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A randomised trial of a hypo-fractionated radiation regimen for the treatment of localized prostate cancer

Catton, et al

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CONFIDENTIAL

A Randomized Trial of a Shorter Radiation Fractionation Schedule for the Treatment of Localized Prostate Cancer

PROFIT

(**PRO**state **F**ractionated **I**rradiation **T**rial)

Version 3
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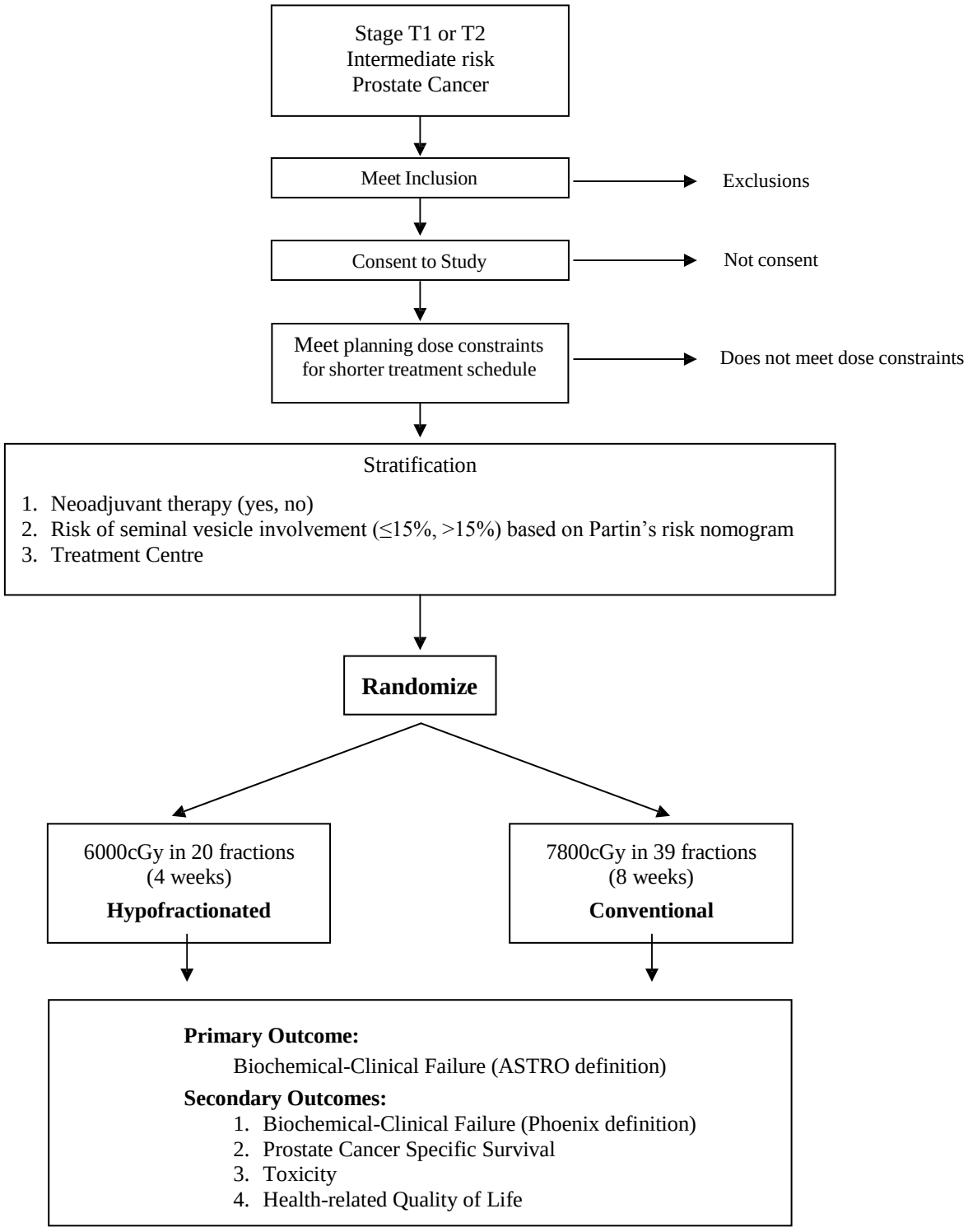
1. SUMMARY

Prostate cancer is the most commonly diagnosed cancer in Canadian men. The increased incidence due to an aging population and prostate specific antigen (PSA) screening has expanded the requirement to provide cancer care services for these men. Men with localized prostate cancer are often treated with external beam radiation. This trial focuses on men with intermediate risk prostate cancer who usually receive 8 weeks of radiation treatment. There is evidence to show that prostate cancer responds more favourably to large size radiation fractions than do most other cancers. Technological advances in radiation planning and treatment have enabled patients to be treated with conformal therapy which reduces radiation toxicity.

This trial is designed to determine whether an 8-week course of escalated dose conformal radiation can be compressed safely, and with similar efficacy into a 4-week course. In this trial, men with intermediate risk prostate cancer will be randomized to a shorter course of radiotherapy (6000cGy in 20 fractions over 4 weeks; hypofractionated) or treatment with a conventional fractionation course (7800cGy in 39 fractions over 8 weeks; standard). Three-dimensional conformal radiation treatment techniques, including intensity modulated radiotherapy will be used for both hypofractionated and standard treatments to avoid normal tissue exposure to radiation and minimize the risk of acute and late treatment related toxicity.

The primary outcome is biochemical-clinical failure (BCF) defined by a cluster of events including PSA failure based on the ASTRO definition, clinical evidence of local or metastatic progression (nodal or distant), post-treatment initiation of hormonal therapy by the treating physician, or prostate cancer-related death. Secondary outcomes include BCF with PSA failure based on the Phoenix definition, mortality from cancer, toxicity and health-related quality of life. In total, 1204 patients will be recruited for the study. If the safety and efficacy of the shorter course are demonstrated, then its adoption would reduce the social, emotional and economic burden of treatment for patients and their families.

2. STUDY SCHEMA



3. BACKGROUND AND RATIONALE

After lung cancer, carcinoma of the prostate is the commonest malignancy to afflict the Canadian male population. The estimated number of new cases of prostate cancer in 2004 across Canada was 20,100. It is estimated that in this year 4,200 men will die of prostate cancer making it the third most common cause of cancer deaths in men [1]. Because of the aging of the population, the increasing emphasis on prostate cancer screening and the increasing usage of prostate specific antigen (PSA), the incidence of prostate cancer appears to be increasing by approximately 3% annually [2]. The treatment of these patients is accounting for an ever-increasing share of health care resources [3].

The most important prognostic factors in the management of patients with localized prostate cancer include tumour stage (TNM staging), grade of tumour (Gleason score) and PSA level. These factors have correlated with local extent of disease and nodal metastases in surgical series [4] and with biochemical disease free survival in patients treated with radiotherapy [5].

The stage of disease at presentation describes the extent to which prostate cancer has spread in the body and is an important determinant of prognosis. Prostate cancer may be staged by the Whitmore-Jewett system or the UICC-TNM system [6] (Appendix 1). Both systems are complimentary to each other. In this protocol, we will use the UICC system and will refer to localized prostate cancer as T1 (intracapsular tumours with no palpable abnormality) or T2 (palpable nodule limited to the prostate). T2 is categorized to describe tumour involving half a lobe or less (T2a), more than half of one lobe (T2b), or both lobes (T2c) of the prostate.

Between 1974-1983, 56% of men newly diagnosed with prostate cancer in the U.S. presented with localized prostate cancer [7]. More recent studies, however, suggest that 75% of patients present with localized disease [8]. This has been attributed to the increased utilization of PSA screening to diagnose patients.

The Gleason score is universally accepted as an extremely important prognostic factor. Reporting of the Gleason score is based on the assignment of a Gleason grade (1 to 5) to the primary and secondary tumour patterns. The primary and secondary pattern scores are summed to derive the Gleason score (2 to 10) for the tumour. Gleason score of 2-6 generally correlates

with a well-differentiated tumour while Gleason score of 7 correlates with a moderately differentiated tumour and Gleason score of 8-10 correlates with a poorly differentiated tumour.

3.1. Risk Group Classification

The three important prognostic factors have been collated into three risk strata: low risk, intermediate risk and high risk, and the criteria for these strata was developed and accepted by the 2000 Canadian Consensus Conference [9] (Appendix 2). The utility of this risk group classification has been validated by D'Amico et al [10] who demonstrated that this risk classification system predicted time to prostate cancer specific mortality after surgery or radiation therapy.

Prostate cancer frequently exhibits a long natural history and long follow-up is necessary to assess the effectiveness of treatment. The time from diagnosis to clinical failure to eventual death from disease will often exceed ten years or more [11]. Investigators have therefore used PSA failure post-treatment as a surrogate outcome.

The management of prostate cancer remains controversial because of the variable natural history, the diversity of available treatments and lack of randomized clinical trials comparing the different treatments available. Low risk patients are candidates for watchful waiting, surgery and radical radiotherapy (either with external beam radiotherapy or brachytherapy). Patients with high-risk disease are usually treated with a combination of radical radiotherapy and adjuvant hormonal treatment.

A detailed discussion of intermediate risk prostate cancer will follow a discussion of the changes in radiation treatment technique over the last decade for treating prostate cancer.

3.2. Radiotherapy Treatment Technique for Prostate Cancer

Until 5-6 years ago, conventional radical radiotherapy fractionation schedules in treating localized prostate cancer ranged between 6600 and 7000cGy over 6 to 7 weeks [12-14]. Treatment techniques included a conventional four-field technique with margins around the prostate of 1.5cm. More recently, technological advances have enabled patients to be treated using conformal radiotherapy. Conformal radiotherapy in the treatment of localize prostate cancer usually involves the utilization of 5-6 field arrangements with maximal shielding. When

conformal techniques are used with appropriate localization, margins of 8-10 mm are used around the prostate. The increased number of beams used, reduced margins and maximum shielding enables the rectal and bladder dose to be reduced. A randomized study using conformal techniques has confirmed reduced toxicity over traditional four-field techniques [15], and in view of the reduced toxicity associated with conformal radiotherapy patients are usually treated with this technique even when moderate doses of radiotherapy are used.

Intensity Modulated Radiotherapy (IMRT) was introduced approximately 4-5 years ago and is being increasingly introduced into clinical practice. IMRT is a specialized form of conformal radiotherapy for delivering external beam radiotherapy to highly conformed treatment volumes by means of segmentation of each beam into hundreds of beamlets – each of which has its radiation intensity under individual control. This enables the high dose volume to be more appropriately "shaped" around the target volume further reducing the dose to normal tissue. Conformal treatment techniques reduce dose to normal tissue, and reduced toxicity also enables patients to be treated to higher doses of radiation with acceptable toxicity. When conformal techniques are used the dose to normal tissue is calculated during treatment planning and radiation doses to these organs are kept below acceptable dose constraint levels.

3.3. Intermediate Risk Prostate Cancer

Patients with intermediate risk disease (T1-2 Gleason 6 and PSA 10-20 ng/ml or T2b-c Gleason 6 and PSA ≤20 ng/ml or T1-2 Gleason 7 and PSA ≤ 20 ng/ml) (Appendix 2) are candidates for surgery or radical radiotherapy. For these patients, the options are either radical prostatectomy or radical radiotherapy. When comparisons are made between the reported studies of radiation and surgery (all retrospective), both treatments appear to be equally effective in terms of local control and survival [16, 17]. The decision to employ radiation rather than surgery is often made on the basis of patient factors such as age, the presence of co-morbid conditions which could make surgery hazardous, and the availability of surgical expertise.

Intermediate risk patients treated with radical radiotherapy may be treated with doses of 7000cGy (moderate dose radiotherapy) with or without neoadjuvant and concurrent hormones, high dose radiotherapy using doses exceeding 7560cGy, and with external dose radiotherapy with implant boost. One small randomized study has shown an improved biochemical relapse-

free rate using this technique compared to moderate dose external beam radiotherapy [18]. No other randomized studies have compared this treatment technique to the other options mentioned above – in particular no randomized study has compared this approach to high dose radiotherapy. The role of hormonal treatment used in a neoadjuvant and concurrent basis with moderate dose or high dose radiotherapy has not been established in the intermediate risk patient population.

3.3.1. Current Recommendations for Radiotherapy in Intermediate Risk Disease

In 2000 the Cancer Care Ontario Program in Evidence Based Care performed a systematic review of the literature and concluded that patients with localized prostate cancer should be treated using conformal radiotherapy techniques to doses exceeding 7560cGy [19] when patients are treated outside of a clinical study. Since that publication, further evidence of an improved biochemical relapse-free rate with use of higher doses of radiotherapy is seen in two other randomized studies comparing higher dose of radiotherapy to moderate dose radiotherapy [18, 20]. The acceptable toxicity of higher doses of radiation therapy using conformal techniques has resulted in doses exceeding 7560cGy (in 180-200cGy fractions) being considered standard practice in the treatment of patients with intermediate risk disease.

In summary, high dose conformal radiotherapy using doses exceeding 7560cGy in 180-200cGy fractions is considered standard treatment for patients with intermediate risk localized prostate cancer. In modern series using doses of greater than 7500cGy the long-term biochemical control rates range from 62-90% depending on selection factors used (Table 1).

3.4. Radiobiology Consideration: Hypofractionation

External beam radiotherapy is given in equal daily increments (fractions), usually for five days a week, to permit normal tissue to repair radiation injury and to allow tumours to re-oxygenate between treatments. A radiotherapy prescription therefore consists of a total dose, a fraction number and an overall treatment time (e.g. 7800cGy in 39 fractions over 8 weeks). Typical curative radiation prescriptions use 180-200cGy fraction sizes (standard fractionation) since this fraction size is believed to offer the best balance between desired tumour kill and unwanted normal tissue injury for most carcinomas.

Larger fraction sizes of more than 250cGy (hypofractionation) are usually avoided for curative therapy of most tumour types because late reacting normal tissues (e.g. late fibrosis effect) are more sensitive to large fractions than are most carcinomas. For these tumours, hypofractionation (rather than standard fractionation) will result in greater damage to late reacting normal tissue compared to tumour [21]. Late reactions (late toxicity) are considered a vital and dose-limiting effect in radiotherapy because unlike acute effects, these may not heal well and may require surgical intervention.

Recent evidence shows that prostate carcinoma does not behave like other carcinomas in its radiation responsiveness. The sensitivity of tissue to radiation fraction size is described by the alpha and beta component of the linear quadratic equation [22]. Most carcinomas, and all rapidly dividing normal tissues (acute reacting tissues), have an alpha/beta of approximately 10Gy. Slowly dividing late reacting normal tissues (e.g. late fibrosis effect) have an alpha/beta of between 3 and 5Gy [21]. A number of studies, however, suggest that the alpha/beta for prostate cancer is 0.9-1.5Gy [23-25]. The outcome of the only randomized trial of hypofractionated vs. conventional prostate radiotherapy is best explained with an alpha/beta for prostate cancer of 0.9 [26].

A low alpha/beta for prostate carcinoma means that hypofractionated radiotherapy is more efficient at tumour killing than standard fractionation is, and will produce equivalent tumour control with a lower total dose and a shorter overall treatment time. Since late reacting normal tissues also have a low alpha/beta, radiation treatment techniques that protect normal tissue from direct radiation exposure, such as 3D conformal therapy, must be used to protect sensitive normal tissues from the effects of hypofractionation and avoid the increased risk of late effects posed by hypofractionation treatment schedules.

3.4.1. Rationale for Hypofractionated Regimen Radiobiological Considerations

While the clinical validity of the alpha/beta model has not been shown for prostate carcinoma, its predictive value for late effects has been shown for cervix cancer [27], and for the proposed trial comparisons of the high dose regimen (7800cGy in 39 fractions and 200cGy fractions) to the hypofractionated regimen (6000cGy in 20 fractions and 300cGy fractions) show that the doses delivered are comparable in the alpha/beta 1-3Gy range. The model would also predict lower

acute toxicity with hypofractionated regimens compared to standard fraction sizes. According to the model, 6000cGy in 300cGy fractions has a lower effect compared to 7800cGy in 200cGy fractions for acute reacting tissues with an alpha/beta of 10.

3.4.2. Clinical Experience with Hypofractionated Regimen

A systematic review of the literature was conducted from 1980-2004 with a Medline search using the key words prostate, radiotherapy, hypofractionation, trials. In addition, scientific abstracts were searched from 2000-2004, and experts in the field consulted.

Only one randomized trial comparing hypofractionation to conventional fractionation was identified. The majority of the literature consists of retrospective institutional reports, and the clinical experience with hypofractionated radiotherapy regimens for prostate cancer can be divided into an early experience using low precision treatment techniques before the PSA era, and a modern experience using 3D conformal therapy reporting biochemical relapse free rates.

Initial experience of hypofractionated regimens was based on clinical series reported from Princess Margaret Hospital [28], Edinburgh [29], Brisbane [30], Manchester [31] and Bristol [32]. The only randomized study of hypofractionation in localized prostate cancer (the PR-5 trial) conducted under OCOG and NCIC-CTG was reported in 2003 and compared treatment with 6600cGy in 200cGy fractions over 6.5 weeks to 5250cGy in 262.5cGy fractions over four weeks [26]. The five-year biochemical relapse-free rates for these regimens were 47.0% vs. 40.0% respectively. The study was designed as an equivalence study and the hypofractionated regimen was within the predefined tolerance of 7.5%. However, the possibility of the hypofractionated regimen being inferior to the conventional regimen could not be excluded. Presentation of this Canadian study has renewed interest in hypofractionated regimens based on the potential radiobiological advantages and advantages to the patient. Recent case series have reported on their other hypofractionated regimens in localized prostate cancer (Table 2). These studies have been conducted since the early 1990's and have had PSA outcomes reported.

The largest retrospective series from the Christie Hospital reported treating patients with 5000cGy in 16 fractions and 313cGy fractions [33].The biochemical relapse-free rates in the low, intermediate and high risk were 82%, 56% and 39% respectively. The late toxicity rates (grade 2) for bowel and bladder were 5% and 9% respectively. There were no grade 3 toxicities.

These patients were treated with small volumes and traditional techniques, and the late toxicity would be anticipated to be lower using conformal techniques.

The Cleveland Clinic [34] has reported on their prospective phase 2 study of treating 116 patients to a dose of 7000cGy in 28 fractions and 250cGy fraction size. The biochemical relapse-free rate at 30 months was 94%. The reported late toxicity rate (grade 3) was 1.5%.

The Princess Margaret Hospital has analyzed their phase 2 study of treating 97 patients with T1-2 disease to a dose of 6000cGy in 20 fractions and 300cGy fraction size [35] (updated to median 14 months follow-up, Catton-personal communication). The PSA failure rate has not yet been analyzed. The regimen has been has been well tolerated with no patient experiencing late bladder or bowel toxicity greater than grade 2.

3.4.3. Rationale for Chosen Hypofractionated Regimen

The alpha/beta model would predict equivalent tumour control and late toxicity with the hypofractionated regimen in this study. The model would predict a lower acute toxicity, and the acute and late toxicity from the phase 2 study conducted at Princess Margaret Hospital confirms the safety of this regimen. Secondly, our investigators are familiar with the technique and fractionation schedule of the hypofractionation arm of this study since it is identical to the regimen used in the phase 2 trial.

4. STUDY OBJECTIVES

4.1. General Objective

To improve the management of patients with early stage prostate cancer.

4.2. Specific Objectives

4.2.1. Primary Objective

To compare the efficacy of a shorter course of radiotherapy (6000cGy in 20 fractions over 4 weeks) with a conventional fractionation course (7800cGy in 39 fractions over 8 weeks) with respect to biochemical-clinical failure (BCF) defined by a cluster of events including PSA progression (based on the American Society of Therapeutic Radiology and Oncology (ASTRO) consensus definition), clinical evidence of local or metastatic progression (nodal or distant), post-

treatment initiation of hormonal therapy by the treating physician, or prostate cancer-related death.

4.2.2. Secondary Objectives

To compare the two treatment groups with respect to: (1) BCF with PSA failure based on the Phoenix definition; (2) mortality from prostate cancer; (3) toxicity; and (4) health-related quality of life (HRQoL).

5. STUDY METHODOLOGY

5.1. Study Design

A multi-centre trial will be performed in which patients with Clinical T1-2 N0M0 intermediate risk prostate cancer will be randomized to either 6000cGy in 20 fractions over 28 days to the prostate or 7800cGy in 39 fractions over 53 days to the prostate (see Study Schema in section 2).

5.2. Patient Population

5.2.1. Inclusion Criteria

1) Histologic diagnosis of carcinoma of the prostate within 6 months of entry without evidence of metastatic disease to the lymph nodes, bone or lung;

2) Intermediate risk prostate cancer (T1-2a, Gleason score <6, PSA 10.1-20.0 ng/ml; T2b-c Gleason <6, PSA ≤ 20.0 ng/ml; T1-2, Gleason 7, PSA ≤ 20.0 ng/ml).

5.2.2. Exclusion Criteria

1) Histologic diagnosis of carcinoma of the prostate more than six months prior to study entry;

2) Previous therapy for carcinoma of the prostate other than biopsy or transurethral resection;

3) Patients previously on more than 12 weeks of hormone therapy for treatment of their prostate cancer;

4) Any other active malignancy (untreated, progressive or recurrent), except for non-melanoma skin cancer. Any inactive malignancy diagnosed within 5 years of entry, except for non-melanoma skin cancer;

5) Treatment plan cannot meet dose constraints for the hypofractionation arm of the trial;

6) Previous pelvic radiotherapy;

7) Inflammatory bowel disease.

5.3. Randomization

Randomization will be conducted centrally by the Coordinating and Methods Centre within the Ontario Clinical Oncology Group (OCOG) located at the Henderson Research Centre in Hamilton, Ontario, Canada. OCOG is affiliated with the Department of Oncology at McMaster University. A computer generated randomization schedule will allocate patients to the standard treatment arm or the experimental arm on a 1:1 ratio. After an eligible patient has given informed consent (Appendix 3), randomization will be performed by means of a telephone call to the Coordinating and Methods Centre.

5.4. Stratification

Patients will be stratified by:

(a) use of neo-adjuvant hormone therapy (yes, no)

(b) risk of seminal vesicle involvement (≤15%, >15%) using Partin's risk nomogram [4] based on pre-treatment PSA, Gleason score and T-category (Appendix 4); and

(c) treatment centre.

5.5. Treatment Plan

5.5.1. Pretreatment Investigations

5.5.1.1. Prior to Randomization

1) Complete history and physical examination.

2) Confirmation of pathological diagnosis within 6 months of entry. Gleason score mandatory.

3) Prostate Specific Antigen (PSA) within 12 weeks prior to commencement of radiotherapy. PSA should be obtained prior to rectal examination.
4) Patients who have received less than 12 weeks of neo-adjuvant hormone therapy are eligible and will have hormones stopped prior to study entry. They will have PSA eligibility determined from a PSA taken within 12 weeks prior to commencement of hormone therapy.
5) Patients who have received less than 12 weeks of neo-adjuvant hormone therapy will have clinical eligibility determined from the Digital Rectal Exam (DRE) recorded prior to commencement of hormone therapy.

5.5.1.2. Baseline before Treatment

1) Hemoglobin, white blood count, and platelet count prior to randomization
2) Blood urea nitrogen (BUN), creatinine prior to randomization
3) Baseline bladder and bowel function according to RTOG toxicity status (Appendix 5)
4) Baseline Quality of Life assessment (Appendix 7)

5.5.2. Anatomic Volume and Desired Dose

A patient cannot be randomized until it is demonstrated that the dose constraints for the hypofractionated arm can be met. All patients must therefore be planned for the hypofractionated arm, whether or not they are eventually treated on that arm. It is assumed that patients who meet the more rigorous dose constraints for the hypofractionated treatment arm will also be able to meet the dose constraints for the standard treatment arm. Randomization will therefore take place after initial treatment planning is complete. For patients subsequently randomized to the longer fractionation schedule, centres may choose at their discretion to re-plan patients or to treat on the plan developed for the hypofractionated treatment arm, assuming that the dose constraints for the longer schedule are met.

The Clinical Target Volume (CTV) will be limited to the prostate only, except for patients at >15% risk of seminal vesicle involvement (Gleason score 7 and PSA 4-20, Appendix 2). The planning target volume (PTV) will be the CTV plus 10 mm in all planes except towards the rectum, where it will be 7 mm. For patients with more than 15% risk of SV involvement, the

CTV will include the proximal seminal vesicles, defined as the portion from its origin with the prostate and extending 1 cm superiorly.

The prescribed dose is either 6000cGy in 20 fractions over 28-31 days or 7800cGy in 39 fractions over 53-56 days. The doses to the CTV and PTV will be such that a minimum of 99% of the CTV will receive the prescribed dose and a minimum of 99% of the PTV will receive 95% of the prescribed dose. No more than 1cc of the PTV should receive more than 105% of the prescribed dose. See Appendix 8.

5.5.3. Radiotherapy Technique

See Appendix 8 for details.

Radiation:	High energy photons (≥ 6 MV)
Position:	Supine with hands on chest.
Immobilization:	Recommended.
Special Instructions:	Bladder to be comfortably full, rectum empty.
Technique:	Not mandated. Must meet specified dose constraints.
Image Guidance:	Daily image guidance required.

5.5.4. Radiotherapy Planning

CT Planning will be required for the study. See Appendix 8 for details.

5.5.5. Dosimetry

IMRT and non-IMRT treatment plans will be prescribed to CTV minimum, and the dose within the CTV should not exceed 7% of the prescribed dose.

5.5.6. Radiotherapy Treatment Verification

On-line daily target verification will be mandatory. This may include imaged implanted fiducial markers, or ultra-sound localization, or tomographic localization (kV or MV).

5.6. Radiotherapy Quality Assurance

All participating radiation centres will be accredited before local trial activation by a Radiation Quality Assurance Committee composed of a Radiation Oncologist, Medical Physicist and a

Radiation Therapist. In addition, each centre will undergo a site visit by the committee during the course of the trial.

5.7. Follow-up and Post Treatment Investigation

Details of the assessments at each visit are shown in Appendix 9.

1) Toxicity assessments will be performed weekly from the start of radiotherapy. Patients receiving 4 weeks of treatment will have telephone follow-up for toxicity during weeks 6 and 8. All patients will have a telephone follow-up during week 10, and a clinic visit at week 14.
2) PSA, done at each follow-up visit starting with the six-month post-randomization visit.
3) Health-related Quality of Life (HRQoL) (Appendix 7) assessment to be done at baseline, 24 months and 48 months post-randomization visits.
4) Clinic visits will be scheduled every six months post-randomization or until clinical evidence of metastatic disease is found.
5) Each patient will be followed for at least nine years, but the usual practice in oncology trials is to follow patients indefinitely.

5.8. Compliance

Physician compliance with the treatment protocol will be monitored by a Radiation Quality Assurance Committee (described above). Patient compliance with radiotherapy is traditionally very high, since treatment is given daily over a period of weeks, and any single missed days are made up during the overall course. Radiation Therapists are trained to contact patients who miss treatments and encourage continuation. Patient compliance with follow-up will be high, since the follow-up schedule is not arduous, and Clinical Research Assistants or nurses will be employed to monitor follow-up. They are trained to re-establish contact with non-compliant patients.

5.9. Outcome Assessment

5.9.1. Primary Outcome: Biochemical-Clinical Failure (BCF)

BCF is defined as a cluster of four outcomes including PSA failure, hormonal intervention, clinical evidence of failure (local or distant) and prostate cancer death [26]. Most failure events

would be expected to be due to PSA failure, and the other criteria defining failure are included for evidence of clinical failure that do not meet the strict ASTRO criteria for PSA failure. It is anticipated that following radiation, the PSA would fall from its baseline level. At the time of protocol development, PSA failure based on American Society of Therapeutic Radiology and Oncology (ASTRO) definition of failure [36] was accepted to be a surrogate endpoint for prostate cancer, while other definitions of PSA failure (Houston and Vancouver) [37, 38] had been reported. For the purposes of this study, BCF using the ASTRO definition of PSA failure will be used as the primary outcome.

5.9.2. Secondary Outcomes

5.9.2.1. BCF using the Phoenix Definition

BCF with PSA failure based on the Phoenix definition (BF_P; nadir + ≥2 ng/mL increase, with the failure dated "at call") will be used as a secondary efficacy outcome.

5.9.2.2. Prostate Cancer-Specific Mortality

Death due to prostate cancer, along with the metric of time from randomization to the date of that death, will be analyzed as a secondary outcome.

5.9.2.3. Toxicity

An important aim of this study is to determine whether there is any difference in toxicity to the normal tissue between the two different radiation schedules. Acute and late toxicity will be assessed by the RTOG toxicity score (Appendix 5 and 6). We have chosen this toxicity scale because it is widely recognized and investigators across the country have experience with its use. This scale will be administered by the physician or clinical designate.

5.9.2.4. Quality of Life

Physician-reported data suggests that urinary, bowel and sexual side-effects are common after external beam radiotherapy, and that the observed incidence of late bowel and bladder effects shows a plateau between 24-36 months after treatment [39]. Urinary symptoms are largely comprised of irritative and obstructive symptoms such as frequency, urgency, nocturia and dysuria, and bowel symptomatology are commonly frequency, urgency and hematochezia.

Several instruments have been developed to measure prostate-intervention related symptoms [40-44]. The HRQoL instrument proposal for this trial is The Expanded Prostate Cancer Index Composite (EPIC) (Appendix 7) which is a validated instrument with broadened sensitivity to irritative urinary symptoms and hormonal symptoms as well as a more comprehensive bother assessment [45]. Adding the Medical Outcomes Study Short Form 12 (SF-12) to the previous instruments allows measurement of more global elements of HRQoL.

5.10. Recommended Treatment at Time of Relapse

In general it is recommended that investigators consider recurrent/relapse only when there is definite evidence that treatment failure has occurred. Investigations and treatment at the time of relapse for metastatic symptoms, local prostate cancer persistence or rising PSA will be at the discretion of the treating physician. Hormonal therapy should not be implemented following radiotherapy before the patient meets the ASTRO consensus definition current at the time, or unless there is radiologic or pathologic evidence of disease progression in the absence of biochemical failure.

5.11. Sample Size and Feasibility

5.11.1. Sample Size

While the cluster of BCF events (i.e., PSA failure, hormonal intervention, clinical local or distant failure, prostate cancer death) is the primary outcome in this trial, the important metric is the time from randomization to the earliest occurrence of any of the component events. The date of PSA failure will be determined using the ASTRO definition of PSA failure. This definition identifies biochemical failure as being three consecutive PSA rises following a post-treatment PSA nadir, and the date of relapse is back-dated to the mid-point between the nadir and the first PSA rise. If the ASTRO definition of failure is modified before the time of the final analysis, then the definition current at the time will be used. Clinical failure will be defined on the date of objective documentation of event. Patients without BCF will be censored at the end of the study period or at death (if not from prostate cancer).

In the original sample size determination, we based the hazard ratio (experimental relative to the conventional regimen) and, therefore, the sample size, on the five-year BCF probability. From the results of previous studies (Table 1), we estimated 30% BCF at five years in the conventional

treatment arm. We postulated that eligible, consenting patients would be accrued over four years, and the last patient would be followed for at least five years. Since this is a non-inferiority design, we used a one-sided alpha of 5%. We were confident that we should have 85% power to demonstrate that the experimental arm will be no worse than 37.5% (i.e., a 7.5% tolerance margin), corresponding to a maximum hazard ratio of 1.32, with 572 patients per arm (378 events overall). Allowing 5% for loss, non-compliance and death unrelated to prostate cancer [2], we would need to recruit a minimum of 1204 patients overall.

The non-inferiority margin of 7.5% at five years was the same as that used in the earlier PR.5 study. Although this translates to a larger relative hazard tolerance than what we observed in the PR.5 trial (1.32 versus 1.21), we feel that the tolerance margin based on the absolute difference at five years is extremely meaningful to oncologists. Patients who experience PSA failure are usually treated with hormonal therapy, which often delays disease progression for an extended period. The combination of the patients' long natural disease history and long periods of disease control with hormonal intervention means that the tolerance margin of 7.5% based on the surrogate marker PSA failure would translate to a clinically non-meaningful difference in an important prostate cancer outcome such as prostate cancer specific mortality.

5.11.2. Recruitment and Feasibility

Eligible patients are identified and recruited by the treating physicians from the new prostate cancer patients seen at Canadian Cancer Treatment Centres. The original anticipated accrual rate was 300 per year, for a total recruitment time to complete the trial of 4 years. However, a more realistic estimate based on our experience to date is that a total accrual period of approximately 5.4 years will be needed to achieve the target sample size.

This trial is investigating the same treatment (radiotherapy) in the same population (patients with localized prostate cancer) as its predecessor trial PR.5 (OCOG and NCIC-CTG). This trial successfully accrued 936 patients at a rate of 300 patients a year from Canada, so our planned target accrual is reasonable. This trial will be conducted by the same investigators and the same coordinating group.

5.12. Data Handling and Analysis

Data will be handled by the Coordinating and Methods Centre of the OCOG unit within the Henderson Research Centre. The primary assessment of non-inferiority will be based on the estimated hazard ratio (experimental relative to the conventional regimen) with respect to BCF as calculated using a Cox proportional hazards model with treatment as the sole predictor adjusted for three stratification factors: neo-adjuvant hormone therapy, risk of seminal vesicle involvement, and centre. For declaration of non-inferiority, the upper limit of the two-sided 90% confidence interval must be less than 1.32. All time-to-event data will be summarized using Kaplan-Meier methods, and comparisons between treatment arms will be undertaken using a log rank test. Toxicity (acute and long-term) in the two arms will be compared using Fisher's exact tests. HRQoL data will be analyzed using a repeated measures mixed models framework. Although we anticipate that missing HRQoL assessments will be minimal, a missing-at-random model will be assumed in the analysis. For prostate cancer-specific survival, toxicity and HRQoL, statistical significance will be based on a two-sided 5% type I error. A supportive analysis for the BCF outcome will also use Cox modeling to assess the impact of the radiotherapy modality (3D vs. IMRT) without stratification on clinical centre. It is anticipated that the first formal analysis of the data will be undertaken shortly after the nine-year anniversary of the study.

Interim Analysis

A single interim analysis of safety and efficacy will be performed at three years after study commencement and will be reviewed by the Data Safety Monitoring Board (DSMB). The DSMB will be expected to recommend to the Steering Committee that the trial should be discontinued early based on the following stopping guidelines:

(a) Excess GU/GI Toxicity

The proportion of patients with an adverse outcome defined as RTOG late grade 3 and 4 bladder or rectal toxicity will be compared between treatment arms. Using the Peto-Haybittle approach, if the proportion is greater in the experimental arm as compared to the control arm with a corresponding one-sided p-value of 0.001 or less, the DSMB will seriously consider recommending early termination of the study.

(b) Lack of Efficacy

The rates of BCF will be compared using a log rank test. If the hazard ratio for the experimental arm as compared to the control arm exceeds 1 with a one-sided $p<0.001$ (using the Peto-Haybittle approach), the DSMB may recommend early termination of the study.

In addition to an interim analysis, the DSMB will also review accumulating study data every six months for toxicity starting approximately twelve months after study commencement.

6. ADVERSE EVENTS

6.1. Adverse Event Reporting

The study will be conducted according to the ICH/GCP guidelines. Adverse events and Serious Adverse Events will be collected and reported (see Appendix 10). Worsening of metastatic prostate cancer is expected and therefore will not be considered an SAE for the purpose of this study. Deaths due to metastatic prostate cancer are Outcome Events and will not be reported as AEs or SAEs. They will be monitored by the DSMB and will not require reporting to Health Canada.

7. TRIAL ORGANIZATION and QUALITY ASSURANCE

7.1. Steering Committee

The Steering Committee will be responsible for the design, execution, analysis and reporting of the study, and will assign appropriate responsibilities to the other study committees. The Steering Committee will hold the primary responsibility for publication of the study results. This committee will convene regularly (at least every three months) by telephone conference or meetings to address policy issues and to monitor study progress, execution and management.

7.2. Radiation Quality Assurance Committee

A RT quality assurance committee will be established consisting of a Radiation Oncologist, Radiation Physicist and a Radiation Therapy planner. This committee will be available for consultation should questions arise concerning the treatment protocol. All centres will be accredited for activation by the committee after providing paper or electronic copy of plans for 5 recent cases demonstrating:

1) CTV and PTV contoured according to protocol.
2) Organs at risk (bladder and rectal walls and femoral heads) contoured according to protocol.
3) DVH for bladder and rectal wall, PTV and CTV that meet dose constraints for the hypofractionated treatment arm.
4) A statement that patients will be treated with an approved daily image guidance technique.

7.3. Central Adjudication Committee

A committee, unaware of the treatment allocation, will review PSA failure profiles and suspected clinical outcome events, including prostate cancer-specific deaths, to establish whether they satisfy criteria for a study outcome event.

7.4. External Data Safety Monitoring Board

An independent external **Data Safety Monitoring Board (DSMB)** will be responsible for monitoring of patient safety. Members will be experts in the fields of clinical trials methodology and oncology and will receive study data pertinent to patient safety every six months starting approximately twelve months after study commencement through the Coordinating and Methods Centre (CMC). They will also review safety and efficacy data for an interim analysis at three years after study commencement.

7.5. Study Coordination

Patient randomization, study coordination, data management and statistical analysis will be carried out by the CMC at OCOG within the Henderson Research Centre in Hamilton, Ontario, Canada. In addition, the CMC will also provide methodological and administrative support to all committees, investigators and other study personnel.

8. ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human patients adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 as amended in 2000 and later revisions; or the laws and regulations of the country, whichever provide the greater protection for the individual.

8.1. Institutional Review Board

Prior to the commencement of the trial at each of the clinical centres, the study protocol must be approved by the local Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

8.2. Informed Consent

Written informed consent will be obtained from all patients prior to enrollment in the study in compliance with ICH/GCP Guidelines and local Institutional Review Boards.

9. SCIENTIFIC REPORTING AND PUBLICATION

The study protocol was developed by the Principal Investigators and Study Steering Committee. The trial is being coordinated by the Ontario Clinical Oncology Group. The Steering Committee is responsible for the scientific reporting, publishing and/or presentation of the study results. All Investigators participating in this study must agree to delegate the primary publication or presentation responsibility to the Steering Committee. Any other publication or presentation related to the study and the results by any investigator or participant must receive prior approval from the Steering Committee. No other publication or presentation is allowed before the primary publication or presentation by the Steering Committee. The information developed during the conduct of this clinical study is considered confidential.

10. SIGNIFICANCE

The move in modern radiotherapy practice toward highly conformed, high precision radiotherapy techniques for prostate cancer treatment has reduced treatment toxicity, and improved biochemical relapse free rates with dose-escalation. Treatment courses have extended from 6-7 weeks to 8-9 weeks, and this has increased radiotherapy requirements without increasing capacity, and more importantly, placed an additional social, emotional and economic burden on patients who must spend additional weeks traveling to cancer centres for treatment. This problem will increase over the next 1-2 years as all Canadian radiotherapy centres acquire the technical facility for dose-escalation and switch to longer treatment schedules.

This trial provides the opportunity to show that high-precision radiotherapy techniques can also be used to shorten treatment courses for intermediate risk prostate cancer, and if the safety and efficacy of the shorter course are demonstrated, then its adoption would reduce the social,

emotional and economic costs of treatment on individuals and their families through almost 4 weeks less time spent receiving treatment.

A positive trial would immediately result in the widespread adoption in Canada of shorter course hypofractionated treatment regimens as the new treatment standard for external beam radiotherapy of intermediate risk prostate cancer. It would also lead to the investigation of even shorter treatment courses. A result that shows non-inferiority for the shorter treatment arm with respect to the primary endpoint of biochemical-clinical relapse free rate, but demonstrates unacceptable late toxicity compared to standard treatment would support the hypothesis that the alpha/beta for prostate is low, but would not be adopted due to excessive toxicity. It would lead to investigation of more innovative treatment strategies to deliver hypofractionated external beam radiotherapy safely.

If the shorter treatment arm shows inferiority for the primary endpoint of biochemical-clinical relapse free rate then the treatment would not be adopted.

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Table 1: Summary of Trials of Radiation Dose-escalation for Prostate Cancer using Standard-sized Fractions

Institution	N of Patients	Clinical stage T1-2	Dose/Fraction size	5-year biochemical relapse-free rate	Late toxicity (RTOG grade)	Notes
MD Anderson [46]	301	80%	70 Gy/2.0 Gy vs. 78Gy/2.0 Gy	Overall 64% PSA>10 43% Overall 70% p=0.03 PSA>10 62% p=0.01 *(reported at 6 years)*	Rectal grade>2 12% Urinary grade≥2 10% Rectal grade>2 26% Urinary grade>2 10%	Randomized 3D conformal radiotherapy trial. All patients had pelvic + prostate radiation.
Harvard [20]	393	100%	70.2 Gy/1.8 Gy vs. 79.2Gy/1.8Gy	62.7% 80.9% p=0.002	Rectal grade>3 1.5% Rectal grade>3 0.5%	Randomized 3D conformal proton trial. Doses given in GyE (Gy equivalents)
Memorial Sloan-Kettering [47]	1100	76%	64.8-70.2 Gy/1.8 Gy 75.6-86.4 Gy/1.8 Gy	Risk category: A. Low 77% B. Intermed 50% C. High 21% D. Low 90% A vs D p=0.05 E. Intermed 70% B vs E p=0.001 F. High 47% C vs E p=0.002	Rectal grade 2 5% Urinary grade 2 4% *(actuarial 5-yr)* Rectal grade 2 14% Urinary grade 2 13% *(actuarial 5-year)* IMRT Rectal grade 2 2% 3DCRT Rectal grade 2 14% *(actuarial 3-yr)*	Median follow-up = 95 months Median follow-up = 69 months Phase 2 trial of sequentially dose-escalated cohorts.
Fox-Chase [48]	618	Not stated	Fraction size 2.1 Gy median 72.8 Gy median 77.5 Gy median 72.8 Gy median 77.3 Gy median 72.8 Gy median 77.3 Gy median 72.4 Gy median 76.9 Gy median 73.3 Gy median 77.3 Gy	Risk category: A. PSA <10 Unfavorable 70% 92% p=0.009 B.PSA 10-19.9 Favorable 72% 86% p=0.10 Unfavorable 51% 82% p=0.005 C.PSA ≥20 Favorable 23% 63% p=0.002 Unfavorable 29% 26% p=0.67	Rectal grade 3-4 < 1% Urinary grade 3-4 4% *(actuarial 5-yr).* Dose-effect detected for grade 2 GI	Sequentially dose escalated cohorts. Favorable: (T1-2a and Gleason score <7 and no perineural invasion) Unfavorable: (T2-3 or Gleason 7-10 or perineural invasion) Toxicity data from earlier report (n=232){Hanks, 1998 #48}

Institution	N of Patients	Clinical stage T1-2	Dose/Fraction size	5-year biochemical relapse-free rate	Late toxicity (RTOG grade)	Notes
3DOG/RTOG [49]	288	Group 1 100% Group 2 91%	Level 1 68.4 Gy/1.9 Gy (95%) equivalent to 72Gy/2.0 Gy (100%) Level 2 73.8 Gy/1.9 Gy (95%) equivalent to 77.7 Gy/2 Gy (100%)	Not stated	Urinary grade 2 12% Rectal grade 2 12% Urinary grade 2 12% Rectal grade 2 12% Urinary grade 3 0.5% *(actuarial 2-yr)*	Sequential dose-escalated cohorts, stratified by risk into 2 groups.

Table 2: Summary of Trials of Hypofractionated Radiotherapy for Localized Prostate Cancer

Institution	N of patients	Clinical stage T1-2	Dose/Fraction size	5-year biochemical relapse-free rate	Late toxicity (RTOG grade)	Notes
OCOG [26]	936	100%	66 Gy/2.0 Gy vs 52.5 Gy/2.62 Gy	51.4% 44.4%	Overall grade>3 3.2% Overall grade>3 2.6%	Randomized phase 3 trial. Outcome is biochemical and clinical failure both
Cleveland Clinic [34]	100	100%	70 Gy/2.5 Gy fractions	85% (ASTRO) 88% (Nadir+2)	Rectal grade 3 3% Rectal grade 2,3 5%	Prospective phase 2 trial. Median follow-up 66 months
Christie [33]	705	70%	50Gy/3.13 Gy fractions	Low risk: 82% Intermediate risk: 56% High risk: 39%	Rectal grade≥2 5% Bladder grade≥2 9%	Retrospective series
Princess Margaret [35]	92	100%	60Gy/3 Gy fractions	Not stated	Rectal grade 0 96% Rectal grade 3 0% Bladder grade 0 92% Bladder grade 3 0% (only ≥12 month follow-up)	Prospective phase 2 trial. Updated to median follow-up of 25 months (Catton, personal communication)

Appendix 1: Staging of Prostate Cancer

UICC – TNM Classification System

Symbol		Meaning
T_x		Primary tumour cannot be assessed
T_0		No evidence of primary tumour
T_1		Clinically inapparent tumour not palpable or visible by imaging
	T_{1a}	Tumour incidental finding in 5% or less of tissue resected
	T_{1b}	Tumour incidental finding in more than 5% of tissue resected
	T_{1c}	Tumour identified by needle biopsy (e.g., because of elevated PSA)
T_2		Tumour confined within prostate†
	T_{2a}	Tumour involves half of a lobe or less
	T_{2b}	Tumour involves more than half of a lobe, but not both lobes
	T_{2c}	Tumour involves both lobes
T_3		Tumour extends through prostatic capsule‡
	T_{3a}	Unilateral extracapsular extension
	T_{3b}	Bilateral extracapsular extension
	T_{3c}	Tumour invades seminal vesicle(s)
T_4		Tumour is fixed or invades adjacent structures other than seminal vesicles
	T_{4a}	Tumour invades any of the following: bladder neck, external sphincter, rectum
	T_{4b}	Tumour invades levator muscles and/or is fixed to pelvic wall

† Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging is classified as T_{1c}

‡ Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T_3, but as T_2.

Appendix 2: Risk Stratification for Prostate Cancer

Key

Low Risk
Intermediate Risk
High Risk

Gleason Score	← T_{1-2} →			T_3
	PSA ≤ 10	**PSA 10.1-20**	**PSA ≥ 20**	
≤ 6	(T_{2a})			
7				
≥ 8				

Appendix 4: Partin's Risk Nomogram

Percentage Risk of Seminal Vesicle Involvement

Partin AW, Kattan MW, Subong EN et al. Combination of prostate-specific antigen, clinical stage and Gleason score to predict pathological state of localized prostate cancer: a multi-institutional update. *JAMA* 277: 1445-51, 1997.

PSA 0 to 4 ng/ml

Gleason Score	Clinical T-Stage						
	1a	**1b**	**1c**	**2a**	**2b**	**2c**	**3a**
2-4	0	1	1	1	2	2	----
5	1	2	1	2	3	3	7
6	1	2	1	2	3	4	7
7	---	6	4	6	10	12	19
8-10	---	11	9	12	17	21	---

PSA 4.1 to 10 ng/ml

Gleason Score	Clinical T-Stage						
	1a	**1b**	**1c**	**2a**	**2b**	**2c**	**3a**
2-4	1	2	1	2	4	5	10
5	2	3	2	3	5	6	12
6	2	3	2	3	5	6	11
7	6	9	8	10	15	18	26
8-10	10	15	15	19	24	28	35

PSA 10.1 to 20 ng/ml

Gleason Score	Clinical T-Stage						
	1a	**1b**	**1c**	**2a**	**2b**	**2c**	**3a**
2-4	2	4	2	4	7	8	----
5	3	5	3	5	8	9	15
6	---	4	4	5	7	9	14
7	8	11	12	14	18	22	28
8-10	---	15	20	22	25	30	34

Appendix 5: Acute RTOG-EORTC Toxicity Scores

Genitourinary Score

0	1	2	3	4
No change	Frequency of urination, or nocturia twice pre-treatment 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., phenazopyridine).	Frequency with urgency and nocturia hourly or more frequently. Dysuria, pelvic pain or bladder spasm requiring regular frequent narcotics. Gross hematuria with or without passage of clot.	Hematuria requiring transfusion. Acute bladder obstruction not due to clot passage, ulceration or necrosis.

Gastrointestinal Score

0	1	2	3	4
No change	Increased frequency or change in quality of bowel habits not requiring medication. Rectal discomfort not requiring analgesics.	Diarrhea requiring parasympatolytic drugs. Mucous discharge not requiring sanitary pads. Rectal or abdominal pain requiring analgesics.	Diarrhea requiring parenteral support. Severe mucous or blood discharge requiring sanitary pads. Abdominal distention with distended bowl loops on plain X-ray.	Acute or sub-acute obstruction, fistula or perforation. GI bleeding requiring transfusion. Abdominal pain or tenesmus requiring tube decompression or bowel diversion.

Appendix 6: Late RTOG-EORTC Toxicity Scores

Genitourinary Score

0	1	2	3	4
No change	Slight epithelial atrophy, mild telangiectasia, microscopic hematuria	Moderate frequency, generalized telangiectasia, intermittent macroscopic hematuria	Severe frequency and dysuria, severe generalized telangiectasia, frequent hematuria, reduction in bladder capacity (<150cc)	Necrosis, contracted bladder (capacity <100cc), severe hemorrhagic cystitis

Gastrointestinal Score

0	1	2	3	4
No change	Mild diarrhea, mild cramping, bowel movement 5 times daily, slight rectal discharge or bleeding	Moderate diarrhea and colic, bowel movement more than 5 times daily, excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis, perforation, fistula

.

Appendix 7: EPIC and SF-12

Expanded Prostate Cancer Index Composite (EPIC)
and
Medical Outcomes Study Short Form (SF-12, version 2)

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

Today's Date (please enter date when survey completed): _____ _____ _____
Day Month Year

Patient Initials: _____ _____ ___
F M L

Date of Birth (optional): _____ _____ _____
Day Month Year

1. In general, would you say your health is:

Excellent..... 1 (Circle one number.)
Very Good.....2
Good.....3
Fair 4
Poor 5

2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(Circle 1, 2, or 3 on each line.)	**Yes, limited a lot**	**Yes, limited a little**	**No, not limited at all**
a. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.....	1	2	3
b. Climbing **several** flights of stairs.....	1	2	3

3. During the **PAST FOUR WEEKS**, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your **physical health**?

(Circle one or two on each line.)	**Yes**	**No**
a. **Accomplished less** than you would like.....	1	2
b. Were limited in the **kind** of work or other activities.....	1	2

4. During the **PAST FOUR WEEKS**, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any **emotional problems** (such as feeling depressed or anxious)?

(Circle one number on each line)	Yes	No
a. **Accomplished less** than you would like.....	1	2
b. Didn't do work or other activities as **carefully** as usual.....	1	2

5. During the **PAST FOUR WEEKS**, how much did pain interfere with your normal work (including both work outside the home and housework)? Circle one number.

Not at all.....1
A little bit.....2
Moderately.....3
Quite a bit.....4
Extremely.....5

6. These questions are about how you feel and how things have been with you during the **PAST FOUR WEEKS**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the PAST FOUR WEEKS...

(Circle one number on each line)	**All of the time**	**Most of the time**	**Some of the time**	**A little of the time**	**None of the time**
a. Have you felt calm and peaceful?	1	2	3	4	5
b. Did you have a lot of energy?	1	2	3	4	5
c. Have you felt downhearted and depressed?	1	2	3	4	5

7. During the **PAST FOUR WEEKS**, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)? Circle one number.

All of the time.....1
Most of the time.....2
Some of the time.....3
A little of the time.....4
None of the time.....5

URINARY FUNCTION

This section is about your urinary habits. Please consider **ONLY THE LAST 4 WEEKS**.
Circle one number only.

8. 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
About once a week 4
Rarely or never..... 5

9. Over the **past 4 weeks**, how often have you urinated blood?

More than once a day 1
About once a day..... 2
More than once a week..... 3
About once a week 4
Rarely or never..... 5

10. Over the **past 4 weeks**, how often have you had pain or burning with urination?

More than once a day 1
About once a day..... 2
More than once a week..... 3
About once a week 4
Rarely or never..... 5

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

No urinary control whatsoever 1
Frequent dribbling..... 2
Occasional dribbling 3
Total control..... 4

12. 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
3 or more pads per day 3

13. 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 Pro	**Very Small Problem**	**Small Problem**	**Moderate Problem**	**Big**
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 stream 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

14. Overall, how big a problem has your urinary function been for you during **the last 4 weeks**? Circle only one number.

No problem.....1
Very small problem.....2
Small problem.....3
Moderate problem.....4
Big problem.....5

URINARY SYMPTOMS

(Please circle one number on each line)	**Not at all**	**Less than one time in five**	**Less than half the time**	**About half the time**	**More than half the time**	**Almost always**
15. Incomplete emptying						
Over the past month, how often have you had the sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
16. Frequency						
Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5
17. Intermittency						
Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
18. Urgency						
Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
19. Weak Stream						
Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5
20. Straining						
Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
21. Nocturia	none	1x	2x	3x	4x	5x or more
Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5

BOWEL HABITS

The next section is about your bowel habits and abdominal pain. Please consider **ONLY THE LAST 4 WEEKS**. Circle only one number.

22. How often have you had rectal urgency (felt like I 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
    About once a week 4
    Rarely or never 5

23. How often have you had uncontrolled leakage of stool or feces?

    More than once a day 1
    About once a day 2
    More than once a week 3
    About once a week 4
    Rarely or never 5

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

    Never 1
    Rarely 2
    About half the time 3
    Usually 4
    Always 5

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

    Never 1
    Rarely 2
    About half the time 3
    Usually 4
    Always 5

26. How often have your bowel movements been painful during **the last 4 weeks**?

    Never 1
    Rarely 2
    About half the time 3
    Usually 4
    Always 5

27. How many bowel movements have you had on a typical day during **the last 4 weeks**?

    Two or less 1
    Three to four 2
    Five or more 3

28. How often have you had crampy pain in your abdomen, pelvis or rectum during **the last 4 weeks**?

    More than once a day 1
    About once a day 2
    More than once a week 3
    About once a week 4
    Rarely or never 5

29. 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
e. Bloody stools	0	1	2	3	4
f. Abdominal/ Pelvic/Rectal pain.....	0	1	2	3	4

30. 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
Moderate problem.....4
Big problem 5

SEXUAL FUNCTION

The next section is about your **current** sexual function and sexual satisfaction. Many of the questions are very personal, but they will help us understand the important issues that you face every day. Remember, THIS SURVEY INFORMATION IS COMPLETELY **CONFIDENTIAL**. Please answer honestly about **THE LAST 4 WEEKS ONLY**.

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

	Very Poor to 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

32. How would you describe the usual QUALITY of your erections 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
Firm enough for intercourse.....4

33. 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
I had an erection MORE THAN HALF the time I wanted one..... 4
I had an erection WHENEVER I wanted one..... 5

34. How often have you awakened in the morning or night with an erection during the **last 4 weeks**?

Never..... 1
Less than once a week..... 2
About once a week..... 3
Several times a week..... 4
Daily 5

35. During the **last 4 weeks**, how often did you have any sexual activity?

Not at all..... 1
Less than once a week..... 2
About once a week..... 3
Several times a week..... 4
Daily 5

36. 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
Several times a week..... 4
Daily 5

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

Very poor 1
Poor..... 2
Fair..... 3
Good 4
Very good 5

38. How big a problem **during the last 4 weeks**, 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. Your level of sexual desire.....	0	1	2	3	4
b. Your ability to have an erection.	0	1	2	3	4
c. Your ability to reach an orgasm.	0	1	2	3	4

39. 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
Moderate problem 4
Big problem..... 5

HORMONAL FUNCTION

The next section is about your hormonal function. Please consider **ONLY THE LAST 4 WEEKS**

40. 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
About once a week 4
Rarely or never..... 5

41. 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
About once a week 4
Rarely or never..... 5

42. 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
About once a week 4
Rarely or never..... 5

43. 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
About once a week 4
Rarely or never..... 5

44. 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
Lost less than 10 pounds 4
Lost 10 pounds or more..... 5

45. How big a problem **during the last 4 weeks**, 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.	Hot flashes	0	1	2	3	4
b.	Breast tenderness/enlargement	0	1	2	3	4
c.	Loss of body hair	0	1	2	3	4
d.	Feeling depressed	0	1	2	3	4
e.	Lack of energy	0	1	2	3	4
f.	Change in body weight	0	1	2	3	4

Overall Satisfaction

46. Overall, how satisfied are you with the treatment you received for your prostate cancer? Circle one number.

Extremely dissatisfied 1
Dissatisfied 2
Uncertain 3
Satisfied 4
Extremely satisfied 5

THANK YOU VERY MUCH!

Appendix 8: Details of Radiotherapy Planning

Radiation Treatment Planning

Patients will be instructed on bowel and bladder filling protocol prior to first planning appointment, and will follow the bowel and bladder protocol for the planning CT scan and during treatment.

All patients will undergo planning CT scan of the pelvis, supine, with the pelvis immobilized (recommended) and with an empty rectum and comfortably full bladder.

Patients with a maximum post-prostate rectal internal diameter of > 2 cm will be rescanned after evacuating their bowels.

The dome of bladder should extend to at least the superior aspect of the femoral heads.

Slice thickness should be 3 mm or less through the prostate. Total scanned volume should be at least 2 cm superior to the dome of bladder superiorly and at least 2 cm inferior to the inferior aspect of the ischial tuberocities.

Target and Organ at Risk Contouring

The CTV is the prostate gland, and will be contoured on each CT image.

Seminal Vesicles (SV): Patients with an estimated risk of seminal vesicle involvement of > 15% based on Partin's nomogram (Appendix 4) will have the proximal seminal vesicles included in the CTV. For patients with more than 15% risk of SV involvement, the proximal seminal vesicles will be defined as the portion from its origin with the prostate and extending 1 cm superiorly.

Bladder and Rectal Wall: The inner and outer bladder wall and inner and outer rectal wall will be contoured for a distance of 18 mm beyond the most inferior and superior contoured prostate slices or seminal vesicles when it is included in the CTV.

Femoral heads: Both femoral head and necks will be contoured.

The Planning Target Volume (PTV) will be expanded beyond the prostate and if applicable the contoured portion of the seminal vesicles. This will be 7 mm posteriorly (toward the rectum) and 10 mm in all other planes.

Planning Dose constraints and prescribed dose

A RT quality assurance committee will be established consisting of a Radiation Oncologist, Radiation Physicist and a Radiation Therapy planner. This committee will be available for consultation should questions arise concerning the treatment protocol. All centres will be accredited for activation by the committee after providing paper or electronic copy of plans for 5 recent cases demonstrating:

- CTV and PTV contoured according to protocol.
- Organs at risk (bladder and rectal walls and femoral heads) contoured according to protocol
- DVH for bladder and rectal wall, PTV and CTV that meet dose constraints for the hypofractionated treatment arm.

- A statement that patients will be treated with an approved daily image guidance technique

Treatment Technique:

IMRT will be the technique used for patients accrued from centres where all study patients can be treated with IMRT. In those centres were IMRT is not routinely available, then IMRT may be used when required to meet dose constraints. In these situations care must be taken to ensure that the CTV and PTV coverage are not compromised to meet dose constraint guidelines. If IMRT is not available then dynamic conformal arc therapy, or 6 or 7-field conformal therapy is acceptable, provided that the dose-constraints outlined below can be met. It is not anticipated that a 4-field conformal technique will be adequate to meet the required normal-tissue dose constraints.

Hypofractionated Treatment arm:

CTV	D99 ≥ 60Gy
PTV	D99 ≥ 57Gy (-5%) The volume of PTV exceeding 63Gy should not exceed 1 cubic centimetre (+5%)
Contoured rectal wall:	50% to receive less than 37Gy 70% to receive less than 46Gy
Contoured bladder wall:	50% to receive less than 37Gy 70% to receive less than 46Gy
Femoral head and neck:	5% to receive less than 43Gy
Dose prescription:	60Gy in 20 (3Gy) fractions over 4 weeks prescribed to CTV minimum

Conventional Treatment arm:

CTV	D99 ≥ 78Gy
PTV	D99 ≥ 74.1Gy (-5%), The volume of PTV exceeding 81.9 Gy should not exceed 1 cubic centimetre (+5%)
Contoured rectal wall:	50% to receive less than 53Gy 70% to receive less than 71Gy
Contoured bladder wall:	50% to receive less than 53Gy 70% to receive less than 71Gy
Femoral head and neck:	5% to receive less than 53Gy

Dose prescription: 78Gy in 39 (2Gy) fractions over 7.8 weeks prescribed to CTV minimum

Treatment Delivery:
Daily image-guidance will be used.

Allowable Techniques:
Implanted fiducial markers
Ultrasound
Cone-beam CT
Tomo-CT

IMRT Quality Assurance

All IMRT plans will undergo quality assurance evaluation with ion chamber measurements or an equivalent method of dose verification to verify the absolute dose for each IMRT field and film dosimetry to measure the relative dose for each IMRT field, as would be required for standard clinical practice. Independent MU calculation may be substituted for ion chamber dosimetry when available.

Appendix 9: Assessment and Follow-up Schedule

Assessment	Prior to randomization	Baseline	Weeks 1-8 from start of RT	Week 10 post start of RT	Week 14 post start of RT	6 months post randomization	Every 6 months thereafter[6]	24 months post randomization	48 months post randomization
Pathology with Gleason score obtained no later than 6 months prior to entry	X								
Physical exam including DRE	X				X[1]	X	X		
PSA	X[2]					X	X		
Hb, WBC, Platelets, BUN, Creatinine		X							
RTOG Toxicity Assessment		X	X[3]	X[4]	X	X	X		
Quality of Life[5]		X						X	X

[1] Rectal exam not mandatory for this visit

[2] PSA done no more than 12 weeks prior to entry, or 12 weeks prior to start of hormonal therapy (if patient has started on hormonal therapy prior to referral, maximum permitted is 12 weeks of hormonal therapy prior to entry)

[3] Weekly during treatment; the 6000cGy/20 group will have a telephone assessment at weeks 6 and 8

[4] Telephone assessment for both the 6000cGy/20 group and 7800cGy/39 group

[5] Self-administered questionnaire (EPIC and SF-12)

[6] Patients followed for more than 9 years may be seen on an annual basis

Appendix 10: Adverse Event Reporting

Adverse Event Classification Definitions

An **Adverse Event (AE)** is any untoward medical occurrence in a patient who is administered a drug or biologic (medicinal product) or for the purposes of this trial, radiation treatment; the event does not necessarily have a causal relationship with that treatment or usage. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study treatment, whether or not related to that treatment. Each AE is to be classified by the Investigator as serious or non-serious.

A **Serious Adverse Event (SAE)** is any adverse event associated with radiation therapy that:

- results in death,
- is life-threatening (i.e., immediate risk of death),
- requires inpatient hospitalization or prolongs an existing hospitalization,
- results in persistent or significant disability / incapacity; or
- is a congenital anomaly / birth defect.

Important medical events, which are not immediately life threatening or requiring hospitalization, but may otherwise jeopardize the patient or may require intervention to prevent other outcomes specified in the above definition of SAE may also usually be considered serious.

An AE is **Unexpected** when the nature or severity of the AE is not consistent with current information on radiation treatment. An AE is considered to be associated with the use of radiation treatment if the attribution is deemed to be "Possible", "Probable" or "Very Likely".

Attribution Definitions

Not Related: An AE which is not related to the use of radiation treatment.

Doubtful: An AE for which an alternative explanation is more likely (e.g., concomitant medications, concomitant diseases), and/or the relation with time suggests that a causal relationship is unlikely.

Possible: An AE which might be due to the use of the radiation treatment. An alternative explanation (e.g., concomitant medications, concomitant diseases) is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be excluded.

Probable: An AE which might be due to the use of the radiation treatment. The relationship in time is suggestive (e.g., confirmed by a de-challenge). An alternative explanation is less likely (e.g., concomitant medications, concomitant diseases).

Very Likely: An AE, which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation (e.g., concomitant medications, concomitant diseases). The relationship in time is very suggestive (e.g., it is confirmed by a de-challenge and a re-challenge).

Adverse Event Reporting Criteria

All radiation therapy-related genitourinary or gastrointestinal AEs will be graded according to the RTOG-EORTC toxicity scores (Appendices 5 and 6). All other radiation therapy-related AEs will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0, March 31, 2003. For each event, the highest severity grade attained since the last assessment period will be reported. If a toxicity score does not exist, the Investigator should assess the event as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening or disabling), or Grade 5 (death), to describe the maximum intensity of the AE.

However, because the study cohort will likely experience considerable medical and surgical AEs during the natural course of their malignancy and cancer treatment, only AEs which meet any one of the following criteria will be recorded on the Adverse Event Form:

1. Classified as Grade 3, 4 or 5 severity resulting from radiation treatment; or
2. Meet the SAE criteria.

Do not report the following as adverse events:

1. AEs resulting from chemotherapy, hormone therapy, or any other systemic cancer therapy;
2. AEs which occur after prostate cancer progression or development of a second primary cancer.

Worsening of metastatic prostate cancer is expected and therefore will not be considered an SAE for the purpose of this study.

Deaths due to metastatic prostate cancer are Outcome Events and will not be reported as AEs or SAEs. They will be monitored by the DSMB and will not require reporting to Health Canada.

Adverse Event Reporting Period

The AE reporting period for this trial begins upon randomization and ends 3 months post-randomization, or at death if it occurs earlier. In addition, any known untoward event of grade 3 or greater severity that occurs subsequent to the AE reporting period that the Investigator assesses as possibly, probably, or very likely related to the protocol radiation treatment should also be reported as an SAE.

Serious Adverse Event Reporting

SAEs considered to be serious, unexpected, and related to protocol radiation treatment must be reported by the local Investigator to OCOG within 24-48 hours from the time when the clinical centre personnel becomes aware of the event, using the OCOG SAE Form accompanied by relevant source documentation. Follow-up reports must be submitted to OCOG when new information becomes available and not later than 10 days after the local study personnel becomes aware of the event. Local Clinical Investigators will be informed of all of these serious adverse events and instructed to notify their local Institutional Review Boards/Ethics Committees of the same.

For each of these SAEs, the CMC will inform the independent external Data Safety Monitoring Board. Patients withdrawn from the study due to an AE will be followed until the AE has resolved. In the case of an SAE, the patient will be followed until clinical recovery or until progression has been stabilized or judged to be chronic. Follow-up of SAEs will be documented on the SAE form submitted to the CMC.

The local Investigator will be responsible for reporting SAEs occurring at the local site to their REB, as per local REB requirements.