IRB# 10-625-A **PROTOCOL**

A feasibility study of oral hormonal therapy and radiation for non-metastatic, intermediate or high risk prostate cancer in men 70 and older or with medical comorbidities

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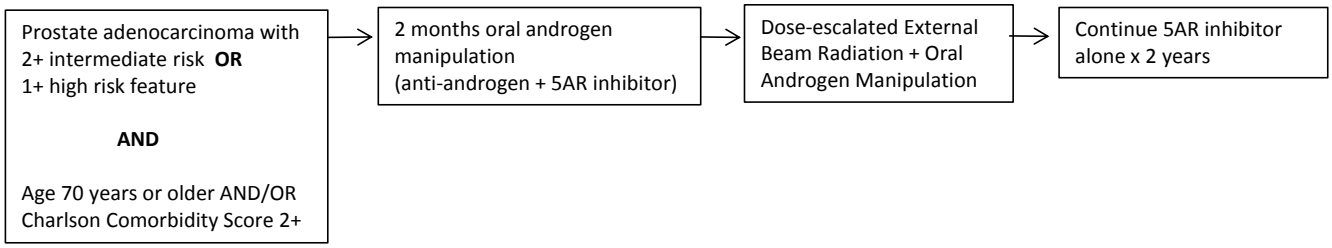
SCHEMA



Patient Population: (see section 3.0 for complete eligibility criteria)

- Age ≥70 and/or Charlson Comorbidity Score ≥2
- Biopsy proven prostate adenocarcinoma
- No clinical or radiographic evidence of metastatic disease
- By risk groupings, 2+ intermediate risk factors or 1+ high risk factor
- Zubrod performance status ≤ 2
- No history of androgen deprivation therapy (ADT) [GnRH agonist or antiandrogen]
- No prior pelvic radiation

Required Sample Size: Minimum of 40 experimental subjects and 30 control subjects (total of 70).

Study Center:
University of Chicago Medical Center,.

Concept and Rationale: Randomized data support the addition of ADT to standard dose external beam radiation (RT) in men with non-metastatic, intermediate and high risk prostate cancer. However, the role of medical castration with ADT is less certain when dose-escalated RT is administered. In particular, the benefit of standard ADT remains unclear in older men and in those with medical comorbidites in whom the risks of therapy may be heightened. Therefore, we propose to de-intensify standard ADT in this population, in favor of dual oral androgen manipulation with an antiandrogen and a 5-alpha reductase inhibitor (5AR). We hypothesize that health-related quality of life (HRQOL) will be improved with the removal of the gonadotropin releasing hormone (GnRH) and that oncologic outcomes will not be compromised. Dual oral androgen manipulation therapy will be delivered prior to and concurrent with dose-escalated radiation with the goal of maximizing its anti-tumoral effect.

Primary Objective: To test the hypothesis that health-related quality of life (HRQOL) of men over 70 and/or with medical comorbidities treated with oral androgen manipulation and radiation (RT) will be improved compared to that of patients undergoing standard ADT and RT.

Secondary Objectives: To test the hypothesis that the oncologic outcomes of patients treated with dual oral androgen manipulation with RT will be comparable to the outcomes of patients undergoing standard ADT with RT.

Study Design: Single arm prospective, feasibility trial. A synchronous control cohort receiving standard ADT will be followed for collection of data on HRQOL endpoints.

Statistical Methods:

Patient reported data will be grouped into summary scores in each relevant quality of life domain (sexual, urinary, bowel, hormonal/vitality. Quality of life and toxicity scores will be compared to those of patients in the synchronous control cohort receiving standard ADT with radiation. Univariate analysis of mean scores will be performed using a two sample t-test. Scores will also be compared between trial patients and the control cohort while controlling for covariates using linear regression analysis.

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1. OBJECTIVES

1.1. Primary Objectives

The broad objective is to test the feasibility of delivering dual oral androgen manipulation with an antiandrogen and a 5-alpha reductase (5AR) inhibitor in conjunction with dose-escalated radiation (RT) in intermediate and high risk prostate cancer patients 70 years of age or older and/or with moderate to severe medical comorbidities. The primary objective is to test the hypothesis that health-related quality of life (HRQOL) in patients treated with dual oral androgen manipulation will be improved compared to that of controls treated with standard androgen deprivation therapy (ADT) including a gonadotropin releasing hormone (GnRH) agonist +/- an antiandrogen.

1.2. Secondary Objectives

The secondary objective is to test the hypothesis that oncologic outcomes including biochemical progression free survival, distant metastasis free survival, cause specific survival, and overall survival after treatment with dual oral androgen manipulation and dose escalated radiation will be comparable to the outcomes of patients treated with standard ADT.

1.3. Tertiary Objectives

For select men who consent to a research biopsy, we would like to analyze the RNA expression of prostate cancers treated with hormonal therapy prior to radiation for prostate cancer. We would a comparison using tissue from the same patient, before any treatment (initial biopsy) and then after two months of ADT (at the time of fiducial marker placement) to show how RNA expression changes in the tumor of the prostate with ADT. We would also compare differences in expression across the 2 cohorts of patients, treated with oral-only ADT and traditional injectable ADT. The hypothesis is that oral-only ADT would induce similar changes within the tumor, thus complementing the clinical outcome evaluation (primary and secondary objectives) with a mechanistic evaluation.

2. BACKGROUND

2.1. Intermediate and High Risk Prostate Adenocarcinoma

Prostate cancer is the most common non-dermatologic malignancy and the second leading cause of cancer-related death in men in the United States. In 2010, an estimated 217,730 men will be diagnosed with prostate cancer, and 32,050 will die of their disease.[1] Prostate cancer is predominately a disease affecting older men, with 75% of cases diagnosed in men aged 65 and older.[2] Despite a trend toward earlier stage at diagnosis with the widespread use of prostate specific antigen (PSA) screening, a significant percentage of patients are diagnosed with advanced disease. In an analysis of over 10,800 men with prostate cancer diagnosed between 1990 and 2007, over 50% of patients entering the cohort between 2004 and 2007 were diagnosed with intermediate or high risk prostate cancer. [3]

Multiple treatment options exists for intermediate and high risk prostate cancer ranging from active surveillance to aggressive combined modality therapy with surgery and/or radiation with or without androgen deprivation therapy (ADT). Treatment decisions involve consideration of disease features including clinical T stage, PSA, and Gleason score. In addition, the therapeutic approach should take into account comorbidities, quality of life concerns, and patient preferences.

Therapeutic decision-making can be particularly complicated in men with a limited life expectancy. In these cases, weighing the oncologic benefits of treatment against the possibility of toxicity related to a given therapy is clouded by competing risks of mortality related to comorbid illnesses and aging. The majority of patients with intermediate or high risk disease will undergo definitive therapy including either surgery or radiation, but advanced age and comorbidities are known to influence the choice of primary treatment. In one series of over 11,000 patients, 4% of those over age 75 underwent surgery as primary therapy compared to 60% of patients under the age of 75. [4] Patients who are elderly or who have multiple medical illnesses are more likely to receive external beam radiation than younger, healthier men.[5]

2.2. Rationale

Extensive evidence from randomized trials demonstrates a benefit in PSA control, cause-specific, and in some cases, overall survival, with the addition of ADT to radiation in men with both intermediate [6, 7] and high risk prostate cancer [8-10]. In these randomized trials, radiation was delivered to doses on the order of 66-70 Gy. With improvements in techniques for radiation delivery, doses can now be safely escalated upwards of 80 Gy with significant improvements in disease control. Multiple randomized trials have demonstrated absolute improvements in 5-year biochemical control in all risk groups by 10 to 20% with doses in the range of 74-80 Gy.[11-15] Dose escalated radiation has therefore become standard practice in patients receiving radiation alone; however, the role of dose escalated radiation in combination with ADT in patients with intermediate and high risk disease has not been fully elucidated. This is, in large part, the rationale for the ongoing Radiation Therapy Oncology Group 0815 trial which randomizes patients with intermediate risk prostate cancer to 79.2 Gy of radiation with or without Leuprolide and Bicalutamide.

While the benefits of ADT have been well-established in randomized trials, so have the toxicities; androgen blockade with a GnRH agonist has well-known potential adverse effects including sexual dysfunction (loss of libido, impotence), decreased bone mineral density, hot flashes, hematologic toxicity (anemia), fatigue, hyperglycemia, hypercholesterolemia, hypertension, anxiety, depression, breast tenderness, and pain. For complete androgen blockage, GnRH agonists are commonly given in conjunction with a nonsteroidal antiandrogen (e.g. bicalutamide). However, the side effects of ADT are, for the most part, driven by the GnRH agonist component of treatment, which induces a castrate state. In a randomized comparison of bicalutamide monotherapy versus leuprolide monotherapy for nonmetastatic prostate cancer, bicalutamide monotherapy increased bone mineral density and resulted in less fatigue, sexual dysfunction, fat accumulation, and vasomotor flushing than leuprolide monotherapy. [16]

Due to the significant toxicities associated with ADT, and the uncertain benefit in the setting of dose escalation, the role of ADT in the elderly and in patients with significant comorbidities is particularly unclear. Some question the role of further testosterone suppression in elderly men in whom up to 80% meet the criteria for hypogonadism before treatment.[17] Furthermore, the elderly may have heightened sensitivity to the adverse effects of ADT resulting in more severe quality of life detriment than in younger patients. In a randomized trial from Harvard showing an overall survival benefit with the addition of short-term ADT to radiation in intermediate and high risk patients, a post-randomization analysis revealed a significant interaction between

comorbidity score and the effect of ADT on survival. In patients with moderate or severe comorbidities, the survival benefit to adding ADT to radiation was lost. [18] The lack of benefit to ADT seen in some groups may in part be due to hastening of cardiovascular disease, and thus death due to causes other than prostate cancer. Furthermore, given the long natural history of prostate cancer, the beneficial effects of ADT may be masked by competing causes of mortality in aging and unhealthy populations who are unlikely to benefit from aggressive therapy.

However, there is some clinical evidence in support of the use of ADT even in the elderly or those with significant comorbidities. A reanalysis of the Radiation Therapy Oncology Group (RTOG) 85-31 trial comparing ADT until progression versus no ADT in patients treated with radiation for high risk non-bulky disease, there was no impact of hormonal therapy on the risk of cardiovascular mortality.[19] In the Harvard randomized study of radiation with or without short term ADT, of 206 patients enrolled, there were 78 with mild or no comorbidity who were over the age of 72. Among the 70% of these men who were healthy, all cause mortality at 8 years was 16% in those treated with ADT plus radiation compared to 41% in those receiving radiation alone.[20] More investigation is warranted to clarify the risks and benefits of ADT in addition to radiation in patients with medical comorbidities and advanced age in order to improve patient selection.

One alternative to medical castration with a GnRH agonist is nonsteroidal antiandrogen monotherapy. Due to the aforementioned toxicity profiles, bicalutamide monotherapy has been studied in the setting of locally advanced, node positive, recurrent, and metastatic prostate cancer as an alternative to gonadal suppression. A multicenter randomized trial comparing bicalutamide monotherapy to medical or surgical castration in patients with locally advanced or metastatic disease revealed no difference in disease progression or overall survival with a median 6.5 years follow-up in the group without metastases. In addition, measures of sexual interest, physical capacity, and bone mineral density were significantly higher in the bicalutamide arm.[21] In contrast, gynecomastia and breast pain were more common in the group treated with bicalutamide alone.

The Bicalutamide Early Prostate Cancer Program is the largest study of bicalutamide monotherapy as an adjuvant to standard treatment in patients with localized or locally advanced prostate cancer. The study was comprised of 3 parallel trials: one in North America (trial 23), one in Mexico, South Africa, Australia, and Europe (trial 24), and one in Scandinavia (trial 25). The trials randomized over 8,000 patients to placebo or bicalutamide (150 mg QD) following the standard therapy of choice including watchful waiting (in trials 24 and 25 only), radical prostatatectomy, or radiation. In 1,370 patients who underwent radiation (median dose 64 Gy) with a median follow-up of over 7 years, patients randomized to bicalutamide after radiation had prolonged biochemical and objective progression free survival compared to those receiving placebo (HR 0.61 and HR 0.75, respectively). Furthermore, patients treated with bicalutamide with locally advanced disease (T3-T4 or N1 M0) had superior overall survival to those receiving placebo (HR 0.65).[22] This overall survival benefit is in line with the 23% reduction in overall deaths seen in RTOG 85-31 which randomized patients with locally advanced, non-bulky disease to radiation followed by goserelin or radiation alone.[23]

Another class of testosterone modulators, 5-alpha reductase (5AR) inhibitors, blocks the intraprostatic conversion of testosterone to its more potent form, dihydrotestosterone. In addition, 5AR inhibitors down-regulate androgen receptor expression and may decrease the rate of subsequent androgen independent prostate cancers. [24] Dutasteride and finasteride are

effective in the treatment of benign prostatic hyperplasia and male pattern baldness, and they are generally well tolerated because serum testosterone levels are maintained. The Prostate Cancer Prevention Trial (PCPT) compared finasteride to placebo in men at high risk for prostate cancer; men randomized to finasteride had a 25% reduction in the incidence of prostate cancer.[25] A similar effect was noted in a randomized study testing dutasteride to placebo for the prevention of prostate cancer in men at high risk; the relative risk reduction with the use of dutasteride was 23% for the incidence of prostate cancer over 4-years.[26] As monotherapy for either localized or advanced prostate cancer, 5AR inhibitors may have some effect on progression of disease, however no studies have confirmed an effect on survival. [27-29]

Several phase II trials have investigated 5AR inhibitors in combination with antiandrogens with promising findings. A CALGB study investigated the role of finasteride plus flutamide in 101 patients with rising PSA after definitive surgery or radiation therapy. In 98.6% of patients, PSA was reduced 80% below baseline. Approximately 2/3 of patients achieved undetectable PSA levels, and amongst this group, only one patient progressed with a median of 16 months follow up. [30] In sequential phase II studies at Walter Reed Army Medical Center, patients with rising PSA after definitive treatment received either combined flutamide and finasteride or flutamide monotherapy. In comparing the two cohorts, those receiving combined therapy had greater PSA decreases and lower nadir values. On multivariable analysis, patients on combined therapy were less likely to progress (HR 0.21). There was no difference in the frequency of side effects between the two arms. [31] In the setting of metastatic prostate cancer, a UK randomized trial compared goserelin plus flutamide versus goserelin plus finasteride versus flutamide plus finasteride. The PSA value at 24 weeks decreased 97-99% from baseline and was no different between the 3 groups, although the group that was spared from goserelin therapy appreciated less sexual toxicity. [32]

Dual oral androgen manipulation has not been formally investigated as definitive treatment for untreated prostate cancer, nor as a concurrent therapy with radiation. The proposed study will investigate the role of dual oral androgen manipulation overlapping with radiation as an alternative to a GnRH agonist. We hypothesize that the proposed treatment will result in less quality of life decline than standard therapy. In this study, we aim to demonstrate the feasibility of administering radiation therapy with oral hormonal therapy to a population of prostate cancer patients of advanced age or with comorbidities and to demonstrate the feasibility of evaluating a number of quality of life endpoints. After some preliminary data are established, we anticipate moving forward with a larger phase II study design, testing radiation therapy with oral only versus standard hormonal therapy, with a primary endpoint of quality of life. Disease outcome would be an important secondary endpoint; we also theorize that dual oral androgen manipulation will impart some anti-tumoral effect or radiosensitization, thus resulting in acceptable oncologic outcomes. The data from this larger randomized phase II study could then potentially contribute towards a phase III, cooperative group, randomized study testing for a quality of life benefit, or for non-inferiority regarding efficacy of therapy.

3. PATIENT SELECTION

3.1. Eligibility Criteria

3.1.1. Age ≥ 70 years

AND/**OR**

Charlson comorbidity index score ≥ 2 (see Appendix C)

(Prostate cancer diagnosis does not contribute to total score)

3.1.2. Pathologically (histologically) proven diagnosis of prostatic adenocarcinoma.

3.1.3. Intermediate or high risk for recurrence according to the following criteria:

Two or more of the following intermediate risk features for recurrence

- Gleason Score = 7
- PSA 10-20 ng/ml
- Clinical Stage T2b-T2c
- Percent positive biopsy cores ≥50%

OR

One or more of the following high risk features for recurrence

- Gleason Score 8-10
- PSA >20 ng/ml
- Clinical Stage T3a-T4

3.1.4. Clinically negative lymph nodes as established by imaging (pelvic +/- abdominal CT or MRI), nodal sampling, or dissection, except as noted immediately below:

- Patients with intermediate risk factors only do not require abdominopelvic imaging, but these studies may be obtained at the discretion of the treating physician.
- For men with any high risk feature (psa > 20, gleason score >8, or clinical stage T3), a pelvic CT or MRI, are required. It is recommended that the duration between these scans and study registration be less than 60 days, but if the time period is >60 days and the opinion of the clinician is that repeat studies would offer limited benefit, then these studies do not need to be repeated. A lymph node will be considered radiographically positive if it is >1.5cm in size, occurs within the expected distribution for prostate cancer metastasis (i.e. internal iliac or obturator fossa), and is without classic benign features (i.e. fatty hilum). Patients with lymph nodes equivocal or questionable by imaging are eligible for inclusion in this study.

3.1.5. No evidence of bone metastases (M0) on bone scan.

- Patients with intermediate risk factors only do not require a bone scan, but these studies may be obtained at the discretion of the treating physician.
- Patients with any high risk factors are required to undergo a bone scan. It is recommended that the duration between these scans and study registration be less than 60 days, but if the time period is >60 days and the opinion of the clinician is that repeat studies would offer limited benefit, then these studies do not need to be repeated.
- Equivocal bone scan findings are allowed if additional imaging (e.g. plain film x-rays, or CT) does not confirmmetastasis.

3.1.6. History/physical examination (to include, at a minimum, digital rectal examination of the prostate and examination of the skeletal system and abdomen, and formal comorbidity assessment via the Charlson Comorbidity Index within 60 days prior to registration.

3.1.7. Zubrod Performance Status 0-2

3.1.8. Age ≥ 18

3.1.9. Baseline serum PSA value performed with an FDA-approved assay (e.g., Abbott, Hybritech) within 60 days prior to registration

3.1.10. Baseline serum testosterone obtained within 60 days prior to registration

3.1.11. Study entry PSA and serum testosterone must not be obtained during the following time frames: (1) 10-day period following prostate biopsy; (2) following initiation of oral androgen manipulation; (3) within 30 days after discontinuation of finasteride or dutasteride

3.1.12. CBC/differential obtained within 60 days prior to registration with adequate bone marrow function defined as follows:

- Absolute neutrophil count (ANC) ≥ 1,800 cells/mm3
- Platelets ≥ 100,000 cells/mm3
- Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥8.0 g/dl is acceptable.)

3.1.13. Patient must be able to provide study-specific informed consent prior to study entry.

3.1.14. Liver function parameters as follows:

- Total Bilirubin ≤2 x institutional upper limit of normal
- AST (SGOT) or ALT (SGPT) ≤2 x institutional upper limit normal

3.2. Exclusion Criteria

3.2.1. Prior radical surgery (prostatectomy), high-intensity focused ultrasound (HIFU) or cryosurgery for prostate cancer

3.2.2. Prior hormonal therapy, such as LHRH agonists (e.g., goserelin, leuprolide), antiandrogens (e.g., flutamide, bicalutamide), estrogens (e.g., DES), or bilateral orchiectomy

3.2.3. Use of 5-alpha reductase inhibitors (finasteride, dutasteride) specifically prescribed for the treatment of prostate cancer.

3.2.4. Prior or concurrent cytotoxic chemotherapy for prostate cancer; prior chemotherapy for a different cancer is permitted.

3.2.5. Prior radiation, including brachytherapy, to the region of the prostate that would result in overlap of RT fields.

3.2.6. Active lupus or scleroderma

3.2.7. Severe, active co-morbidity, including but not limited to:

3.2.7.1. Unstable angina within the last 6 months without subsequent corrective cardiovascular procedure.

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

3.2.7.3. Hepatic insufficieny with AST, ALT, or Bilirubin > 2 x upper limit of normal, clinical jaundice, and/or coagulation defects

3.2.7.4. Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. Patients who are HIV seropositive but do not meet criteria for diagnosis of AIDS are eligible for study participation.

3.3. Inclusion of Minorities and Women

All races and ethnic groups are eligible for this trial. Women are not eligible as the natural history and epidemiology of prostate cancer is such that only men develop the disease.

4. TREATMENT PLAN

4.1. Dual Oral Androgen Manipulation

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 6.

After study enrollment, patients will initiate dual oral androgen manipulation therapy consisting of an androgen receptor blocker and a 5AR inhibitor according to the following dose and route schedules:

- Bicalutamide 50 mg PO daily
- Dutasteride 0.5 mg PO daily (recommended) or Finasteride 5 mg PO daily

During week 6-8 of oral androgen manipulation therapy, patients will undergo CT simulation for radiation planning. After 8 weeks of hormonal therapy, patients will begin dose escalated radiation with concurrent androgen manipulation for approximately 7-8 weeks, Monday through Friday. Details regarding planning and administration of RT are described in Section 5.

Following completion of radiation, having completed 4 total months of dual androgen manipulation, patients will discontinue Bicalutamide. All patients will continue taking the 5AR inhibitor as monotherapy for 2 years after completion of radiation for a total of 2 years, 4 months of treatment.

4.2. Measuring Health-Related Quality of Life and Toxicity

Patient-reported outcome measures will include a modified version of the Expanded Prostate Cancer Index Composite (EPIC-26) which has been validated as an alternative to the complete questionnaire (EPIC-50).[33] The questionnaire will include all EPIC-26 items as well as additional items in the hormonal/vitality domain drawn from the full length EPIC-50. General

health-related quality of life, including fatigue, will be assessed with the PROMIS v1.0 Global short form and the EQ-5D visual scale for quality of life. All items will be consolidated into 2 questionnaires. The first questionnaire is the standard questionnaire administered to all patients with prostate cancer in the department of radiation oncology (see Appendix A). A supplemental four page questionnaire will be administered to all patients on trial and to all consenting control patients at baseline (see Appendix B). Both questionnaires will again be administered at 1-2 months after initiation of hormonal treatment (before RT), at 3-4 months (during RT), and at 6 months after initiation of study therapy. Questionnaires will be completed in writing by the patient. Questionnaires at 12, 18, and 24 months after completion of radiation therapy will not be required, although any collected data over this time frame will be recorded and available for analysis.

The evaluation period of acute radiation-related toxicity will be defined by the period from the start of radiation to three months following the completion of radiation. Toxicity will be graded according to Radiation Therapy Oncology Group (RTOG) acute toxicity scale (see Appendix D). Toxicity will be recorded on a weekly basis during radiation treatment and at the first follow up visit. Chronic toxicities will also be graded according to the RTOG toxicity scale and will be recorded at each point of clinical contact beyond the third month after completion of radiation.

4.3. Experimental Controls

Patients who meet eligibility criteria of the study but who do not enroll on the trial who receive standard ADT with radiation will be approached for participation in the parallel data collection study. These patients will serve as the control group with which to compare HRQOL outcomes of patients treated on trial. Patients consenting to enrollment on the parallel data collection study will receive standard of care treatment, follow-up, imaging, and laboratory studies not subject to the plan described in this protocol. Health information may be recorded from the electronic medical record. Patients on the data collection study will be asked to complete the same supplemental four-page questionnaire (see Appendix B) as those on trial at baseline, 1-2 months after initiation of standard ADT (before RT), and at 6 months. Completion of the supplemental questionnaire will not be required at 12 18, and 24 months after initiation of radiation, however any collected data over this time frame will be recorded and available for analysis. In addition, all controls will complete the six-page questionnaire which is standard practice for all patients treated in the department of radiation oncology according to usual practice.

4.4. General Concomitant Medication and Supportive Care Guidelines

Development of painful mastitis and gynecomastia are potential side effects of antiandrogen therapy in the absence of gonadal suppression. There is no restriction towards the use of radiation for the prophylaxis or treatment of breast tenderness or gynecomastia. Patients should not receive Tamoxifen or other estrogen modulating therapy during treatment on the trial given concern for unknown effects on the hormonal milieu. Treatment with breast radiation to breast tissue should be clearly documented for each patient in whom it is employed. If prophylactic or therapeutic intervention is sought, a dose of 12 Gy in 3 fractions using en face electrons is preferred.

4.5. Duration of Therapy

Duration of dual oral androgen manipulation will be 4 months in all patients. The duration of 5AR inhibitor use will be 2 years, 4 months. Radiation therapy should be delivered over the course of 7-

8 weeks (Monday through Friday) beginning after the initial 8 weeks of oral androgen manipulation. Treatment delays should be avoided unless:

- Intercurrent illness prevents further administration of treatment
- There are unacceptable adverse event(s)
- The patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

The use of continued treatment with 5AR beyond 2 years, 4 months is at the discretion of the treating physician.

4.6. Duration of Follow Up

Patients will be followed on protocol through the completion of therapy (2 years after completion of radiation therapy). Beyond this time point, further data collection will be at the discretion of the treating physician. It is encouraged to continue follow-up every six months until 5 years after completion of radiation therapy, and monitor serum PSA over each of these visits, according to standard practice.

4.7. Criteria for Removal from Study

Patients will be removed from the study when any of the criteria listed in Section 4.5 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

4.8 Registration Procedures

- Guidelines for the Lead (University of Chicago):
  All patients should be registered by the responsible Clinical Research Associate and or Research Nurse in the Velos Database after consent and prior to the start of treatment. The appropriate eligibility criteria in 3.1 should be confirmed prior to registration.

4.9 Tissue Collection

For patients consenting to tissue collection portion of the study, the first block of FFPE tissue will be taken from the left over samples of Prostate biopsy done at initial diagnosis. If the patient has more than one diagnostic biopsy then tissue will be taken from the most recent biopsy sample.

A research biopsy will be collected at the time of intra-prostatic fiducial marker placement, after the initial 2 months of hormonal therapy. The marker placement is considered standard of care therapy, using a transrectal ultrasound probe (similar to the approach for a prostate biopsy). The biopsy would include patients in both treatment and control group. If the patient has had prior MRI, these images can be fused to the ultrasound using software (UroNav) which will increase the yield of the biopsy for tumor. The tissue collected will be stored at HRTC.

The following tables outline the requirements for tissue banking. Tissue will be collected and stored for batched future analysis.

Biospecimen Type	Collection time point	Number of samples

A paraffin embedded tissue block of primary prostate cancer taken at initial diagnostic biopsy (left over sample)	Pretreatment, before starting any hormonal therapy	1 block
2 cores of paraffin embedded tissue of tumor	After 2 months of hormonal therapy at the time of fiducial marker placement , for consenting patients	2 blocks of FFPE

Tumor biopsy for molecular analysis will be conducted. Either fresh tissue or archived paraffin embedded specimens will be used for analysis. RNA from tumor samples will be isolated using standard techniques. We would like to 1) analyze intra-patient differences in RNA expression at initial biopsy specimen and after two months of hormonal therapy, and 2) compare the inter-patient differences in RNA expression in the oral ADT cohort versus the traditional injectable ADT cohort to test the hypothesis that oral-only ADT results in a similar RNA expression profile to traditional therapy.

5. RADIATION THERAPY GUIDELINES

5.1. Treatment Planning Procedures

5.1.1. Placement of fiducial markers in the prostate gland (e.g. gold markers) for image guidance is recommended but not required.

5.1.2. Simulation will be CT-based in all cases. The use of urethral contrast at the time of simulation is recommended but not required. Patients will be positioned supine on a flat tabletop with a customized thermoplastic immobilization cast or a molded foam cradle for stabilization and setup reproducibility.

5.2. Dose Specifications: 3D Conformal Radiotherapy (3DCRT) or IMRT

The prostate and seminal vesicles will be treated to a dose of 50-50.4 Gy in 1.8-2 Gy fractions prescribed to the PTV1. Subsequently, the prostate and any additional gross disease will be treated to a cumulative total dose of 75.6-79.2 Gy in 1.8-2 Gy fractions prescribed to the PTV2. The PTV2 prescription dose may be reduced to 72 Gy at the discretion of the treating radiation oncologist only if it is felt that critical structure dose constraints cannot be met for that particular case at a prescription dose of 75.6-79.2 Gy. All attempts should be made to deliver the dose with the heterogeneity constraints and adherence to the critical structure parameters listed below in Table 1. If 3DCRT is used, more relaxed rectal and bladder constraints are acceptable, but the rectal V70Gy must be ≤20% in all cases.

5.3. Suggested Critical Structure Dose Constraints

Table 1.

Target or Tissue (priority)	Parameter	Target
PTV (++++)	V100% (%)	≥ 95%
	V95% (%)	≥ 98%
	V105%*	≤ 10%

	V110%*	≤ 5%
	Max dose to voxel	≤ 115%
Rectum (+++)	V70Gy (%)	≤ 10%
	V65Gy (%)	≤ 20%
	V40Gy (%)	≤ 40%
Bladder (++)	V70Gy	≤ 15%
	V65Gy	≤ 30%
	V40Gy (%)	≤ 60%
Femoral heads (+)	V50Gy (%)	≤ 10%
Penile bulb (++)	V50Gy	≤ 50%

5.4. Technical Factors

RT will be delivered with megavoltage equipment at energies ≥6 MV.

5.5. Treatment Planning/Target Volumes

The definition of volumes will be in accordance with the ICRU Report #50: Prescribing, Recording, and Reporting Photon Beam Therapy.

5.5.1. The recommended CTV1 includes the entire prostate gland and the proximal 2 cm of the seminal vesicles. In general, it is recommended that patients with intermediate risk disease and no evidence of seminal vesicle involvement should have at least the proximal 1.0 cm of seminal vesicles included in the target volume. The entire seminal vesicles should be included for any patients who have prostate cancer involving any portion of the seminal vesicles.

5.5.2. The CTV2 is defined by the physician as the entire prostate gland. If there is seminal vesicle involvement, it is recommended to include the entire seminal vesicles . If the rectal V70Gy ≤20% cannot be met, then the uninvolved portion of the seminal vesicle may be excluded from the final CTV2 volume.

5.5.3. The Planning Target Volume (PTV1) will provide a margin around the CTV1 to compensate for the variability of treatment set up and internal organ motion. A range of 5-10 mm around the CTV1 is required to define the PTV1. Superior and inferior margins (capping) should be 5-10 mm depending on the thickness and spacing of the planning CT scan. Careful consideration should be made when defining the 5-10 mm margin in 3 dimensions.

5.5.4. The Planning Target Volume (PTV2) will provide a margin around the CTV2 to compensate for the variability of treatment set up and internal organ motion. A range of 5-10 mm around the CTV2 is required to define each respective PTV. Superior and inferior margins (capping) should be 5-10 mm depending on the thickness and spacing of the planning CT scan. Careful consideration should be made when defining the 5-10 mm margin in 3 dimensions.

5.5.5. The ICRU Reference Points are to be located in the central part of the PTV and, secondly, on or near the central axis of the beams. Typically these points should be located on the beam axes or at the intersection of the beam axes.

5.5.6. Normal Critical Structures to be defined on the treatment planning CT scan will include the following: bladder (the outer bladder wall), rectum (from its origin at the rectosigmoid flexure to the inferior-most extent of the ischial tuberosities), bilateral femora (to the level of ischial tuberosity), penile bulb, and skin. Any small bowel within the primary beam aperture should be defined as well. All structures will be contoured in their entirety as solid organs.

5.5.7. A dose reduction to 72 Gy minimum PTV dose is permitted if the above constraints cannot be met at the planned dose level of 78 Gy. Of note, the penile bulb constraint is to be regarded as a suggested guideline, and adherence to this should not, in any way, result in compromised coverage of the dose delivery to the target volume.

5.6. Treatment Verification

5.6.1. First day port films or orthogonal pair portal images must be obtained. Thereafter, weekly verification films or images of orthogonal isocenter views (anterior to posterior and lateral projection) are required. The use of daily image guided therapy (using fiducial markers or transabdominal ultrasound) is highly recommended.

5.6.2. For IMRT the intensity profiles of each beam must be independently verified and compared to the planned field intensity. Portal films are not required for IMRT but orthogonal verification films are required, just as for 3DCRT. These images are to be archived by the institution for later review if requested by the study chair.

6. RISKS AND BENEFITS

The study will be fully explained to the subjects emphasizing the potential risks and benefits of their participation: the potential loss of their confidentially with regards to their prostate cancer, the closer monitoring of their progress due to both research and medical staff working on their case, and the altruistic aspect of helping men in the future with prostate cancer. No monetary gain will be offered to the subjects and they will be informed that that their decision will have no impact on the quality of care they will receive. The primary investigator will answer any and all questions in full. Subjects will be given a copy of the consent for their own records and will be given instructions as to how to withdraw from the study if they change their mind.

Medication and radiation side effects will be discussed with all patients. Adverse events will be monitored and reported.

6.1. Adverse Events

6.1.1. **Dutasteride:**

Side effects of dutasteride may include serum testosterone increase, thyroid-stimulating hormone increased, impotence, libido decreased, ejaculation disorders (≤1%), gynecomastia, breast tenderness or pain, hypersensitivity (pruritus, rash, urticaria, swelling face/lips,

angioedema), dizziness, edema, diminished urinary flow, hepatic impairment. Pregnant women or women trying to conceive should not handle the product.

6.1.2. **Finasteride**

Side effects of finasteride may include, impotence, decreased libido, neuromuscular or skeletal weakness, postural hypotension, edema, dizziness, somnolence, ejaculation disturbances, gyncomastia, dyspnea, rhinitis, hypersensitivity (pruritus, rash, urticaria, swelling face/lips), breast tenderness, testicular pain, and diminished urinary flow. Women should not handle finasteride as its active ingredient is absorbed through skin; pregnant women should not handle finasteride as it may negatively impact fetal development.

6.1.3. **Antiandrogen (Bicalutamide)**

Side effects of antiandrogen therapy may include gynecomastia, breast tenderness or pain, hepatotoxicity (including rare cases of fatal hepatitis), inhibition of spermatogenesis, hot flashes, gastrointestinal disorders, diarrhea, nausea, weakness, pruritus, decreased libido, erectile dysfunction, and rash. Bicalutamide should be discontinued if ALT rises above two times the upper limit of normal or the patient develops jaundice.

6.1.4. **Radiation**

Radiation side effects are limited to the area involved in the treatment field. Acute and late toxicity related to radiation therapy may include fatigue, skin erythema, diarrhea or loose stools, damage to the bowel or rectum (including stricture or obstruction, bleed, fistula formation, or perforation), radiation enteritis, dysuria, hematuria, increased urinary frequency, urethral stricture, urinary incontinence, decreased sexual function, and impotence.

6.2. Reporting

All life threatening Grade 4 or fatal toxicities (grade 5) must be reported immediately and evaluated.

- University of Chicago Reporting Guidelines:
    - If the reaction requires reporting, the Research Nurse or MD reports the adverse reaction to the Cancer Clinical Trials Office (CCTO) at 773-702-5149 by the end of the business day when he/she becomes aware of the event. Events occurring after business hours will be reported to the CCTO by 12 pm (noon) the next business day.
    - The following information is required when calling in the event:
        - Caller's Name and Telephone Number
        - Patient Initials
        - Patient Medical Record Number
        - IRB Protocol Number
        - PI of Study
        - Attending Physician
        - Date of Event
        - Description of Event (including grade of even and attribution of the even and if the event required hospitalization).
    - Email is sent to the research nurse, attending physician, and PI of the study informing them that adverse reaction notification has been received
    - The University of Chicago's IRB Serious Adverse Event Form must be sent to the CCTO within 5 calendar days of event occurrence. The UC IRB Serious Adverse Event for is available on line at http://ors.bsd.uchicago.edu/HS/newirbforms. This

form must be typed. Once the forms are completed, the original is forward to the study PI to review and sign. The signed report is delivered to the QA Coordinator. A weekly report of delinquent or pending documents will be forwarded to the applicable person who reported the event. All delinquent reporting (great than 10 days from the even occurrence) must include documentation of reason fro delinquency and may require implementation of an action plan.

- Once the appropriate AE documents have been received, the CCTO forwards these to the IRB. A copy will be forward to the appropriate Research Nurse.

6.3. Data and Safety Monitoring

A weekly meeting in the department of radiation oncology will be held for data and safety monitoring of patients enrolled at the University of Chicago site.

The primary endpoint, HRQOL, will be formally evaluated at 6 months.

Stopping rules include excessive failures defined by biochemical failure in > 70% of patients at 2 years or excessive toxicity defined as >15% of patients with acute or late Grade 3+ toxicity.

7. STUDY CALENDAR

Baseline evaluations (including performance status, history and physical, scans) are to be conducted within 60 days prior to the start of protocol therapy.

	Baseline	Month 2 (pre-RT)	Month 3-4 (during RT)	Month 6 (2 mos post-RT)	Month 10 (6 mos post-RT)	Month 16 (12 mos post-RT)	Month 22 (18 mos post-RT)	Month 28 (24 mos p RT)
Inclusion/ exclusion	X							
Informed Consent	X							
Path confirms cancer	X							
History and Physical	X	X	X**	X	X	X	X	X
Vital Signs, weight	X		X**	X	X	X	X	X
Zubrod Performance status and Charlson index	X							
Document Current Medicines	X	X	X**	X	X	X	X	X
CT Ab/Pelvis OR MRI*	X							
Bone Scan *	X							
Tumor tissue collection	X	X						
CBC with differential and CMP	X	X	X#	X		X		X
Toxicity Assessment			X**	X	X	X	X	X
Patient Outcome Questionnaire	X	X		X	X	X≠	X≠	X≠
PSA	X	X		X	X	X	X	X

Total, serum Testosterone	X	X				X		X

^ This evaluation will occur at the planning stage before radiation therapy has begun (e.g. fiducial marker placement or simulation)

* See Section 3 for requirements/exceptions ** Weekly during radiation treatment

These labs will be drawn in the last week of radiation therapy

≠ Optional

Note that the protocol allows for 1 month of flexibility to meet any follow-up appointment time (e.g. the month 6 visit may occur at month 5 or month 7.)

Beyond month 10, follow-up is recommended but not required. All data collected between month 10 and month 28 will be registered under this study so that longer term quality of life data (beyond the primary endpoint of 6 months) may be analyzed.

8. MEASUREMENT OF EFFECT

Disease Control

Although disease control is not the primary endpoint of this trial, patients will be assessed by standard criteria for disease response with serum PSA and clinical examinations. For the purposes of this study, patients should undergo serum PSA and testosterone testing at baseline, 2 months (at start of RT), and every three to six months until completion of androgen manipulation at 2 years, 4 months according to the study calendar. After completion of study treatment, it is recommended that PSA should be drawn every 6 months until 5 years post-treatment. Clinical exams should be performed on a regular basis at the discretion of the treating physician, but a least biannually during the course of therapy and at least annually thereafter. Screening for distant metastases will be based on clinical information and is at the discretion of the treating physician.

9. STATISTICAL CONSIDERATIONS

9.1. Study Design/Primary Endpoint

The study is designed as a feasibility study to determine quality of life endpoints for men treated with oral androgen deprivation therapy in conjunction with dose-escalated radiation. Data gathered from this preliminary cohort will aid in defining the expected range of quality of life changes as to facilitate a subsequent Phase II randomized comparison of oral therapy with standard ADT.

The primary endpoint is HRQOL at 6 months after initiation of therapy; at this time point, symptoms and side effects are expected to stabilize. In a large study of HRQOL in patients treated with standard ADT, scores at 6 months were comparable to those at 24 months in all domains.[34] Analysis at the six month time point will allow an early evaluation of what is expected to persist during longer term follow-up. HRQOL will be summarized using a score reflecting reported symptoms in sexual, hormone/vitality, fatigue, and global quality of life domains. A composite score inclusive of each of these domains except for breast tenderness and gynecomastia will also be analyzed; assessments of breast tenderness and gynecomastia will be excluded from this summary score as it is expected that some patients may receive additional therapies directed at reducing this side effect which may confound the analysis. Incidence of breast symptoms and signs will be recorded and reported separately from the other HRQOL endpoints. Mean scores in each quality of life domain will be calculated and confidence intervals will be derived.

Quality of life and toxicity scores will be compared to those of patients in the synchronous control cohort receiving standard ADT with radiation. Univariate analysis of mean scores (continuous

variables) will be performed using a two sample t-test. Scores will also be compared between trial patients and the control cohort while controlling for covariates using linear regression analysis.

9.2. **Sample Size/Accrual Rate**

Success will be defined as a decline in hormonal/vitality domain score by no more than 30% from baseline. The required rate of success is p=0.6. A minimum sample size of n=40 experimental subjects will provide a 95% confidence interval width of + 15%. We anticipate that approximately 30 patients will be entered into the control group. In total, we plan to accrue 70 patients.
The expected accrual rate for patients in the experimental group is 2 per month at each participating site. The expected accual rate for patients in the control group is 1 to 2 per month. We will collect tumor tissue only for the 14 patients who will be enrolled on the study. 8 in the treatment arm and 6 in the control arm.

9.3. Analysis of Secondary Endpoints

As secondary endpoints, the study will investigate oncologic outcomes of the prescribed protocol therapy including biochemical progression-free survival, distant metastasis-free survival, cause specific survival, and overall survival. Kaplan-Meier curves will be generated for each endpoint. Findings will be compared to a synchronous cohort of controls.

Biochemical progression free survival will be defined to be the time from the start of therapy with oral androgen manipulation until PSA failure occurs as defined by the Phoenix definition of a rise to 2 ng/ml above the nadir PSA value. The relative hazard for a PSA failure in patients on protocol therapy compared to those in the control cohort will be calculated using the proportional hazards regression model of Cox, but formal statistical conclusions will not be drawn from this analysis.

Hematologic effects of dual oral androgen manipulation will be assessed using hemoglobin levels from scheduled CBC's. Changes in mean hemoglobin between baseline and various time points throughout treatment will be assessed. Univariate analysis of mean scores will be performed using a two sample t-test.

10. CONFIDENTIALITY

Study records that identify patients will be kept confidential. Study records will contain patients' name, address, and medical history number, and will be available to the study doctor, research nurse, and data coordinator. Data collected in this study will be maintained on a password protected computer that only the principal investigator, co-investigators, research nurse, and data coordinator will be able to access. Study records will be secured in locked offices in the Department of Radiation and Cellular Oncology. Neither patient names nor other personally identifying information will be used in any publication resulting from the research study.

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APPENDIX A:

THE UNIVERSITY OF CHICAGO MEDICAL CENTER

DEPARTMENT OF RADIATION AND CELLULAR ONCOLOGY

DIVISION OF THE BIOLOGICAL SCIENCES AND
THE PRITZKER SCHOOL OF MEDICINE

This questionnaire is designed to measure Quality of Life issues in patients with Prostate Cancer. To help us get the most accurate measurement, it is important that you answer all questions honestly and completely. **Please note that there are 2 sides on each page.**

Remember, as with all medical records, information contained with this survey will remain strictly confidential.

Name : _____ Today's Date: Month _____ Day___ Year _____

The following questions are about your **general health**.

List any health problems, including diagnosis of any other cancers, that have required new therapy (such as medicines or procedures) or hospitalization **since your last visit**:

List the date of any recent colonoscopy (examination of the colon using a camera): _____
List the date of any recent cystoscopy (examination of the bladder using a camera): _____

Include the names, addresses, and phone/fax numbers of any physicians who are actively involved with your medical care. We will send documentation of your clinic visit to any physicians listed here.

Physician use only		Grade	Comment
	GI		
	GU		
	Sexual		
	Other		

The following questions are about your **urinary function**.

1. Over the **past 4 weeks**, how often have you leaked urine?

   More than once a day…… 1
   About once a day…….. 2
   More than once a week……. 3 (Circle one number)
   About once a week.....……..... 4
   Rarely or never …… 5

2. Which of the following best describes your urinary control **during the last 4 weeks**?

   No urinary control whatsoever…….. 1
   Frequent dribbling……. 2 (Circle one number)
   Occasional dribbling……. 3
   Total control…….. 4

3. How many pads or adult diapers per day did you usually use to control leakage **during the last 4 weeks**?

   None…….. 0
   1 pad per day……. 1
   2 pads per day…… 2 (Circle one number)
   3 or more pads per day…….. 3

4. How big a problem, if any, has each of the following been for you **during the last 4 weeks**?

(Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a. Dripping or leaking urine …….	0	1	2	3	4
b. *Pain or burning on urination* …	0	1	2	3	4
c. *Bleeding with urination* ……	0	1	2	3	4
d. Weak urine steam or incomplete emptying ……..	0	1	2	3	4
e. Waking up to urinate ……	0	1	2	3	4
f. Need to urinate frequently during the day ……..	0	1	2	3	4

5. Overall, how big a problem has your urinary function been for you **during the last 4 weeks**?

   No problem…… 1
   Very small problem……... 2
   Small problem……3 (Circle one number)
   Moderate problem……..4
   Big problem……..... 5

6. International Prostate Symptom Score (IPSS). The following questions are about symptoms **during the last 4 weeks**.

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your score
a. Incomplete emptying How often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5	
b. Frequency How often have you had to urinate again less than two hours after you finish urinating?	0	1	2	3	4	5	
c. Intermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
d. Urgency How often have you found it difficult to postpone urination?	0	1	2	3	4	5	
e. Weak stream How often have you had a weak urinary stream?	0	1	2	3	4	5	
f. Straining How often have you had to push or strain to begin urinating?	0	1	2	3	4	5	
	None	1 time	2 times	3 times	4 times	≥5 times	
g. Nocturia How many times did you most typically get up to urinate **each night** from the time you went to bed at night to the time you got up the next morning?	0	1	2	3	4	5	

TOTAL IPSS SCORE:

Quality of life: If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	Delighted	Pleased	Mostly satisfied	Mixed	Mostly dissatisfied	Unhappy	Terrible
	0	1	2	3	4	5	6

The following questions are about your **bowel function**.

7. How often have you had rectal urgency (felt like you had to pass stool, but did not) **during the last 4 weeks**?

More than once a day …… 1
About once a day ……..... 2
More than once a week …… 3 (Circle one number)
About once a week ……..... 4
Rarely or never ……..5

8. How often have you had stools that were loose or liquid (no form, watery, mushy) **during the last 4 weeks**?

Never…… 1
Rarely…….....2
About half the time……..... 3 (Circle one number)
Usually…….....4
Always……... 5

9. How often have you had bloody stools **during the last 4 weeks**?

Never…… 1
Rarely…….....2
About half the time……..... 3 (Circle one number)
Usually…….....4
Always……... 5

10. How big a problem, if any, has each of the following been for you? (Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a. Urgency to have a bowel movement ……..	0	1	2	3	4
b. Increased frequency of bowel movements ……	0	1	2	3	4
c. Watery bowel movements.	0	1	2	3	4
d. Losing control of your stools …….....	0	1	2	3	4
d. Bloody stools ……..	0	1	2	3	4
e. Abdominal/Pelvic Rectal pain ……..	0	1	2	3	4

11. Overall, how big a problem have your bowel habits been for you **during the last 4 weeks**?

No Problem…… 1
Very Small Problem……..... 2
Small Problem……... 3 (Circle one number)
Moderate Problem……..... 4
Big Problem……... 5

The following questions are about your **sexual function**.

12. How would you rate each of the following **during the last 4 weeks**? (Circle one number on each line)

	Very Poor/ None	Poor	Fair	Good	Very Good
a. Your level of sexual desire?	1	2	3	4	5
b. Your ability to have an erection?	1	2	3	4	5
c. Your ability to reach orgasm (climax)?	1	2	3	4	5

13. How would you describe the usual QUALITY of your erections WITHOUT assistance of medicines or devices **during the last 4 weeks**?

None at all…….. 1
Not firm enough for any sexual activity…… 2
Firm enough for masturbation and foreplay only…….. 3 (Circle one number)
Firm enough for intercourse…….. 4

14. How would you describe the usual QUALITY of your erections (WITH assistance of medicines or devices if needed) **during the last 4 weeks?**

None at all…….. 1
Not firm enough for any sexual activity…… 2
Firm enough for masturbation and foreplay only…….. 3 (Circle one number)
Firm enough for intercourse…….. 4

15. Regarding the use of any medications or devices to aid or improve erections:

	Have NOT tried it	Tried it, but was NOT HELPFUL	It HELPED, but I am NOT using it NOW	It HELPED, and I use it sometimes	It HELPED, and I use it always
a. Viagra or other pill (name if not viagra): _____ Dose used: _____	1	2	3	4	5
b. Vacuum erection device (such as erect-aid)	1	2	3	4	5
c. Muse (intra-urethral alprostadil suppository)	1	2	3	4	5
d. Penile injection therapy (such as caverject)	1	2	3	4	5
e. Other (if not listed): _____	1	2	3	4	5

16. How would you describe the FREQUENCY of your erections **during the last 4 weeks?**

I NEVER had an erection when I wanted one…….. 1
I had an erection LESS THAN HALF the time I wanted one…….. 2
I had an erection ABOUT HALF the time I wanted one…….. 3 (Circle one number)
I had an erection MORE THAN HALF the time I wanted one……. 4
I had an erection WHENEVER I wanted one…… 5

17. **During the last 4 weeks**, how often did you have sexual intercourse?

Not at all …… 1
Less than once a week ……..... 2
About once a week ……...…… 3 (Circle one number)
Several times a week ……..... 4
Daily …….. 5

18. Overall, how would you rate your ability to function sexually **during the last 4 weeks**?

Very poor…… 1
Poor……. 2
Fair…….. 3 (Circle one number)
Good…… 4
Very good…… 5

19. Overall, how big a problem has your sexual function or lack of sexual function been for you **during the last 4 weeks**?

No Problem……. 1
Very small problem……. 2
Small problem……. 3 (Circle one number)
Moderate problem……... 4
Big problem……..... 5

20. Sexual Health Inventory for Men (SHIM). Answer the following questions, including the use of medications or devices if you use them.

a. How do you rate your confidence that you could get and keep an erection?

Very low	Low	Moderate	High	Very high
1	2	3	4	5

b. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?

No sexual activity	Almost never or never	A few times (much less than half the time)	Sometimes (half the time)	Most times (much more than half the time)	Almost always or always
0	1	2	3	4	5

c. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?

Did not attempt intercourse	Almost never or never	A few times (much less than half the time)	Sometimes (half the time)	Most times (much more than half the time)	Almost always or always
0	1	2	3	4	5

d. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?

Did not attempt intercourse	Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult
0	1	2	3	4	5

e. When you attempted sexual intercourse, how often was it satisfactory for you?

Did not attempt intercourse	Almost never or never	A few times (much less than half the time)	Sometimes (half the time)	Most times (much more than half the time)	Almost always or always
0	1	2	3	4	5

TOTAL SHIM SCORE: ☐

APPENDIX B

THE UNIVERSITY OF CHICAGO MEDICAL CENTER

DEPARTMENT OF RADIATION AND CELLULAR ONCOLOGY

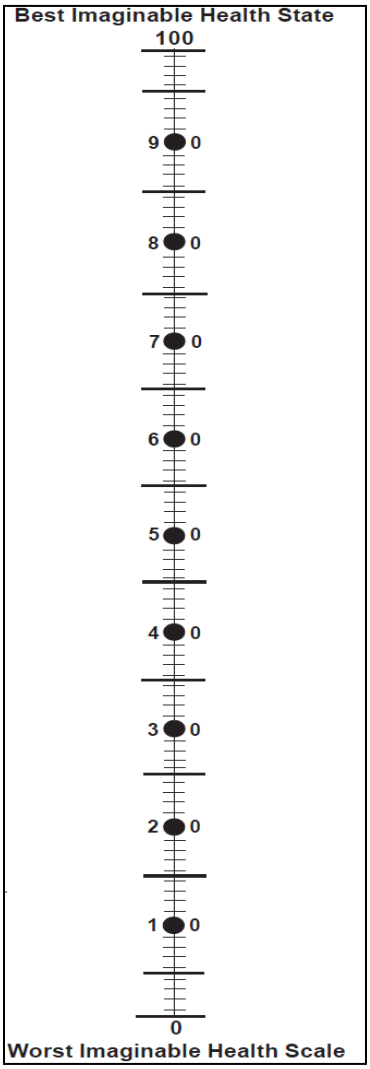
DIVISION OF THE BIOLOGICAL SCIENCES AND
THE PRITZKER SCHOOL OF MEDICINE

This questionnaire is a supplement to the standard of care questionnaire used for all patients treated for prostate cancer in our department. These questions are aimed at further describing your general state of well being, under the study IRB:____: "A Phase II study of oral hormonal therapy and radiation therapy for non-metastatic, intermediate or high risk prostate cancer in men with advanced age or medical comorbidity."

Please note that there are 2 sides on each page.

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked by 100 and the worst state you can imagin is marked by 0.

We would like you to indicate in this scale how good or bad is your own health today, in your opinion. Please do this by drawing an **"X"** on the line at whichever point on the scale indicates how good or bad your current health is.



Physician use only:

Baseline	***Pre-ADT***	***Pre-RT***	***2 mos post-RT***	***6 mos post-RT***	***12 mos post-RT***	***18 mos post-RT***	***24 mos post-RT***
STUDY VISIT: (circle month)	0	2	3-4	10	16	22	28

The following questions are about your **energy and overall well being**.

2. **Over the last 4 weeks**, how often have you experienced hot flashes?

   More than once a day……1
   About once a day……2
   More than once a week……...3 (Circle one number)
   About once a week……..4
   Rarely or never……5

3. How often have you had breast tenderness **during the last 4 weeks?**
   More than once a day…….……..1
   About once a day……..2
   More than once a week…….3 (Circle one number)
   About once a week……...…4
   Rarely or never…….5

4. **During the last 4 weeks**, how often have you felt depressed?
   More than once a day……1
   About once a day……...2
   More than once a week……..3 (Circle one number)
   About once a week……4
   Rarely or never……..5

5. **During the last 4 weeks**, how often have you felt a lack of energy?
   More than once a day……1
   About once a day……...2
   More than once a week……..3 (Circle one number)
   About once a week……4
   Rarely or never……..5

6. How much change in your weight have you experienced **during the last 4 weeks,** if any?
   Gained 10 pounds or more…….....1
   Gained less than 10 pounds…….....2
   No change in weight……...3 (Circle one number)
   Lost less than 10 pounds…….4
   Lost 10 pounds or more……...5

7. How big a problem **during the last 4 weeks**, if any, has each of the following been for you?

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a. Hot flashes…….…….. ...	0	1	2	3	4
b. Breast tenderness/ enlargement……...0		1	2	3	4
c. Feeling Depressed…….....0		1	2	3	4
d. Lack of energy……..0		1	2	3	4
e. Change in body weight ……0		1	2	3	4

8. Overall, how big a problem has hormonal therapy been for you **during the last 4 weeks**?

No Problem……...1
Very small problem……..2
Small problem……..3 (Circle one number)
Moderate problem……....4
Big problem…….....5

9. Please respond to each by circling one number per row.

	Excellent	Very Good	Good	Fair	Poor
a. In general, would you say your health is:…….,…….....1		2	3	4	5
b. In general, would you say your quality of life is: …….…….....1		2	3	4	5
c. In general, how would you rate your physical health? :……..1		2	3	4	5
d. In general, how would you rate your mental health, including your mood and your ability to think? ……..1		2	3	4	5

	Excellent	Very Good	Good	Fair	Poor
e. In general, how would you rate your satisfaction with your social activities and relationships? ……..1		2	3	4	5
f. In general, please rate how well you carry out your usual social activities and roles (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.) …….……..1		2	3	4	5

10. To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?

Never…….…....1
Rarely……..….. 2
Sometimes……..…….….. 3 (Circle one number)
Often……..... 4
Always …….....5

11. In the past 7 days, how often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?

Not at All……....1
A Little……...2
Moderately……..……...3 (Circle one number)
Mostly……....4
Completely ……....5

12. In the past 7 days, how would you rate your fatigue on average?

None……....1
Mild…..……...…2
Moderate……..…….....3 (Circle one number)
Severe..……....4
Very Severe ……....5

Signature_____ Date___/____/_____

APPENDIX C:

Charlson Comorbidity Index:

Comorbidity should be recorded according to the defined criteria in the original publication of Charlson, et al.

Myocardial infarct: Includes patients with one or more definite or probable myocardial infarctions; these patients have been hospitalized and had electrocardiographic and/or enzyme changes. Patients with electrocardiographic changes alone were no designated as having had an infarction.
Congestive heart failure: Includes patients who have had exertional or paroxysmal nocturnal dyspnea and who have responded symptomatically (or on physical examination) to digitalis, diuretics, or afterload reducing agents. It does not included patients who are on medication but have had no symptomatic response and no evidence of improvement of physical signs.
Peripheral vascular disease: Includes patients with intermittent claudication or those who had a bypass for arterial insufficiency and those with gangrene or acute arterial insufficiency and those with an untreated thoracic or abdominal aneurysm. (6 cm or more).
Hypertension: Includes patents with diastolic pressure over 100 mmHg and those with controlled hypertension on medications.
Chronic Pulmonary Disease: Moderate pulmonary disease is Dyspneic with slight activity, with or without treatment and those who are dyspneic with moderate activity despite treatment. Severe pulmonary disease includes patients who are dyspneic at rest, despite treatment, those who require constant oxygen, those with CO_2 retention and those with a paseline P02 <50 mmHg.
Cerebrovascular disease: Includes patients with a history of a cerbrovascular accident with minor or no residua and transient ischemic attacks
Dementia: Includes patients with chronic cognitive deficit.
Renal Disease: Moderate renal disease includes patients with serum creatinine of >3 mg/dl. Severe renal disease includes patients on dialysis those who had a transplant and those with uremia
Liver disease: Severe liver disease consists of patients with cirrhosis, portal hypertension, and a history of variceal bleeding. Moderate liver disease consists of cirrhosis with portal hypertension and without bleeding.
Lymphoma includes patients with Hodgkins, lymphosarcoma, waldenstroms macroglobulinemia, myeloma, and other lymphomas.
Leukemia includes patients with acute and chronic myelogenous leukemia, acute and chronic lymphocytic leukemia, and polycythemia vera.
Tumor consists of patients with solid tumors without documented metastases but initially treated in the last 5 years including breast, colon, lung, and other tumors. Does not include the diagnosis under study (prostate cancer).

Table 3. Weighted index of comorbidity

Assigned weights for diseases	Conditions
1	Myocardial infarct
	Congestive heart failure
	Peripheral vascular disease
	Cerebrovascular disease
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Ulcer disease
	Mild liver disease
	Diabetes
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end organ damage
	Any tumor
	Leukemia
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS

Assigned weights for each condition that a patient has. The total equals the score. Example: chronic pulmonary (1) and lymphoma (2) = total score (3).

Charlson, M.E., et al., *A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.* J Chronic Dis, 1987. **40**(5): p. 373-83.

Hall, W.H., et al., *An electronic application for rapidly calculating Charlson comorbidity score.* BMC Cancer, 2004. **4**: p. 94.

APPENDIX D:

RTOG Toxicity Scale

GU Toxicity

	Grade 1	Grade 2	Grade 3	Grade 4
Acute RTOG	Frequency of urination or nocturia twice pretreatment habit/ dysuria, urgency not requiring medication	Frequency of urination or nocturia which is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic (e.g., Pyridium)	Frequency with urgency and nocturia hourly or more frequently/ dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/gross hematuria with/ without clot passage	Hematuria requiring transfusion/ acute bladder obstruction not secondary to clot passage, ulceration or necrosis
Late RTOG BLADDER	Slight epithelial atrophy Minor telangiectasia (microscopic hematuria)	Moderate frequency Generalized telangiectasia Intermittent macroscopic hematuria	Severe frequency and dysuria Severe generalized telangiectasia (often with petechiae) Frequent hematuria Reduction in bladder capacity (<150 cc)	Necrosis/ Contracted bladder (capacity <100 cc) Severe hemorrhagic cystitis

GI Toxicity

	Grade 1	Grade 2	Grade 3	Grade 4
Acute RTOG	Increased frequency or change in quality of bowel habits not requiring medication/ rectal discomfort not requiring analgesics	Diarrhea requiring parasympatholytic drugs (e.g.Lomotil)/ mucous discharge not necessitating sanitary pads/ rectal or abdominal pain requiring analgesics	Diarrhea requiring parenteral support/ severe mucous or blood discharge necessitating sanitary pags/abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Acute or subacute obstructionfistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion
Late RTOG SMALL/LARGE INTESTINE	Mild diarrhea Mild cramping Bowel movement 5 times daily Slight rectal discharge or bleeding	Moderate diarrhea and colic Bowel movement >5 times daily Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis/ Perforation Fistula