Research Narrative

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Study Title: Stereotactic Hypofractionated Radiotherapy of the Prostate

Principal Investigator: Geoffrey Weinstein, MD

Explain the research project according to the outline below. Be sure to complete all sections – for the research to be conducted at Sharp HealthCare do not refer reviewer to attached protocol. If you build your research narrative from this template please delete all of the instructional directions given.

Explanation/Purpose:

Please provide a precise statement of the purpose of this research and the hypotheses that serve as the basis for this research. Specific aims may be used if they clearly define the purpose and intent of the proposed research.

External beam radiation therapy for prostate cancer, while effective, takes up to 9 weeks to deliver on a Monday through Friday basis. Recent phase I/II studies out of Seattle and Palo Alto using stereotactic guidance to deliver high doses of radiation to the prostate over a 1 to 2 week period of time suggest that outcomes may be equal or superior to standard approaches (1,2). These data, combined with markedly improved convenience for patients, make radiosurgery for early-stage prostate cancer an enticing option. The goal of this study is to offer a radiosurgical option to patients within the Sharp system under the umbrella of an IRB-approved study.

Background and Significance:

Please provide a succinct discussion of relevant background information and the rationale for the current study. Appropriate references should be included. Please provide a summary of results obtained by others pertinent to this project. Appropriate references should be included.

Use this section to provide an account of the Principal Investigator's previous or preliminary studies pertinent to this application and/or any information that will help to establish the experience of the principal investigator to pursue the proposed project. If this is an extension of a previous project (by this researcher or another), please reference past research project(s) along with the IRB number, and summarize findings pertinent to this project.

Radiobiology of prostate cancer indicates a low alpha/beta ratio which is suggestive of relative radioresistence (1,2). One way to overcome radioresistence using standard daily doses is to increase the dose given each day and to shorten the overall duration of theapy. This also is attractive from a patient standpoint, since the entire treatment can be done in one week rather than the traditional 8 to 9 weeks.

Research Design and Methods:

Describe the research design and the procedures to be used to accomplish the specific aims of the project. Define in clear terms exactly what will be done to the human subjects, including data to be collected or samples to be taken. Be sure to indicate which procedures are part of the routine care and which are experimental. Provide a precise description of the planned data collection, data analysis plan and anticipated study results. This should include criteria for determining statistical significance and sample size.

All patients used in the study would have been referred to the Radiation Oncology department for standard consultation for a newly-diagnosed prostate cancer. During the course of the initial consultation the patients will be given various options depending on their tumor characteristics. If appropriate they would also be given the option of being treated on-protocol using the stereotactic body radiosurgery approach.

Inclusion criteria include male gender of any age (typically 50 to 70 y/o) with a low risk disease. This is defined as a Gleason's score of 7 or less, clinical stage of T2a or less, and a PSA of less than or equal to 15. No patients with prior surgery or radiotherapy will be included.

Prostate localization will be accomplished each fraction using cone beam CT scanning Micromultileaf collimation will be used to shape the radiation field and either VMAT technique or static field IMRT technique will be employed to maximize dose conformality and limit dose to normal tissues, especially rectum and bladder. Patients will be immobilized using vacuum-assisted devices. A rectal balloon will be used to minimize motion of prostate gland during each treatment.

Dose will be delivered every other day at a 7 Gy/fraction for a total of 5 fractions. The Stanford data (DVH) on normal tissue tolerance will be used as a guideline for treatment planning (1). We anticipate that each fraction will take approximately 30-45 minutes.

A data collection sheet (see attached) will be used for each patient. This will summarize acute and late toxicity to the GU and GI systems based on the RTOG definitions. In addition, the efficacy of treatment will be monitored. Since this is not a randomized trial there will be no need for a p-value or sample size determination but we anticipate accruing 20 patients. We expect a 1-year biochemical control rate greater than 90%.

Protected Health Information (PHI)

If the use of PHI is a necessary component of this research, please list the information needed, who will be accessing the information, and via what process (i.e., Health Information Department, Electronic Record, Paper Record, etc.). If PHI will be accessed, used or disclosed prior to or without individuals' authorization (i.e., for recruitment, assessment of eligibility, or for studies where a waiver of informed consent is being requested), an explanation of who will access the PHI, what PHI will be used/disclosed,

where from or how the PHI is obtained, and the start and end dates (or timeframe) for the use/disclosure of the PHI.

We will not be accessing PHI prior to having the patient enroll in the study. All information used to follow efficacy and toxicity outcomes will be accrued after enrollment by one of the IRB-approved investigators and will therefore be implicitly approved by the study subject.

Potential Risks:

Describe and assess any potential or known risks - physical, psychological, social, legal or other, and assess their likelihood and seriousness. Where appropriate, describe alternative treatments and procedures that might be advantageous to the subjects.

The risks of radiosurgical approach are similar to those from standard radiotherapy in the sense of acute and chronic toxicity to bladder, rectal and erectile function. Our initial experience at Palomar suggests that acute toxicity, especially to the bladder, is less with the radiosurgery. Stanford found higher rates of grade 3 toxicity with qd fractionation (38%) but this decreased to 0% with the qod approach. Urinary frequency, nocturia, dysuria, rectal urgency, tenesmus, and rectal bleeding will all be managed aggressively in the same way as is done with patients undergoing standard 36-40 fractions.

Risk Management/Confidentiality:

Describe the procedures for protecting against or minimizing any potential risks, including risks to confidentiality, use or disclosure of protected health information, and assess their likely effectiveness. Where appropriate, discuss provisions for ensuring medical or professional intervention in the event of adverse effects to the subject. Also, where appropriate, discuss the provisions for monitoring the data collected to ensure the safety of subjects.

Only the listed investigators will be participating in data analysis and the data sheet will be kept in a locked physician's office at all times so confidentiality should be well protected. Patients' treatment information is protected as per Sharp Healthcare policies.

Potential Benefits:

Discuss potential benefits to be gained by the individual subject, as well as those benefits that may accrue to society in general. If there is no direct benefit to the subject, this must be stated.

Protocol participants will benefit from the significantly decreased treatment time (5 fractions over 1 ½ weeks rather than 39 fractions over 8 weeks) while experiencing equivalent or superior outcomes to traditional XRT. We expect toxicity to be similar to fully-fractionated courses of therapy.

Expense to Subject:

If the research activity involves the possibility of added expense to the subject (longer hospitalization, additional tests, blood draws, etc.) indicate how this will be handled. In cases where the FDA has authorized the drug or device company to charge the patient for the experimental drug or device, a copy of the authorization letter from the FDA must accompany the application.

The radiosurgical approach will not be offered unless we receive authorization from the patient's insurance company. We anticipate that coverage will be provided without difficulty with most insurance plans. For those where coverage is an issue, enrollment on a national protocol may be necessary to ensure approval.

REFERENCES

1. King Christopher et al. Stereotactic body radiotherapy for localized prostate cancer: interim results of a prospective phase II clinical trial. *International Journal of Radiation Oncology Biology and Physics*, 73(4) 1043-1048.
2. Madsen Berit et al. Stereotactic hypofractionated accurate radiotherapy of the prostate (SHARP), 33.5 Gy in five fractions for localized disease: first clinical trial results. *IJROBP*, 67(4) 1009-1105.
3. Mantz et al. A phase II tiral of trilogy-based prostate SBRT: initial report of favorable acute toxicity outcomes. *IJROBP*, 69(3), S334.
4. Olsen CC et al. Stereotactic body radiation therapy (SBRT) vs. high-dose brachytherapy (HDR) as hypofractionated radiation therapy for prostate cancer: a comparison of achievable tumor and normal tissue tolerances. *IJROBP* 69(3), S383.
5. Boike T et al. Intra-fraction and inter-fraction prostate motion associated with stereotactic body radiation therapy (SBRT) and image guided radiation therapy (IGRT). *IJROBP* 69(3) S355.
6. Hara et al. Hypofractionated stereotactic radiotherapy for prostate cancer: early results. *IJROBP* 66(3), S324.
7. Pawlicki T et al. Investigatoin of linac-based image-guided hypofractionated prostate treatment. *IJROBP* 63(2) S518.
8. Wiegner et al. Sexual function after stereotactic body radiotherapy for prostate cancer: results of a prospective clinical trial. *IJROBP* (in press).
9. Buyyounouski M et al. Stereotactic body radiotherapy for primary management of early-stage, low- to intermediate-risk prostate cancer: report of the American society for therapeutic radiology and oncology emerging technology committee. *IJROBP* 76(5) 1297-1304.