Phase I/II Trial Examining Dose-per-fraction Escalation using Intensity Modulated Radiation Therapy in the Treatment of Prostate Cancer

A University of Wisconsin Tomotherapy Group Study

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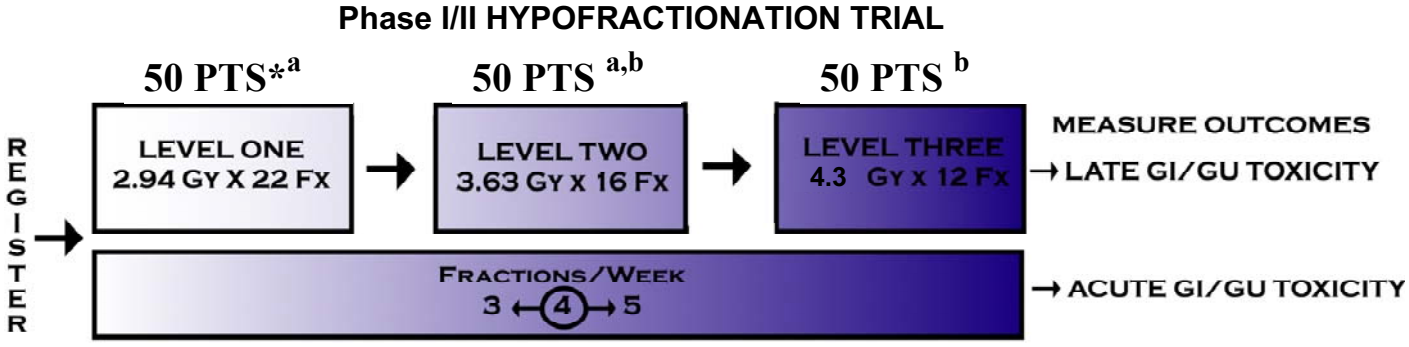

*** As described in Section 5.1, institutions joining the study after Level I is filled will treat two patients at Level I before proceeding to enter patients at the level that the overall trial is currently accruing to.**

[a] 50 evaluable patients will be enrolled per dose/fraction level and followed for toxicity. These 50 patients will be analyzed for dose-per-fraction escalation and fraction-per-week escalation. Additional patients may be enrolled in Levels one and two while waiting for higher dose level data and toxicity information to mature per Section 4.0

[b] An additional 100 patients will be enrolled at the MTS (Maximum Tolerated Schedule) level in addition to the 50 patients already accrued at that level

1.0 BACKGROUND

1.1 Introduction

Prostate cancer is the most common non-skin cancer in American men, resulting in over 30,000 deaths annually in this country. Optimal treatment for localized, potentially curable, prostate cancer has not been determined, but radiation therapy has an established and major role in the management of localized disease, a role supported by evidence that disease control rates comparable to radical prostatectomy are achieved but with less toxicity.

The probability of achieving biochemical control after radiation therapy is related to the pre-treatment PSA, tumor grade and local stage, with PSA and grade being the most important factors. For example, patients with pre-treatment PSAs of less than 6 ng/ml and Gleason scores less than or equal to 6, have 5-year biochemical control rates of 87%, whereas patients with PSAs 10 – 20 ng/ml and Gleason scores of 7 have control rates of only 45%. Radical prostatectomy outcomes are also influenced strongly by these same pre-treatment predictors.

It has long been felt that one of the most important factors limiting the success of radiation therapy has been the inability to deliver adequate radiation dose without producing unacceptable toxicity. More recently, however, innovations in cancer imaging, radiation treatment planning and treatment delivery technology have created opportunities for safe dose escalation.

1.2 The rationale for dose escalation

Retrospective studies have indicated a substantial dose response for prostate cancer. Hanks et al (1) examined Patterns of Care data and found actuarial local recurrence rates of 37% for Stage C patients treated to less than 60 Gy, 36% for doses of between 60-64.9 Gy, 28% for 65-69.9 Gy and 19% for doses of 70 Gy or more. Similarly, Perez et al (2) found 38% local recurrences for doses less than 60 Gy, 20% for doses between 60 and 70 Gy and only 12 % for doses of 70 Gy or greater. More recently, a number of retrospective studies (3-7) and one randomized trial (8) have demonstrated superior PSA recurrence-free survival when doses higher than 70 Gy are delivered, at least for intermediate or higher risk patients (**Figure 1)**. These results and the unsatisfactorily high rates of disease persistence in intermediate to higher risk patients after conventional dose radiation therapy (66-70 Gy) provide a strong rationale for the delivery of higher than conventional radiation doses.

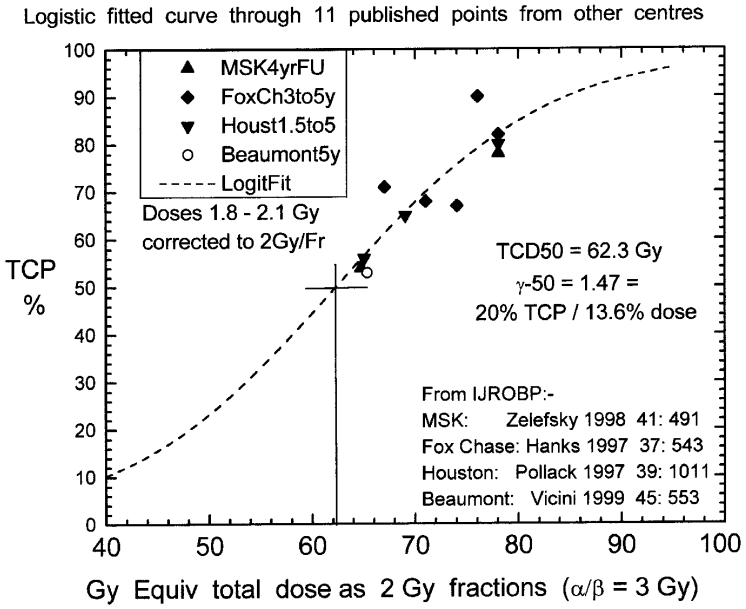

Figure 1.
Tumor control probabilities for "intermediate risk" patients. Data derived from 4 published series (Fowler, unpublished)

When delivered with conventionally planned techniques, however, doses higher than 70 Gy are associated with higher complication risks (9). It has now become clear that 3D conformal radiotherapy demonstrates better than historically expected tolerance of normal tissues to higher doses (6, 10, 11) but complication rates, particularly rectal bleeding, can still be substantial. Various analyses suggest that the total area of rectal wall exposed to greater than 60 or 70 Gy predicts the rate of rectal bleeding or more severe grade 4 complications such as ulceration **(Figure 2)**. Therefore, the implementation of intensity modulated radiotherapy, with its ability to further reduce rectal irradiation, should further reduce toxicities, as has indeed been reported by Zelefsky et. al. (12).

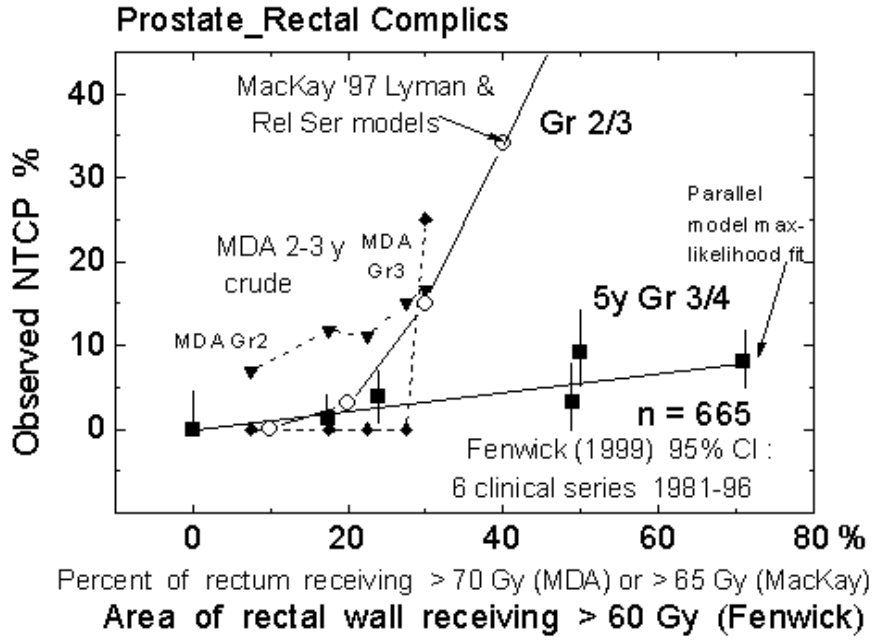

Figure 2. Grade 2 or higher rectal complications versus rectal area receiving higher than specified radiation doses. A summary of 6 clinical trials. (13)

With these advancements in delivery precision for radiation to a planned treatment volume, the minimizing of daily uncertainties regarding patient setup reproducibility and the change of position of the prostate within the pelvis because of rectal and/or bladder filling takes on a significant role. Currently at the University of Wisconsin Department of Radiation Oncology, we are using an optically guided 3D-ultrasound target localization system (SonArray^{TM}, Zmed, Inc., Ashland, MA) to correct daily for these misalignments at the time of treatment to within 2 mm along each axis (Tome, in press, 2001). As an alternative, the implantation of small metal seeds into the prostate to serve as fiduciaries during daily portal imaging has also proven reliable as a means of localizing the prostate

In addition, it has been demonstrated that the use of a rectal balloon catheter can immobilize the prostate and facilitate localization on port films potentially allowing tighter margins for the treatment volume. Also, the lateral and posterior aspects of the rectal wall are displaced out of the high dose region by the rectal balloon, which should offer the potential for significant rectal sparing (14, 15).

1.3 Hypofractionated Radiotherapy for prostate cancer

While the above-described physical improvements in dose delivery have permitted larger total doses of radiation to be delivered to the prostate without undue toxicity, the added number of fractions of radiation required have produced an increasing burden in terms of cost, utilization of resources and inconvenience to the patient. Some dose escalation regimens currently exceed 43 treatments and exceed 8 weeks in duration. Evidence has emerged over the past two years, however, of a unique prostate cancer radiobiology that may offer the opportunity to dramatically improve the efficiency and safety with which radiation therapy is delivered.
Conventional fractionation schemes employing fraction sizes of 1.8 – 2.0 Gy are based upon the premise that tumors typically are less responsive to fractionation than are late-responding normal tissues. The α/β ratios are one measure of fractionation response, with low ratios (high β 's) being more associated with late responding normal tissues, indicating greater repair between fractions with an accompanying greater relative sparing with small fraction sizes than for tumors with their higher α/β ratios. Under these conditions, an improved therapeutic ratio is achieved with multiple small fractions.

In contrast, prostate cancers appear to be <u>better</u> able to repair radiation injury than late responding normal tissues. This is probably related to the very slow growth fractions and growth rates typical for prostate cancer. Growth fraction (or average cell cycle time) has often been associated with fractionation response, with slowly proliferating normal tissues (and some slowly proliferating tumors) generally displaying strong fractionation responses (low α/β ratios). This relationship has been demonstrated for melanomas (16) and for some sarcomas (17), for example. In the case of prostate cancer, there is ample evidence for slow proliferation, based both upon direct measurement of potential doubling times and labeling indices (18) and upon analysis of the kinetics of rising PSA during tumor recurrence (19). Recent analyses of clinical tumor response data have argued for a low α/β ratio for prostate cancer as well (20, 21). Brenner and Hall (20), for example, analyzed dose response data for both external beam radiation and I-125 brachytherapy data and derived a very low α/β ratio of 1.5 Gy for prostate cancer. Duschene and Peters (21) argue in analogous fashion that the α/β ratio for prostate cancer may be more similar to that expected for late responding normal tissue than for the typical, more rapidly proliferating tumor.

Our own analysis of tumor control versus dose response for external beam and brachytherapy also indicates a very low α/βratio of 1.49 (95% CI of 1.25 to 1.76) (22), significantly lower than the ratio of 3 expected for most late responding normal tissues.

Under these unusual conditions, in which the α/β ratio of the tumor is lower (the radiation repair capacity is higher) than that for the limiting normal tissue, a new paradigm is created in which it becomes advantageous to use larger fractions; in other words, to use hypofractionation, rather than the traditionally larger number of smaller fraction size radiation treatments employed when treating most other tumor types. In fact, the old way of fractionating would be the least efficient method. Using the linear quadratic model, one can predict that it should be possible to improve the ratio of tumor control to normal tissue toxicity (the therapeutic ratio) for prostate cancer by using hypofractionation.

Although begun before this unique prostate cancer radiobiology was understood, a relatively large clinical trial has already been carried out using hypofractionation for prostate cancer. Cleveland Clinic investigators have carried out a trial of hypofractionation consisting of 28 fractions of 2.5 Gy each for a total dose of 70 Gy (23). Intensity modulated radiotherapy (IMRT) and daily pretreatment ultrasound-based prostate localization were employed to improve treatment precision and reduce radiation dose to the rectum. These investigators are now reporting 2-year follow-up in which rectal and bladder toxicities are no greater and likely lower that previously experienced with conventional fractionation of 2 Gy per day to 76 Gy using conventional 3D conformal radiotherapy techniques (Mohen, in press, 2002). Furthermore, these early results appear to indicate better tumor control (PSA recurrence-free survival) that was seen with standard fractionation, although follow-up is too short to reach definitive conclusions regarding tumor control.

1.4 Biomarkers of Prostate Cancer Radiation Response

There is increasing evidence that cancers can have molecular alterations that render them poorly responsive to radiation therapy and that are associated with a significant proportion of treatment failures. Preliminary findings indicate, for example, the status of certain biomarkers, such as p53, and Bcl-2, correlate with success or failure of radiation therapy treatment for prostate cancer (30-36) but more such studies are needed to further identify markers and to define the strength of these correlations with treatment outcome, particularly in favorable or intermediate risk patients, the type of patient most frequently diagnosed today and the type treated in this present study.

We will therefore study certain biomarkers in the diagnostic biopsy specimens of patients treated on this protocol. These biomarkers have been selected based upon prognostically useful prevalences in early to intermediate risk prostate cancer and based upon their having pathways linked to radiation response. We will immunohistochemically measure the levels of p53, Bcl-2, and Ki-67 in pre-treatment diagnostic biopsy specimens from patients enrolled on this study and will analyze correlations between these markers and clinical outcomes (freedom from biochemical and metastatic failure) in univariate and multivariate fashion, taking conventional prognosticators such as stage, grade and PSA into account.

1.5 Study Rationale

Hypofractionation Trial

The purpose of this study is to examine the clinical feasibility of using IMRT combined with daily pretreatment prostate localization to deliver increasingly hypofractionated treatment courses. Progressively larger fraction sizes will be delivered in a phase I design based on both acute and long-term tolerances to the treatment. The dose-per-fraction escalation design utilizes schemas that maintain an isoeffective dose for late effects, while predicting that tumor control will actually improve. A natural consequence of these constraints is that the total dose of radiation that can be delivered over an entire course of therapy must decrease as the dose delivered with each fraction increases.

Late effects increase with fraction size and total dose delivered whereas acute toxicities increase with total dose and as overall treatment time is shortened. Excessive shortening of overall treatment time could be a natural consequence of hypofractionation if treatments continue to be delivered daily even as fraction size is increased. Thus, any hypofractionation trial design must guard against an unacceptable increase in acute toxicities by considering whether treatments can continue to be delivered daily (5 days per week), as is generally the case with conventional treatment, or whether treatment frequency needs to be reduced. The proposed study will therefore initiate treatment at each fraction size level with only 4 fractions per week and will only increase to 5 fractions per week if tolerated.

The delivery of fewer, larger fractions of radiation, if proven effective and safe, would result in significant cost saving and a more efficient use of resources. In addition, patients would be spared the burden of undergoing the 40 or more treatments required in most current, conventionally fractionated, dose escalation regimens. Time and effort saved could be applied to upgrading pretreatment verification of patient and organ position.

Biomarker Study

The purpose of the biomarker study is to identify tumor biomarkers useful in predicting which prostate cancers are or are not likely to respond to radiation therapy. If successful, this proposed study will define biomarkers that are clinically useful in predicting response to radiation therapy in favorable-to-intermediate risk patients. This will provide insight into the mechanisms of resistance to radiation therapy and will potentially allow future therapies, including novel biologic/molecular therapy approaches, to be prospectively individualized to optimize clinical outcome.

Participation in the tissue study is optional and is also dependent on the availability of tissue. The decision to participate in Biomarker study will not affect nor influence any patient treatment according to the remainder of this hypofractionation protocol. Subjects agreeing to tissue study participation will sign a consent indicating this decision.

2.0 OBJECTIVES

2.1 To evaluate acute and long-term tolerances to dose-per-fraction escalation in the treatment of prostate cancer using optimized treatment delivery that employs IMRT, daily rectal balloon displacement, and transabdominal ultrasound localization of the prostate.

2.2 To clinically evaluate local tumor control and biochemical progression-free survival and metastasis-free survival.

2.3 To immunohistochemically measure the levels of p53, Bcl-2, and Ki-67 in pre-treatment diagnostic biopsy specimens from patients enrolled on this study and will analyze correlations between these markers and clinical outcomes (freedom from biochemical and metastatic failure) in univariate and multivariate fashion, taking conventional prognosticators such as stage, grade and PSA into account.

3.0 SELECTION OF PATIENTS

- Histologically proven adenocarcinoma of the prostate.
- Stage ≤ T2b disease, as defined by 1997 AJCC classification
- Predicted risk of lymph node involvement (by standard nomograms) of 15% or less (24), OR histologically negative pelvic nodes
- Gleason score ≤ 7
- No evidence of distant metastasis
- Age 18+
- Informed consent signed in accordance with institutional protocol
- Pretreatment evaluations must be completed as specified in Section 7.0.
- ECOG performance status 0-1
- No previous or concurrent cancers, other than localized basal cell or squamous cell skin carcinoma, unless continually disease free for at least 5 years
- No prior pelvic irradiation, prostate brachytherapy, or bilateral orchiectomy
- Gonadotropin-releasing hormone agonist (GnRH-a) use permitted (maximum of 6 months duration). Anti-androgen therapy permitted concurrently with GnRH-a.
- No previous or concurrent cytotoxic chemotherapy
- No radical surgery or cryosurgery for prostate cancer
- The absence of any co-morbid medical condition which would constitute a contraindication for radical radiotherapy
- The absence of serious concurrent illness of psychological, familial, sociological, geographical or other concomitant conditions which do not permit adequate follow-up and compliance with the study protocol.
- No current use of anticoagulation therapy, other than aspirin.

4.0 REGISTRATION PROCEDURES

Patients can be registered only after eligibility criteria are met. Patients must have signed informed consent. Patients are registered prior to any protocol treatment by faxing the registration page to 608-263-3526 and calling 608-263-8500. The UW data managers will verify eligibility, assign a case number, dose level, and confirm the number of fractions per week.

Patients will be enrolled on the highest available dose level open to accrual. If the highest dose level has reached full accrual with insufficient follow-up for further dose-per-fraction escalation, accrual will take place at one dose level lower, if one exists.

Enrollment will be permanently closed when the maximum tolerated dose per fraction is reached or when the dose per fraction escalation is complete.

5.0 TREATMENT PLAN

5.1 General

The accrual goal will be 50 evaluable patients in each of the three dose levels. An additional 100 patients will be enrolled at the determined MTS (Maximum Tolerated Schedule). An exception to this accrual target will be made for any new institutional participant joining the trial after Level I accrual has been completed, in which case that institution will treat two patients to completion at Level I (22 fractions, 5 treatments a week) irrespective of the current hypofractionation level the overall trial currently is treating. After two such patients have been treated, these institutions will then be allowed to accrue to the Level currently open in the trial. In addition, if the highest dose level has reached full accrual with insufficient follow-up for further dose-per-fraction escalation, accrual will take place at one dose level lower. As a result, patients will be enrolled on the highest available dose level open to accrual.

Both acute and late toxicities will be monitored and will dictate subsequent accrual. The level of acute toxicity observed will dictate the number of fractions delivered per week, whereas the level of late toxicities will determine both whether accrual to a dose-per-fraction level is continued and whether escalation to the next dose-per-fraction level is allowed. The escalation rules are as stated in 5.2 and 5.3, with the statistical rationale being described in Section 8. Given this study design, predicting the overall number of patients accrued is difficult. Assuming we are able to complete Levels 1-3 without dose limiting toxicity and taking into account the possibility of further enrollment into a lower dose level per escalation rules, the enrollment could be as high as 400 patients.

5.2 Dose-per fraction escalation

Escalation to the next higher dose-per-fraction level (or the accrual of an additional 100 patients to the MTS) will only be allowed when there is at least 20 patient years of follow-up and at least 5 patients have been followed for at least 12 months. A rate of 20% grade 2 or higher late rectal toxicity per patient follow-up year will be considered dose limiting. Late toxicities will be scored > 90 days from completion of therapy. The statistical rationale and methodology for this dose-per-fraction escalation strategy is described in section 8.0. Of note, statistical fluctuations in measured toxicity rates could occasionally lead to an initial over- or underestimation of these rates. Therefore, cumulative toxicity rates will be updated every 6 months throughout the life of the protocol and will be utilized according to the rules stated above.

The expected accrual timetable, the proposed dose-per-fraction and total fraction levels, and patient accrual goals for this phase I/II trial are shown in Table 1 below.

Table 1: Fraction size dose escalation protocol

Level	*Approx. Interval (mo)*	*Dose per Fx (Gy)*	*# Fxs*	*# pts*	*Treatments per week*	*Total dose (Gy)*	*Equiv. dose (Gy)*
I	1-15	2.94	22	50*	3 ← 4 → 5	64.68	82.6
II	16 - 30	3.63	16	50	3 ← **4** → 5	58.08	85.1
III	31 - 45	4.3	12	50	3 ← 4 → 5	51.6	85.5

* See section 5.1 for exceptions. Patients are initially treated 3 or 4 times per week, with this treatment frequency subsequently increasing, decreasing or remaining the same based upon the number of acute toxicities observed, as described in Section 5.3.

All of the three above levels are predicted to be approximately isoeffective for late effects at BED_3 equals approximately 128 Gy_3. In other words, each of these dose-per-fraction levels would be predicted to produce about the same level of late toxicity, all other factors such as high dose rectal wall volume remaining constant. Furthermore, the above schemas are all predicted to produce the same late toxicity as the fractionation regimen successfully piloted by Kupelian and Mohan(23) of 2.5 Gy times 28 fractions.

An additional **100** patients may be accrued to the MTS if toxicities observed in the first patients at the level are within the limits specified in the standard escalation rules.

The accrual intervals for each level stem directly from the escalation rules that will be followed, which are described in detail in Section 8. While not shown, predicted tumor control at each of the levels can be extrapolated from the fitted model of actual tumor control data in Figure 1, combined with the increased biologically effective doses calculated for each dose-per fraction-level as shown in the last column of Table 1. Such calculations are theoretical, but provide the rationale to believe that the hypofractionation schemas proposed here may produce increasingly better tumor control with fewer fractions.

5.3 Number of fractions per week and acute toxicities

Acute toxicities, as defined in section 5.6, will be assessed to determine the number of fractions at the given fraction size that can be delivered per week. The first 10 patients enrolled at each fraction size level will receive either 3 or 4 fx/week, depending upon how well tolerated previous fractionation levels and weekly treatment frequencies were tolerated. Acute toxicities will be reanalyzed and acted upon if necessary for subsequent groups of 10 patients. For toxicities observed within the first 10 patients at each hypofractionation level, ≥20% acute grade 3 or higher GI or GU toxicity will constitute a threshold toxicity level and will dictate a decrease in frequency of treatment by one treatment per week for the next 10 patients to be treated at that hypofractionation level. If > 20% acute toxicity is also observed in this second group of 10 patients, treatment frequency will be further reduced by one treatment per week for all remaining patients in that hypofractionation level. If excess toxicity is not seen **after changing to a** lower treatment frequency, then all remaining patients in that hypofractionation level will continue to be treated at that frequency.

- If exactly 20% of patients within the first group of ten patients at any hypofractionation level experiences acute grade III or higher GI or GU toxicity, then the next ten patients at that hypofractionation level will remain at the same weekly frequency of treatment,

subject to the usual treatment frequency de-escalation if excess acute toxicities are observed.

- If < 20% of the first ten patients within the level experience this threshold toxicities, then the subsequent patients will be treated at the next higher treatment frequency sublevel, again subject to de-escalation if excess acute toxicities are observed.

- For an individual patient who develops acute toxicity at or above the Grade 3 level, that patient will be placed on treatment break for one week and treatments will then resume at the next lower treatment frequency. For example, if that patient was being treated 4 times per week at the time grade 3 or higher acute toxicities developed, he would subsequently be treated 3 times per week. A longer treatment break can also be prescribed if the treating physician feels that it is clinically indicated.

- At any hypofractionation level, a reduction in treatment frequency to two fractions per week will be allowed for a given patient if that patient experiences a threshold or higher toxicity at 3 fractions per week.

- Acute toxicities will be scored from the start of treatment through 90 days post completion of radiation therapy. Late radiation toxicities will be scored from 90 days post completion of radiation therapy.

5.4 Target volume and rectal dose limits.

Target volume. The GTV will generally be defined to include the entire prostate gland as visualized on CT scan. Seminal vesicles will be included in the GTV for 75% of the prescription dose if the estimated risk for seminal vesicle involvement is ≥15% (24). For situations where there is less than 15% risk of seminal vesicle involvement, the base of the seminal vesicles may be included in the GTV at the discretion of the treating physician. The CTV will represent the same volume as the GTV plus a 0.3 cm margin in all dimensions except at the prostate-rectal interface, for which a margin of between 0 and 0.3 cm can be used. The PTV will include the CTV with a margin to account for patient and organ motion. This margin beyond the CTV is expected to range between 0 – 0.4 cm depending upon the accuracy of the daily pretreatment localization method used. Some form of pretreatment prostate localization must be used, either transabdominal ultrasound, Megavoltage CT (using Tomotherapy) or fiducial markers. Block margins will be chosen to provide adequate coverage of the PTV with no more than 10% dose heterogeneity across the PTV. At least 95% of the PTV must receive the prescription dose or higher. All planning will be carried out using an intensity modulated radiation therapy treatment planning system and delivered with an IMRT capable LINAC or with the tomotherapy machine.

Rectal dose limits. The rectal wall volume (outer minus inner) will be contoured for a total length of 11-12 cm beginning at approximately the inferior-most portion of the ischial tuberosities and extending to at least one cm above the most cranial extent of the treatment fields. Rectal wall percent volumes versus dose, as derived from the dose volume histogram, should be kept at or below values given in Table 2 whenever possible:

Table 2: Rectal Percent Limits vs. Dose

Level	*Dose per Fx (Gy)*	*# Fxs*	*Total dose (Gy)*	*Dose (Gy)*					
				30	35	40	50	55	60
I	2.94	22	64.68	-	-	37%	25%	-	13.5 %
II	3.63	16	58.08	-	38%	32%	19%	12%	-
III	4.3	12	51.6	40%	-	26.5%	12%	-	-

5.5 Patient Positioning and Treatment delivery

Patients will be positioned supine. Use of a rectal displacement balloon is optional but daily pretreatment prostate localization is required. Treatments will be carried out using Intensity Modulated Therapy with 6 MV or higher photons, using either a LINAC or tomotherapy.

5.6 Adverse Effects

5.6.1 Acute toxicity

Acute toxicities will be scored from the start of radiation to 90 days after completion of radiation. Early urinary and GI toxicity will be used to determine the number of fractions deliverable per week as described in Section 5.2. Toxicity grading will be based on a modified RTOG grading criteria (25) (see below).

	Grade 1	Grade 2*	Grade 3	Grade 4
Acute GU	Requiring no medication	Frequency of urination or nocturia, which is less frequent than every hour, dysuria, urgency, bladder spasm requiring local anesthetic. **New obstructive symptoms requiring an alpha blocker**	Frequency with urgency and nocturia hourly or more frequently/dysuria, pelvis pain or bladder spasm requiring frequent narcotic; gross hematuria with or without clot formation.	Hematuria requiring transfusion; acute bladder obstruction not secondary to clot passage, ulceration, or necrosis
Acute GI	Requiring no medication	Diarrhea requiring parasympatholytic drugs; mucous discharge not necessitating sanitary pads; rectal or abdominal pain requiring narcotic analgesics.	Diarrhea requiring parenteral support; severe mucous discharge necessitating sanitary pads, abdominal distension.	Acute or sub-acute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus, requiring tube decompression or bowel diversion

* The pre-existing use of an alpha blocker for GU symptoms or of an antidiarrheal agent for GI symptoms does not constitute a Grade 2 toxicity

5.6.2 Late toxicity

Rectal toxicities

Late toxicities will be scored > 90 days from completion of radiation therapy. Late rectal complications will be used as the primary endpoint for dose-per-fraction escalation in this study, from which the maximum tolerated dose-per-fraction will be determined. The most common clinical syndrome of radiation proctitis is rectal bleeding, urgency/tenesmus, and loose bowel movements. Other, less common late complications include perforation, fistula, and bowel obstruction. Toxicity grading will be based on the FC-LENT grading criteria (see below). Patients will be monitored after treatment at regular intervals, and toxicity determined by history and physical examination. Greater than 40% Grade 2 or higher late rectal toxicity at 2 years will be considered dose limiting and the escalation rules are described in section 8

*FC-LENT rectal toxicity scale**

Grade 1	Symptoms not requiring medication
Grade 2	>4 stools daily above baseline for ≥ 3 months; regular blood in stool for at least 6 months; pain not requiring narcotics; minor outpatient therapies (≤ 3 coagulations; enemas; steroids; antibiotics; opiates)
Grade 3	Dysfunction requiring non-surgical hospitalization for management; bleeding requiring transfusion and/or more than 3 coagulations; pain requiring narcotics
Grade 4	Dysfunction requiring surgery; perforation; life-threatening bleeding
Grade 5	Fatal complications

* pre-existing use of opiates does not constitute Grade 2 toxicity

Late GU toxicities

Late GU	Requiring no medication	Moderate frequency; generalized telangiectasia, intermittent macroscopic hematuria	Severe frequency and dysuria; severe generalized telangiectasia; frequent hematuria; reduction in bladder capacity (<150 cc)	Necrosis; contracted bladder (capacity <100 cc); severe hemorrhagic cystitis

5.6.3 Serious Adverse Events

Serious adverse events (SAE) will be defined as all Grade 4 and Grade 5 toxicity. SAE'S will be phoned in to the Study Chairman at 608-263-8500 within one working day of the event. SAE's will be reported by the UW data managers to the DSMB and the Clinical Trials Monitoring Committee administrator within one business day of notification of SAE. These will also be discussed at regularly scheduled Disease Oriented Working Group meetings.

5.6.4 Quality of Life

Quality of life will be assessed by three separate questionnaires with special emphasis on bowel, bladder, and erectile function. Questionnaires will be performed prior to treatment, one , two and three years after completion of treatment. Overall quality of life will be assessed using The Spitzer Quality of Life Index *(SQLI)* (26). Bowel and bladder quality of life will be assessed using a questionnaire developed at Fox Chase Cancer Center (27). Erectile function will be assessed

using the International Index of Erectile Function Questionnaire (IIEF) (28). Data will be used to compare these patients to those who received conventional external beam radiation therapy.

5.7 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study.

5.8 Duration of Therapy

Study treatment will be stopped if:

- The patient refuses the study treatment
- The patient's physician feels that continuing the study treatments would not be in the patient's best interest.
- The patient experiences severe treatment related toxicities as outlined in section 5.6.3.
- There is clear evidence of progressive disease.
- Treatment interruption more than 2 weeks.

All patients will be followed for disease status until progression and for survival until death.

5.9 Biomarker Assessment

Biomarker studies will be carried out at UW Hospital by performing immunohistochemistry analyses on the original diagnostic biopsy material whenever this is available. In most cases, this will be needle biopsy material. The emphasis will be on a proliferation markers, Ki-67 and apoptotic pathway markers (e.g., p53, bcl-2, bax and mdm-2). The apoptotic markers are all involved in molecular radiation response pathways and have shown promise in predicting prostate cancer patient outcome after radiotherapy, while the proliferation marker, Ki-67, may have particular relevance for hypofractionation since the slow proliferation typical of many prostate cancers is thought to be causally related to their high capacity for interfraction repair and their suitability for a hypofractionated radiotherapy approach. All of these markers will be determined by quantitative immunohistochemistry, using the ACIS Chromavision system, as has been used, for example, in immunohistochemistry studies carried out in RTOG 86-10 (37).

Clinical outcomes (biochemical control) determined from the trial described here will not be ready for correlative analysis comparisons with these biomarker analysis for approximately 7 years. This analysis is for research purposes only and is not expected to have an impact on the patients enrolled on this study.

6.0 MEASUREMENT OF EFFECT

6.1 General

The primary objectives of this study are to potentially establish the maximum tolerated hypofractionation intensity (or to determine whether the most hypofractionated schedule tested in this study is tolerated) for prostate cancer patients and to determine clinical response. Analyses for

clinical tumor control and PSA disease free survival will be performed when median 5-year follow-up is obtained. Data will be collected for efficacy evaluation as stated in section 6.2 and 6.3.

6.2 Disease-free Status

Patients will be considered to be without biochemical recurrence if either the PSA is still declining or the PSA nadir has been reached and is below 1.0 ng/mL, there is no palpable or radiologic evidence of disease, PSA is not rising (defined as 3 successive increases in measured PSA levels each at least two months apart) and there is no evidence of metastasis. Patients not meeting these criteria will be judged to have a recurrence.

6.3 Progressive Disease

Any patient with rising PSA on 3 successive serum measurements will be considered to have recurrent or progressive disease. The date of failure will be taken as midway between the nadir PSA date and the date of the first of the three rising PSAs.

7.0 STUDY PARAMETERS

7.1 All pre-study laboratory tests must be done within 6 weeks of registration.

7.2 Patients will be evaluated weekly during radiotherapy by one of the clinical study investigators to assess acute toxicities and functional status

7.3. The follow-up schedule and evaluations are outlined below:

	Pre-study	Weekly during RT	4 weeks post-RT	3 months post-RT	Subsequent follow-up[a]
H & P	X		X	X	X
Weight	X	X	X	X	X
Performance status	X	X	X	X	X
PSA	X		X	X	X
CBC/platelets	X				
Toxicity notation	X	X	X	X	X
QOL assessment	X				X[b]
IPSS score	X		X	X	X

[a] Subsequent follow-up will be every 3 months x 1 year post-treatment, every 4 months during years 2 - 3, every 6 months years 4 – 5 and then annually. Follow-up frequency can be increased if thought medically necessary by the treating physician

[b] QOL assessment will be completed pre-treatment and at 12, and 24 and 36 months post-treatment.

* For patients for whom travel to the treating institution creates a hardship, scheduled follow-ups, with the exception of the 4 week and all annual follow-ups, can be conducted via telephone interview with PSA and any other indicated testing being carried out at a facility near to the patient.

8.0 STATISTICAL CONSIDERATIONS

8.1 Treatment and Toxicities

This phase I/II trial will be conducted with three potential fraction size levels, with a potential of 50 patients per level (plus an additional 100 patients at MTS if permitted by the escalation rules) and an accrual rate of approximately 50 patients per year anticipated. This may estimate the maximum tolerated dose-per-fraction (MTD), defined as that fractionation schema that yields at most a 40% rate of late grade 2 rectal toxicity at 2 years. A modified LENT grading system for rectal toxicity will be used (28). That outcome is chosen for its clinical relevance; however, the extended follow-up makes the standard sequential designs impractically long at 3 years (one year accrual plus two years follow-up for each of three cohorts). We therefore use the simply modified class of prorated designs (R. Chappell and K. Cheung, Simple designs for phase I clinical trials of long-term toxicities, abstract presented at the 1998 meeting of the Society for Clinical Trials). Proration implies, for example, that two patients observed for one year each, constituting two patient-years of follow-up, are equivalent in information to one patient followed for two years. This implicitly uses the result of Teshima (29) that the cumulative incidence of late grade 2 rectal complications reaches 50% of the final value within twelve months of treatment and that the cumulative incidence of complications is approximately linear with time.

The prorated design will require the following conditions for escalation: at least twenty patient-years of observation; and a minimum of 5 patients followed for one year; and at most a 40% toxicity rate per two years (i.e., at most 2 toxicities per 10 patient-years) observed. Proration allows a great reduction in the overall time of the trial - with fifty patients accrued at a uniform rate over each year, the first two conditions will be satisfied after 15 months. Thus the entire study will take at most 45 months. The requirement of 5 patients being followed for one year is made for safety's sake. The situation may arise that the maximum 50 patients have been accrued at a particular dose-per-fraction step, but there is insufficient follow-up to allow escalation to the next dose-per-fraction step. Under these circumstances, additional patients may be accrued at the previous (next lower) dose-per-fraction level until follow-up conditions for the next escalation are met.

8.2 Disease-free Survival

A primary endpoint is Disease-Free Survival (DFS), as defined in Section 6.2. The 95% confidence interval for DFS observed on 150 fully followed patients will have half-width of 8% or less; that is, it will be the observed DFS rate plus or minus 8%. This figure is conservative in that the width will be less for DFS rates far from 50%. It is slightly anticonservative in the presence of loss to follow-up.

The DFS estimate and its confidence interval will be compared to similar statistics observed for patients treated with standard care fractionation schedules such as those presented in [Zelefsky et al. High dose rate radiotherapy delivered by intensity modulated conformal radiotherapy improves the outcome of localized prostate cancer, J. Urol. 166: 876, 2001]. In addition, efficacy in these data will be modeled with the linear-quadratic formula [Chappell, R., Nondahl, D., and Fowler, J.F. Modeling dose and local control in radiotherapy. Journal of the American Statistical Association. Vol. 90 (1995), pp. 829-838] to examine the hypothesis, which underlies the logic of fractionation, that prostate cancers have an alpha/beta ratio which makes them better able to repair radiation injury than surrounding late responding tissues.

8.3 Correlation of Biomarkers with Clinical Outcome

The percent labeling observed immunohistochemically with each biomarker studied will ultimately be analyzed for correlations with clinical outcome once sufficient clinical follow-up is achieved (median follow-up of at least 5 years. Three markers (p53, bcl-2, and Ki-67) will be analyzed for prognostic significance using a Cox proportional hazards regression analysis accounting for each of the 250 patients' follow-ups, and adjusting for pretreatment PSA and tumor grade. For purposes of power calculations only, we will assume that marker scores will be divided at their medians and modeled as binary covariates, so that prevalences are by definition 50%. Also, we compute power using binary failure/no-failure five year outcomes; these produce conservative (slightly too small) estimates of power. We invoke the usual two-sided test of significance at the conducted .05 level, divided by three using a Bonferroni adjustment to avoid bias due to multiple comparisons.

Suppose that the relative risk induced by positive markers is 3. This, by the proportional hazards assumption, implies five-year failure rates of approximately 22% vs. 8% which average to 15%, a failure rate consistent with that reported in a patient population such as this treated with dose-escalated radiotherapy. Then by the above assumptions the power to detect each marker's effect, after adjusting for multiple comparisons, is approximately 79%. This is reasonable for an exploratory study. Should failure rates be higher than the assumed 15%, then the power would be greater.

8.4 DSMB

Hypofractionation of radiation therapy for prostate cancer was identified in the funded Tomotherapy Program Project Grant as a key investigational area, irrespective of whether the treatment was delivered by a tomotherapy device or by conventional LINAC-based equipment. Therefore, the DSMB established for tomotherapy-related protocols will also be utilized in this study. This Data Safety Monitoring Board (DSMB) has been formally constituted for the “Improving Cancer Outcome With Adaptive Helical Tomotherapy” NIH grant. The DSMB consists of one statistician who will chair the Board (Associate Professor Mary Lindstrom, Ph.D.), one radiation oncologist (Professor Emeritus Richard Steeves, Ph.D., M.D.), and one medical physicist (Heath Odau). None of these individuals are involved with this study. The DSMB meetings will be held semi-annually and more often depending on the nature and progress of the trial. The DSMB will be responsible for recommendations regarding specific actions or no action for the continuing conduct of this trial. The DSMB will be notified immediately (within 24 hours) if any grade 4-5 toxicities are observed.

9.0 DATA COLLECTION

This protocol will be conducted according to Good Clinical Practice Guidelines. Participating investigators/institutions agree to permit trial related monitoring, audits, IRB review, and regulatory inspections, providing direct access to source documents/data.

All data identified in patient evaluation table, section 7.0 will be collected. The following dosimetry data will be collected within 10 days of the end of radiation: copy of DVH plan, copy of daily treatment record, and axial CT cuts at several levels with superimposed isodose curves. Follow-up data and signed informed consents will be kept for a minimum of five years. Forms will be labeled with name codes and sequence numbers.

For patients that agree to participate in the Biomarker study the following info will be collected: one paraffin tissue block containing tumor* (*any unused tissue will be returned to the site) and the corresponding pathology report. Tissue and report will be labeled with name codes and sequence numbers.

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