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Phase I-II trial of hypo-fractionated conformal proton beam radiation therapy for favorable-risk prostate cancer

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Protocol
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1.0 INTRODUCTION

1.1 Rationale for Hypofractionation

Radiation therapy has a long and established role in the curative treatment of organ-confined prostate cancer[1]. However, the optimal radiation dose and treatment schedule remain unknown[2]. Typically, patients treated with external beam radiation therapy [EBRT] receive daily treatment five days per week for a total duration of 7-8 weeks[3]. More recently, published non-randomized and randomized data strongly suggests that radiation doses in the range of 78-81 Gy result in an improvement in five year biochemical freedom from relapse, even in "low risk (for regional/distant metastasis) patients [4] [5]. Delivery of these doses via highly conformal radiation techniques (including conformal proton beams) has been associated with minimal and acceptable significant acute and late treatment-related morbidity. At LLUMC, our current institutional standard for early-stage disease is to treat the prostate and immediately adjacent paraprostatic tissues with conformal proton beams alone to a radiation dose of ~81 CGE [Cobalt-Gray Equivalent, in which 1 proton Gy is assumed to equal 1.1 photon Gy], delivered over a period of nine weeks. This prolonged course, although well tolerated, can lead to logistical difficulties in terms of requiring patients (many of whom reside outside of the immediate area) to remain at LLU for periods of up to three months; this can serve as an absolute treatment barrier to some patients who would otherwise be candidates for conformal proton beam therapy but who are unable to remain at LLU for such a prolonged treatment course. A reduction in treatment time could therefore allow more patients to take advantage of this treatment modality that is currently possible.

Radiation induced mammalian cell death (including human cells) is classically described according to the linear-quadratic equation. Per this formula, the survival rate of a given cell will depend upon multiple factors including the overall radiation dose, the dose per treatment fraction, and the overall treatment time. The dose-response of tumors and normal tissue to fractionated radiotherapy can be described according to the alpha-beta ratio. This ratio is a parameter which numerically describes the fractionation sensitivity of a particular cell type. For example, the α/β ratio is typically high ($\geq$10 Gy) for early-responding normal tissues (skin, mucosa) and most tumors, and low (< 5 Gy) for late-responding normal tissues (spinal cord, brain, bone). An obvious implication of the difference in α/β ratios between tumor and normal tissue is that it may therefore be possible to increase the "therapeutic ratio" by employing unconventional fractionation schedules.

Over the last 5-10 years there have been several published reports suggesting that the α/β ratio for prostate cancer cells is very low and is in fact lower than that for some of the surrounding adjacent normal tissues (bladder, rectum) [6] [7]. Although the absolute number varies, most publications suggest that the α/β ratio is between 1 and 3 [8] [9]. Should this be true, then treatment with hypofractionated regimens (shorter overall treatment time, larger treatment fractions) may prove to be more effective

than conventional fractionation. As will be mentioned below, this hypothesis has already been successfully tested in conformal proton beam treatment of numerous malignancies. This protocol is designed to investigate the safety and efficacy of conformal proton beam therapy of early stage prostate cancer in which treatment is administered via a hypofractionated regimen designed to be biologically equivalent to our current conventional fractionation schemata.

1.2 Hypofractionated Conformal Proton Beam Therapy of other tumors

The use of hypofractionation has a long and generally successful history in conformal proton beam therapy. Its use has been predicated by both the superior physical characteristics of protons as compared to x-rays (i.e., low entrance dose, sharply defined high dose area, lack of exit dose) and, until recently, the limited number of proton beam treatment centers in existence. Hypofractionated conformal proton beam therapy is routinely employed in the treatment of intra-ocular tumors, intra-cranial tumors (both benign and malignant), lung cancer, and early breast cancer. It is, therefore, reasonable to assume that an analogous level of success can be achieved in treatment of organ-confined prostate cancer, and this hypothesis is worthy of testing in a Phase I-II clinical trial.

1.3 Calculation of Biologically Equivalent Dose [BED]

In order to facilitate a comparison between our current institutional standard (81 CGE/45 Fractions) and the fractionation schedule to be employed in this protocol (60 CGE/20 Fractions) biologically equivalent doses [BED] will be calculated and the isoeffect model using the linear-quadratic equation will be used. Also, for the purposes of calculating the BED and isoeffective doses in this protocol two underlying assumptions will be made 1) complete repair of radiation-induced DNA injury between fractions and 2) there is no time factor. The calculated BED depends on the assumed α/β ratio, which in this protocol will be assumed to be 1.5 for tumor, 4.0 for rectum (a late responding tissue), and 10 for early responding tissues. The assumed α/β ratio used in each calculation will be indicated by a subscript e.g., $BED_{1.5}$ indicates that the BED reported was calculated using an α/β of 1.5. The calculated BED's for the hypofractionated treatment and our current institutional protocol are as follows:

	$BED_{1.5}$	$BED_{4.0}$	$BED_{10.0}$
Conv	178	117	96
Hypofx	180	105	78

1.4 Phase I-II Trials of Hypofractionation Regimens in Prostate Cancer

Several reports detailing the efficacy and safety of hypofractionated conformal radiation therapy (with x-rays) of prostate cancer can be found in the literature. In the United States, Kupelian et al have recently reported five year bNED survival and morbidity in a group of patients treated with hypofractionated radiotherapy delivered via an IMRT approach [10]. One hundred patients with organ-confined prostate cancer were treated to 70 Gy delivered in 28 fractions (2.5 Gy/fx). Patients were treated in 1998, and the median follow up was 66 months. Androgen deprivation therapy was administered to 51% of the patients, with the duration of ADT limited to no more than six months. The PTV-CTV margin was 4mm posteriorally and 5-8 mm elsewhere. Freedom from biochemical failure was reported using both the ASTRO Consensus definition [11] and the RTOG Phoenix definition (nadir + 2 ng/ml). Results were reported according to prognostic groups, and the RTOG morbidity scoring system was used to report GI and GU morbidity.

The estimated rate of FFBR at five years post-treatment was 85% according to the ASTRO definition and 88% per the Phoenix definition. These biochemical results were similar to a group of contemporaneously treated patients who were treated with 3-D CRT to 78 Gy/39 fx. In the hypofractionated patients the combined rate of Grade 2-3 rectal morbidity was 11% at five years; again, this compares favorably to patients treated in a conventional manner to 78-80 Gy.

LLUMC has treated sixty-two patients with low-risk prostate cancer on a Phase I-II hypofractionation trial, in which they received 60 Gy/20 fractions. With a minimum follow-up of one year, to date there have been no Grade $\geq$3 complications, and the rate of Grade 2 GI/GU morbidity is 1.6%. These toxicity numbers compare favorably with those from our randomized dose-escalation trial and strongly suggest that further dose-escalation via hypofractionated techniques is medically feasible.

1.5 Randomized Trials of Hypofractionation

To date, the preliminary results from two randomized trials have been published. The Australian Trial compared 64 Gy/32 fx to 55 Gy/20 fx in men with favorable risk stage T1-T2 prostate cancer [12]. The primary trial endpoint was morbidity, and the total sample size of 220 patients (110 per arm) was powered to determine a difference in the frequency of mild late radiation morbidity of 20% with 90% power. Efficacy was considered to be a secondary endpoint. An interim analysis included the first 120 consecutively treated men. Median follow up was 43 months (range 23-62 months). Two dimensional EBRT was employed in each arm; no 3-D or IMRT was used or allowed. Morbidity was measured with the LENT-SOMA questionnaires. The GI component of this questionnaire emphasizes six symptoms (stool frequency, stool consistency, rectal pain, mucus discharge, tenesmus, and rectal bleeding). GU morbidity measures four symptoms (urinary frequency, urgency, dysuria, and

hematuria). Treatment efficacy was assessed both clinically and biochemically; the latter utilized PSA nadir and three consecutive rises as indications of biochemical relapse.

Of the ten symptoms measured only the prevalence of rectal bleeding at two years was different between the two arms, with bleeding reported in 42% of the hypofractionated patients vs. 24% in the conventionally treated arm ($p<0.05$). The prevalence of late rectal bleeding in the conventionally treated arm is higher than expected and is most likely due to the two-dimensional methods employed. If one only considers those patients experiencing moderate to severe bleeding there is no difference between the arms (20 vs. 14%, $P < 0.05$). In terms of efficacy, there was no difference in the nadir PSA and the PSA levels 2 years following treatment between the arms. Using the ASTRO definition the 4-year estimated freedom from biochemical failure was 85.5% in the conventionally treated arm (BED_{10} 76.8, $BED_{1.5}$ 149.3) and 86.2% in the hypofractionated arm (BED_{10} 70.1, $BED_{1.5}$ 155.8).

Preliminary results of a Canadian randomized trial have also been recently published [13]. This trial compares 66 Gy/33 fx (standard arm) to 52.5 Gy/20 fx (hypofractionated arm) in patients with low and intermediate risk prostate cancer. Dose was prescribed to isocenter and the CTV-PTV margin was 15 mm, except, 10 mm posterioraly (at investigators discretion). Patients were treated via a four-field arrangement and although CT data was used for treatment planning in most patients, IMRT was not performed. It must be noted that the two arms were not designed to be isoeffective and that the biologically equivalent dose of the short arm is considerably less than the long arm (BED_{10} 66.3 vs. 79.2, $BED_{1.5}$ of 144 vs. 154). It is therefore not surprising that the five year failure rate (biochemical or clinical) is higher in the hypofractionated arm (59.95% vs. 52.95%, $P < 0.05$). At a median follow up of 5.7 years there is no difference in five year actuarial rate of grade 3+ GI/GU toxicity between the two arms.

1.6 Trial Justification

As has been previously described, hypofractionated conformal proton beam radiation therapy has become our institutional routine for the treatment of numerous solid tumors. Conformal proton beams, by virtue of their physical characteristics, permit a degree of normal tissue sparing that is simply not possible with x-rays [14]. In the treatment of prostate cancer, this difference is almost exclusively in the volume of normal tissue which receives a low to moderate radiation dose. This difference may and probably does have a profound impact in late normal tissue morbidity as radiation-induced late effects are moderated by many factors including total dose, dose per fraction, and volume of organ receiving any radiation dose. Given the degree of normal tissue sparing possible with protons, it is reasonable to assume that results achieved with x-ray therapy can be duplicated and quite possibly exceeded (in terms of reducing late effects) by treating in a similar fashion with conformal proton beams. Since ample support exists in the medical literature regarding the safety and apparent

efficacy of hypofractionated prostate cancer treatment via x-rays, it is reasonable and desirable to pursue an identical strategy with protons.

1.7 Patient Selection

This trial will be restricted to patients with low-risk prostate cancer, defined as Stages T1-2C, and Gleason Score 2-6 and PSA < 10. In this patient population the risk of seminal vesicle and lymph involvement is low enough (< 10%) to permit excluding these structures from the treatment volume.

1.8 Dose Selection

The hypofractionated dose of 60 CGE/20 Fx has been chosen because, as per the linear-quadratic equation (and assuming a BED of 1.5 for prostate cancer cells) it should be isoeffective in terms of biochemical DFS with our current institutional standard of 81 CGE/ 45 fractions [4]. In addition, the hypofractionated dose is similar to that which has been reported by Kupelian et al.

2.0 Objectives

2.1 Primary Objective

To determine if hypofractionated conformal proton beam radiation therapy of prostate cancer can result in late RTOG ≥ Grade 3 treatment-related morbidity which is no worse than that engendered by our current institutional standard with conventional fractionation (81 CGE/45 fx). In PROG 9509, late Gr 2 and Gr3+ GI toxicity was 17 & 1 % respectively, Gr2 & Gr3+ GU toxicity was 20 & 3%.

2.2 Secondary Objectives

2.2.1. To determine if hypofractionated conformal proton beam treatment will result in local progression (5-year rate in PROG was 7%), disease-specific survival, freedom from biochemical failure (3-Year Actuarial rate in PROG was 96% for low risk patients, 90% for intermediate/high risk patients), and overall survival (5 year OS in PROG was 97%) that are no worse than those achieved with our current institutional standard.

2.2.2. To determine the incidence of acute and late GI and GU morbidity treated with hypofractionated conformal proton beam treatment.

3.0 Patient Selection

3.1. Criteria for eligibility

3.1.1. Histologically confirmed adenocarcinoma within 180 days of registration.
3.1.2. History and Physical Examination, including digital rectal exam, within eight weeks prior to registration
3.1.3. Histologic evaluation of prostate biopsies at LLUMC with assignment of Gleason's Score to the specimen
3.1.4. Clinical stage T1-T2C as per the AJCC, 6th edition, and Gleason Score 2-6, and PSA < 10 ng/ml within 180 days prior to registration
3.1.5. KPS ≥ 90
3.1.6 Age > 18
3.1.7 Patient must sign study-specific informed consent

3.2 Conditions for Ineligibility

3.2.1. Prior or concurrent invasive malignancy (excluding non-melanomatous skin cancer) or lymphomatous or hematologic malignancies unless continuously disease-free for a minimum of five years
3.2.2. Evidence of distant metastasis
3.2.3. Regional lymph node involvement
3.2.4. Previous radical surgery (radical prostatectomy) or cryosurgery for prostate cancer
3.2.5. Previous pelvic irradiation, prostate brachytherapy, or bilateral orchiectomy
3.2.6. Previous hormonal therapy
3.2.7. Previous or concurrent cytotoxic chemotherapy for prostate cancer
3.2.8. History of Ulcerative Colitis or Crohn's Disease
3.2.9. Concurrent Coumadin administration
3.2.10. AIDS

4.0 Pretreatment Evaluation.

4.1. History and Physical Examination, including digital rectal examination.
4.1.1. Completion of baseline urinary status questionnaire.
4.1.2. Evaluation of pelvic lymph node status by non-contrast CT 3-D planning scan.
4.1.3. MRI/MRS. Endo-rectal MRI/MRS is optional and recommended in patients who are clinically stage T2B-T2C. MRI evidence of upstaging to T3a-T3b will not be taken into account for eligibility determinations unless these findings are collaborated pathologically however, MRI/MRS data on staging will be used to analyze impact of MRI upstaging on biochemical freedom from relapse, disease-specific survival, and overall survival.
4.1.4. Pre-treatment PSA as per Section 3.1.5.
4.1.5. Histologic review of biopsy specimens as per Section 3.1.3.

5.0 Registration

5.1 Patient registration as per LLUMC institutional standards for participation in clinical trials.

6.0 Radiation Therapy

6.1. All treatment will be delivered with conformal proton beams. Minimum beam energy will be 225 MeV.

6.1.1. All fields will be treated daily.

6.2 Immobilization, and CT Scanning

6.2.3. All patients will be immobilized in a full body immobilization device, while positioned supine. A water balloon will be placed into the rectum at the time of immobilization as per our institutional standard.

6.2.4. Following immobilization a treatment planning CT will be performed as per our institutional protocol, with scanning beginning at the iliac crests superiorly and extending inferiorly to beyond the perineum. Image thickness will be 3mm, with images acquired every 2mm, thus providing sufficient image overlap to minimize the effects of patient motion on image quality and to provide for the creation of a high-resolution DRR. Patients will be encouraged to fill their bladder by drinking 8-16 ounces of fluid prior to CT scan, but no specific bladder filling guidelines will be mandated.

6.2.5. Daily treatment localization will be achieved by acquiring orthogonal radiographs immediately prior to each daily treatment. To ensure adequate coverage of the prostate gland, wherein daily position can be influenced by varying amounts of bladder and rectal filling, the daily patient alignment will be performed with reference to bony landmarks. Alignment via reference to bone landmarks will remain our primary alignment technique.All positioning images and table shifts are to be reviewed by a physician prior to each day's treatment.

6.3 Treatment Planning/Target Volumes

6.3.1. The GTV is defined by the physician as all known disease as defined by the planning CT scan, additional imaging studies (ultrasound, MRI) and clinical information. The GTV for the purposes of this protocol is the prostate gland only.

6.3.2. The CTV is the GTV plus areas considered to be at risk for containing microscopic tumor. The CTV for the purposes of this protocol is the GTV.

6.3.3. The PTV (Planning Target Volume) will provide a margin around the CTV to compensate for patient motion, variations in daily set-up position, and beam physics. For the purposes of this protocol, the PTV will be defined as the CTV + 12 mm in all directions.

6.3.4. Treatment will be administered to the PTV via multiple conformal proton beams, with all fields being treated daily. It is anticipated that for most if not all patients a lateral beam arrangement will be employed, although other beam configurations may be permitted subject to the normal tissue constraints listed in section 6.3.6. and the approval of the principal investigator.

6.3.5. Critical Normal Structures

6.3.5.1. DVH data will be generated for the following normal tissues:
Bladder-with organ contoured from dome to neck.
Rectum-Contoured from the recto-sigmoid junction to the inferior border of the ischial tuberosities. The entire outer circumference should be contoured.
Femoral heads-Contoured from the acetabular roof to the inferior edge of the greater trochanter.

6.3.6. Normal Tissue Constraints (adapted from arm II of the RTOG 0415 Study, assumes an α/β of rectum and bladder=3).

	No more than 15% volume exceeds	No more than 25% volume exceeds	No more than 35% volume exceeds	No more than 50% volume exceeds
Bladder	60 CGE	55 CGE	51 CGE	48 CGE
Rectum	60 CGE	55 CGE	50 CGE	45 CGE

6.3.7. The prescription dose is to the isocenter of the PTV. The maximum dose to the PTV should not exceed the Rx dose by >5%, and the minimum dose to the PTV should not be < 90% of the Rx dose.

The Rx is 3 CGE/Day to isocenter, one treatment per day, 5 days per week, for 20 treatments (=60 CGE to isocenter/20 fractions).

6.4 **Radiation Toxicity**

6.4.1. All patients will be seen and examined weekly by their attending radiation oncologist during treatment. Any and all observations regarding radiation reactions will be recorded and should include particular attention to the following side effects:

6.4.1.1. Small bowel or rectal irritation manifesting as abdominal cramping, diarrhea, rectal urgency, proctitis, or hematochezia.

6.4.1.2. Bladder complications including urinary frequency/urgency/dysuria, hematuria, urinary tract infection, incontinence, nocturia.

6.4.1.3. Radiation dermatitis.

6.4.1.4. Clinical discretion may be exercised to treat radiation-induced side effects with the appropriate OTC and/or prescription medications.

7.0 Drug Therapy-N/A

8.0 Surgery-N/A

9.0 Other Therapy

9.1. Neoadjuvant or Adjuvant Hormonal Therapy.

Neoadjuvant or adjuvant hormonal therapy is not allowed in this trial. The patient population for this trial was chosen to include only those patients who did not stand to benefit from the use of hormonal therapy (by virtue of their favorable disease status). As a secondary goal of this trial is to determine the effect of hypofractionated conformal proton beam radiation therapy on bNED survival, hormonal therapy would simply confound the impact of hypofractionated radiation on bNED survival and freedom from relapse.

9.2 Subsequent disease progression.

Patients who have failed as defined by criteria described in Sections 11.4 (criteria for biochemical recurrence), 11.5 (criteria for local recurrence), or 11.6 (criteria for non-local recurrence) may receive additional medical and/or surgical therapy as appropriate for the clinical situation. These would include salvage prostatectomy, salvage cryosurgery, androgen-ablation therapy, cytotoxic chemotherapy, observation, or participation in an appropriate clinical trial.

11.0 Patient Assessments

11.1 Study parameters

Assessments	Pre-Entry	Weekly During RT	Follow-Up (months)							
			3	6	9	12	15	18	21	24
History, physical exam	X	X	X	X	X	X	X	X	X	X[c]
Prostate biopsy with Gleason Score	X									X[d]
PSA	X[a]		X	X	X	X	X	X	X	X[c]
Digital Rectal Exam	X		X	X	X	X	X	X	X	X[c]
MRI/MRS	X[b]									
Baseline urinary status evaluation	X									
Toxicity evaluation		X	X	X	X	X	X	X	X	X[c]
Bone scan										X[e]

a. PSA < 10 ng/ml within 180 days of registration
b. Per Section 4.1.3
c. Follow-up will continue every 6 months for the next 3 years, then annually thereafter
d. Per Section 11.3.4
e. Per Section 11.3.3

11.2. Evaluation During Treatment

11.2.1. Patients will be seen and evaluated at least weekly during treatment with documentation of treatment tolerance and the presence/absence/magnitude of acute reactions.

11.3 Evaluation Following Treatment

11.3.1. At each visit the patient will have an interval history, disease-focused physical examination (including DRE) and assessment of any specific GI/GU toxicity.

11.3.2. PSA will be drawn at each follow up visit: 3 months post radiation therapy, then every three months for two years, then every six months for three years, then annually.

11.3.3. A Bone scan will be performed as clinically indicated e.g., if the patient develops a PSA recurrence with a rapid doubling time (< 6 months) or if the patient develops symptoms suggestive of metastatic disease.

11.3.4. A needle biopsy is encouraged from the site of original tumor within the prostate and/or other sites or within the gland as identified by TRUS and/or MRI for rising PSA or clinical failures (see Sections 11.5.1. and 11.6.1).

11.4 Criteria for Biochemical Recurrence

11.4.1. Biochemical (PSA) recurrence will be defined as per the new RTOG/ASTRO criteria known as the RTOG Phoenix definition: an increase of the PSA level of at least 2 ng/ml greater than the post-treatment nadir. To ensure valid comparisons with our institutional data, the ASTRO Consensus Conference definition (three successive > 10% rises in PSA above a nadir) will also be used, although this definition will not be the primary definition of biochemical failure.

11.5 Criteria for Local Recurrence

11.5.1. Clinical criteria for local recurrence are progression (increase in size of a palpable abnormality) at any time, failure of regression of the palpable tumor by two years post-treatment, and redevelopment of a palpable abnormality after complete disappearance of the previously appreciated abnormality. The presence of palpable disease must be recorded on the data collection forms for initial and follow up patient evaluations.

11.5.2 Histologic criteria for local recurrence are presence of prostate carcinoma upon biopsy and positive biopsy of the palpably normal prostate > 2 years from the end of treatment.

11.6 Criteria for non-local recurrence.

11.6.1. Distant metastasis will be documented if clinical, bone scan, or other imaging studies (Prostascint, MRI) demonstrates evidence of its existence. Whenever possible, distant metastasis should be documented by histologic confirmation. In addition, TRUS/ biopsy of the prostate is recommended at the time distant metastasis are reported.

11.6.2. Regional metastasis will be documented if there is imaging evidence of lymphadenopathy and histologic confirmation.

12.0 Statistical Considerations

12.1 Study Endpoints

12.1.1. Rate of late GI and GU toxicities ≥ grade 3 (see Appendix for scoring scheme)
12.1.2. Three-year actuarial rate of freedom from biochemical failure.

12.2. Sample Size

12.2.1. Sample Size

12.2.1.1. Phase I Component: Between 1990 and 2007, we have treated 4260 patients with early stage prostate cancer (clinical stage T1 or T2, initial PSA <10 ng/ml, KPS 90 or 100) with protons only. The 3-year actuarial rectal/urinary grade 3 toxicity rate was 0.69% ± 0.15% SE in this cohort. We will conservatively assume the standard toxicity rate p_0 to be 1% and set the unacceptable toxicity rate p_1 at 5%. Statistical error rates will be set at α=10% for a false positive result (calling the treatment too toxic when it is not) and β=10% for a false negative result (accepting that the treatment is not too toxic when in reality it is) when using a one-sided test of significance. The sample size meeting these requirements is 105 patients.

12.2.1.2. Phase II Component: In the same patient cohort, the 3-year actuarial rate of biochemical progression free survival (bPFS) was 96%. We will conservatively assume the standard 3-year biochemical failure rate p_0 to be 5% and set the unacceptable failure rate p_1 at 10%. Statistical error rates for false positive and false negative results will again be set at 10%. The required sample size is 187 patients, which exceeds the required sample size for the toxicity endpoint. An additional 35% will be added to this number to guard against ineligible or inevaluable cases, resulting in 288 patients**.** In order to be conservative the sample size for the Phase I/II study will be set to 300 patients.

12.2.1.3. Assuming we accrue the target goal of 187 evaluable patients, a 5% late toxicity rate equates to 9.34 patients with toxicity. If we have 9 or fewer patients with toxicity, the protocol therapy will be considered for further study. In addition, we must also meet the goals for tumor control. Assuming the target goal of 187 patients, tumor control will be considered acceptable if 12 or fewer patients have biochemical failure within the first three years. For the protocol therapy to be recommended for further study, both the toxicity and tumor control outcomes must be considered acceptable. This equates to 9 or fewer patients with late toxicity, and 12 or fewer patients with recurrence. If the study accrues more or less than 187 evaluable patients, these cut-off numbers will be adjusted accordingly.

With a sample size of 187 patients and an assumed late toxicity rate of 2%, we have an upper = 95% confidence limit of 5% for (grade ≥3) late toxicity. This upper bound corresponds to the limit we would accept in terms of toxicity.

12.3. Stopping Rules for Excessive Acute Effects

The acute toxicity rate (>=grade 2) in our previously treated patient with early stage prostate cancer was less than 15% (12.6% grade 2, 0.8% grade 3) . We wish to ensure that the hypofractionation treatment does not increase the acute toxicity rate within the first three months after treatment commenced. The following table

gives the numbers of patients with acute toxicity (>= grade 2) that are considered unacceptable at interim check points as calculated by the method of Fleming. For example, if there are 17 or more acute toxicities reported in the first 50 patients, the accrual will be stopped and the treatment protocol will receive a special review. Note that these are the first 50 patients entered (and eligible) consecutively onto the trial and not the first 14 patients for whom we have collected data up to three months. The last column lists the power to detect a 10% increase from an assumed 15% toxicity rate to 25% based on the number of patients available at each stage.

Number of Patients with acute Toxicity	Number of Patients Available	Power (%) (1-β)
15	50	20.7
22	100	75.6
30	150	92.1
35	187	97.6

12.4 Patient Accrual

It is projected that there will be approximately a 2-month period with initial slow accrual (5-10 patients per month) at the beginning of this study to allow for establishing the procedures. After this initial period, it is projected that this study will accrue approximately 25 patients per month. At this rate, it will take 13 months to complete accrual. If the average monthly accrual is less than 15 patients per month, the study will be reevaluated with respect to feasibility.

12.5 Analysis Plan

12.5.1 Interim Analyses of Accrual and Toxicity Data

• Interim reports will be prepared every six months until the final analysis. In general, the interim reports include information about:
• accrual rate with projected completion date
• Pre-treatment characteristics of patients accrued
• frequency and severity of toxicity.

12.5.2 Analysis and Reporting of Initial Treatment Results

The analysis to report the initial results of treatment will be undertaken when each patient has been potentially followed for a minimum of 15 months. The emphasis of this analysis will be on acute toxicity. The usual components of this analysis are:
• patients excluded from the analyses with their reasons for exclusion
• distribution of the important baseline prognostic variables
• patient accrual rate
• observed results with respect to the endpoints described in Section 12.1

12.5.3 Analysis and Reporting of Final Treatment Results (10/29/01)

The analysis to report the final results of treatment will be undertaken when each patient has been potentially followed for a minimum of 3 years. The emphasis of this analysis will be on biochemical control. The usual components of this analysis are:

- patients excluded from the analyses with their reasons for exclusion
- distribution of the important baseline prognostic variables
- patient accrual rate
- observed results with respect to the endpoints described in Section 12.1.

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