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Prostate radiotherapy

# Prostate stereotactic ablative body radiotherapy using a standard linear accelerator: Toxicity, biochemical, and pathological outcomes

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ABSTRACT

*Background and purpose:* Biological dose escalation through stereotactic ablative radiotherapy (SABR) holds promise of improved patient convenience, system capacity and tumor control with decreased cost and side effects. The objectives are to report the toxicities, biochemical and pathologic outcomes of this prospective study.

*Materials and methods:* A phase I/II study was performed where low risk localized prostate cancer received SABR 35 Gy in 5 fractions, once weekly on standard linear accelerators. Common Terminology Criteria for Adverse Events v3.0 and Radiation Therapy Oncology Group late morbidity scores were used to assess acute and late toxicities, respectively. Biochemical control (BC) was defined by the Phoenix definition.

*Results:* As of May 2012, 84 patients have completed treatment with a median follow-up of 55 months (range 13–68 months). Median age was 67 years and median PSA was 5.3 ng/ml. The following toxicities were observed: acute grade 3+: 0% gastrointestinal (GI), 1% genitourinary (GU), 0% fatigue; late grade 3+: 1% GI, 1% GU. Ninety-six percent were biopsy negative post-treatment. The 5-year BC was 98%.

*Conclusions:* This novel technique employing standard linear accelerators to deliver an extreme hypofractionated schedule of radiotherapy is feasible, well tolerated and shows excellent pathologic and biochemical control.



Among North American men, prostate cancer is the most common non-cutaneous malignancy. In 2011, it is estimated that 265,000 North American men will be diagnosed with prostate cancer; [1,2] the global incidence is estimated to be over 900,000 men [3]. Given recommended lowering of PSA thresholds for biopsy, the ageing population, improved sensitivity for biopsy and increased prevalence of prostate cancer screening, it is estimated that the incidence of prostate cancer in North America could increase to over 600,000 by the year 2021 [4].

Surgery, external beam radiotherapy (EBRT), brachytherapy and/or combinations thereof are commonly used in the treatment of localized prostate cancer. According to CAPSURE and registry data from British Columbia, Canada, 12–23% of patients are treated with EBRT [5,6]. Several randomized studies of EBRT support the concept that higher biological doses of radiation therapy (RT) improve biochemical disease-free survival (bDFS), distant-metastatic free survival and overall survival (OS) in localized prostate cancer [7,8]. These studies were conducted using conventional simulation or 3D conformal RT.

Intensity modulated RT (IMRT) allows the delivery of more complex treatment volumes and has been associated with lower gastrointestinal side effects when doses above 70 Gy (in 1.8–2 Gy per day fractions) were delivered [9]. SABR and stereotactic body radiotherapy (SBRT) are often used synonymously. SBRT is defined as:

> "The precise delivery of highly conformal, image-guided, hypofractionated (≥5 Gy/fraction) external beam radiotherapy delivered in a single or few fraction(s) to an extra-cranial body target, with doses at least biologically equivalent to those doses considered radical when given over a protracted conventionally (1.8–3.0 Gy/fraction) fractionated course" [10].

The more accurate treatment delivery systems allow tighter margins on the clinical target volume (CTV) which allows more sparing of normal tissues. Lastly, there is accumulating evidence that prostate cancer is preferentially killed using higher doses

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per day of radiation therapy supporting the notion of fewer but higher dose per day treatments of prostate cancer may allow further biologic dose escalation without incremental toxicities [11].

Several groups have previously published their prospective SABR experience of prostate cancer, [12–16] including our group [17]. However, to our knowledge there is a paucity of outcome data from patients with more than 5 years of follow-up and none of the previous studies reported routine post-treatment biopsy data. Of note, many of these reported outcomes were on patients who had SABR delivered using specialized treatment units (such as CyberKnife or Tomotherapy) whereas our experience is based entirely on standard linear accelerators with electronic portal imaging. Herein, we update our prospective phase 2 experience of SABR for low-risk localized prostate cancer including toxicity, biochemical, and pathological outcomes.

## Materials and methods

This study was approved by Sunnybrook Health Sciences Centre Research Ethics Board (REB 371-2006) and was registered on ClinicalTrials.gov (NCT01578902). Informed written consent was obtained from all patients participating in the study.

### *Patient selection*

Inclusion criteria were men over 18 years of age with histologically confirmed diagnosis of adenocarcinoma of the prostate. The histology slides were all reviewed by an Uropathologist. Only patients with clinical stage T1-T2b (TNM 2002) [18] Gleason Sum $\leqslant$6 and PSA $\leqslant$10 ng/ml were eligible. Neoadjuvant androgen deprivation therapy (ADT) was allowed for cytoreduction, however prehormonal PSA had to be performed within 2 months prior to the start of ADT. If ADT had been started, it was continued for a minimum of 3 months before radiation therapy planning in order to separate out the impact of RT and ADT on the quality of life (collected but to be reported separately).

Patients were excluded if they had prior pelvic radiation therapy, a bleeding diathesis which precluded safe gold seed insertion, the presence of hip prosthesis or pelvic girth >40 cm. Lastly, prostate size >90cm$^3$ on imaging or severe lower urinary tract symptoms (International Prostate Symptom Score (IPSS) [19] >19) also made patients ineligible.

### *Treatment planning and delivery*

All patients were planned to receive 35 Gy in 5 weekly fractions over 29 days, with Day 0 being 1st day of radiation treatment and Day 28 being the last day. The weekly treatment was designed to allow maximal normal tissue repair without allowing for tumor repopulation, concepts subsequently reported by other groups [14,20]. The planning procedure has been described previously [17]. In short, all patients had ultrasound guided insertion of 3 fiducial gold seeds transperineally followed by a planning CT scan. The planning and all treatments were performed in the supine position with a comfortably full bladder and empty rectum. This was achieved by asking patients to empty their bowels and bladder 1 h before simulation and treatment and drink 250–500 cc of water. A custom vacuum lock bag was used for pelvic immobilization (VacLock, MED-TEC. Inc., Orange City, IA) for simulation and treatment.

The clinical target volume (CTV) was the prostate only; seminal vesicles were not part of CTV. No patients had a pelvic MRI or endorectal balloon [12]. The rectum was contoured as a single solid organ from the bottom of the ischium to the sigmoid flexure (typically 11 cm). The bladder and penile bulb were also contoured as single solid organs. The planning target volume (PTV) was the CTV plus a uniform 4 mm margin to account for intrafractional prostate motion. This margin was based on our previous work where patients were administered a mild hypofractionated IMRT boost using the same daily image guidance protocol as was used in this protocol [21]. Planning objectives stipulated that the volume of CTV receiving 35 Gy (CTV V35 Gy) was to receive >99% and PTV V33.25 Gy >99%. The maximal dose (Dmax) was $\leqslant$105%. The normal tissue DVH constraints were rectal V28 $\leqslant$ 40%, rectal V32 $\leqslant$ 33%, bladder V32 $\leqslant$ 40%, and penile bulb V20 $\leqslant$ 90%. Pinnacle 7.6 h-8.0 d (Philips Medical Systems, Cleveland, OH) inverse planning software was used to generate an optimized IMRT plan.

Patients were treated on standard linear accelerators (Siemens Primus, Concord, CA; Elekta Synergy, Stockholm, Sweden) with multi-leaf collimators capable of delivering IMRT plans using a "step and shoot" technique. Six MV photons were used in all plans. 10 MV is not available on many of our machines and therefore was not used; 18 MV photons were not used to reduce neutron dose [22].

Prior to each radiation treatment, patients were initially setup based on skin tattoos and tri-planar lasers. The prostate position was then calculated by capturing orthogonal electronic portal imaging and if necessary, any table shifts applied before treatment. This image guidance technique allowed the therapists to adjust for any deviations that may have been introduced due to daily changes in bowel/bladder filling or slight variations in patient positioning the treatment was setup using orthogonal megavoltage electronic portal images of the fiducial markers. As part of quality assurance, starting from the 23rd patient, another set of orthogonal portal images were taken after each treatment delivery, to quantify the amount of intrafractional movement (imaging doses were incorporated into the plan) [23]. Steroids, [12] laxatives [24] or alpha antagonists [12] were not used prophylactically.

### *Study endpoints and follow-up*

Time zero was defined as commencement of radiation therapy. The co-primary endpoints were acute genitourinary (GU), gastrointestinal (GI) toxicities and fatigue (defined as toxicities before 6 months of follow-up) and measured using the Common Terminology Criteria for Adverse Events Version 3 (CTCAEv3) [25]. Acute and late GU and GI toxicities were recorded at baseline, weekly during treatment, and at 3 months. At 6 months and every 6 months until 5 years toxicities were scored using the Radiation Therapy Oncology Group (RTOG) [26] late toxicity scales for GI and GU. The worst new GI and GU toxicity scores were reported for each patient as well as the prevalence at last follow-up. To clarify, if a patient had baseline GU 2 "toxicity" and had grade 2 GU toxicity post-treatment, the patient was assigned grade 0 GU toxicity. Alternatively, if the same patient had grade 3 GU toxicity at any point post-treatment, he was assigned grade 3 GU toxicity. Suspected grade >3 toxicities were judged by an independent adjudication team who were not study co-investigators and probability of association to treatment assigned (unlikely, possible, probable, and certain) [27].

PSA was assessed at the baseline, at 3 months, 6 months, and every 6 months until 5 years. The study mandated 5 years of follow-up but willing participants were followed annually thereafter for biochemical outcomes. The Phoenix definition (i.e., nadir + 2 ng/ml) of biochemical failure and time-to-failure analysis was used for this study [28]. The American Society of Therapeutic Radiology and Oncology (ASTRO) definition is also reported. A benign bounce was defined as a rise over the relative nadir of greater than 0.2 ng/ml with a subsequent drop below the relative nadir PSA [14]. At 3 years, patients had a minimum 10 $\times$ 12 mm core transrectal or 6 $\times$ 22 mm core transperineal biopsy. The areas to be biopsied were left to the biopsy physician's discretion. For the transrectal biopsy, the same pattern used to diagnose prostate can-