Phase II Study Assessing the Potential for Reduced Toxicity Using Focal Brachytherapy in Early Stage, Low Volume Prostate Cancer

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Men diagnosed with early stage, low volume prostate cancer (defined as clinical stage T1c-T2a, prostate-specific antigen (PSA) <10 ng/mL, biopsy with a minimum of 10 cores, Gleason grade 7 in two cores or less with no primary Gleason grade 4 or 5 in any core, no individual biopsy core with >50% cancer, unilateral cancer and no more that 25% of cores containing cancer) and a total prostate volume of < 60 cc at the time of treatment are eligible for this study. Patients will undergo a repeat transrectal or transperineal ultrasound-guided prostate biopsy (minimum of 12 cores) to confirm the early stage, low volume nature of their cancer. In order to be enrolled into this study, patients must meet the original pathology entry criteria on this repeat biopsy. If the patient meets the eligibility criteria as stated above, he will be treated with focal brachytherapy to the involved lobe of the prostate containing cancer.

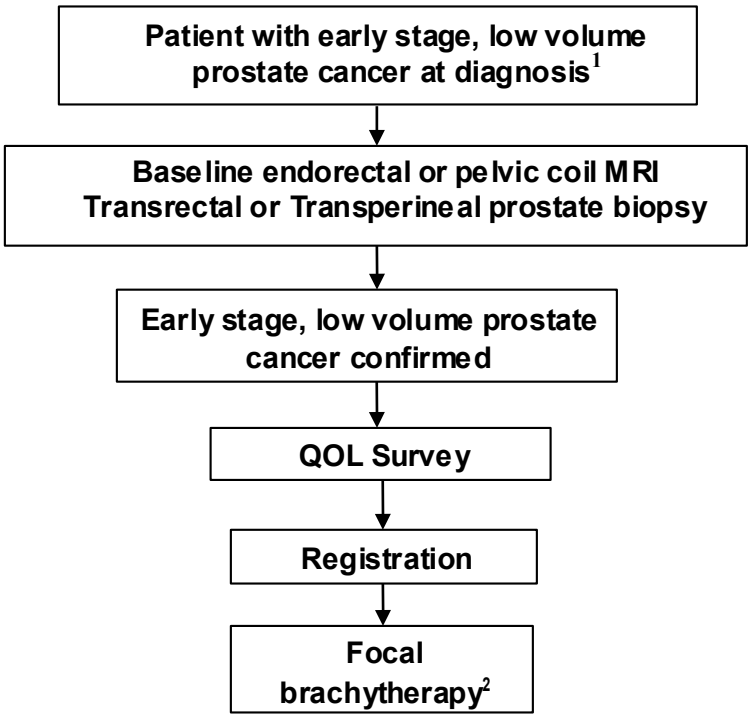
As the primary endpoint of this study is to determine if this treatment approach would be associated with significantly less late grade 2 and higher urinary or rectal toxicities compared to whole gland brachytherapy, patients will be monitored at 3 month intervals during the first two years. Efficacy is a secondary endpoint of this study and is defined as all negative biopsy cores in the treated lobe on a repeat biopsy 12 and 24 months after completion of focal brachytherapy.

At baseline (prior to the transrectal or transperineal biopsy) and at 3, 6, 12, 18, and 24 months (prior to the repeat biopsies used to define efficacy), the patient will be monitored for side effects including urinary and rectal related effects as well as sexual function and serial quality-of-life (QOL) questionnaires will be administered. Digital rectal examination (DRE) and PSA tests will be performed at the 3 (DRE optional at 3 months) and 6 month follow-up visits and every 6 months for 24 months. Transrectal or transperineal ultrasound-guided biopsies will be performed at the 12 and 24 month follow-up visit. Imaging (endorectal or pelvic coil MRI) will be performed at baseline and at 6 (optional), 12, and 24 months after the completion of focal brachytherapy procedure. Endorectal coil MRI is preferred, though not required.

Following completion of the study, patients will undergo standard care procedures, including a DRE and serum PSA level every 6 months for 5 years and annually thereafter**.** The need for any future prostate biopsies will be at the physician's discretion.

Target accrual for this study is 80 patients, approximately 20 per site, to be achieved in 2-3 years of accrual.

Schema



Endorectal or pelvic coil MRI at baseline, 6 (optional), 12, and 24 months
QOL survey at baseline, 3, 6, 12, 18 and 24 months
Transrectal or transperineal prostate biopsy at baseline, 12 and 24 months after brachytherapy

[1]Clinical stage T1c-T2a, PSA <10 ng/mL, unilateral cancer, biopsy with a minimum of 10 cores, Gleason grade 7 in two cores or less with no primary Gleason grade 4 or 5 in any core, no individual biopsy core with >50% cancer, and no more than 25% of cores containing cancer.

[2] If there is greater than 30 days between consent and treatment start, patients will need to be re-consented prior to treatment.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective

To assess the late, 6 months to 2 years, toxicity outcomes of focal brachytherapy in patients with early stage, low volume prostate cancer. Given the reduced volume of the treated region, we expect significantly less rectal, urinary and sexual dysfunction among treated patients compared to expected tolerance outcomes with whole gland brachytherapy.

Secondary Objectives

1. To evaluate the local tumor control after focal brachytherapy as measured by the ability to obtain all negative biopsy cores 12 and 24 months after completion of therapy in the hemi-

gland of where the focal therapy was administered. “All negative” means no prostate cancer; if the biopsy contains inflammation, or pre-cancerous changes (high-grade prostatic intraepithelial neoplasia and/or atypical small acinar proliferation, or adenocarcinoma with severe treatment effect) it will be considered negative for study purposes.

2. To evaluate the change from baseline in QOL indicators following focal brachytherapy in patients with low-risk localized prostate cancer.

3. To correlate post-treatment MRI findings with post-treatment biopsy outcomes

3.0 BACKGROUND AND RATIONALE

Epidemiological data demonstrate a marked increase in the number of men diagnosed with prostate cancer, and a profound migration towards earlier-stage disease at the time of diagnosis. Implementation of large-scale serum PSA screening programs and more extensive biopsy strategies are largely responsible for the increase in diagnosis. An analysis of the control group in the Prostate Cancer Prevention Trial illustrates the potential for extensive biopsy to result in over-diagnosis of prostate cancer (1). Among 2,950 men with negative DRE and PSA levels <4.0 ng/mL, 15.2% harbored prostate cancer by biopsy, as did 6.2% of men with PSA levels ≤ 0.5 ng/mL. In an era of increasing prostate cancer incidence and stage migration towards earlier disease, appropriate management of the disease requires assessment of risk: How likely is a given man’s cancer to progress or metastasize over his remaining lifetime? What is the probability of success with treatment? What are the risks of side effects and complications with each treatment?

Prostate cancer is relatively slow growing, with doubling times for local tumors estimated at 2 to 4 years. Some prostate cancers prove to be so small, low-grade, and noninvasive that they appear to pose little risk to the life or health of the host. A recent review of the Memorial Sloan-Kettering Cancer Center (MSKCC) radical prostatectomy series suggests that 25%-30% of men undergoing radical prostatectomy have pathologic features in the radical prostatectomy specimen consistent with an insignificant or “indolent” cancer that posed little threat to life or health (organ-confined cancer <0.5 cm^3, no Gleason grade 4 or 5 component). However, the biological potential of histologically detectable cancers is difficult to characterize with certainty, and a traditional 10 to 12 core transrectal prostate biopsy may underestimate the extent of cancer in the prostate in up to 50% of men with low-risk cancer.

There are ongoing studies in various institutions exploring the role of focal therapy for early stage prostate cancer (2-8). While the tumor control outcomes for such therapy should be comparable to whole gland therapy, it has not been established or tested whether these highly selected early stage tumors require treatment to the whole gland. Indeed, the irradiation of the whole gland subjects the patients to increased risks of morbidity including chronic urethritis, rectal bleeding and erectile dysfunction. Given the fact that the dominant reasons patients with early stage therapy select a specific treatment intervention such as surgery or irradiation is often based on quality of life and psychological issues, exploring modes of treatment intervention for early stage of disease which could be associated with significantly lower rates of morbidity and impairment on their quality of life is important.

Advantages of Focal Therapy:

While deferring definitive therapy (active surveillance, watchful waiting, expectant management) until evidence that the cancer is sufficiently aggressive to warrant therapy may be appropriate for many patients with a favorable (early stage, low volume) cancer, most men with a diagnosis of 'cancer' do not accept this approach. As such, there appears to be a role for therapy solely targeting the cancer (focal therapy; the male 'lumpectomy'). This has the theoretical advantage of treating/curing the cancer while at the same time having fewer side effects than traditional whole-gland treatments. The major disadvantage of watchful waiting is that the cancer is not treated, while the major disadvantage of surgery/radiation is that there is a significant risk of urinary, bowel, and sexual side effects. Using real-time intraoperative techniques, brachytherapy is amenable and well suited for focal treatments.

The other advantage for focal brachytherapy which is the primary objective of our study is to corroborate reduced toxicity outcomes with the treatment of a smaller target volume. Such an approach can more easily spare the urethra, rectum and neurovascular bundles more effectively from the high doses of irradiation. Many studies have demonstrated that the volume of irradiated normal tissue correlates with morbidity outcomes. In these studies higher doses to the urethra, rectum and neurovascular bundle were directly associated with increased rates of dysfunction and morbidity (9-11). In our published experience using whole gland brachytherapy in 448 patients the incidence of late grade 2 rectal bleeding is 5%, the risk of late grade 2 chronic urethritis is 15% and the incidence of erectile dysfunction is approximately 40% (12). We hypothesize that treatment of a hemilobe of the prostate rather than whole gland treatment for selected early stage tumors will reduce by $\geq$30% these respective morbidities. A future goal is also to compare these side effect profiles to contemporarily treated patients who receive whole gland brachytherapy. Once we obtain from this study the incidence of side effects experienced with focal brachytherapy we would consider the design of a randomized trial to compare to similar patients who receive standard whole gland brachytherapy.

This protocol will investigate the tolerance profile of focal brachytherapy in a well-defined, early stage, low volume prostate-cancer population and in addition will examine treatment efficacy (elimination of the cancer) as well as changes from baseline in QOL. While PSA is often used to assess the response of treatment and while biochemical control is considered a surrogate for local tumor control, this marker is recognized to be insufficient to assess the response after focal therapy. For this reason serial MRI studies as well as 12 and 24 month biopsies will be used to monitor the response of focal therapy. Local control will also be considered negative if the biopsy contains inflammation or pre-cancerous changes (high-grade prostatic intraepithelial neoplasia and/or atypical small acinar proliferation, or adenocarcinoma with severe treatment effect). It will also be considered negative for study purposes if no recurrence of cancer is noted within the irradiated lobe. Given the limited scope of the irradiated area we would not anticipate significant risk or morbidity if the area was subsequently treated with whole gland irradiation or salvage surgery.

Our QOL survey is based on the previously validated MSKCC prostate cancer QOL outcomes instrument (13). Erectile function will be assessed using the six-question version of the International Index of Erectile Function, a validated and widely used measure. For urinary function, we will use a five-question scale that constitutes a subset of the urinary outcomes on the MSKCC instrument: correlation between the score on these five questions and the scores on the complete instrument is 0.9. In a limits-of-agreement analysis, the difference was 1.7, with an 80% confidence interval of −7.5, 10.8. We feel that these are acceptable properties for a 0-100 scale. The Cronbach's α for

these six items was also good, at 0.82. Two bowel questions from the full questionnaire, "How often have bowel problems or bowel pain made it difficult to enjoy your life?" and "How big a problem have your bowel habits been for you?" had a high Pearson's rho (0.91) compared to the full domain score (limits of agreement difference of −2.3; 80% confidence interval −13.9, 9.3). These two questions will therefore be used in the questionnaire. Finally, we will ask a general health-related QOL question using a 0-10 scale. The full instrument is given in appendix A.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a multi-center, non-randomized, Phase II study examining the tolerance profile (primary endpoint) as well as the secondary endpoints of QOL changes, efficacy and the correlation of post-treatment MRI findings with post-treatment biopsy outcomes in men with early stage, low volume prostate cancer treated with focal brachytherapy. We will test the hypothesis that the 2-year probability of rectal bleeding, grade 2 urethritis or erectile dysfunction for patients treated with focal ablation will be reduced by 30% or greater compared to our aforementioned published experience of whole gland brachytherapy.

4.2 Intervention

Patients will undergo a re-staging transrectal or transperineal ultrasound-guided prostate biopsy as currently performed at participating institutions. Prostate biopsy will be performed under general or local anesthesia using a standard transrectal or transperineal approach that obtains no fewer than 12 biopsy cores. For patients to be eligible for treatment with focal brachytherapy under this protocol, they must meet the original entry criteria on this re-staging biopsy.

If after the re-staging biopsy the patient does not meet the criteria for focal brachytherapy, he will be considered for other treatment options for prostate cancer including active surveillance, radical prostatectomy, external beam radiation therapy, or whole-gland brachytherapy.

Focal brachytherapy will be performed at least 8 weeks following the transrectal or transperineal biopsy, though it may be performed sooner if the patient has recovered from the repeat biopsy and the treating physician determines it is safe to proceed with treatment. Focal brachytherapy is performed under a spinal or general anesthesia and will include the hemilobe of the prostate containing cancer, based on the re-staging biopsy. The regions will be targeted with the prescription dose and receive 144 Gy of Iodine-125 (I-125). This is an outpatient procedure. Prior to discharge, the Foley catheter (inserted routinely during the brachytherapy procedure) will be removed.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Whole-gland brachytherapy is a standard and accepted treatment for clinically localized prostate cancer. Focal brachytherapy will merely entail the treatment of the involved lobe where the biopsy cores are positive and sparing the rest of the gland from the high-dose therapy. The actual brachytherapy procedure itself will be otherwise identical to standard whole-gland brachytherapy procedure in technique, treatment-planning aspects, and treatment delivery as described in section 9.0.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Men ≥ 21 years of age with a life expectancy estimated to be > 10-years
- Diagnosis of adenocarcinoma of the prostate confirmed by MSKCC or participating site pathology review
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1(Appendix C)
- Prostate cancer clinical stage T1c-T2a
- PSA < 10ng/mL (this will be the PSA level prompting the prostate biopsy)
- MRI evidence of one-sided disease performed within 3 months of registration
- Prostate size <60 cc at time of treatment- if the prostate is larger, hormonal therapy is allowed to achieve the required size

Screening biopsy parameters:

- Minimum of 10 biopsy cores
- Gleason grade 7 in two cores or less, with no primary Gleason grade 4 or 5 in any cores
- Unilateral cancer (only right-sided or left-sided, not bilateral)
- No more than 50 % cancer in any one biopsy core
- No more than 25 % of cores containing cancer

Repeat transrectal or transperineal prostate biopsy that must meet the following parameters:

- Minimum of 12 biopsy cores
- Unilateral cancer (only right-sided or left-sided, not bilateral)
- Gleason grade 7 in two cores or less, with no primary Gleason grade 4 or 5 in any cores
- No more than 50 % cancer in any one biopsy core
- No more than 25 % of cores containing cancer

6.2 Subject Exclusion Criteria

- Medically unfit for anesthesia
- Evidence or suspicion of extracapsular extension on MRI
- IPSS score > 18
- Unable to receive MRI
- Prior radiotherapy for the current disease

7.0 RECRUITMENT PLAN

Recruitment Plan (with Limited waiver of Authorization)

Investigators and their research teams at University of Colorado, MD Anderson Cancer Center and North Shore-LIJ Health Systems will recruit patients at their respective sites.

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC). If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the

research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

We plan to accrue 80 patients (approximately 20 per site) within 2-3 years.

8.0 PRETREATMENT EVALUATION

The baseline clinical evaluation is to be completed before the transrectal or transperineal, ultrasound-guided prostate biopsy. These procedures, which are standard of care, will include:

- Medical history
- Physical examination including DRE
- Review of prostate biopsy information including Gleason score and clinical staging (TNM staging). Note: If the patient had his diagnostic biopsy performed at an outside institution, these biopsy slides must be reviewed at either MSKCC or one of the participating centers prior to determining patient eligibility. If there is a discrepancy between the pathology reviews, we will rely on the MSKCC or participating center review to determine eligibility.
- QOL assessment
- Endorectal or pelvic coil MRI (within 3 months of registration)
- PSA

9.0 TREATMENT/INTERVENTION PLAN

9.1 Re-staging Prostate Biopsy

9.1.1 Transrectal Prostate Biopsy:

Preparation/anesthesia: The patient will be administered prophylactic antibiotics as per standard of care. The biopsy is performed by the urologist on an outpatient basis under local anesthesia. With the patient in the left lateral decubitus position, 2% lidocaine gel is instilled per rectum followed by the ultrasound probe. Serial images of the prostate are taken in transverse and sagittal planes.

Approximately 5 cc of lidocaine may be injected in the angle between the seminal vesicle and base of the prostate on each side.

A minimum of 12 prostate biopsy specimens are obtained. Cores are placed in the same specimen container containing formalin and submitted to pathology for histologic examination.

Required equipment and setup: Techniques for transrectal prostate biopsy will employ an endocavity ultrasound probe with biopsy needle guide. The lubricated probe will be placed in the rectum and the prostate gland will be imaged manually by hand to identify the base, mid and apex anatomy. Core biopsies will be taken from medial and lateral portions of the prostate. The biopsy needle is capable of obtaining core lengths of 2.2 cm.

9.1.2 Transperineal Prostate Biopsy:

The location and grade of the subject's prostate cancer may be documented via transrectal ultrasound guided transperineal 3-dimensional prostate mapping biopsy as described by Crawford et al. (Clinical Staging of Prostate Cancer: A Computer-simulated Study of Transperineal Prostate Biopsy, BJU Intl., Vol. 96, pp. 999-1004, 2005).

This procedure is performed under general anesthesia. A Foley catheter may be placed to mark the location of the urethra and assess the subject for post-biopsy hematuria for a recommended 2-5 days. A biplane transrectal ultrasound probe may be placed in the rectum to visualize the prostate and assist in needle guidance and placement.

The G *x* axis of the brachytherapy grid may be placed in the midline urethral plane for ultrasound prostate orientation. A 5mm Civco Brachytherapy Grid with coordinates of A-M on the *x axis* and 0-12 on the *y axis* may be used to identify biopsy location and to guide biopsy needles in relation to the ultrasound generated biopsy grid**.** To assist in this location, two fiducial markers may be placed, one in each hemisphere approximately midline within the prostate, in an apex/base relationship. Prior to placement of the fiducial seeds, the two coordinates selected for these markers may be biopsied in the appropriate fashion. The fiducial seeds may be dropped in their respective locations as described, and the fiducial needles may be left in place to stabilize the prostate throughout the remaining biopsy procedure. Prior to biopsy, multiple jpeg images may be sampled under ultrasound guidance at 5mm increments from extreme apex to extreme base utilizing the mounted stepping unit in order to aid in 3D reconstruction. These images may be saved to a removable storage device. Using a 22mm, 18 gauge automated biopsy gun with a 2 cm specimen size, biopsies may be obtained every 5 mm throughout the volume of the prostate under transrectal

ultrasound guidance.

Depth of the needle placement may be monitored with the ultrasound longitudinal view in order to sample the entire length of the prostate and avoid punctures to the bladder base. The axial ultrasound view may be checked periodically to confirm that samples are taken in the correct *x y* coordinates, corresponding to the grid rendered on the BK Falcon (or newer) ultrasound machine. Where the length of the prostate is greater than the specimen size of a single biopsy at a given coordinate, additional biopsies may be obtained at that location in order to sample the full length of the prostate. Biopsies in the area of the urethra or neurovascular bundles may be avoided in order to prevent any subsequent damage.

Biopsy samples may be inked utilizing Davidson Marking Systems # 1003-3 ink at their distal end (distal in relation to the biopsy needle body), placed in a formalin biopsy jar, labeled with their respective *x y* brachytherapy grid coordinates, and sent to a respective pathology lab for analysis. If more than one biopsy is taken at a given *x y* coordinate, it may also be labeled as to whether it was base, apex, or midline.

Dependent on the size of the prostate, the number of biopsy samples may vary between 30-150 samples. The whole procedure can last anywhere between 60-90minutes.

Patients meeting our definition of early stage, low volume prostate cancer (clinical stage T1c-T2a, PSA <10 ng/mL, Gleason grade 7 in two cores or less, with no primary Gleason grade 4 or 5 in any core, unilateral cancer, no single biopsy core containing >50% cancer, no more than 25% of cores containing cancer) will undergo focal brachytherapy of the regions/lobe containing cancer on the biopsy.

9.2 Focal Brachytherapy of the Prostate

The focal brachytherapy procedure will be performed in the Department of Radiation Oncology Brachytherapy Suite 8 weeks following the transrectal or transperineal biopsy, or sooner if the patient has recovered from the repeat biopsy and the treating physician determines it is safe to proceed with treatment. The procedure is performed in the exact fashion as conventional whole gland brachytherapy except the target is restricted to the involved lobe of the prostate. The patient is placed in the extended lithotomy position and transrectal ultrasound is placed as well as a urinary catheter. Axial ultrasound images are obtained with peripherally placed needles through the perineum into the involved hemilobe. The images are downloaded into the brachytherapy planning computer and a computer-based conformal treatment plan is generated which will determine the optimal seed loading to treat the involved lobe of the prostate to 144 Gy with I-125 while minimizing the dose to the urethra (V100<130% of the prescription dose) and rectum (V100 < 100% of the prescription dose). A mobile cone-beam computed tomography (CT) unit, which is routinely used in the department for intraoperative planning of permanent I-125 implants, may be employed for the focal brachytherapy procedure. The procedure itself will take about 60-90 minutes to perform, similar to a standard whole gland brachytherapy procedure.

The information/coordinates from the biopsy as to the dominant visible tumor on the pre-operative endorectal or pelvic coil MRI may be fused to the intraoperative ultrasound images. This visible area will constitute the gross tumor volume. The clinical target volume (CTV) will represent a 3 mm margin beyond the GTV and the planning target volume will represent the involved hemi-lobe of the

prostate gland. The 144 Gy prescription dose may be prescribed to the isodose line from the intraoperative computer plan which completely encompasses the PTV.

Routine intraoperative planning methods may be used to treat the designated hemilobe of the prostate.

An intraoperative cone-beam CT scan may be used to confirm accurate placement of the seeds. If it is determined based on this scan that there is a deficient dose region, this will be corrected with the placement of additional seeds after regeneration of the treatment planning prior to reversal of anesthesia. Several hours later, a routine post-implantation CT scan will be obtained for quality-assurance assessment of the adequacy of the implanted region.

9.3 Assessment of QOL

The quality-of-life assessment will focus on erectile function, urinary function, bowel function, and general health related quality of life (See Appendix A). The scales to measure these domains were derived from the previously validated MSKCC Prostate-Health Related Quality of Life Questionnaire (PHRQOLQ (13)). The patients will complete this assessment at baseline and then approximately 3 ± 1 months, 6 ± 1 months, 12 ± 2 months, 18 ± 2 months, and 24 ± 2 months after treatment. Consistent with Wagner and colleagues' discussion of methodological issues associated with collection of patient-reported outcomes in Phase II studies (8), these measure will provide pilot data which will help describe these symptoms/side effects of brachytherapy and determine general effect sizes to appropriately power quality of life outcomes in future studies.

Erectile Function: Erectile function will be assessed using 7-questions from the sexual function subscale of the MSKCC Prostate Health-Related Quality-of-Life Questionnaire (PHRQOLQ (13)). The PHRQOLQ includes items from the Erectile Function Doman (EFD) of the International Index of Erectile Function Questionnaire (IIEF (6)). The 7-item EFD subscale has demonstrated Cronbach's alpha values greater than 0.73 and strong test-retest reliability. The EFD also displayed a high degree of sensitivity and specificity to the effects of treatment. One additional question has been added to the EFD for this study, and asks men if they have been using medication to treat erectile dysfunction. This question is for descriptive purposes only, and will not be included in the total score for the EFD.

Urinary Function: To assess urinary function, we will use 5-questions which come from the urinary function subscale of the MSKCC Prostate Health-Related Quality-of-Life Questionnaire (PHRQOLQ (13)). The validation of this subscale is based on data from MSKCC prostate cancer patients. The correlation between the scores on these 5-question subscales used in this study and the scores on the full urinary subscale is 0.9. In a limits-of-agreement analysis, the difference was 1.7, with an 80% confidence interval of −7.5, 10.8. The Cronbach's α for these five-items was also good, at 0.82.

Bowel Function: Bowel function will be assessed with two 2 questions from the bowel function subscale of the PHRQOLQ questionnaire. These questions are: "How often have bowel problems or bowel pain made it difficult to enjoy your life?" and "How big a problem have your bowel habits been for you?" These two questions produced a high Pearson's rho (0.91) compared to the full bowel domain of the PHRQOLQ (limits of agreement difference of −2.3; 80% confidence interval −13.9, 9.3).

General Healthy Related Quality-of-Life: This will be assessed with 1 question which asks the

subjects to rate their general health status on a 0-10 scale. As with the urinary function and bowl function, this 1-item assessment is from the PHRQOLQ.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

3 ± 1 month after focal brachytherapy:

- DRE (optional)
- Assessment of toxicity relevant to the protocol therapy
- QOL questionnaires

6 ± 1 month after focal brachytherapy:

- DRE
- PSA
- QOL questionnaires
- Assessment of toxicity relevant to the protocol therapy
- Endorectal or pelvic Coil MRI (optional)

12 ± 2 months after focal brachytherapy:

- Endorectal or pelvic Coil MRI
- DRE
- PSA
- QOL questionnaires
- Assessment of toxicity relevant to the protocol therapy
- Second transrectal or transperineal ultrasound-guided prostate biopsy

18 ± 2 months after focal brachytherapy:

- DRE
- PSA
- QOL questionnaire
- Assessment of toxicity relevant to the protocol therapy

24 ± 2 months after focal brachytherapy:

- DRE
- PSA
- QOL questionnaire
- Assessment of toxicity relevant to the protocol therapy
- Endorectal or pelvic Coil MRI
- Third transrectal or transperineal -guided prostate biopsy

11.0 TOXICITIES/SIDE EFFECTS

This study will utilize the toxicity grading scale Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 for the following:

Transrectal or transperineal prostate biopsy

- Blood in semen (50%)
- Bleeding from the rectum, bladder (<3%)
- Anemia (<1%)
- Pelvic pain (<5%)
- Infection (1%)
- Urinary retention (5%)- which would be temporary and require a catheter for several days

Focal brachytherapy

- Bleeding (1%)
- Infection (<1%)
- Blood in the stools (3%)
- Defecation urgency (1%)
- Defecation incontinence (1%)
- Urinary retention (5%)
- Urinary incontinence (< 1%)
- Erectile dysfunction (25%)
- Urinary urgency (10%)
- Urinary frequency (10%)
- Dysuria (20%)
- Rectal fistula (<1%)

Endorectal or pelvic Coil MRI

- Discomfort of placing probe in rectum and exacerbation of hemorrhoids if present

This type of prostate radiation can affect an unborn baby and thus birth control methods must be used during participation in this study. Patients will be instructed not to father a baby for two years following implantation of the seeds. If a patient's partner should become pregnant during this period, the patient must notify the study team as soon as possible. The progress of the pregnancy and delivery will be monitored by the study team to ensure that any complications are properly documented and reported.

If the patient's partner is currently pregnant, at the time of protocol treatment, they must be instructed to use a condom for at least the first 5 ejaculations after treatment. They should also be reminded not father any other children for two years following protocol treatment.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12 ± 2 months and 24 ± 2 months following focal brachytherapy the patient will undergo a second and third biopsy to assess the local tumor response, as well as to assess treatment efficacy. The rationale for a complete (bilateral) biopsy after brachytherapy, rather than just sampling the regions that were treated, is to confirm a prostate cancer-free status, since prostate cancer is commonly found to be multifocal and the remainder (non-treated portion) of the prostate remains at risk for the presence of cancer. If all biopsies are found to be negative within the hemi-gland where the focal therapy was administered this will be considered for the purposes of this study as a complete response after therapy and indicative of a successful outcome. In addition, the post-treatment MRI studies will be correlated with the biopsy findings to determine the specificity and sensitivity of this diagnostic study as a tool to follow patients who were treated with this focal therapy approach.

13.0 CRITERIA FOR REMOVAL FROM STUDY

The patient may withdraw consent from the study at any time.

The study will be terminated if there is a 3% or greater incidence of rectal fistula as a result of treatment.

If at any time the patient develops progressive disease he will be withdrawn from the study and referred for alternative therapy.

If at any time the patient is found to be ineligible for the protocol as designated in the section on Criteria for Subject Eligibility (i.e., a change in diagnosis), the patient will be removed from the study.

14.0 BIOSTATISTICS

The primary objective of this study is to assess for the reduction of treatment related long-term morbidity rates associated with focal brachytherapy, compared to our published historical morbidity rates associated with whole gland brachytherapy for patients with low-risk, clinically localized prostate cancer. The treatment would be considered to have achieved the study's primary objective if a 30% or greater (relative) reduction in either rectal, urinary toxicities or sexual dysfunction is observed between 6 months and 2 years after treatment compared to our published toxicity profile of whole gland brachytherapy.

Our published data showed that the late toxicity rate (patients having either grade 2 or higher rectal or urinary toxicity after 6 months but within 2 years of the treatment, or having sexual dysfunction after 6 months but within 2 years of the treatment) was 53% for whole gland brachytherapy. Therefore, a late toxicity or sexual dysfunction rate of 53% or higher is considered definitely unacceptable while a late toxicity or sexual dysfunction rate of 37% or less is definitely acceptable. Using a cohort of 70 patients, we will claim the focal brachytherapy procedure significantly reduces the late toxicity/sexual dysfunction rate if no more than 31 patients have grade 2 or higher rectal or urinary toxicity or sexual dysfunction after 6 months but within 2 years of the treatment. For this decision rule we have a type I error rate as 9% and a power of 92%.

We will also report the sample proportions of the acute toxicity rate (occurred within 6 months of the treatment) and the late toxicity and sexual dysfunction rates with its confidence interval and tabulate and summarize all tolerance profiles based on all patients.

We expect to accrue 2-3 patients per month. Thus the trial should be completed within 2-3 years. Efforts will be made to follow-up every patient for at least 2 years. Since patients may drop off (for reasons not related with toxicity or sexual dysfunction) or be lost to follow-up, we will enroll an extra 15% of patients to make a total of 80 patients, approximately 20 per site, for our accrual goal. However, only the first 70 patients who have been followed for at least 2 years will be analyzed towards the primary objective.

For secondary objectives, the local control rate will be examined using proportions of patients who obtain all negative biopsy cores 12 and 24 months after completion of therapy in the hemi-gland of where the focal therapy was administered. QOL data will be presented descriptively, giving summary statistics for the change in sexual, erectile, bowel, and QOL scores over time. Post-treatment MRI

outcome is defined as a 3-level categorical variable: positive, negative and undetermined. Post-treatment biopsy outcome is defined as a binary variable: positive and negative. We will examine the correlation between the 12-month MRI and 12-month biopsy, and between the 24-month MRI and 24-month biopsy. The correlation will be assessed by a Fisher exact test. We will also examine the sensitivity and specificity of MRI by using biopsy as the gold standard (for this analysis we will omit patients with undetermined MRI results). All patients enrolled will be used for the analysis of secondary objectives.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. The PPR fax numbers are (646) 735-0008 and (646) 735-0003. Registrations can be phoned in or faxed. The completed signature page of the written consent and a completed Eligibility Checklist must be faxed to PPR.

15.1.1 For Participating Sites:

Central registration for this study will take place at Memorial Sloan Kettering Cancer Center (MSKCC).

To complete registration and enroll a participant from another institution, the study staff at that site must contact the designated research staff at MSKCC to notify him/her of the participant registration. The site staff then needs to fax registration/eligibility documents to the Radiation Oncology department at MSKCC 212-639-2417.

The following documents must be sent for each enrollment within 24 hours of the informed consent form being signed:

- The completed or partially completed MSKCC eligibility checklist
- The signed informed consent and HIPAA Authorization form
- Supporting source documentation for eligibility questions (pathology report, radiology reports, MD notes, physical exam sheets, medical history and prior treatment records).

Upon receipt, the research staff at Memorial Sloan Kettering Cancer Center will conduct an interim review of all documents. If the eligibility checklist is not complete, the patient will be

registered PENDING and the site is responsible for sending a completed form within 30 days of the consent.

If the eligibility checklist is complete, participant meets all criteria, all source documentation is received, the participating site IRB has granted approval for the protocol, and the site is in good standing with MSKCC, the MSKCC research staff will send the completed registration documents to the MSKCC Protocol Participant Registration (PPR) Office to be enrolled as stated in section 15.1. The participant will be registered.

Once eligibility has been established and the participant is registered, the participant will be assigned an MSKCC Clinical Research Database (CRDB) number (protocol participant number). This number is unique to the participant and must be written on all data and correspondence for the participant. This protocol participant number will be relayed back to study staff at the registering site via e-mail and will serve as the enrollment confirmation.

15.2 Randomization

There is no randomization for this trial.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team.

The data collected for this study will be entered into CRDB. Source documentation will be available to support the computerized patient record.

16.0.1 Data and Source Documentation for Participating Sites

Data
Standardized Case Report Forms (CRFs), directions for use and sign off requirements have been generated for this study. Blank case report forms will be sent to the study staff at each participating site for use. The participating Site PI is responsible for ensuring these forms are completed accurately, legibly and in a timely manner.

Source Documentation
Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into CRFs. Relevant source documentation to be submitted throughout the study includes:

- Baseline measures to assess pre–protocol disease status (ex. MRI, PSA)
- Treatment records
- Toxicities/adverse events not previously submitted with SAE Reports
- Response designation

16.0.2 Data and Source Documentation Submission for Participating Sites

Participating sites should email CRFs and source documentation to MSKCC to the contact provided below. Submissions should include a cover page listing all CRFs enclosed per participant.

EMAIL: Michael Zelefsky, MD, zelefskm@mskcc.org and
Rebekah Dunn, CRC, dunnr@mskcc.org

16.0.3 Data and Source Documentation Submission Timelines for Participating Site
Data and source documentation to support data should be transmitted to MSKCC according to the following chart:

	Baseline	*Biopsy Visit*	*Treatment Visits*	*Follow Up*	*SAE*	*Off Study*
SUBMISSION SCHEDULE						
Source Documentation	**Within 24 hours (see section 15.1.1)**	**within 14 days of visit**		**Within 14 days of visit (see section 10.0 for schedule)**	**Within 3 days of event (see section 17.3; updates to be submitted as available**	**Within 14 days of visit**
CRFs	**Within 7 days of enrollment**					
Required Forms						
Demographics Form	**X**					
Medical History Form	**X**					
Treatment Form			**X**			
Disease Status Form	**X**			**X**		**X**
Biopsy Form	**X**	**X**		**X**		**X**
Adverse Event Form				**X**	**X**	**X**
Serious Adverse Event Form					**X**	
Off Study Form						**X**
Questionnaires	**X**			**X**		

16.0.4 Data Review and Queries for Participating Site Data

Research staff at MSKCC will review data and source documentation as it is submitted. Data will be monitored against source documentation and discrepancies will be sent as queries to the participating sites. Queries will be sent by MSKCC Research staff twice a month.

Participating sites should respond to data queries within 14 days of receipt

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data-quality reports will be generated to assess missing data and inconsistencies. Accrual rates, and extent and accuracy of evaluations and follow-up, will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.1.1 Quality Assurance for Participating Sites

Each site participating in the accrual of participants to this protocol will be audited by the staff of the MSKCC study team for protocol and regulatory compliance, data verification and source documentation. Audits may be accomplished in one of two ways: (1) selected participant records can be audited on-site at participating sites or (2) source documents for selected participants will be sent to MSKCC for audit. Audits will usually be determined by participant accrual numbers and rate of accrual, but can also be prompted by reported SAEs or request of MSKCC PI.

Audits will be conducted at least once shortly after initiation of participant recruitment at a site, annually during the study (or more frequently if indicated), and at the end or closeout of the trial. The number of participants audited will be determined by available time and the complexity of the protocol.

The audit will include a review of source documentation to evaluate compliance for:

- Informed consent documents and procedures
- Adherence to eligibility criteria
- Protocol defined treatment
- Required baseline, on study and follow-up protocol testing
- IRB documents (submitted amendments, annual continuing review reports, SAEs)
- Case Report Form submissions to MSKCC: time lines and accuracy

A wrap-up session will be conducted at the participating site and preliminary findings will be discussed with the participating site PI and research team. The preliminary results will be sent to the MSKCC PI.

Each audit will be summarized and a final report will be sent to the PI at the audited participating site within 30 days of the audit. The report will include a summary of findings, participant by participant case review, specific recommendations on any performance and/or shortcomings and request for corrective action, when necessary. When corrective action is required, the participating site must reply within 45 days of receipt of audit report with their corrective action plan.

A copy of the audit report and corrective action plan (if applicable) submitted by the participating site must be sent to the MSKCC IRB/PB, CRQA and maintained in the department's protocol regulatory binder.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: *http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1*. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://smskpsps9/dept/ocr/OCR%20Website%20Documents/Clinical%20Research%20Quality%20Assurance%20(CRQA)/MSKCC%20Data%20and%20Safety%20Monitoring%20Plan.pdf*
There are several different mechanisms by which clinical trials are monitored for data, safety, and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research quality assurance) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees, *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., National Institutes of Health sponsored, in-house sponsored, industrial sponsored, National Cancer Institute cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

16.3 Regulatory Documentation

Prior to implementing this protocol at MSKCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSKCC Institutional Review Board/Privacy Board (IRB/PB). Prior to implementing this protocol at the participating sites, approval for the MSKCC IRB/PB approved protocol must be obtained from the participating site's IRB.

The following documents must be provided to MSKCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Participating site laboratory certifications and normals for PSA

Upon receipt of the required documents, MSKCC will formally contact the site and grant permission to proceed with enrollment

16.3.1 Amendments

Each change to the protocol document must be organized and documented by MSKCC and first approved by the MSKCC IRB/PB. Upon receipt of MSKCC IRB/PB approval, MSKCC will immediately distribute all non expedited amendments to the participating sites, for submission to their local IRBs.

Participating sites must obtain approval for all non expedited amendments from their IRB within 90 calendar days of MSKCC IRB/PB approval. If the amendment is the result of a safety issue or makes eligibility criteria more restrictive, sites will not be permitted to continuing enrolling new participants until the participating site IRB approval has been granted.

The following documents must be provided to MSKCC for each amendment within the stated timelines:

- Participating Site IRB approval
- Participating Site IRB approved informed consent form and HIPAA authorization

16.3.2 Additional IRB Correspondence

Continuing Review Approval
The Continuing Review Approval letter from the participating site's IRB and the most current approved version of the informed consent form should be submitted to MSKCC within 7 days of expiration. Failure to submit the re-approval in the stated timeline will result in suspension of study activities.

Deviations and Violations
A protocol deviation on this study is defined as a request to treat a research participant who does not meet all the eligibility criteria, pretreatment evaluation, or who requires alteration in their study plan. If a deviation from this protocol is proposed for a potential or existing participant at MSKCC or a participating site, approval from the MSKCC IRB/PB is required prior to the action. Participating sites should contact the MSKCC PI who will in turn seek approval from the MSKCC IRB/PB.

A protocol violation is anything that occurs with a participant, which deviated from the protocol without prior approval from the MSKCC IRB/PB. For protocol violations that are identified after they occur, the participating site should report to MSKCC as soon as possible. The MSKCC PI will in turn report the violation to the MSKCC IRB/PB.

Participating sites should report deviations and violations to their institution's IRBs as soon as possible per that site's institutional guidelines. Approvals/acknowledgments from the participating site IRB for protocol deviations and violations should be submitted to MSKCC as received.

Other correspondence
Participating sites should submit other correspondence to their institution's IRB according to local guidelines, and submit copies of that correspondence to MSKCC.

16.3.3 Document maintenance

The MSKCC PI and the Participating Site PI will maintain adequate and accurate records to enable the implementation of the protocol to be fully documented and the data to be subsequently verified.

The participating sites will ensure that all participating site IRB correspondence (IRB approval letters referencing protocol version date and amendment number, IRB approved protocol, appendices, informed consent forms, deviations, violations, and approval of continuing reviews) is maintained in the regulatory binder on site and sent to MSKCC.

A regulatory binder for each site will also be maintained at MSKCC; this binder may be paper or electronic.

After study closure, the participating site will maintain all source documents, study related documents and CRFs for 3 years.

16.4 Noncompliance
If a participating site is noncompliant with the protocol document, accrual privileges may be suspended and/or contract payments may be withheld, until the outstanding issues have been resolved.

17.0 PROTECTION OF HUMAN SUBJECTS

This protocol does not include children because children do not develop prostate cancer. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects. Since only men have prostates, participants in the study are limited to this gender. Therefore, women will be excluded from the study. In conformity with the National Institute of Health Revitalization Act of 1993 with regard to the inclusion of minorities in clinical research, every effort will be made to include participants of all ethnicities. There will be no restrictions based on racial/ethnic background.
The risk of participating in this protocol is related to the risk of prostate biopsy (infection, bleeding, pelvic pain, urinary obstruction) and/or the focal brachytherapy (infection, bleeding, pelvic pain, urinary obstruction, urinary incontinence, erectile dysfunction) and/or the risk of under-treating the patient's prostate cancer. Each of these risks appears low and certainly appears to have a more favorable risk/benefit profile than any active treatment. Alternative treatment options include active surveillance (watchful waiting; whereby definitive treatment is delayed until the patient demonstrates signs of prostate cancer local progression), radiation therapy or radical prostatectomy.

The subjects will be responsible for all charges associated with the items that are part of the routine clinical care, including the prostate biopsy (clinical and pathological charges) as well as the focal brachytherapy procedure. The subjects will not be compensated for their participation. If the patient is injured as a result of being in this study, emergency care, hospitalization, and outpatient care will be made available by the hospital and billed to the patient and his insurance company as part of his medical expenses.

The exams, tests or procedures in the study are part of regular cancer care. The patient and/or health plan/insurance company will need to pay for the following tests in the study:

- Physical exam
- Digital rectal examinations
- Endorectal or pelvic coil MRIs
- Prostate-Specific Antigens (PSA)
- Transrectal and transperineal prostate biopsies
- Focal brachytherapy

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization Form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization Form. A Research Authorization Form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

17.2 Serious Adverse Event (SAE) Reporting

Any serious adverse event must be reported to the IRB as soon as possible but no later than 5 calendar days.

An SAE is defined as any untoward medical occurrence that

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in congenital anomaly and/or birth defects
- Is an important medical event that jeopardizes the participant AND requires medical or surgical intervention to prevent one of the outcomes above

The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from the CRDB

- Subject's name (generate the report with only *initials* if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the adverse event was expected
- The severity of the adverse event
- The intervention
- Detailed text that includes the following information:
  - A explanation of how the adverse event was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
  - If an amendment will need to be made to the protocol and/or consent form

The principal investigator's signature and the date it was signed are required on the completed report.

17.3 Serious Adverse Event (SAE) Reporting for Participating Sites

Responsibility of Participating Sites

- Participating sites are responsible for reporting all SAEs to the MSKCC PI and CRC by email within 24 hours of learning of the event. The SAE form is due to MSKCC via fax or e-mail within 3 calendar days of learning of the event.
- Participating sites should notify the MSKCC PI of any grade 5 event immediately.
- Participating sites should use the SAE Report Template (in the CRF packet) to report SAEs to MSKCC.

SAE contact information for the Coordinating Center is listed below:
Michael Zelefsky, MD, ZelefskM@mskcc.org and
Rebekah Dunn, CRC, DunnR@mskcc.org

Responsibility of MSKCC

- The MSKCC Research Staff is responsible for submitting all SAEs to the MSKCC IRB/PB as specified in 17.2
- The MSKCC PI is responsible for informing all participating sites about unexpected SAEs within 30 days of receiving the stamped SAE from the MSKCC IRB/PB.
- Any report pertaining to a grade 5 event will be distributed to the participating sites as soon as possible.

17.4 Safety Reports

- MSKCC will distribute outside safety reports to the participating sites immediately upon receipt.
- MSKCC must submit outside safety reports to the MSKCC IRB/PB according to institutional guidelines.
- Participating sites must submit safety reports to their institution's IRBs within 30 days of receipt from MSKCC or per participating site guidelines.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.

5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information.

In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

18.1 FOR PARTICIPATING SITES

The investigators listed on the protocol cover page and their qualified designees at each participating site may obtain informed consent and care for the participants according to good clinical practice and protocol guidelines.

Signed copies of the informed consent should be distributed as follows: One copy will be given to the participant to be retained for their personal records. One copy will be maintained on file at the MSKCC. The third copy will be confidentially maintained by the participating institution.

A note will be placed in the medical record documenting that informed consent was obtained for this study, and that the participant acknowledges the risk of participation.

19.0 REFERENCES

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20.0 APPENDICES

Appendix A: QOL questionnaire used in the Department of Urology
Appendix B: QOL directions
Appendix C: ECOG performance status scale