CLINICAL STUDY PROTOCOL

Protocol Title: CyberKnife Dose Escalation Prostate Cancer Trial (CK-DESPOT)

Hypothesis: Dose Escalated Stereotactic Body Radiation Therapy (DE-SBRT) is adequate for biochemical control of Unfavorable Intermediate and High Risk Prostate Cancer.

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1.0 INTRODUCTION

External Beam Radiation Therapy in the Management of Clinically Localized Prostate Cancer: Rationale for Dose Escalation

Local tumor control with radiation is dose-dependent, following a sigmoid dose-response relationship. Results of early clinical applications of conventional external-beam radiation treatment (60–70 Gy in 2-Gy fractions) yielded 10-year disease-free survivals ranging from 40%–70% prompting investigations of dose escalation (1-6). The randomized dose escalation trial performed at the M. D. Anderson Cancer Center compared 70 Gy to 78 Gy (7). As expected, the 78-Gy arm resulted in improved local control, but, at the price of increased rectal complications. Similar results have been obtained in other reported randomized trials (8-9). The risk of rectal bleeding appears to be dependent on both the radiation dose and the volume of the rectum subjected to high doses (10-12).

It has become clear that increases in the total dose delivered to the prostate enhance local tumor control, offering a therapeutic benefit, as long as normal tissue tolerances are respected. Intensity modulated radiation therapy (IMRT) is considered a dosimetric improvement over 3DCRT. Dosimetric comparisons of conventional treatment plans with IMRT plans have revealed that IMRT is capable of sparing adjacent normal tissues (13, 14). Use of IMRT for prostate cancer treatment allows for high levels of clinical and biochemical local control with lower complication rates as compared to conventional external-beam techniques (14, 15).

Rational for Hypofractionation

The optimal radiation schedule for the curative treatment of prostate cancer remains unknown. Prostate cancer patients receiving IMRT are typically treated 5 days per week for 8-9 weeks. This prolonged treatment time is inconvenient for many patients and increases treatment costs. Recent data suggest that large radiation fraction sizes are radio-biologically favorable over lower fraction sizes in prostate cancer radiotherapy (16). The sensitivity of a tumor or normal tissue to fraction size of radiation can be approximated by the alpha-beta ratio (α/β). Recently, Brenner and Hall (17) suggested that the α/β for prostate cancer is actually as low as 1.5. These results imply that the current radiation therapy paradigm for prostate cancer treatment might be fundamentally flawed, as high fraction sizes would be expected to damage tumor more readily. These findings are of considerable interest for prostate cancer treatment and could be exploited with high fraction-size radiation therapy.

Stereotactic Body Radiation Therapy In the Management of Prostate Cancer

The term stereotactic refers to precise positioning which safely allows higher radiation doses per fraction and fewer fractions (hypofractionation) than conventional RT. Multiple single institution experiences suggest high biochemical control rates with acceptable toxicity (18-24).

These series suggest that clinically significant late Grade 3 toxicities are infrequent and lower or similar to rates observed in series of IMRT patients. Early quality of life data indicate that treatment is well tolerated with acceptable declines in patient reported urinary, bowel and sexual function (25). Recent updates have confirmed a 5-10 year biochemical disease-free survival in excess of 90% and local control greater than 98% (26-28). The use of SBRT has accelerated in the last few years largely due to early efficacy and safety data and high degree of penetration of IMRT techniques in the radiation oncology community. As such, the learning curve associated with SBRT compared to IMRT is not as steep. A survey of 500 radiation oncologists in 2010 found that approximately 64% had reported using SBRT in their practice for some type of cancer (29). Second, the number of SBRT-capable radiation platforms has expanded significantly since the introduction of CyberKnife SBRT in 1999. Additionally, cost is also significantly less for SBRT compared to IMRT or proton therapy and this has become increasingly important with scarce healthcare dollars (30).

Clinical Experience with Hypofractionation for Unfavorable Clinically Localized Prostate Cancer

Large radiation fraction sizes have been clinically utilized in the treatment of unfavorable prostate cancer for many years. HDR brachytherapy as a boost to external-beam radiotherapy (EBRT) has shown promise in this regard (31-36). Initial trials combined external beam radiation therapy (36-50.4 Gy) with high dose rate (HDR) brachytherapy (2-4 fractions of 3-11.5 Gy). HDR brachytherapy was employed to escalate the dose to gross disease within the prostate and seminal vesicles. HDR brachytherapy allows greater flexibility in dose delivery which provides for intraprostatic dose escalation and optimization of periprostatic doses. Supplemental EBRT was designed to treat the prostate and seminal vesicles with a margin to encompass adjacent microscopic disease. Draw backs relate to associated hospitalization with the patient confined to bed and remaining supine for 24–48 hours to accommodate treatment. Even so, catheter migration between treatments is common and must be corrected (36-38).

Similarly, recent long term data from the ASCEND-RT trial utilizing LDR brachytherapy boost in similar fashion showed a dramatic 21% improvement in biochemical control at 9 years favoring LDR brachytherapy boost compared to conventional dose escalated EBRT although no corresponding benefit was identified in overall survival, incidence of bone metastases or prostate cancer specific mortality (39). Unfortunately, the incidence of late grade 3 or higher urinary toxicity was increased 3-fold (18 vs 6%) in the LDR brachytherapy arm compared to the EBRT arm. Given the associated toxicity and resources with brachytherapy boosts, recent research has focused on utilizing prostate SBRT to deliver escalated doses similar to HDR or LDR brachytherapy since SBRT is well tolerated and non-invasive (42-43).

Radiation Dose Selection

In this protocol, CK-SBRT will be used to target the microscopic and gross disease in the prostate, seminal vesicles. An escalated dose of 40Gy in 5 fractions will be delivered to the entire target volume while any nodules visible within the prostate gland on endorectal MRI will receive 50Gy in 5 fractions. The linear quadratic formula was used to calculate equivalent doses and three assumptions were made: 1) Sublethal damage is completely repaired between fractions, 2)

No repair of sublethal damage occurs during a given fraction, and 3) No repopulation occurs during the treatment course (i.e., there is no time factor). Data analysis from grouped prostate hypofractionation trials (1) suggests that an EQD_2 of > 80 Gy may be required to achieve long term biochemical disease free survival in the 96-98% range. In this protocol, this dose will be achieved by five SBRT treatments (Minimum EQD_2 108.6 Gy calculated 3 mm from the prostate border). The feasibility and safety of DE-SBRT for treating localized prostate cancer has been shown in two recently completed prospective trials (44). These studies confirm that DE-SBRT is technically feasible and reproducible with acceptable toxicity similar to or lower than patients receiving DE-IMRT.

Evaluating Quality of Life After the Treatment of Prostate Cancer.

The treatment alternatives for clinically localized prostate cancer provide similar local control and survival (46). Quality of life (QOL) outcomes are thus an important factor in selecting treatment (47). Several studies have demonstrated that radiation treatment for prostate cancer can adversely affect urinary, bowel and sexual function (25, 26). The severity and duration of these toxicities varies among patients. The expanded prostate cancer index composite (EPIC) has been developed as a disease specific, patient-administered instrument to measure quality of life in men with prostate cancer (48). Thus, acceptance of a novel regimen for treatment of unfavorable-risk prostate cancer patients must not only be effective and have minimal impact on short- and long-term quality of life, but it must also be cost effective (30,49). Quality-Adjusted Life Years (QALYs) are well-established for measurement of cost-effectiveness for many different types of diseases, and can be calculated through use of clinical quality of life measurements, such as the EuroQol EQ-5D (50). These tools will be utilized for longitudinal QOL assessments for the duration this study.

The Philadelphia CyberKnife Experience

The Philadelphia CyberKnife center is a highly specialized radiation oncology facility within the Crozer Keystone Health System with a sole focus on stereotactic radiation therapy services and delivery. As one of the early adopters and pioneers of SBRT techniques, our expertise and experience is on par with nationally renowned academic centers and our physicians serve on national committees and lead multi-institution prospective trials. Our published experience with CyberKnife prostate SBRT has shown favorable biochemical control compared to IMRT cohorts with low toxicity rates (51, 52). We have also compared prostate SBRT to IMRT using a large national database showing no detriment to SRBT compared to IMRT (53, 54). We will leverage our experience, expertise and national standing to conduct this pivotal prospective study.

Updated Clinical Experience for SBRT

Since initiation of the current trial two important randomized studies have been published which support the current trial structure and importance. Focal boost to the intraprostatic MRI documented tumor has been studied in a recently completed randomized Phase III trial for external beam radiotherapy with standard IMRT 77Gy/35 fractions (2.2Gy per fraction) vs same dose to the prostate with integrated focal boost up to 95Gy (2.7Gy per fraction). The recently completed trial published January 2021coined the FLAME trial revealed an improvement of biochemical disease free survival for patients with intermediate and high risk prostate cancer

with integrated boost without impacting toxicity and quality of life. (56) More importantly, a phase III trial (HYPO-RT-PC) of 1200 men with intermediate to high risk prostate cancer found ultra-hypofractionation 42.7Gy/7fx to be non-inferior to conventional fractionation 78Gy/39fx with late toxicity similar in both treatment arms. (57) The National Comprehensive Cancer Network (NCCN) version 4.2022 defines SBRT as an acceptable standard radiation treatment option for unfavorable, high and very high risk prostate cancer using 5 fractions with dose of 36.25-40Gy, www.nccn.org. Therefore, the experimental aspect of this research is the additional boost to MRI defined nodule with dose painting.

Defining Unfavorable Risk Prostate Carcinoma

For this study, 3 sub-classifications of unfavorable risk prostate carcinoma will be defined.

1. Unfavorable Intermediate Risk Carcinoma: Any patients with intermediate risk prostate cancer not meeting favorable risk classification.
    a. Gleason score 4+3=7
    b. Gleason score 3+4=7 with more than 50% of cores positive
    c. Gleason Score 3+4=7 and PSA 10-20 ng/ml
    d. Gleason Score 3+4=7 and >T2a

2. High Risk Prostate Cancer:
    a. T3a (ECE only) or
    b. Gleason score 8 or
    c. PSA >20 ng/ml

3. Very High Risk Prostate Cancer:
    a. T3b or
    b. Gleason Score 9-10 or
    c. PSA >20 ng/ml

STUDY SCHEMA

1. Registration

2. Endorectal/Multi parametric MRI and Staging Studies

3. Ultrasound with fiducial and SPACE OAR placement

4. Planning CT and MRI

5. SBRT treatment to the prostate and proximal seminal vesicles (4000 cGy in 5 treatments)

PATIENT ELIGIBILITY

Histologically confirmed adenocarcinoma of the prostate diagnosed within 360 days of enrollment.

PSA documented within 90 days prior to registration.

Clinical staging completed within 90 days of registration.

No Nodal or Distant Metastases documented on CT or MRI of the pelvis and bone scan (PSMA

PET/CT may be substituted for bone scan).

Unfavorable Risk Prostate Carcinoma as Described is documented.

No prior pelvic radiotherapy.

No prior TURP.

Prostate volume < 100 cc
AUA score < 20

No recent (within 5 years) or concurrent cancers other than non-melanoma skin cancers.

Patient must have no medical or psychiatric illnesses that would interfere with treatment or follow-up.

No implanted hardware adjacent to the prostate that would prohibit appropriate treatment planning and treatment delivery is allowed.

Patient must speak and comprehend the English language to complete questionnaires.

Patient's with very high risk prostate cancer must be seen in consultation by medical oncology as per NCCN guidelines version 4.2022 for consideration for abiraterone or docetaxel following radiation.

ELIGIBILITY CHECKLIST

_____(Y) 1. Is there histologically confirmed adenocarcinoma of the prostate within 360 days of enrollment?

_____ 2. What is the Gleason score?

_____ 3. What is the T stage?

_____ (N0 or Nx) 4. What is the N stage?

_____ (M0 or Mx) 5. What is the M stage?

_____ (ng/ml) 6. What is the PSA (< 90 days prior to registration)?

_____ (N) 7. Has the patient had prior pelvic radiation?

_____ (N) 8. Has the patient had a TURP?

_____ (< 100 cc) 9. Is the prostate volume < 100 cc?

_____ (N) 10. Has the patient had previous (within the last 5 years) or concurrent cancer other than basal cell or squamous cell skin cancer?

_____ (N) 11. Are there any major medical or psychiatric illnesses which would prevent the completion of treatment or interfere with follow-up?

_____ (Y) 12. Has the patient signed a study-specific consent form?

_____ (AUA < 20) 13. Is the patient's AUA score < 20?

_____(N) 14. Does the patient have implanted hardware adjacent to the prostate that would prohibit appropriate treatment planning and treatment delivery?

2.0 OBJECTIVES

This is a phase II study designed to prospectively evaluate the efficacy and safety of DE CK-SBRT for unfavorable risk prostate cancer in a community setting.

Hypothesis

1. Dose Escalated Stereotactic Body Radiation Therapy is adequate for biochemical control of Unfavorable Intermediate and High Risk Prostate Cancer.

Primary Objective

1. To assess efficacy endpoints: Biochemical disease-free survival (bDFS) assessed using the Phoenix definition (55), duration of local control, distant failure and site of distant failure, disease-free survival, disease-specific survival and overall survival.

Secondary Objectives

1. To estimate the proportion of patients who develop late (> six months) grade 3-5 gastrointestinal and genitourinary toxicity observed following SBRT for prostate cancer.

2. To evaluate Quality of life (QOL) using standardized instruments.

3.0 PRETREATMENT EVALUATION

Evaluations Required for Eligibility:

1. Complete history & physical examination

2. Assessment of performance status

3. Serum PSA (<90 days prior to registration)

4. Pathologic confirmation of adenocarcinoma of the prostate

5. Bone scan (PSMA PET can be substituted for bone scan)

6. Ultrasound of prostate, MRI or CT of pelvis

7. Endorectal/Multi parametric MRI

8. Patient questionnaires (see appendix VI).
   1 Expanded Prostate Cancer Index Composite (EPIC)-26 questionnaire
   EuroQol EQ-5D-5L

4.0 RADIATION THERAPY

DE-SBRT will be delivered using the CyberKnife robotic radiosurgery system. Patients will be treated with five SBRT treatments (8 Gy per fraction to the PTV, and 9-10 Gy per fraction to any nodules identified on endorectal MRI) over 7-10 days.

1 MARKER/SPACE OAR PLACEMENT

All patients will have fiducial markers placed in the prostate prior to treatment planning. At least three fiducial markers or electromagnetic transponders will be placed under transrectal ultrasound guidance, using either transperineal or transrectal approach, with local anesthesia and/or sedation as required. At least three markers must be usable for tracking during treatment. Space OAR hydrogel is a spacer providing space between the rectum and the prostate, making it much less likely that the rectum is exposed to high dose radiation must be utilized in all patients undergoing treatment.

2 TREATMENT PLANNING IMAGING AND CONTOURING STRUCTURES

To allow marker stabilization and resolution of swelling, planning studies will be imaged > 7 days after placement. Immobilization devices will be used as needed. CT scans will be taken for treatment planning. Planning MRI images will be obtained simultaneously with CT images and are utilized for treatment planning.

The structures listed below will be contoured on the CT scan and evaluated with DVH analysis. Bowel peristalsis and bladder filling change the size and location of normal structures. For treatment plans utilizing MRI, if the CT and MRI show normal tissues in different locations immediately adjacent the prostate, the contoured structure shall be a larger composite of both image sets.

1. Rectum: For this study, the rectum is defined as the solid structure, including the lumen and rectal wall, extending from the level of the ischial tuberosity to the sigmoid flexure.

2. Bladder: For this study, the bladder is defined as a solid structure including the bladder wall and lumen.

3. Femoral heads: For this study, the femoral heads are defined as the femoral head and neck.

4. Sigmoid colon or other bowel: Bowel lying within 2 cm of the PTV should be contoured. For non-isocentric treatment plans, distal hot spots need to be avoided.

5. Prostatic urethra: For this study, the prostatic urethra is defined as the lumen-mucosal interface, extending from bladder neck to the membranous urethra.

6. Membranous urethra: For this study, the membranous urethra is defined as the lumen-mucosal interface, extending from the prostatic apex to the penile bulb.

7. Penile Bulb: For this study, the penile bulb is defined as the portion of the bulbous spongiosum that lies inferior to the urogenital diaphragm.

8. Bladder Neck: For this study, the bladder neck is defined as the most proximal portion of the bladder extending from the prostate base and urethral junction.

3 SBRT:

SBRT delivery:

The protocol requires image guidance via radio-opaque fiducial markers or electromagnetic transponders implanted in the prostate. At least three fiducial markers must be identified for each treatment. If fewer than three can be tracked, then additional fiducial markers will be placed, and the patient re-planned. Live fiducial tracking is required. No rectal balloons are allowed.

Dose specifications:

Patients will receive five SBRT treatments of 8 Gy each. The total dose will be 40 Gy. The five treatments will be completed in 7-10. A minimum of 20 hours should elapse between treatments. The total duration of treatments should take no longer than 10 days.

Target Volumes:

Gross Tumor Volume (GTV): The GTV shall include the prostate and any gross extension. 2cm of the SV will be contoured separately. Malignant Nodules identified on MRI will be contoured separately.

Planning Tumor Volume (PTV): The prescription dose (8 Gy) shall be delivered to the PTV. The PTV shall equal the CTV expanded 3 mm in all other directions. Any malignant nodules identified on endorectal/Multi parametric MRI will be prescribed an integrated boost of 10Gy per fraction while respecting all dose constraints. (9 Gy per fraction will be considered an acceptable variation if dose constraints cannot be met.) The PTV-SV will receive 7.25 Gy per fraction.

SBRT Dose Specifications:

PTV: The prescription dose of 40 Gy shall be the dose to the PTV: Per protocol, the volume of the PTV receiving 40 Gy (V40 Gy) shall be at least 95%. The PTV-SV will be treated to 36.25 Gy and the PTV-SV receiving 36.25 Gy shall be at least 95%.

Rectum: Per protocol, the volume of the rectum receiving 36 Gy (V36 Gy) shall be < 1cc. The rectal dose-volume histogram (DVH) constraints are < 50% rectal volume receiving 50% of the prescribed dose, < 20% receiving 80% of the dose, < 10% receiving 90% of the dose, and < 5% receiving 100% of the dose

Bladder: Per protocol, the volume of the bladder receiving 40Gy (V40 Gy) shall be < 5 cc. Although not required, the bladder dose-volume histogram (DVH) goals are < 40% bladder volume receiving 50% of the prescribed dose, < 10% receiving 100% of the dose.

Bladder Neck: Per protocol, the maximum dose (0.03 cc) to the bladder neck should be ≤ 40 Gy.

Sigmoid colon and other bowel: Per protocol, the volume of the sigmoid colon and other bowel receiving 36 Gy (V36Gy) shall be < 1cc.

Prostatic urethra: Per protocol, the maximum dose (0.03 cc) to the prostatic urethra should be < 43 Gy.

Membranous urethra: Per protocol, the maximum dose (0.03 cc) to the membranous urethra should be < 43 Gy.

Penile bulb: Per protocol, the volume of the penile bulb receiving 35 Gy (V35Gy) shall be < 50%. Minor variations: V35Gy ≥ 50%, but < 75%. Major variations: V35Gy > 50%.

5.0 ANDROGEN SUPPRESSION

Androgen suppression (ADT) consists of LHRH agonist for a total of 6 months for unfavorable intermediate risk patients and 18 months for high and very high-risk patients. The choice of LHRH agonist is at the discretion of the treating physician. ADT should proceed initiation of SBRT however there is no minimum interval of ADT prior to initiation of SBRT which is patient/physician defined but should not exceed 6 months.

Risks of Androgen Suppression

ADT has several reported adverse and serious adverse reactions that have been reported in patients with advance prostate cancer who received Orgovyx (ADT oral use tablets). The most common adverse reactions hot flush, musculoskeletal pain (including arthralgia, back pain, pain in extremity, musculoskeletal pain, myalgia, bone pain, neck pain, arthritis, musculoskeletal stiffness, non-cardiac chest pain, musculoskeletal chest pain, spinal pain, and musculoskeletal discomfort), fatigue, diarrhea, and constipation.

Serious adverse reactions occurred in 12% of patients who received ADT. Serious adverse reactions in ≥ 0.5% of patients included myocardial infarction (0.8%), acute kidney injury (0.6%), arrhythmia (0.6%), hemorrhage (0.6%), and urinary tract infection (0.5%). Fatal adverse reactions occurred in 0.8% of patients receiving ADT including metastatic lung cancer (0.3%), myocardial infarction (0.3%), and acute kidney injury (0.2%). Fatal and non-fatal myocardial infarction and stroke were reported in 2.7% of patients receiving Orgovyx.

6.0 PATIENT ASSESSMENTS

Assessment	Pre-entry				Follow-up interval: months post therapy				
			1	3	6	12	18	24	36-60
History (SHIM, AUA)	X		X	X	X	X	X	X	X
Physical exam (DRE)	X			X	X	X	X	X	X
ECOG Performance Scale	X			X	X	X	X	X	X
Prostate Biopsy	X								
PSA	X			X	X	X	X	X	X
Prostate volume assessment	X								
Bone scan	X								
Pelvic imaging	X								
Toxicity evaluation (AUA)	X		X	X	X	X	X	X	X
EPIC-26 Questionnaire	X				X	X		X	X
EuroQol EQ-5D-5L	X				X	X		X	X

Assessment schedule: Quality of life measurements will take place per the table, then annually through 5 years post-treatment.

7.0 CLINICAL ENDPOINTS:

Patients will have toxicity evaluation weekly during treatment. At 1 month following treatment, patients will be assessed for acute toxicity. At 6, 12, 18, and 24 month intervals (and every year thereafter, through year 5- 10, if investigators opt to continue past year 5), patients will be seen and evaluated, including a history, physical exam, performance status, PSA, toxicity evaluation. In addition, at 6 months, 12 months and annually thereafter, EPIC-26 will be administered. Examination and studies may be done at outside facility. Prostate biopsy, bone scan (PSMA PET/CT may be substituted for bone scan) and pelvic MRI will be performed at time of biochemical or clinical failure.

Criteria for toxicity:

Acute side effects (<=90 days of treatment start) and late side effects (> 90 days of treatment start) will be assessed using the NCI Common Toxicity Criteria version 4.0 (see appendix V).

Criteria for disease control:

1. Biochemical disease free survival (bDFS):
    a. Phoenix definition (55): failure occurs when the PSA is ≥ 2 ng/ml more than the lowest PSA measurement before the current one, with no backdating. Administration of salvage therapy will be considered failure.

2. Duration of local control: clinical evidence of local progression or recurrence. Clinical failure includes a palpable abnormality that has increased in size, failure of regression of a palpable abnormality by 2 years after treatment, or redevelopment of a prostate abnormality after complete response. Patients with a prostate abnormality compatible with local recurrence, or a PSA failure shall undergo a prostate biopsy. Histologic criteria for local failure is a positive prostate biopsy more than 2 years after treatment. Patients

with a normal exam and no evidence of PSA failure shall be considered controlled locally. Patients with clinical failure and no biopsy are considered local failures. If a patient is locally controlled at the time of orchiectomy or androgen ablation, he is censored and considered "not evaluable" for further local control.

3. Distant failure (includes regional failure): documented if clinical, bone scan, CT or other imaging study shows metastatic disease. Biochemical failure with a negative prostate biopsy shall be considered distant only failure. Biopsy of metastatic site required if radiographic or clinical findings are equivocal. Type of metastatic failure (distant and/or regional) shall be recorded if known. Prostate biopsy recommended at this time.

4. Disease-free survival: for any measure of disease, including PE, PSA, bone scan, CT/MRI and biopsy, or death.

5. Disease-specific survival: for any of the following: Death due to prostate cancer. Death due to other causes, with active malignancy (defined by clinical or biochemical evidence of progression). If a patient suffered a previous relapse, but has inactive disease, this is not considered a disease-specific death. Death due to complications of treatment.

6. Overall survival: for death from any cause.

Quality of Life/Health Outcomes instruments (See Appendix VI):

1. Disease-specific quality of life: The **Expanded Prostate Cancer Index Composite (EPIC)-26** is a validated comprehensive instrument developed to assess patient function and bother after prostate cancer treatment. It was developed by an expert panel of urological oncologists, radiation oncologists, survey researchers, and prostate cancer nurses, to address symptoms related to radical prostatectomy, radiotherapy, and hormonal symptoms.

Quality-Adjusted Life Years (QALY): **EuroQol EQ-5D-5L** is a validated instrument which provides a single index value for a patient's overall health status (otherwise known as "utility"). It is widely used in cancer clinical trials (56, 57). Five of the items are scored on a 3-point Likert scale (mobility, ability for self-care, ability to perform usual activities, pain/discomfort, anxiety depression), and one item assesses a patient's overall health state on a visual analog scale ranging from 0 (worse imaginable state) to 100 (best imaginable).

8. STATISTICAL CONSIDERATIONS:

Endpoints:

Primary Endpoint

1. **Toxicity** will be assessed using the NCI Common Toxicity Criteria version 4.0.

Secondary Endpoints

1. **Biochemical disease-free survival (bDFS)** will be defined as the time in months from completion of SBRT to biochemical failure. Patients who are free from biochemical failure on the date of closing follow-up will be censored on that date. The Phoenix definition will be used to assess biochemical failure as described in Section 10.

2. **Duration of local control** will be defined as the time in months from SBRT completion to local failure.

3. **Distant failure (includes regional failure)** will be defined as the time in months from SBRT completion to distant failure.

4. **Disease-free survival** will be defined as the time in months from the date that the patient is determined to be free of disease to the date of known disease recurrence for any measure of disease. Patients who are alive and free from disease recurrence on the date of closing follow-up will be censored on that date.

5. **Disease-specific survival** will be defined as the time in months from completion of SBRT to death due to prostate cancer, other causes with active malignancy, or complications from treatment. Patients who are alive or dead with disease relapse but with inactive disease on the date of closing will be censored on that date.

6. **Overall survival** will be defined as the time in months from SBRT completion until death. Patients who are alive on the date of closing will be censored on that date.

7. **Quality of life**

Study Design:

The target sample size is 100 patients for this Phase II study. Allowing for a 15% ineligibility rate, the total sample size is 115 patients. Accrual is anticipated to be completed within 5 years of institutional IRB approval. This Phase II trial will provide information to guide future Phase III studies. Sample size determination is based on the late toxicity endpoint. A single-stage Fleming design will be used to test the null hypothesis that the late unacceptable radiation toxicity probability at 2 years p is < 0.05 versus the alternative hypothesis that toxicity probability at 2 years is > 0.15. Unacceptable toxicity will be defined as grade 3 or higher toxicity. If 10 or fewer patients experience late radiation toxicities at 2 years, the null hypothesis will not be rejected and then the regimen will be considered for a phase III study. If at least 10 patients experience late radiation toxicities at 2 years, the null hypothesis will be rejected. This design has a power of 89% and a type I error rate of 0.10.

Analysis Plan

1. Number and percentage of subjects for each toxicity will be summarized overall by body system and by onset time (acute: ≤90 days of treatment start and late: >90 days of treatment start). The tabulation will also be separated by toxicities of Grade 3 and above. **Future studies incorporating DE-SBRT would be worthwhile if the rate of grade 3 GU/GI toxicity was ≤ 10%.**

2. Biochemical disease-free survival, disease-free survival, disease-specific and overall survival curves will be calculated and presented by the methods of Kaplan and Meier.

3. The proportion of patients with local and distant failure will be reported with a 95% binomial confidence interval.

4. General health related and disease specific quality of life measurements will be summarized over time. Graphical displays will be created for each patient's trajectory over time and also summarized using the average for all patients.

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