

A Phase II Randomized Pilot Study of Low Dose Rate compared to High Dose Rate Prostate Brachytherapy for Favorable Risk and Low Tier Intermediate Risk Prostate Cancer

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Introduction

Prostate cancer is the most common non cutaneous malignancy in Canadian men and the third leading cause of cancer death; approximately 23,600 cases were diagnosed in 2014 and due to the wide acceptance of PSA screening, the majority are non-metastatic. Definitive treatment, using either surgery or radiation, is associated with satisfactory disease-free rates of 80-95% at 5 years and 70-90% at 10 years for favorable and intermediate-risk disease. Unfortunately, quality of life may suffer due to short and/or long-term surgical or radiation side effects. Active surveillance is commonly offered in Canada for favorable risk disease, but about one-third of newly diagnosed men (about 8,500 annually) have intermediate-risk disease for which active surveillance is generally not recommended. Since treatment is necessary to avoid progression to metastases and eventual death from prostate cancer, an improved side effect profile would be welcome(1).

Background and rationale

Low-dose rate brachytherapy (LDR) using Iodine-125 seeds is a highly effective option for favourable and low-tier intermediate-risk prostate cancer (2-4). Mature data from Canadian institutions report PSA-progression-free survival (PFS) in the range of 90-95% at 5-10 years (5). High-dose rate brachytherapy (HDR) used as a single modality (monotherapy) is accepted in both North America and Europe as an alternative to LDR (6-8), but the mature data for HDR brachytherapy involves multi-fraction regimens of 4 or more fractions. Such HDR fractionation schemes achieved very comparable PFS at 5 years > 93% (8-10). Recently, however, advances in imaging and software have resulted in more efficient HDR delivery with reduction in the number of fractions to two (often given in separate implants) or even in one single large fraction. Early results with follow-up of only 2-4 years are promising (5,6,11,12) but no intermediate or long-term data is yet available. The larger fractions dose is calculated to be radiobiologically equivalent to the multi-fraction regimens and the interest in pursuing this form of brachytherapy relates to an improved side effect profile, specifically lower rates of acute and late urinary toxicity compared to LDR(13).

HDR has several potential advantages over LDR:

- Dose optimization by manipulation of dwell times and dwell positions of the “stepping source” can correct for slight deviations in needle placement
- Potential to reliably push extra prostatic dose where it is needed
- Critical organ doses (rectum, urethra) can be tightly controlled
- Fewer radioprotection issues for patients and staff
- The low α/β ratio for prostate cancer (1.2-1.5) imparts a radiobiological advantage to large fraction sizes(14-16).
- HDR is cost-effective since a single radioactive source delivers treatment to a large number of patients(7)

Potential disadvantages of HDR compared to LDR:

- Efficacy equivalent to that of LDR brachytherapy has not been established in controlled clinical trials

- Efficacy data is shorter term for HDR, with less than 5 years of follow up for fractionation schemes of two or a single large fraction, compared to LDR where 10- year data are available
- Experience with HDR in BC is much less than that with LDR and is as yet still only available in one of the provincial cancer centers.

The major advance that has led to the improvement in HDR delivery is the introduction of intra-operative Ultrasound-based HDR treatment planning (17,18) which allows needle placement, treatment planning and treatment delivery in a single 2-hour procedure under anaesthesia.

The reasons to consider HDR as an alternative to LDR brachytherapy

1. *Reliability of dose delivery:* Although highly effective, there are some drawbacks to LDR seed implants. The procedure is highly operator-dependent and, even in the most experienced hands, there can be discrepancies between planned and actual seed positions. Although uncommon in experienced hands, areas with too much or too little dose cannot be corrected after the implant is completed.
2. *Acute Toxicity:* With an LDR implant, the radiation dose is delivered over 6 months (half-life of Iodine-125 is 60 days; 87.5% of the dose is delivered in 3 half lives) compared to 10-15 minutes for HDR. For this reason LDR is associated with a more prolonged recovery period, especially concerning acute urinary toxicity compared to HDR (13,19)(7,10,17). The median time to return to baseline urinary function after LDR brachytherapy is 6 months and is achieved by 80% in 12 months. In the BCCA experience, acute urinary RTOG grade 3 toxicity was 16%(20) (23). A recent prospective non randomized comparison of QOL after HDR vs. LDR brachytherapy boost (combined with 4.5 weeks of external radiotherapy) similarly showed a return to baseline International Prostate Symptom Score (IPSS) at 6 months with LDR compared to only 12 weeks with HDR(22). No randomized trial has yet reported on HDR and LDR brachytherapy side effects and Quality of Life.
3. *Late Toxicity:* Late grade 3 toxicity is reported between 0 and 3% for HDR brachytherapy compared to LDR where long-term grade 3 urinary toxicity was still 10% at a median follow up of 55 months (21).

LDR prostate brachytherapy is still the most common approach; over 5000 cases have been performed in British Columbia since 1998. Although HDR brachytherapy is widely accepted when used as a boost in combination with EBRT, and is available as such as a standard treatment option at the Center for the Southern Interior in BC, HDR has yet to be employed as monotherapy in this province. In order to introduce HDR monotherapy, we propose this randomized pilot study with a QOL endpoint. Based on the findings of the non -randomized prospective study completed at CCSI reporting decreased urinary and bowel toxicity for men treated with external beam radiotherapy and an HDR brachytherapy boost compared to an LDR boost(22), a randomized phase III trial is under way (H13-02139). Since in that study the EBRT component was identical for both arms, the improvement seen should translate to the monotherapy scenario.

Hypothesis and Objectives

HDR monotherapy for favorable and low tier intermediate risk prostate cancer will result in improved Quality of Life as determined using the Expanded Prostate Cancer Index Composite (EPIC) and QOL scores in the urinary domain, and faster IPSS (International Prostate Symptom Score) resolution compared to Iodine 125 permanent seed implant. The standard arm of the trial will be LDR brachytherapy and will be compared to the experimental arm, HDR monotherapy, in a randomized Phase II clinical Pilot Study. If feasibility of patient acceptance is demonstrated in the initial pilot, with accrual of 60 patients within 18-24 months, a larger-scale phase III randomized trial will continue for a total of 200 patients.

Primary objective:

To evaluate the difference in QOL in the urinary domain between LDR and HDR brachytherapy. The urinary domain of the EPIC prostate cancer specific QOL questionnaire will be assessed at baseline, 1, 3, 6, 12, 24 and 36 months after the procedure. The EPIC has been shown to be the most robust instrument for assessing prostate cancer-specific quality of life (33-35). For each domain, a function and bother score can be calculated (0-100) with higher scores indicating better function and less bother.

Secondary objectives:

- The EPIC score in the bowel and sexual domains will be evaluated at baseline, 1, 3, 6, 12, 24 and 36 months.
- The IPS Score will be assessed at baseline, 1, 3, 6, 12, 24 and 36 months. The IPS Score, designed to assess lower urinary tract symptoms in men, is widely used to assess urinary function after prostate cancer treatment. The time to return to baseline +/- 3 points will be determined.
- Acute and long-term toxicity will be graded using the Common Terminology Criteria for Adverse Events (CTCAE V4) at each follow up time point
- TRUS- MRI fusion will be developed within our planning software to facilitate treatment planning
- Two standard predictors of outcome will be evaluated as secondary objectives to assess treatment efficacy;
 - PSA nadir predicts for long-term outcome following radiotherapy (23-28) and will be recorded every 6 months to 5 years and then annually to 10 years
 - Prostate re-biopsy will be performed at 36 months after radiotherapy (29-31) to assess the local efficacy of radiation.

For those patients consenting to targeted biopsies under anaesthesia at the start of their brachytherapy procedure (separate optional consent)

- MRI-TRUS fusion accuracy will be verified by targeted biopsies under anaesthesia at the beginning of each brachytherapy procedure (LDR or 1st HDR).
- Biopsy material will be sent for genetic testing to determine Cell cycle Progression scores for both arms of the trial to ultimately correlate with outcome.

This proposal represents the first instance of collaboration between the BC Cancer Agency and Myriad Genetics where evaluation of the CCP score will be performed (Prolaris™). With further experience and follow up the CCP score may become increasingly important in helping to determine the appropriate aggressiveness of treatment. A recent presentation at the American Urologic

Association Meeting (2015) reported that the use of the Prolaris™ test for 1206 men with localized prostate cancer resulted in alteration of treatment in 48%, ¾ being for a less aggressive approach and ¼ for more aggressive. Indiscriminate over-treatment of indolent disease is not acceptable but a blanket conservative approach to prostate cancer known to be of “moderate” aggressiveness is also not without severe adverse consequences. In addition to reducing the toxicity of treatment, more reliable means of selecting patients for aggressive treatment are urgently needed. CCP scores may allow appropriate triage of intermediate risk patients to focal therapy, brachytherapy monotherapy, combined EBRT + brachytherapy, or combination with systemic agents.

Patient eligibility:

Favorable risk and low-tier intermediate-risk prostate cancer with estimated life expectancy of at least 10 years.

- Clinical stage T1c-T2b, PSA < 20, Gleason < 8
- ECOG 0-1
- Low tier intermediate-risk prostate cancer is defined by;
 - a single NCCN intermediate risk factor (either Gleason 7(3+4) and PSA < 10 ng/ml OR Gleason 6 and PSA 10-20 ng/ml)
- Extensive favorable-risk disease is defined as:
 - clinical stage T1c-T2a
 - PSA < 10
 - Gleason 6
 - ≥ 50% of biopsy cores containing cancer
 - PSA density > 0.2 ng/cc
- Selected intermediate risk patients not defined above
 - - T1c/T2a
 - - PSA < 10
 - -Gleason 4+3
 - -< 33% of cores involved
 - -Max tumour length in any core 10 mm
- No androgen deprivation therapy (ADT)
- Prostate volume by TRUS ≤ 60 cc.
- Not eligible for, or accepting of, active surveillance according to NCCN guidelines.
- Signed study specific informed consent.

Exclusion criteria

- Prior radical surgery for carcinoma of the prostate,
- Prior pelvic radiation
- Prior chemotherapy for prostate cancer,
- Prior TURP or cryosurgery of the prostate
- Claustrophobic or unable to undergo MRI

Investigations:

All of the required investigations are standard of care for a patient undergoing prostate brachytherapy.

- CBC, electrolytes, creatinine, glucose, INR
- PSA/testosterone
- Pathology review of diagnostic biopsy
- ECG
- Staging bone scan and CT abdomen/pelvis
- Multiparametric MRI of the prostate. (This imaging modality is standard of care in staging of both intermediate and favorable risk prostate cancer in many health jurisdictions. Recently it has become more readily available in BC and is being incorporated into the treatment paradigm. In this study it will be used for demonstration of the dominant intraprostatic lesion for both dose prescription and biopsy guidance)

Additional investigations:

- 2 biopsy cores taken from the region of interest under anesthesia using a transperineal template-guided approach and a Bard Magnum Biopsy Gun and 18 gauge biopsy needles (same gauge as implant needles just prior to brachytherapy to confirm what was interpreted on mpMRI as the location of the dominant site of cancer (separate consent for this biopsy)
- Follow up biopsy at 36 months in Diagnostic Radiology under TRUS guidance to evaluate pathologic eradication of tumour

Brachytherapy

Arm 1: Low-dose rate brachytherapy using Iodine-125 seed implant

LDR brachytherapy requires a preplanning Transrectal Ultrasound (TRUS) 3-6 weeks before the procedure to plan the number and location of the required seeds and to allow the order and delivery of these seeds to the Cancer Centre. The actual brachytherapy implant will be performed within 8 weeks of randomization.. It is performed under general or spinal anesthesia as an outpatient procedure under TRUS guidance and takes about 1 ½ hours. The patient is discharged home when they have recovered from anesthesia and are able to void. The prescription dose for Iodine-125 is 144 Gy delivered to the prostate plus a margin (5mm laterally and caudally, 0 mm cranially and posteriorly, and 3 mm anteriorly. Four weeks later the patient returns to the Cancer Centre for Quality Assurance (QA) which involves the combination of a CT and an MRI (single sequence; non multiparametric) of the prostate region. A dose-volume histogram (DVH) will be generated and the following values shall be reported:

- prostate V100 (percentage of the prostate volume receiving at least 100% of the prescription dose)
- D90 (isodose enclosing 90% of the prostate volume)
- V150 (percentage of the prostate volume receiving at least 150% of the prescription dose)
- urethra D5 (dose to maximally irradiated 5% of urethra)
- rectum RV100 (volume in cc of rectal wall receiving 100% of prescription dose.

Evaluation criteria: Prostate D90> 100% but less than 130% of the prescription dose, prostate V100> 90%.

Arm 2: High dose rate brachytherapy

HDR brachytherapy has been available at the Center for the Southern Interior since June 2011 with over 200 procedures performed and an experienced team of 5 Medical Physicists and 2 Radiation Oncologists. It is a Provincial Standard of Care for use as a boost combined with external beam radiotherapy for more advanced prostate cancers.

HDR brachytherapy will be performed within 8 weeks of randomization, using US-based planning systems such as available from Varian. The procedure is performed as an out patient procedure under either spinal or general anesthesia and takes 1 ½ to 2 hours. Similar to LDR brachytherapy, the patient is set-up in dorsal lithotomy and TRUS images are acquired, followed by needle insertion. When all needles are appropriately placed and locked in the template, repeat TRUS imaging is performed with the needles in place for needle track identification and treatment planning. When the plan is complete and approved, transfer tubes are connected to each needle and the treatment is delivered using a stepping source of high activity Iridium 192 attached to a cable such that it steps through each needle in turn at 3 mm increments delivering the required dose at that site. Treatment takes 15-20 minutes depending on the exact strength of the source on the treatment day. The needles are then removed and the patient awakened and transferred to the recovery suite for discharge the same day after recovered from anesthesia and able to void.

The dose prescription is 27 Gy in 2 fractions, with one fraction per implant, 1-2 weeks apart. The following dosimetry parameters will be met: V100 > 95% (> 95% of prostate volume receives prescription dose)

V125: 55-65% (55-63% of prostate volume receives 125% of prescription)

V200 < 8%

UV115%: 0 (urethral max dose < 115%)

RV1cc; 7.5 Gy (1 cc of rectal wall receives < 7.5 Gy per fraction)

D90_{DIL}: 125% of prescription (for those patients where DIL visible)

Evaluation During and After Protocol Treatment:

At baseline, 1, 3, 6, and 12 months and then yearly up to 5 years, patients will be evaluated with IPSS and EPIC questionnaire. PSA measurements will be done every 6 months during the first 3 years then annually.

The mpMRI demonstrating intra prostatic tumour will be electronically registered (fused) with the TRUS images in order to transfer the target for treatment planning. For patients consenting to biopsy, 2 biopsy cores will be obtained under anesthesia using a template-guided transperineal approach, and targeting the demonstrated lesion as seen on mpMRI. Biopsies will be formalin fixed and processed in the pathology department at Kelowna General Hospital for pathologic interpretation to confirm the presence of tumor, and stored for subsequent oncotype testing. 7 unstained slides with 5u sections will be sent to Myriad Genetics (Seattle) for micro-dissection and evaluation.

Prostate re-biopsy will be performed at 36 months and assessed for the presence or absence of residual tumour. Cores will be evaluated by Dr. Terry Bainbridge, the BCCA reference pathologist in Kelowna.

Statistical analysis and justification of sample size

This initial randomized pilot study is to accrue 60 patients, to assess feasibility in terms of acceptance of the protocol. Patients will need to be willing to accept randomization to treatment that will require 2 implant procedures and thus 2 anesthetics. This was not problematic in our initial HDR experience in Kelowna with protocols H10-01987 and H12-00557. We expect to achieve this in 18-24 months; if not we will conclude that a 2-implant option is not acceptable and will not embark on an expanded protocol to include a total of 200 patients.

A study of 60 patients was sufficient to show a significant difference in EPIC urinary and bowel scores in the non-randomized prospective evaluation of HDR and LDR boost treatment. Thus, we estimate that HDR brachytherapy is associated with half the acute toxicity seen with LDR. For the 60 men receiving an HDR or LDR boost, on average, bowel domain scores decreased by 20.1 points for LDR and 10.4 points for HDR. Four months after treatment, LDR patients still had significantly worse urinary health compared to HDR ($p = 0.012$). Urinary domain scores for LDR were on average 12.6 points lower compared to the pre-treatment assessment, while for HDR patients the mean difference was only 1.4 points. A two sample T-test will be used to compare mean differences at each time point of assessment. For the expanded protocol a minimum of 172 patients would be needed to achieve 90% power with a difference between the means of 50%.

The treatment effect with respect to all endpoints will be analyzed by the log rank test. All eligible and evaluable patients will be included in the intent-to-treat analysis. The cumulative incidence method will be used to estimate the five-year and 10-year rates of biochemical and clinical failure because of the competing risk of dying of other causes.

Proof of reduced toxicity and improved QOL will help to establish HDR monotherapy for this group of patients, and will save the health-care system the costs of non-reusable, permanently implanted seeds for up to 300 patients per year (\$750,000 for the province of BC).

We do not expect to see a difference in PSA nadirs or prostate re-biopsy results and cannot mount an equivalence trial in this regard at a single center or even in a single province. Nonetheless, our data will offer additional support to the presumed equivalence already evident in the literature.

| Assessments | Pre-treatment | | | Follow up (months) | |
|------------------|-----------------|-----------------|-------|----------------------|----------|
| | Within 6 months | Within 3 months | Day 0 | 1-3-6-12-18-24-30-36 | Annually |
| Biopsy | X | | | X (36 months) | |
| History/physical | | X | | X | X |

| | | | | | |
|------------------------|--|---|---|---|---|
| PSA/testosterone | | X | | X | X |
| CT/Bone scan/ mpMRI | | X | | | |
| IPSS/IIEF | | | X | X | X |
| EPIC | | | X | X | X |

Budget

Permanent seed implant is the standard of care in BC for this group of patients and all costs are covered.

HDR brachytherapy is available as a standard of care when used as a boost combined with EBRT and performed as a single procedure with a single fraction. All costs are covered and are considered to be roughly equivalent to the cost of an LDR implant. Since HDR monotherapy in this protocol is delivered in 2 fractions in 2 separate implants, the second of these procedures represents an additional cost. The approximate cost per 2 hour OR procedure is \$2000.

2 circulating nurses

1 recovery room nurse (2 nurses/2 patients)

1 anesthetist

2 radiation therapists

Total x 30 = \$60,000

The cost of this additional procedure to the health care system is offset by the saving from not having to purchase single-use radioactive seeds. (average number of seeds per implant: 100; cost per seed \$22 = \$2200 per patient. Total \$66,000 for 30 patients.

Pathology processing and interpretation \$180 per patient = \$10,800.

Cell Cycle Progression Gene profile using Prolaris test from Myriad Genetics: \$1200 USD per patient.

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