challenging in patients with unfavorable anatomy.

Therefore, another potential strategy to improve dosimetry has been developed recently. This involves the use of an anatomic modulating strategy to distance the anterior rectum from the prostate in order to reduce dose to the rectum. This approach is now being investigated both in conventional fractionated radiation therapy and in SABR for prostate cancer patients, and involve the use of an injectable rectal spacers [33-38]. These spacers would likely be particularly effective at reducing the high dose associated with vascular/stromal injury and will likely lead to significant reduction of high grade rectal toxicity events. It should also improve acute lower grade events, as such events also will likely be mitigated if we can limit the 24 Gy dose/5 fractions to treate < 50% of rectal circumference. Multiinstitutional clinical trial of rectal spacers ability to improve dosimetric parameters when using conventional intensity modulated radiation therapy has been completed with positive outcome[39] further supporting use of this strategy. This same group has recently published safety profile of use of this spacer for conventional IMRT based radiation therapy for prostate cancer[40]. Effectiveness in reducing acute toxicity using another rectal spacer for brachytherapy/IMRT application has been reported in abstract form[41]. Its safety/efficacy in SABR has not yet been established.

1.4 Rationale

Stereotactic Body Radiation therapy (SBRT)/ Stereotactic ablative body radiation therapy (SABR) in Localized Prostate Cancer.

Studies using SBRT/SABR approaches for extreme hypofractionation to reduce further treatment time, convenience, and possibly treatment efficacy, has been performed at multiple institutions including ours [13, 14, 30, 31]. We were the first institution to perform a multiinstitutional phase I dose escalation study which was completed successfully. This study included cohorts of 15 patients per dose group with doses escalated from 45 Gy → 47.5 Gy → 50 Gy in 5 fractions. In the phase I study at the 45 Gy dose (9Gy x 5 fractions) arm, first ten patients underwent anoscopic evaluation by study P.I. (R.T.) at 6, 12, 24, and 36 weeks post SABR. 10/10 (100%) patients were found to have development of a small ulcer in the anterior rectum adjacent to the prostate, which was mostly asymptomatic. This mucosal lesion shrunk in size and disappeared in all 10 cases by 24-36 weeks post therapy ({Kim, 2014 #203} and personal communication, R. Timmerman).

Using 90 day toxicity as the endpoint for dose escalation, acute toxicity at 50 Gy was found to be tolerable[13], and we proceeded to treat additional patients in phase II studying late toxicity using that dose. An unacceptable 6.6 % (6/61) of patients treated developed high grade rectal toxicity, 5 of whom required colostomy {Kim, 2014 #203}. The data from these patients were analyzed to determine clinical and radiation dose parameters that may have been related to such high grade toxic event. We found that Grade 3+ delayed rectal toxicity felt related to vascular/stromal damage was strongly correlated with volume of rectal wall receiving 50 Gy (V50) > 3 cm^3 (p=.002), and treatment of > 35% circumference of rectal wall to 39 Gy (p=.03) related to stem cell eradication. Grade 2+ acute rectal toxicity felt related to stem cell depletion was significantly correlated with treatment of > 50% circumference of rectal wall to 24 Gy (p=.006) {Kim, 2014 #203}.

1.4.1 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 higher risk prostate cancers may be better controlled using large dose per fraction treatments such as might be delivered by stereotactic body radiation therapy (SBRT/SABR)[19]. However, the results of our phase I/II study clearly demonstrates that on long term follow up delayed rectal toxicity events can occur, but this is likely preventable if we can respect rectal tolerance by reducing the radiation dose to the rectal wall. In addition to having rectal tolerance parameters defined from our previous study, which we will incorporate to this study, there are now rectal spacers made from polyethyleneglycol hydrogel material available for use[33-38, 40, 41]. These spacers are designed for stability for up to 1- 3 months, which will allow for stability of anatomy during the SABR treatment phase.

We plan to perform a phase II study to assess safety and efficacy of the spacer injection process, ability of the spacer to effectively provide the space necessary to reduce acute events in the rectum, and also meet the SABR based rectal constraints, and to monitor stability of this process during SABR. Unlike IMRT, which uses smaller dose/fraction, when using such high dose/fraction, even a few mm of shift in spacer positioning may impact the dose that the rectum receives, and therefore, a rigorous study of stability of material during the SABR

treatments will need to be determined. If there is some shift, by doing this study, we may be able to determine the margin of error that will be necessary in considering rectal organ dosimetry, based on the possible shift in positiong that may occur with the spacer over time.

As the SABR 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 of low and intermediate risk patients to minimize risk of extraprostatic spread, seminal vesicle invasion, and nodal spread. Hormonal therapy may also be used to shrink prostates that are massively enlarged as this may also help further reduce length of rectum that will be irradiated. 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, inflammatory bowel disease) and immunosuppressed individuals based on our phase I experience[13]. In this way, patients will be uniformly selected in a fashion that would identify patients likely to receive benefit from the therapy.

Based on our phase I/II experience, we will select 9 Gy/fraction with a total of 5 fractions, as this dose was well tolerated, and appears thus far to have been extremely effective at controlling the prostate cancer. With a median f/u of 25.5 months (range 1-68.4m), at last analysis, PSA control remains at 99%. Given there will be only 5 treatments, daily enemas, rectal tubes, and even urethral catheters for simulation are all feasible undertakings which were well tolerated, and found to be helpful for optimizing setup and the therapy.

1.4.2 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. Extended exposure to 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 SABR may in fact be a better option for some men with prostate cancer. High risk patients benefit by the hypofractionated nature of the treatment, and may also require doses higher than what can be delivered safely with this approach (based on our phase I/II data, and other institutional experiences as noted above). These patients are in need of better therapy, and higher dose SABR approach may prove to be an important therapeutic gain for this group of patients. Furthermore, findings of our study will have further clinical ramifications beyond prostate cancer. It will be applicable to design of studies of tumor sites in close proximity to bowel structures in general, where higher SABR doses are being contemplated due to perceived clinical needs as such tumors may not share the same alpha beta ratio as prostate cancer does. Development of an effective paradigm for spacer placement to displace critical structures reliably away from the high dose region may lead to design of additional spacer studies in other anatomical sites.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To reduce acute periprostatic rectal ulcer events from 90%+ to <70% (particularly in the anterior rectum)

2.1.2 To establish rates of creation of >= 7.5 mm space (anticipated to be 95% [39]).

This is to determine if use of rectal spacers are effective at improving protection of rectum from high dose radiation, using rate of rectal ulceration as a surrogate measure of acute effects. It is also to determine whether it provides sufficient dosimetric benefits to warrant further clinical investigation in future SABR related clinical studies.

2.2 Secondary Objectives

Secondary objective is to determine radiation related toxicity outcomes in the acute and delayed setting, as well as to follow PSA control. HRQOL will be measured as part of current clinical practice, and not necessarily related to this treatment protocol.

2.2.1 Assess for spacer related acute toxicity. Spacer related toxicity could be related to the procedure itself (bleeding, infection, pain), or secondary effects of spacer (erectile dysfunction, persistent pain and discomfort).

2.2.2 Determine spacer's ability to decrease percent rectal circumference (PRC) receiving 24 and 39 Gy by at least 50%.

2.2.3 Assess for acute (within 270 days of treatment) and chronic (>270 days from treatment) SABR-related genitourinary (GU) and gastrointestinal (GI) toxicities, as well as non-GU/GI toxicities during follow up.

2.2.4 Assess oncologic outcomes, including biochemical recurrence, overall survival, disease-specific survival, rates of local/regional/distant relapse

2.2.5 Assess effect on quality of life (QOL)

2.3 Endpoints

2.3.1 Primary Endpoint

The primary endpoint of this study is to determine whether use of a rectal spacer with SABR will decrease the rate of rectal toxicity when performing SABR treatments for prostate cancer, and the effectiveness of space creation by the spacer. To this extent, our primary objectives are

- to measure rectal mucosal ulceration rate, and
- to determine ability of spacer to create >=7.5 mm space: rate of space creation of >=7.5mm.

2.3.2 Secondary Endpoints

- To assess spacer related acute toxicity, defined as toxicities occurring in the two week period between spacer placement and start of radiation treatment.
- To determine spacer's efficacy as measured by its ability to decrease the PRC 24 Gy and 39 Gy parameters by at least 50%. This will be determined by using CT planning studies for dosimetric analysis before and after spacer placement.

- Acute GU and GI toxicity is defined as grade 1-5 toxicity occurring prior to 270 days from the start of protocol treatment. It is graded based on CTCAE v4.0.
- Delayed GU and GI toxicity is defined as grade 1-5 toxicity occurring after 270 days from the start of protocol treatment. It is graded based on CTCAE v4.0.
- 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
- HRQOL questionnaires

3.0 SUBJECT ELIGIBILITY

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

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

3.1.2 Eligible patients must have appropriate staging studies identifying them as AJCC stage T1 (a, b, or c) or T2 (a, b, or c) 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 performed within 180 days of registration.

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

3.1.4 The Gleason score should be less than or equal to 7.

3.1.5 The serum PSA should be less than or equal to 15 ng/ml
Study entry PSA must not be obtained during the following time frames: (1) 10-day period following prostate biopsy; (2) following initiation of ADT; (3) within 30 days after discontinuation of finasteride; or (4) within 90 days after discontinuation of dutasteride.

3.1.6 Age ≥ 18 years.

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

3.1.8 The ultrasound, MRI, or CT based volume estimation of the patient's prostate gland should be ≤ 80 grams.

3.1.8.1 For patients with prostate size > 60 grams cytoreduction therapy with ADT is recommended

3.2 Exclusion Criteria

3.2.1 Subjects who have had previous pelvic radiotherapy or have had chemotherapy or surgery for prostate cancer.

3.2.2 Subjects who have plans 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.

3.2.3 Subjects who have undergone previous transurethral resection of the prostate (TURP) or cryotherapy to the prostate.

3.2.4 Subjects who have significant urinary obstructive symptoms; AUA score must be ≤ 18 (alpha blockers allowed).

3.2.5 Subjects who have a history of significant psychiatric illness.

3.2.6 Men of reproductive potential who do not agree that they or their partner will use an effective contraceptive method such as condom/diaphragm and spermicidal foam, intrauterine device (IUD), or prescription birth control pills.

3.2.7 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).

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

- **3.2.8.1** Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months.
- **3.2.8.2** Transmural myocardial infarction within the last 6 months.
- **3.2.8.3** Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration.
- **3.2.8.4** Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days before registration.
- **3.2.8.5** Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol.
- **3.2.8.6** Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.
- **3.2.8.7** **Patients with history of inflammatory colitis (including Crohn's Disease and Ulcerative colitis) are not eligible.**

3.2.9 Subjects with a known allergy to polyethylene glycol hydrogel (spacer material) or contraindication to spacer products (Duraseal or SpaceOAR).

3.2.10 Subjects with evidence of extraprostatic extension (T3a) or seminal vesicle involvement (T3b) on clinical evaluation.

3.2.11 Subjects with uncontrolled bleeding disorder which cannot be controlled with anticoagulants

4.0 TREATMENT PLAN

4.1 Treatment Dosage and Administration

RADIATION THERAPY

4.1.1 Dose Specifications

4.1.1.1 *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/SABR) has become a treatment that is well beyond just stereotactic targeting. Indeed SABR 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.

4.1.1.2 *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 be 45 Gy.

4.1.1.3 *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 SABR. 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 SABR treatment and continue for 3 months post finishing all SABR 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.

4.1.1.4 *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.

4.1.2 Technical Factors

4.1.2.1 *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.

4.1.2.2 *Dose Verification/Rectal Dose Verification at Treatment*

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

4.1.3 Localization, Simulation, and Immobilization

4.1.3.1 *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). 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%).

4.1.3.2 *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 include 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. Based on our prior experience, we do not anticipate significant issues with adequately controlling for inter and intrafractional motion using our setup techniques, including pretreatment enema.

4.1.3.3 *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 be 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. We will perform daily enemas prior to each treatment. 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.

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.

4.1.4 Treatment Planning/Target Volumes

4.1.4.1 *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 evacuation with enemas. The treatment planning scans may 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. Alternatively, MRI delineation or urethrogram may be used. 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.

CT simulation will be performed for this study. The first simulation (scan #1) will involve all of the above procedures, and will be performed prior to rectal spacer placement. The patient will then undergo rectal spacer placement, and return for repeat simulation (scan #2) under exact same condition as above.

Image fusion with other imaging modalities such as MRI that might be useful in delineating the target and normal tissues will be performed. **T2 MRI sequence optimized for seed localization will be allowed. This will only be performed for second simulation with rectal spacer in place, which will be the study used for final treatment.**

Planning will be performed twice for this study using same guidelines as below. Once without the rectal spacer, using CT simulation scan #1. Then plan will be performed again with the rectal spacer in place using CT simulation scan #2. We anticipate that the rectal dose constraints will be far easier to meet with rectal spacer placed. The dosimetrist and physicians will be expected to create as conformal a plan as feasible to truly determine the extent of rectal dose sparing that can be achieved without sacrificing PTV coverage, and other normal tissue tolerance limits.

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 0.3-1.0 cm in the longitudinal plane (cranio-caudal) will be added to the CTV to constitute the planning treatment volume (PTV) depending on the institution's accuracy and treating physician's preference. UT Southwestern has determined that uniform expansion of 0.3 cm is sufficient margin for PTV.

4.1.4.2 *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 4.1.5 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.

4.1.5 Critical Structures

4.1.5.1 *Critical Organ Dose-Volume Limits*

The following table lists maximum dose limits to a point or volume within several critical organs. These are limits, and treatment delivery that exceeds these limits will constitute a possible protocol violation (See Section 4.1.7). 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/Parameters	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)
Rectal wall	Less than 3 cc	50 Gy
Percent Rectal Circumference*	< 33% of circumference	39 Gy
	< 50% of circumference	24 Gy
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 18 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	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
Neurovascular bundle (right and left)	Maximum point dose	No more than 105% of prescription dose

*Planning efforts should be made to keep the percent rectal circumference receiving 39 Gy < 20% and < 24 Gy under 25% in the post-spacer plan.

4.1.5.2 *Contouring of Normal Tissue Structures*

4.1.5.2.1 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). Contouring this structure is unnecessary if it is >3cm above the superior extent of the PTV.

4.1.5.2.2 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).

4.1.5.2.3 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 contour.

4.1.5.2.4 Peri-prostatic Rectal wall
The circumference of the rectum adjacent to the prostate will be contoured. Only the outer rectal wall will be included in these contours. Rubber catheter and MRI can be used to help delineate rectal volume.

4.1.5.2.4.1 *Peri-prostatic Rectum*
Starting inferiorly just above the anal sphincter, the outer rectal wall should be contoured up to 1 cm above the superior extent of the prostate.

4.1.5.2.4.5 Percent Rectal Circumference
L_{24} = axial length of rectal wall treated by 24 Gy
L_{39} = axial length of rectal wall treated by 39 Gy.
At the level of mid prostate gland, the L_{24} and L_{39} were estimated by measuring the distance from the 24 Gy, and 39 Gy isodose lines at the right and left edge of the rectal wall to the mid anterior rectal wall.
Percent Rectal Circumference (PRC): The circumference of the rectum at the same level was estimated using formula π x diameter. The percent rectal circumference (PRC) treated by 24 Gy, and 39 Gy at mid prostate gland level was estimated by formula $L_{24or\ 39}$/(circumference).

4.1.5.2.5 Rectum Superior to Prostate
Starting inferiorly at the superior extent of the Peri-prostatic Rectuml described above, the entire wall and lumen of the rectum should be contoured up to the level of the sacral promontory.

4.1.5.2.6 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.

4.1.5.2.7 Prostatic Urethra
The prostatic urethra will be identified by the urethral catheter plus 1-2 mm of tissue radially into the prostate, or on comparison with MRI. 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.

4.1.5.2.8 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).

4.1.5.2.9 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.

4.1.5.2.10 Femoral heads
The femoral heads will be contoured bilaterally as one structure.

4.1.5.2.11 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.

4.1.5.2.12 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.

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

4.1.5.2.14 Neurovascular Bundles
The neurovascular bundles will be contoured as separate structures within 1cm of the prostate volume, as visualized on the planning MRI.

4.1.6 Documentation Requirements

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.

4.1.7 Compliance Criteria

4.1.7.1 *Dosimetry Compliance*
Section 4 describes appropriate conduct for treatment planning dosimetry. In addition to the criteria in section 4.1.4.2, the table in Section 4.1.5 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.

4.1.7.2 *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.

4.1.8 R.T. Quality Assurance Reviews

Dr. Timmerman, along with a medical physicist, will perform an RT Quality Assurance Review once 5 cases have been enrolled at the University of Texas Southwestern. They will perform the next review after complete data for the next and subsequent 5-10 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.

4.2 Toxicities and Dosing Delays/Dose Modifications

Any subject who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events table (Section 5). Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

4.2.1 Radiation Adverse Events

4.2.1.1 *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).

4.2.1.2 *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.

4.2.1.3 *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).

4.2.1.4 *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).

4.2.1.5 *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).

4.2.1.6 *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

4.3 Concomitant Medications/Treatments

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.

Below is a non-comprehensive list of categories of medications permitted.

4.3.1 Obstructive flow medicines (alpha blockers) 5 alpha reductase inhibitors)

4.3.2 Antiemetics

4.3.3 Anticoagulants
4.3.4 Antidiarrheals
4.3.5 Analgesics
4.3.6 Hematopoietic Growth Factors
4.3.7 Herbal products
4.3.8 Nutritional supplementation
4.3.9 Antibiotics for Rectal spacer procedure at Urologist discretion.
4.3.10 Rectal corticosteroid medications

4.4 Other Modalities or Procedures

4.4.1 RECTAL SPACER AND FIDUCIAL PLACEMENT

Fiducial placement for image guidance is a routine procedure being performed by qualified/trained physicians at UTSW and Parkland Medical Center. There will be no significant changes in this routine procedure. Fiducials will be placed by qualified physicians no less than 10-14 days prior to SABR planning CT simulation. In addition, rectal spacer placement will be performed by qualified trained physicians, many of whom are members of the Urology department (Physicians and P.A.s) or the Radiation Oncology departments of UTSW and MSKCC (Physicians with significant brachytherapy and fiducial placement experience). Technique for spacer insertion is outlined below, based on excellent methods paper from [37]).

Rectal Spacer (SpaceOAR):
The rectal Spacer system consists of components for the preparation of the absorbable hydrogel spacer with its delivery mechanism provided in a single-use kit. The spacer hydrogel is formed by simultaneously injecting two solutions, the precursor and the accelerator, into the perirectal space. The solutions mix during injection, initiating a cross-linking reaction that result in the formation of a soft PEG-based gel within 10 s, without a measurable temperature rise. The hydrogel remains in the body for 12 weeks (SpaceOAR), after which hydrolysis causes the implant to liquefy, resulting in complete absorption.

Hydrogel injection technique:
The hydrogel is injected transperineally using hydrodissection to facilitate placement. The potential perirectal space for hydrogel placement is between Denonvilliersfascia and the rectal wall (Fig. 1). Denonvilliers' fascia consists of a single fibromuscular structure covering the posterior aspect of the prostate. This important anatomical boundary separates the prostate from the anterior rectal wall. It is important that the hydrogel is injected on the posterior side of Denonvilliers ' fascia and anterior to the anterior rectal wall to minimize the risk of pushing cancer cells away from the high dose radiation fi eld [42]. In addition, care must be taken to avoid inadvertent injection into the rectal wall which can potentially lead to ischaemia or increased rectal wall stresses. The spacing hydrogel is injected using a transperineal approach under TRUS guidance. A transrectal approach cannot be used because of potential bacterial contamination. Hydrodissection is a technique used to separate tissue planes through the use of fluid. The insertion of the hydrogel spacer is facilitated with the use of hydrodissection. Small volumes of fluid are carefully injected through an 18-G needle between Denonvilliers' fascia and the anterior rectal wall to open the potential space before injecting the hydrogel. By this means, enough space for the spacer hydrogel is created and steady dispersion of the spacing agent is ensured.

Insertion Procedure: The insertion procedure itself is a short procedure that can be performed under local, spinal or light general anaesthesia in an outpatient setting. Prophylactic antibiotics will be given. Transperineal fiducial placement will be performed before the hydrogel injection.\ The patient will be placed in the

lithotomy position. A TRUS probe, covered by a stand-off balloon will be used for ultrasonography imaging and proper needle and anatomical visibility (Figure 2A). The device is mounted to an adjustable stepper unit, freeing both the physician's hands. Under real-time TRUS guidance in the sagittal plane, the injection needle (18G × 15 cm), with an attached syringe containing saline or lidocaine 0.5 – 1.0% diluted in 15 mL saline, is inserted ~ 1 cm above the TRUS probe through the perineum and carefully advanced to the pelvic floor muscles at an angle parallel to the TRUS probe. After penetration of the rectourethralis muscle, the tip is positioned inferior to the prostatic apex, just between Denonvilliers' fascia and the anterior rectal wall. Hydrodissection is started using small volumes of fluid to slowly open up the potential space between Denonvilliers' fascia and the anterior rectal wall. Once the correct space starts to open, the needle is advanced into the space, and saline injection/needle advancement continued until the needle tip reaches mid-gland. By this means, space for the spacer hydrogel is created (Fig. 2b). After confirming the correct position of the needle with both sagittal and axial ultrasound views, and aspirating to ensure the needle tip was not in vessel, the saline syringe is removed. The syringe assembly is then attached, maintaining needle position, and 10 mL of hydrogel will be administered in one continuous motion in 8 – 10 s without moving the needle during injection (figure 2c). In the case of insufficient hydrodissection or unintentional rectal wall perforation, spacer hydrogel injection is aborted. The distance from the rectal wall to the prostate/Denonvilliers' fascia will be measured before and after the injection procedure. Adverse events, if any, during and after the spacer injection procedure will be assessed and documented.

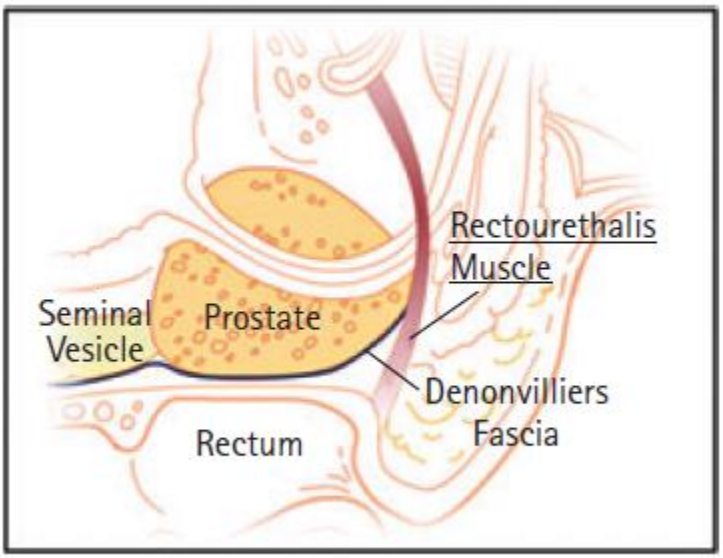


Figure 1. Anatomy of Rectum/Prostate Region (Sagittal View) taken from [37]

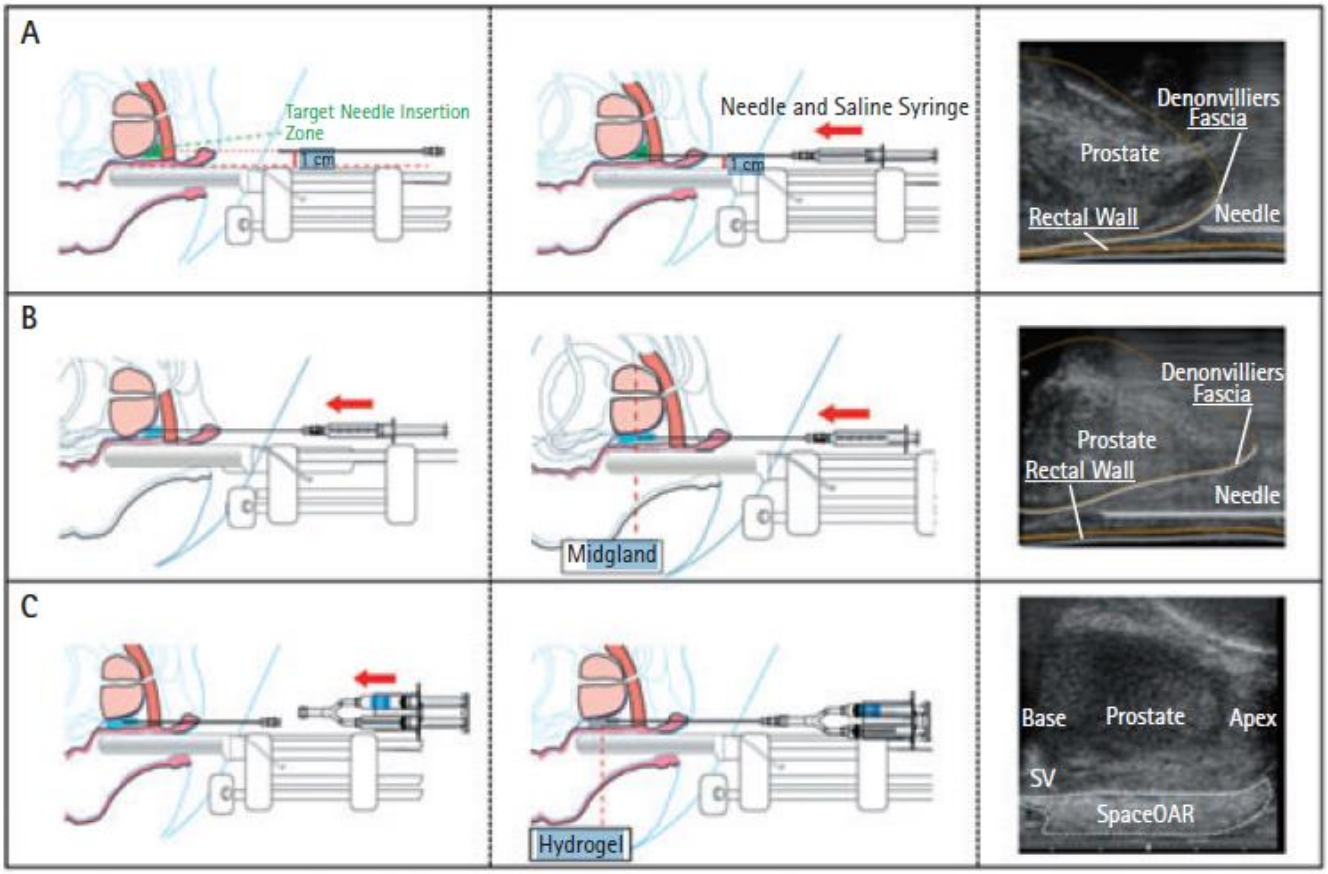


Figure 2. Procedure for TRUS guided transperineal spaceOAR placement. Taken from [37]

4.4.2 Hydrogel Placement Procedure Related Adverse Events

Safety events that could be attributed to device and procedure will continuously be monitored:

4.4.2.1 *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). This will be monitored periprocedural period, and for the duration of spacer presence in the body (3 months) post procedure.

4.4.2.2 *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). This will be monitored periprocedural period, and for the duration of spacer presence in the body (3 months) post procedure.

4.4.2.3 *Infection*
Monitored procedure related toxicity including fever, urinary tract infection, bacteremia, sepsis. This will be monitored in the periprocedural period and for the duration of spacer presence (3 months) post procedure.

POST TREATMENT: GI, GU EVENTS, BASED ON CTCAE V4.0.

4.5 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Subject decides to withdraw from the study, **OR**
- General or specific changes in the patient's condition render the subject unacceptable for further treatment in the judgment of the investigator.

4.6 Duration of Follow Up

Initial follow-up visit at 6 weeks from the end of treatment.

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

4.6.2 Then every six months until five years post treatment.

4.6.3 Then annually for years 5-10; follow up after year 3 on protocol is performed on a voluntary basis at the enrolling investigator's discretion; all patients should be followed even off protocol as per standard clinical practice.

4.7 Removal of Subjects from Protocol Therapy

Subjects will be removed from therapy when any of the criteria listed in Section 5.5 apply. Notify the Principal Investigator, and document the reason for study removal and the date the subject was removed in the Case Report Form. The subject should be followed-up per protocol.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed prior to registration. The screening procedures include:

5.1.1 ***Informed Consent***

5.1.2 ***Medical history***

Complete medical and surgical history, history of infections

5.1.3 ***Demographics***

Age, gender, race, ethnicity

5.1.4 ***Review subject eligibility criteria***

5.1.5 ***Review previous and concomitant medications***

5.1.6 ***Physical exam including vital signs, height and weight***

Vital signs (temperature, pulse, respirations, blood pressure), height, weight

5.1.7 *Performance status*

Performance status evaluated prior to study entry according to Appendix II.

5.1.8 *Serum chemistries (within 90 days prior to registration)*

PSA, BUN, creatinine, CBC w/ diff

5.1.9 *Tumor assessment*

5.1.10 *CT or MRI prostate (within 90 days prior to registration)*

Diagnostic MRI is preferred, at physician's discretion; a pre-spacer simulation CT scan may be used to satisfy this requirement

5.1.11 *QOL questionnaires (AUA; EPIC – may be done after registration)*

5.1.12 *Prostate biopsy (within 180 days prior to registration)*

Repeat prostate biopsy for patients with biopsy >180 days from study entry is not required unless the PSA taken prior to study entry is greater than the PSA taken at the time of biopsy by more than 5 ng/ml.

5.2 Procedures During Treatment

Study Parameters:.

- For each patient, plan will be evaluated to assess:
- Was >=7.5 mm space created between prostate and rectum by the spacer?
  - (Yes/No, document space distance)
- Was PRC 24 Gy and 39 Gy of treatment plan with spacer reduced by at least 50% compared to prerectal spacer plan?
  - (Yes/No, and documentation of PRC 24 Gy and 39 Gy)
- Document spacer related toxicity during and 3 months post procedure.

5.2.1 At Each Treatment Cycle

- Physical exam, vital signs (once per course)
- CT or MRI (cone beam CT acceptable) prior to each treatment fraction
- AE evaluation (once per course)

5.3 Follow-up Procedures

5.3.1 Initial follow-up visit at 6 weeks from the end of treatment.
For each patient, anoscopic evaluation of the periprostatic rectum will be performed at 6, 12, 24, and 36 weeks by the treating physician, and presence or absence of ulcer will be documented.

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

5.3.3 Then every six months until five years post treatment.

5.3.4 Then annually for years 5-10; follow up after year 3 on protocol is performed on a voluntary basis at the enrolling investigator's discretion; all patients should be followed even off protocol as per standard clinical practice.

5.4 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
SABR dosimetry information	Within 1 week after completion of SABR
Follow-up H&P data including PSA, anoscopic findings	After last SABR treatment, post SABR follow-up at 1.5, 3, 6, 9, 12 months, then every 6 months to 5 years; then annually for years 5-10
AUA and EPIC post treatment forms	After last SABR treatment, post SABR follow-up at 1.5, 3, 12, and 18 months
Adverse Event assessment	After each SABR treatment, then post SABR follow-up at 1.5, 3, 6, 9, and 12 months, then every 6 months to 5 years; then annually for years 5-10. Followup after year 3 on protocol is performed on a voluntary basis at the enrolling investigator's discretion; all patients should be followed even off protocol as per standard clinical practice.

5.5 Time and Events Table

	Pre-Treatment				During Treat-ment	Follow-Up (months after therapy)													
	Within 180 days prior to study entry	Within 90 days prior to study entry	Within 30 days prior to study entry	After study entry	With each treatment	1.5	3	6	9	12	18	24	30	36	42 [i]	48 [i]	54 [i]	60 [i]	Every 12 months for years 5-10 [i]
Prostate Biopsy with Gleason Score for Diagnosis	X[e]																		
PSA		X[a]				X	X	X	X	X	X	X	X	X	X	X	X	X	X
Rectal Spacer Measurements				X[aa]															
Rectal Dosimetric Parameters Measurements				X[aa]															
History/ physical			X		X[j]	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	X	X
Performance Status			X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
CT or MRI of prostate		X[ccc]		X[bb]	X[b]														
AUA Symptom index			X			X	X			X	X								
EPIC Questionnaire			X[h]	X[h]		X	X			X	X								
BUN, creatinine, CBC, & platelets		X[c]																	
Blood Draw for Translational Research			X[f]		X[g]			X											
Tumor response evaluation			X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event evaluation					X[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Anoscopic Evaluation						X	X	X	X										

X = required

[a]Baseline PSA should be recorded as pre-hormonal level if taking hormones even if >60 days prior to entry.

[aa] When plan is available to review prior to treatment

[bb]CT simulation in Radiation Oncology Department with immobilization and set up as directed in section 6.3.1 for baseline study prior to rectal spacer placement. [The first CT simulation may be substituted for diagnostic scan at physician's discretion; in this case, the first (pre-spacer) CT simulation will be done prior to study entry. A second CT simulation will be performed after rectal spacer placement. Limited protocoled MRI for fusion/planning will be performed.]

[ccc] MRI is preferred; CT can be performed instead; pre-spacer CT performed within 30 days prior to study entry may be substituted at physician's discretion

[b]CT or MRI prior to each treatment fraction may include conebeam CT.

[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 prior to 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, if patient consents to tissue procurement study.
[g]Immediately after first treatment, immediately before second treatment, immediately after fifth treatment if patient consents to tissue procurement study.
[h]Epic questionnaire can be completed either prior to or after study entry.
[i] Follow up after year 3 on protocol is performed on a voluntary basis at the enrolling investigator's discretion; all patients should be followed even off protocol as per standard clinical practice.
[j] Required once during treatment course

5.6 Removal of Subjects from Study

Subjects can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.5.1 Subject voluntarily withdraws from treatment (follow-up permitted);

5.5.2 Subject withdraws consent (termination of treatment and follow-up);

5.5.3 Subject is unable to comply with protocol requirements;

5.5.4 Subject demonstrates disease progression (unless continued treatment with study drug is deemed appropriate at the discretion of the investigator);

5.5.5 Subject experiences toxicity that makes continuation in the protocol unsafe;

5.5.6 Treating physician judges continuation on the study would not be in the subject's best interest;

5.5.7 Subject becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

5.5.8 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;

5.5.9 Lost to follow-up. If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented Measurement of Effect

5.6 Antitumor Effect- Solid Tumors

5.6.1 Disease Parameters

Measurable Disease: Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
1. 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
2. 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
3. 20 mm by chest x-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30

mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

Note: Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Non-measurable disease.
All other lesions are considered non-measurable, including small lesions (longest diameter < 10mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, and inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses /abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Target lesions.
All measurable lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the five target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

6.1.2 Other Response Parameters

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).

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.

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.

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.

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.

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.

6.1.4 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

5.6.5 Response Criteria

5.6.5.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be “0” if there are target nodes). Determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): > 20% increase in the SLD taking as reference the smallest SLD recorded since the treatment started (nadir) and minimum 5 mm increase over the nadir.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started. There can be no unequivocal new lesions.

5.6.5.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Incomplete Response/Stable Disease (Non-CR/Non-PD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

5.6.5.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Time point response: patients with target (+/– non-target) disease.			
Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, NE = not evaluable, PD = progressive disease, PR = partial response, SD = stable disease.

Time point response: patients with non-target disease only.		
Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, NE = not evaluable, PD = progressive disease

A 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

5.6.6 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as

reference the smallest measurements recorded since the treatment started.

5.6.7 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

5.7 Safety/tolerability

Analyses will be performed for all subjects having received at least one dose of study drug. The study will use the CTCAE version 4.0 for reporting of non-hematologic adverse events (http://ctep.cancer.gov/reporting/ctc.html) and modified criteria for hematologic adverse events.

6.0 ADVERSE EVENTS

7.1 Experimental Therapy

For the most recent safety update, please refer to the current Investigator's Brochure or Study Agent Prescribing Information.

7.1.1 Risks Associated with Placement of Rectal Spacer
Gastrointestinal- colitis, dehydration, diarrhea, enteritis, fistula, nausea, vomiting, obstruction, proctitis, fecal incontinence, stricture/stenosis, hemorrhage, and ulcer
Renal/Genitourinary/Sexual/Reproductive - cystitis, fistula, urinary incontinence, urinary obstruction, stricture/stenosis, hemorrhage, and urinary retention.
Infection – fever, urinary tract infection, bacteremia, sepsis

6.2 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

All subjects experiencing an adverse event, regardless of its relationship to study drug, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

6.2.1 Definition

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam, imaging finding or clinically significant laboratory finding), symptom, clinical event, or disease, temporarily associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on

occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Acute Adverse Events

Adverse events occurring in the time period from the signing of the informed consent, through **30** days post treatment will be considered acute adverse events. All acute adverse events will be assessed and reported as per below.

Late Adverse Events (as applicable)

Adverse effects occurring in the time period from the end of acute monitoring, to 5 years post treatment, will be defined as late adverse events. These events will include all adverse events reported directly to a member of the study team and will be captured, assessed, graded and reported as appropriate.

In addition, the study team will only review encounters in records from Radiation Oncology and Urology providers and limit reporting to events in the GI/GU system.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE V4.0) and version number 4.0 specified in the protocol. Adverse events not specifically defined in the NCI CTCAE V4.0 will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE V4.0 and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

Serious Adverse Events

ICH Guideline E2A and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization[1,2] or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research

project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring ≥24 hour inpatient admission to the hospital would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death which occurs during the protocol-specified period of monitoring for adverse and serious adverse events would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

[1]Pre-planned hospitalizations or elective surgeries are not considered SAEs. Note: If events occur during a pre-planned hospitalization or surgery, that prolong the existing hospitalization, those events should be evaluated and/or reported as SAEs.

[2] NCI defines hospitalization for expedited AE reporting purposes as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the adverse event and should only be used for situations where the AE truly fits this definition and NOT for hospitalizations associated with less serious events. For example: a hospital visit where a patient is admitted for observation or minor treatment (e.g. hydration) and released in less than 24 hours. Furthermore, hospitalization for pharmacokinetic sampling is not an AE and therefore is not to be reported either as a routine AE or in an expedited report.

6.2.2 Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs):

The phrase “unanticipated problems involving risks to subjects or others” is found, but not defined in the HHS regulations at 45 CFR 46, and the FDA regulations at 21 CFR 56.108(b)(1) and 21 CFR 312.66. For device studies, part 812 uses the term unanticipated adverse device effect, which is defined in 21 CFR 812.3(s). Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ALL three (3) of the following criteria:

- Unexpected in terms of nature, severity or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

AND

- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);

AND

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

Follow-up

All adverse events will be followed up according to good medical practices.

6.2.3 Reporting SAEs and UPIRSOs to the Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC)

All SAE/UPIRSOs at all sites, which occur in research subjects on protocols for which the SCCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. All SAEs/UPIRSOs occurring during the protocol-specified monitoring period should be submitted to the SCCC DSMC within 5 business days of the PI or delegated study team members awareness of the event(s). In addition, for participating centers other than UTSW, local IRB guidance should be followed for local reporting of serious adverse events.

The UTSW study team is responsible for submitting SAEs/UPIRSOs to the SCCC DSMC Coordinator. Hardcopies or electronic versions of the eIRB Reportable Event report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE/UPIRSO documentation that is available are also submitted to the DSMC Chair who determines if further action is required. *(See Appendix III of the SCCC DSMC Plan for a template Serious Adverse Event Form which may be utilized when a sponsor form is unavailable and SAE submission to the eIRB is not required).*

If the event occurs on a multi-institutional clinical trial coordinated by the UTSW Simmons Comprehensive Cancer Center, the DOT Manager or lead coordinator ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chairperson reviews all SAEs/UPIRSOs upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

Telephone reports to: **Dr. Michael Folkert MD, PhD** Phone number: 214-645-8525
Written reports to: Investigator: Michael Folkert, MD, PhD Department of Radiation Oncology Clinical Research Office The University of Texas Southwestern Medical Center Attention: **Sarmistha Sen, Project Manager** 2201 Inwood Road Dallas, Texas 75390-9303 FAX #: 214-648-5923 UTSW SCC Data Safety Monitoring Committee Coordinator Email: SCCDSMC@utsouthwestern.edu Fax: 214-648-7018 or deliver to NB 2.418 UTSW Institutional Review Board (IRB) Submit via eIRB with a copy of the final sponsor report as attached supporting documentation

Reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) to the UTSW HRPP/IRB

UTSW reportable event guidance applies to all research conducted by or on behalf of UT Southwestern, its affiliates, and investigators, sites, or institutions relying on the UT Southwestern IRB. Additional reporting requirements apply for research relying on a non-UT Southwestern IRB.

According to UTSW HRPP/IRB policy, UPIRSOs are incidents, experiences, outcomes, etc. that meet **ALL three (3)** of the following criteria:

1. Unexpected in nature, frequency, or severity (i.e., generally not expected in a subject's underlying condition or not expected as a risk of the study; therefore, not included in the investigator's brochure, protocol, or informed consent document),AND
2. Probably or definitely related to participation in the research, AND
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

For purposes of this policy, UPIRSOs include unanticipated adverse device effects (UADEs) and death or serious injury related to a humanitarian use device (HUD).

UPIRSOs must be promptly reported to the UTSW IRB within 5 working days of PI awareness.

For research relying on a non-UT Southwestern IRB (external, central, or single IRB):

Investigators relying on an external IRB who are conducting research on behalf of UT Southwestern or its affiliates are responsible for submitting **LOCAL** UPIRSOs to the UT Southwestern IRB within 5 working days of PI awareness. Investigators must report to their relying IRB according to the relying IRB's policy. In addition, the external IRB's responses or determinations on these local events must be submitted to the UT Southwestern IRB within 10 working days of receipt.

Events NOT meeting UPIRSO criteria:

Events that do NOT meet UPIRSO criteria should be tracked, evaluated, summarized, and submitted to the UTSW HRPP/IRB at continuing review.

For more information on UTSW HRPP/IRB reportable event policy, see https://www.utsouthwestern.edu/research/research-administration/irb/assets/policies-combined.pdf.

1. SAEs

Local serious adverse events (SAEs) for studies where SCC DSMC is the DSMC of record require reporting to the DSMC coordinator within 2 working days of PI awareness, or as described in the protocol.

2. Unanticipated Problems

Local unanticipated problems require reporting to the UTSW IRB within 2 working days of PI awareness of the event.

Unanticipated problems, including those that occur as non-local events, require reporting to the UTSW IRB within 10 working days of PI awareness of the event.

For further guidance for Investigators regarding safety reporting requirements for INDs and BA/BE studies, refer to FDA Draft Guidance document: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf

6.3 Steps to Determine If a Serious Adverse Event Requires Expedited Reporting to the SCCC DSMC and/or HRPP

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4).

Step 2: Grade the adverse event using the NCI CTCAE v4.

Step 3: Determine whether the adverse event is related to the protocol therapy
Attribution categories are as follows:
- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *may NOT be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly up to 5 years post-treatment.

Step 4: Determine the prior experience of the adverse event.
Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:
- the current known adverse events listed in the Agent Information Section of this protocol (if applicable);
- the drug package insert (if applicable);
- the current Investigator's Brochure (if applicable)
- the Study Agent(s)/Therapy(ies) Background and Associated Known Toxicities section of this protocol

6.4 Stopping Rules

Early stopping of this study will be based on unacceptable toxicity, defined as grade 3 - 5 toxicity related to the following organ systems: infectious disease, 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 or rectal spacer injection procedure occurring in higher than 30% 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.

The following early stopping rules will be implemented:

2 or more cases of unacceptable toxicities out of the first 5 evaluable patients, or
4 or more cases of unacceptable toxicities out of the first 10 evaluable patients, or
6 or more cases of unacceptable toxicities out of the first 15 evaluable patients
7 or more cases of unacceptable toxicities out of the first 20 evaluable patients

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.

7.0 DRUG INFORMATION

Not applicable to this study.

8.0 CORRELATIVES/SPECIAL STUDIES

There are no correlative studies associated with this protocol.

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Design/Study Endpoints

Phase II Study Endpoints

10.1.1 Primary Endpoint

The primary endpoint of this study is to determine determine whether use of a rectal spacer with SABR will decrease the rate of rectal toxicity when performing SABR treatments for prostate cancer and the effectiveness of space creation by the spacer. To this extent, our primary objectives are

- to measure mucosal ulceration rate, and
- to determine ability of spacer to create >=7.5 mm space: rate of space creation of >=7.5mm,

10.1.2 Secondary Endpoints

- To assess spacer related acute toxicity, defined as toxicities occurring in the two week period between spacer placement and start of radiation treatment.
- To determine spacer's efficacy as measured by its ability to decrease the PRC 24 Gy and 39 Gy parameters by at least 50%. This will be determined by using CT planning studies for dosimetric analysis before and after spacer placement.
- Acute GU and GI toxicity is defined as grade 1-5 toxicity occurring prior to 270 days from the start of protocol treatment. It is graded based on CTCAE v4.0.
- Delayed GU and GI toxicity is defined as grade 1-5 toxicity occurring after 270 days from the start of protocol treatment. It is graded based on CTCAE v4.0.
- 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

- HRQOL questionnaires

9.2 Sample Size and Accrual

We plan to enroll 45 patients for this study. This sample size is based on considerations of two primary endpoints: mucosal ulceration rate and rate of space creation of >=7.5mm. Forty-five patients will ensure less than 13.5% margin of error (95% confidence) for estimated mucosal ulceration rate and 6.5% margin of error (95% confidence) for estimated rate of space creation of >=7.5mm. The calculations assume new mucosal ulceration rate of <70% and 95% rate of space creation of >=7.5mm. This sample size also has >90% power in detecting significant reduction in mucosal ulceration rate from current observed rate of 90% (alpha=0.05, two sided exact test).

10.2.1 Patient Accrual and Study Duration

It is expected that it will take approximately 1-2 years to complete the accrual for the phase II study. Primary endpoints can be determined for each patient within 24-36 weeks of treatment initial period based on our phase I study's experience of anoscopic evaluation. The analysis for secondary endpoints such as 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 other 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.

9.3 Data Analyses Plans

10.3.1. The Analysis of Rectal Spacer Efficacy

For primary endpoints, numbers and rates of spacer related mucosal ulceration and success of spacer to create >=7.5 mm space will be summarized along with their 95% confidence intervals. Rectal ulceration rate will be measured at specified time points by physician by anoscopic evaluation of the periprostatic rectum. Photographs and/or video images will be taken, and size and location of ulcers if present will be documented at each visit. Rate of mucosal ulceration for patients with spacers will also be compared with currently observed rate using exact test. Analysis on other measures will be all descriptive. Success in decreasing the PRC 24 Gy and 39 Gy parameters by at least 50%will be tabulated for examination in determining future studies.

10.3.2 ***The Analysis of 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. Numbers and rates of toxicities will be tabulated for report. We will not be performing inferential statistical analysis as this study is not powered for such analysis.

10.3.3 ***Estimation of Secondary Endpoints Related to the Efficacy:*** We will examine all the secondary endpoints in relation to efficacy.

10.0 STUDY MANAGEMENT

10.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the UTSW COI Committee and IRB according to UTSW Policy on Conflicts of Interest. All investigators will follow the University conflict of interest policy.

11.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB must approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

10.3 Required Documentation (for multi-site studies)

Before the study can be initiated at any site, the following documentation must be provided to the Research Office.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list or Federal wide Assurance letter
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Form FDA 1572 appropriately filled out and signed with appropriate documentation (NOTE: this is required if {institution} holds the IND. Otherwise, the affiliate Investigator's signature on the protocol is sufficient to ensure compliance)
- A copy of the IRB-approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

10.4 Registration Procedures

All subjects must be registered with the Clinical Research Office, Department of Radiation Oncology, UTSW, before enrollment to study.
New subjects will receive a 3-digit number. The first subject enrolled receives the number 101, the second subject enrolled receives the number 102, etc.

Each newly consented subject should be numbered using the schema provided above. Upon registration, the registrar will assign the additional registration code according to the numbering schema outlined above, which should then be entered as the patient study id in Velos upon updating the status to enrolled.

10.5 Data Management and Monitoring/Auditing

REDCap is the UTSW SCCC institutional choice for the electronic data capture of case report forms for SCCC Investigator Initiated Trials. REDCap will be used for electronic case report forms in accordance with Simmons Comprehensive Cancer Center requirements, as appropriate for the project. All subjects consenting to participate in any aspect of the trial must be registered on REDCap before initiating protocol activities. All research data will be recorded and entered into Case Report Forms using REDCap. Toxicity will be reviewed on an ongoing basis and will be reported per SCCC-DSMC guidelines.

In order to facilitate remote source to case report form verification, the Simmons Comprehensive Cancer Center study team will require other institutions participating in this trial as sub-sites to enter data into the selected EDC system and upload selected de-identified source materials when instructed

Trial monitoring will be conducted no less than annually and refers to a regular interval review of trial related activity and documentation performed by the DOT and/or the CRO Multi-Center IIT Monitor. This review includes but is not limited to accuracy of case report forms, protocol compliance, timeless and accuracy of Velos entries and AE/SAE management and reporting. Documentation of trial monitoring will be maintained along with other protocol related documents and will be reviewed during internal audit.

For further information, refer to the UTSW SCCC IIT Management Manual.

The UTSW Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCCC clinical trials. As part of that responsibility, the DSMC reviews all local serious adverse events and UPIRSOs in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The QAC works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study; the type of investigational agent, device or intervention being studied; and monitoring required to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles.

Clinical trials are assessed for safety on a continual basis throughout the life of the trial. All SAE's and any AEs that are unexpected and possibly/likely related to study participation are reported to UTSW IRB through an electronic research system per UTSW IRB guidelines. SAEs are reported to the sponsor per specific sponsor requirements. These SAEs are reported to the SCCC DSMC on a real time basis. All local SAEs will be reported to the SCCC DSMC. SAE reports can be either scanned/emailed to the coordinator of SCCC DSMC or sent through interoffice mail.

10.6 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

10.6.1 Exceptions (also called single-subject exceptions or single-subject waivers): include any departure from IRB-approved research that is *not due to an emergency* and is:

- intentional on part of the investigator; or
- in the investigator's control; or
- not intended as a systemic change (e.g., single-subject exceptions to eligibility [inclusion/exclusion] criteria)

➢ **Reporting requirement**: Exceptions are non-emergency deviations that require ***prospective*** IRB approval before being implemented. Call the IRB if your request is urgent. If IRB approval is not obtained beforehand, this constitutes a major deviation.

10.6.2 Emergency Deviations: include any departure from IRB-approved research that is necessary to:

- avoid immediate apparent harm, or
- protect the life or physical well-being of subjects or others

➢ **Reporting requirement**: Emergency deviations must be promptly reported to the IRB within 5 working days of occurrence.

10.6.3 Major Deviations (also called **violations**): include any departure from IRB-approved research that:

- Harmed or placed subject(s) or others at risk of harm (i.e., did or has the potential to negatively affect the safety, rights, or welfare of subjects or others), or
- Affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)

➢ **Reporting requirement**: Major deviations must be promptly reported to the IRB within 5 working days of PI awareness.

10.6.4 Minor Deviations: include any departure from IRB-approved research that:

- Did not harm or place subject(s) or others at risk of harm (i.e., did not or did not have the potential to negatively affect the safety, rights, or welfare of subjects or others), or
- Did not affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)

➢ **Reporting requirement**: Minor deviations should be tracked and summarized in the progress report at the next IRB continuing review.

10.7 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. A summary of changes document outlining proposed changes as well as rationale for changes, when

appropriate, is highly recommended. When an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

10.8 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.9 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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12.0 APPENDICES

APPENDIX I
Toxicity from Phase I/II study

	All Patients (n = 91)		45 Gy (n = 15)		47.5 Gy (n = 15)		50 Gy (n = 61)	
Grade	Acute No. (%)	Late No. (%)	Acute No. (%)	Late No. (%)	Acute No. (%)	Late No. (%)	Acute No. (%)	Late No. (%)
0	39 (42.9)	38 (41.8)	9 (60.0)	10 (66.7)	7 (46.7)	8 (53.3)	23 (37.7)	20 (32.8)
1	33 (36.3)	27 (29.7)	6 (40.0)	4 (26.7)	4 (26.7)	2 (13.3)	23 (37.7)	21 (34.4)
2	17 (18.7)	21 (23.1)	0 (0.0)	1 (6.7)	4 (26.7)	5 (33.3)	13 (21.3)	15 (24.6)
3	1* (1.1)	3 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1* (1.6)	3 (4.9)
4	1 (1.1)	2 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	2 (3.3)

*For this patient, toxicity occurred on day 225 (acute period), but persisted to day 470, well into the delayed toxicity time period. Therefore, this patient was reported as having high grade acute and delayed toxicity. While 7 total toxicities are reported, this occurred in a total of 6 patients

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, 7th 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).

APPENDIX III (continued)

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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.

Stage Grouping

Stage I	T1a, T1b, or T1c	N0	M0	PSA<10	Gleason≤6
	T2a	N0	M0	PSA<10	Gleason≤6
	T1-2a	N0	M0	PSA X	Gleason X
Stage IIA	T1a, T1b, or T1c	N0	M0	PSA <20	Gleason 7
	T1a, T1b, or T1c	N0	M0	PSA≥10<20	Gleason≤6
	T2a	N0	M0	PSA≥10<20	Gleason≤6
	T2a	N0	M0	PSA<20	Gleason 7
	T2b	N0	M0	PSA<20	Gleason≤7
	T2b	N0	M0	PSA X	Gleason X
Stage IIB	T2c	N0	M0	Any PSA	Any Gleason
	T1-2	N0	M0	PSA ≥20	Any Gleason
	T1-2	N0	M0	Any PSA	Gleason ≥8
Stage III	T3a-b	N0	M0	Any PSA	Any Gleason
Stage IV	T4	N0	M0	Any PSA	Any Gleason
	Any T	N1	M0	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

APPENDIX IV

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 V
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 VI

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 VII

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, 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.
Anoscopic Evaluations at 6, 12, 24, 36 weeks	Discomfort, bleeding, bruising, dizziness, fainting, infection	An experienced professional will perform this procedure
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.

Stereotactic body radiation therapy (5 treatments)	Dermatologic: Very likely: Skin redness or tanning, rash, itching, peeling, temporary hair loss in treatment area	Referral to a dermatologist if necessary.
	Gastrointestinal. 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.
	Genitourinary. 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.
	Sexual/Reproductive. Very likely: Impotence (may be irreversible); Less likely: Ejaculatory dysfunction (may be irreversible), sterility	Restriction of dose on penile bulb.
	Teratogenic: possible harm to an unborn child	Use of contraception required for participation; need for immediate reporting of causing a pregnancy stressed
	Constitutional: 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 SABR and concomitant medications	Strong encouragement to report any difficulties and keep researchers aware of any change in medications

APPENDIX VIII
SpaceOAR Package Insert

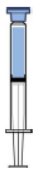
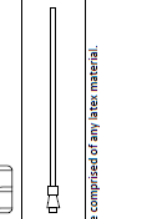
SpaceOAR® System
Product Code SO-1010
INSTRUCTIONS FOR USE

Indication: SpaceOAR System is intended to temporarily position the anterior rectal wall away from the prostate during radiotherapy for prostate cancer and in creating this space it is the intent of SpaceOAR System to reduce the radiation dose delivered to the anterior rectum.

Overview:
The SpaceOAR System consists of components for preparation of a synthetic, absorbable hydrogel spacer and a delivery mechanism packaged in a single use kit. The in situ formed hydrogel spacer creates a temporary space between the prostate and rectum during radiation therapy. The spacer is formed by mixing two solutions, the Precursor and the Accelerator. The Precursor solution is formed through the mixing of the Diluent solution (Trilysine buffer solution) with the PEG powder. The Accelerator solution is a salt buffer solution. When mixed together, the solutions cross-link to form a soft hydrogel. The mixing of the solutions is accomplished as the materials pass through a static mixer in the Y-Connector prior to passing through the injection needle.

The hydrogel spacer maintains space for approximately 3 months and is absorbed in about 6 months, sufficient time to support the intended use.

The SpaceOAR System is provided sterile and consists of the following components:

Powder Vial, with blue label	
Diluent Syringe (10cc), with blue label	
Accelerator Syringe (10cc)	
Y-Connector	
Syringe Holder	
Plunger Cap	
18G x 15cm Needle	

* No components are comprised of any latex material.

Warnings:
- SpaceOAR System must only be administered via a transperineal route.
- SpaceOAR System must not be administered via transrectal injection.
- If the needle enters the rectal lumen at any time during the procedure, abandon the procedure to avoid infection.

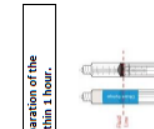
Precautions:
- Users of SpaceOAR System should be familiar with ultrasound needle placement during transperineal procedures.
- The SpaceOAR System is provided sterile. Do not use if packaging or seal has been damaged or opened. Do not re-sterilize.
- Do not use if the PEG powder is not free flowing.
- All kit components are intended for single-patient single-use only. SpaceOAR components cannot be re-used. The assembly device will clog after a single use due to the polymerization of the hydrogel material in the Y-connector and needle.
- Discard opened and unused product.
- Use only with delivery system provided. Appropriate mixing of the Precursor and Accelerator solutions will not occur if the supplied Y-Connector is not used.
- Use within 1 hour of preparing the Precursor solution.

Risks:
Potential complications that may be associated with the use of SpaceOAR System include, but are not limited to: pain associated with SpaceOAR hydrogel injection; pain or discomfort associated with SpaceOAR hydrogel; needle penetration of the prostate, rectal wall, bladder, urethra; injection of SpaceOAR hydrogel into prostate, rectum, bladder or urethra; local inflammatory reactions; infection; injection of air, fluid, or SpaceOAR hydrogel intravascularly; urinary retention; rectal mucosal damage, ulcers, necrosis; bleeding; constipation; and rectal urgency.

Detailed Kit Preparation

The use of SpaceOAR System consists of three steps:
A. Preparing the Precursor Syringe
B. Assembling the delivery components for injection
C. Positioning the needle and injection of SpaceOAR hydrogel

A. Preparing the Precursor Syringe
1. Using sterile technique, transfer the contents of the SpaceOAR System onto the sterile field.
2. Remove the blue cap from the Diluent Syringe and discard.
3. Attach the Diluent Syringe (blue label) to the Powder Vial (blue label)
4. Without depressing the syringe plunger, pierce the vial seal by pushing the syringe into the vial cap until it is fully depressed (twisting not required). The entire reference line should disappear below the vial rim.
5. Inject syringe contents into the vial.



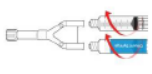
6. Shake the vial/syringe assembly until the powder is completely dissolved and set aside for approximately one minute. The solution may appear to be milky with bubbles.
7. Invert the vial/syringe assembly and draw the vial contents (approximately 5 mL of Precursor) back into the syringe, while being careful to minimize small bubbles in the syringe. This is the Precursor Syringe.
8. Unscrew the Precursor Syringe from the Powder Vial and discard the vial.

NOTE:	Use of kit must occur within 1 hour of preparation of the Precursor. Discard entire kit if not used within 1 hour.

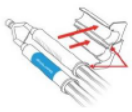
B. Assembling the Delivery Components for Injection
1. Remove the cap from the Accelerator Syringe. Check that the Diluent and the Accelerator Syringe fluid levels are level. If not equal, expel fluid out of the fullest syringe until levels are equal in both syringes.

Then pull back 1 mL of air into each syringe.

2. With the syringes held upright attach Precursor and Accelerator Syringes to the Y-Connector. Saline may be used to prime the Y-Connector prior to assembly, as needed.



3. Attach Syringe Holder to syringe barrels.



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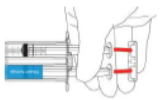
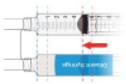
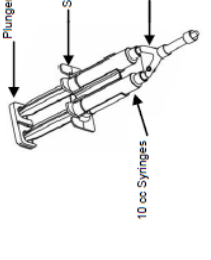
APPENDIX VIII (cont.)
SpaceOAR Package Insert

4. Carefully attach the Plunger Cap to the plungers of both syringes while holding the plungers to avoid dispensing solutions into the Y-Connector



5. Advance the syringe plungers to expel most of the air, but not all, introduced in Step B1. Do not prime.





Detailed Procedure Instruction

C. Positioning the Needle and Injection (See Figure 1)

WARNING:	The needle must be inserted using a transperineal approach.

NOTE:	1) For this procedure a side-fire transrectal ultrasound (TRUS) probe and a stepper are required; a stand-off balloon is recommended. 2) If placing fiducials, do so prior to SpaceOAR injection using a transperineal approach.

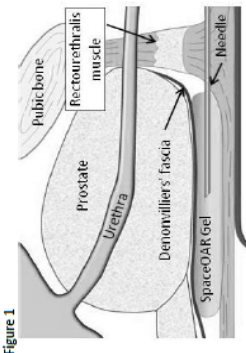
1. Position the transrectal ultrasound (TRUS) probe to enable visual guidance of the needle into the space between the prostate and rectum.
2. Attach the 18G x 15cm needle (provided) to a syringe containing saline or other suitable liquid (not provided).
3. Insert the needle approximately 1 cm anterior to the anal opening. Position the needle parallel to the TRUS Probe.
4. Advance needle through the rectourethralis muscle and position the tip inferior to the prostatic apex. Confirm needle position in sagittal and axial views.
5. Inject small amounts of fluid (e.g. saline or lidocaine) to dissect the space between Denonvilliers' fascia and anterior rectal wall ("hydrodissection").
6. When the space opens advance the needle to the midgland of the prostate. Only advance the needle if there is clear separation between Denonvilliers' fascia and the rectal wall.

NOTE:	Do not advance the needle unless space develops during hydrodissection. Inject more fluid if space does not develop during hydrodissection.

7. Access axial view to confirm needle is in the correct location (mid-gland and centered) and aspirate to ensure needle is not intravascular.
8. While maintaining the desired position, carefully disconnect the syringe from the 18G needle. Recheck the axial image to assess if the needle is halfway between the rectal wall and the posterior prostatic capsule
9. Being careful to maintain needle position, attach the SpaceOAR System delivery assembly to the 18G needle. A second person may be required to assist in the attachment of the assembly to the needle.
10. Under ultrasound guidance, use a smooth, continuous injection technique to dispense the SpaceOAR hydrogel into the space between the prostate and rectal wall. Inject entire syringe contents without stopping until desired space has been created between the prostate and the anterior rectal wall. The entire syringe contents is approximately 10mL.

NOTE:	SpaceOAR System injection should proceed uninterrupted, without stopping. Stopping during injection may result in device plugging, requiring the preparation of a replacement kit.

Figure 1



NOTE:	Avoid excessive anterior force on rectum by TRUS probe during injection, so that space may be formed.

11. Withdraw the needle/syringe assembly and discard the SpaceOAR System using appropriate precautions for sharp objects.

NOTE:	If assembly becomes clogged, discard and prepare replacement kit as needed.

SpaceOAR System must be stored at or below 25°C (77°F) in order to maintain product performance.

Manufacturer:	Authorized Representative:
Augmenix, Inc. 204 Second Avenue Lower Level Waltham, MA 02451 USA	MedPass International, Ltd. Windsor House Barnett Way Barnwood, Gloucester GL4 3RT United Kingdom

SpaceOAR is a registered trademark of Augmenix, Inc.

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