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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-

cer was employed (apex, medial/lateral midgland, mid/lateral base for each side plus directed biopsies of clinical or sonographic abnormality). For the transperineal biopsies, a typical pattern was anterior, mid-lateral and posterior-medial for each side plus directed biopsies into areas of abnormality. MRIs were not performed to guide the biopsies. Each biopsy was read by an Uropathologist at Sunnybrook.

Patient reported outcomes were measured using the Expanded Prostate Cancer Index Composite (EPIC) [29] and the full analysis will be reported separately. Sexual quality of life (sQOL) was included in this paper. Scores were transformed to a 0–100 scale where higher score represented better sQOL. A significant change in sQOL was defined as patients have an average sQOL score on follow-up less greater than 0.5*standard error of the baseline sQOL scores [30].

Sample size and statistical analysis

The phase 1 component of this study was a two-stage Simon design and had a calculated sample size of 30 patients. With an expected grade $\geqslant 3$ toxicity of 5%, the proposed treatment strategy was considered too toxic if greater than 20% of patients had unacceptable toxicity (alpha = 0.033, power = 50%, one-sided, H0: $p = .20$, HA: $p = 0.5$) [31,32]. A stopping rule was built into the study such that if 4 or more of the first 7 patients experienced grade $\geqslant 3$ GU or GI toxicity, the study would be terminated. After a minimum of 6 months of follow-up, none of the 30 patients experienced grade 3 or greater GU or GI acute toxicity (Fisher's exact, 95% confidence interval 0–12%) [17].

Based on these favorable results, the study was expanded to a convenience sample of 100 patients. We calculated that for outcomes occurring in 5%, 10% and 50% of patients, this sample would give us 95% confidence estimates of +/− 4%, +/− 6% and +/− 10%, respectively [17].

Descriptive analysis was summarized as median and range for continuous variables, and proportions for categorical variables. Time to PSA failure (in months) was analyzed by the Kaplan–Meier curve with 95% CI. Patients free of PSA failure at the end of the study or by the time they withdrew from the study had censored times. Cumulative Nelson–Aalen toxicity curves were graphed in GU and GI toxicities grade 2 or 3 [33]. The Nelson–Aalen estimate is the cumulative sum of estimated conditional probabilities of event from I_1 through I_k where $t_k \leqslant t \leqslant t_{k+1}$. The estimator of cumulative hazard to time t was defined as $\hat{H}(t) = \sum_y(i) \leqslant t \frac{d_i}{r_i}$, where d_i denoted number of events at time y_i and r_i denoted number of risk just before time y_i. Patients with toxicity grade <2 or <3 at the end of the study or withdrawal in the study had censored times. All analyses were conducted by Statistical Analysis Software (SAS version 9.2 for Windows).

Results

The study was activated in October 2006. Due to acute financial issues in our clinical trials department in 2008, the last 16 patients could not be accrued. By July 2008, 95 patients were screened for the study. There were 3 screen failures (1 patient exceeded protocol defined girth limit of 40 cm; 2 patients had hip replacements) and 8 chose not to participate in the study. This left 84 patients accrued into the study.

Eight patients withdrew from the study before 5 years of follow-up with no evidence of disease: 2 patients died of other causes, 1 patient had a kidney transplant, 2 patients had a synchronous malignancy, 1 patient left the country, and 2 patients withdrew from study follow up as they found the visits to the cancer center too burdensome. The median follow-up was 55 months (range 13–68 months).

Table 1
Patient characteristics at baseline.

Characteristic	N (%)	
Age, years	84	
Median		67
Range		42–82
T category	84	
T1a	1 (1%)	
T1c	77 (92%)	
T2a	6 (7%)	
Gleason sum	84	
3 + 3	84 (100%)	
PSA, ng/ml	84	
Median		5.3
Range		0.8 – 9.8
Prostate volume	80	
Median		37.2 cc
Range		15–90 cc
Urinary score (IPSS)	84	
Median		5
Range		0–18

IPSS – International prostate symptom score.

One patient had received neoadjuvant androgen deprivation therapy for cytoreduction; for cohort homogeneity he was excluded from pathologic and biochemical outcome analyses. With a follow-up of 61 mo, this patient had a negative biopsy, and remains under biochemical control (last PSA 0.25 ng/ml, testosterone normal).

The median age was 67 years (range 42–82 years). All patients were confirmed to have Gleason 6 adenocarcinoma; 1 (1%) patient was T1a, 77 (92%) were T1c, and 6 (7%) were T2a. The median pretreatment PSA was 5.3 ng/ml (range 0.8–9.8 ng/ml). The baseline patient characteristics are detailed in Table 1.

Toxicity analyses

Eighty-four patients were eligible for the toxicity analyses. At baseline, 16% and 39% had grade 2 and 1 GI "toxicities" while 8% and 29% had grade 2 and 1 GU "toxicities", respectively. In the acute setting, 0%, 10% and 67% developed new grade 3, 2 and 1 GI toxicities, while 1%, 19% and 71% developed new grade 3, 2 and 1 GU toxicities, respectively. The one patient with grade 3 GU toxicity was a man with a 300 cc bladder diverticulum who required temporary catheterization.

In the late setting, 0% and 7% patients had new grade 3 or 2 GI toxicities, respectively. Three patients had hematochezia requiring treatment to resolve the issue (1 required multiple rectal laser treatments, 2 required suppositories). One patient with a history of diverticulitis developed a fistula-in-ano post-radiation and refused definitive surgical correction. While not life-threatening, this

Table 2
Maximum genitourinary and gastrointestinal toxicities at any time and at last follow-up (prevalence). Toxicities were adjusted for initial symptoms.

Toxicity	1	2	3	4	5
Acute (CTCAE v3)					
Gastrointestinal	67%	10%	0%	0%	0%
Genitourinary	71%	19%	1%	0%	0%
Maximum Late (RTOG)					
Gastrointestinal	35%	7%	0%	1%	0%
Genitourinary	2%	5%	0%	0%	0%
Prevalence* Late (RTOG)					
Gastrointestinal	7%	0%	0%	1%	0%
Genitourinary	0%	0%	0%	0%	0%

CTCAE v3 – common terminology criteria for adverse events version 3; RTOG – radiation therapy oncology group late toxicity scale; *highest grade of toxicity at last follow-up.

was assigned grade 4 toxicity. The adjudication committee considered his history of RT and diverticulitis as probably causing the event. This was the only persistent grade 2+ toxicity at last follow-up.

Four (5%) patients developed grade 2 GU late toxicity. Two required transurethral resection of the prostate (TURP – according to RTOG toxicity scale, this is not a grade 3 toxicity) and two required alpha antagonists. At last follow-up, there were no persistent grade 2+ toxicities for any patient. Table 2 summarizes the toxicities and Fig. 1 shows the Nelson–Aalen cumulative risk of toxicity curves (grade 2 or higher).

Seventy-two men provided baseline and adequate follow-up sQOL responses. The median (range; standard deviation) baseline sexual quality of life score (sQOL) was 68 (8–98; 24). After treatment, the median sQOL overall was 50.7; 33/72 (43%) had a significant worsening in sQOL post-treatment.

Biochemical and pathological outcomes

Eighty-three patients were available for these analyses. One patient had biochemical failure (Phoenix definition) resulting in a five-year biochemical control (BC) rate of 98% (95% confidence interval 96–100%). This patient has a history of chronic non-bacterial prostatitis and had a negative biopsy at 31 months. The ASTRO 5-year BC rate was 97% (95% confidence interval 93–100%; data not shown). Eighty-five percent of patients have reached their nadir PSA on follow-up (median time to nadir 12 months). Of these, the median nadir PSA was 0.51 ng/ml (range 0.01–2.5 ng/ml). Thirty-five patients (42%) had at least one "benign bounce" during follow-up; 8 and 1 patient had 2 and 3 benign bounces, respectively. The median time to first benign bounce was 18 months (6–42 months).

Seventy-four patients reached 36 months of follow-up and were eligible for biopsy. Of these, 71 (96%) agreed to undergo a repeat protocol mandated transrectal ($n = 39$) or transperineal ($n = 32$) biopsy. Of the 71 patients, 3 patients (4%) had positive biopsies.

Discussion

In this prospective study, we showed that 5 weekly fractions (or treatments) of SABR were feasible and well tolerated in patients

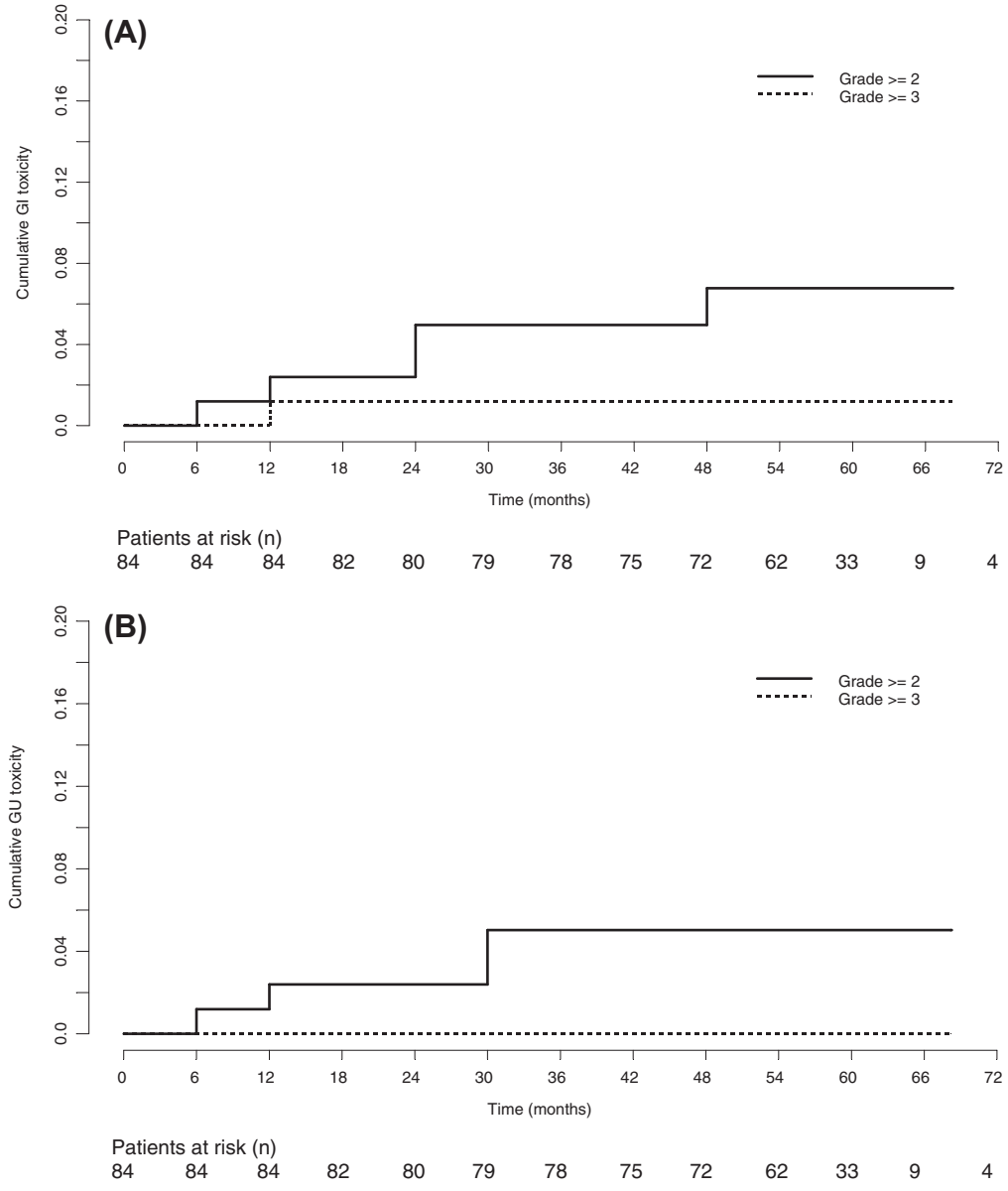

Fig. 1. Cumulative RTOG grade 2 or higher late toxicities: A. gastrointestinal, B. genitourinary. Toxicities were corrected for initial symptoms.

with localized prostate cancer. A summary of other prospective SABR protocols for prostate cancer is shown in Supplementary Table 1. A large multi-institutional retrospective series has been recently presented with similar results. [34] It should be emphasized that, while impossible to draw conclusions about relative tolerability across studies (due to varying toxicity scales and scoring methods), for the purposes of hypothesis generation, our results using standard linear accelerators appear no worse than those using dedicated SABR machines.

While overall the follow-up is short for many of these studies, on weighted average 29 months, we believe this is adequate to judge the acute and late effects of SABR. Overall, these outcomes are comparable to modern dose-escalated, image-guided radiation therapy (IGRT) techniques using standard fractionation schemes (79.4–86.4 Gy) [24,35]. Despite the low rates of serious late toxicities, there may still be a role for performing SABR with an endorectal balloon as it may further decrease rates of hematochezia and anal hypotonia and improve bowel quality of life [36]. However, further study is required to articulate these benefits and weigh them against the potential costs, workflow issues and patient discomfort.

Unfortunately, the follow-up of these SABR studies is too short to make conclusions about efficacy. Post-treatment biopsies have been shown to predict long-term bDFS [24,37] but very few studies outside of the current study have performed routine post-treatment biopsies on the majority of patients. In our series, almost all patients due for biopsy complied (96%) and 96% of these was negative. This compares favorably to the Princess Margaret Hospital standard fractionation IGRT experience where 26 of 259 men underwent biopsies, 14 (54%) of which were negative [24].

Moreover, the biochemical outcomes of patients treated with SABR do not appear worse than standard fractionation IGRT. With a median follow-up of 55 months, our series of low risk patients had a 98% 5-year bDFS. By comparison, with a median of 53 months, Memorial Sloan Kettering reported a 5-year bDFS for low- and intermediate-risk patients of 98% and 85%, respectively, when treating with 86.4 Gy in 48 fractions [35]. The Princess Margaret Hospital experience of 79.6 Gy in 42 fractions (median follow-up 68 months) reported 5-year bDFS rates of 88% and 77%, respectively. [24] The favorable SABR results are consistent with a low alpha/beta ratio. With an alpha/beta of 1.4 Gy, [11] the equivalent dose in 2 Gy per fraction (EQD2) of our protocol, Memorials' and Princess Margaret's is 86.5 Gy, 81.3 Gy and 77.1 Gy, respectively. However, biochemical failures after 5 years are common and further follow-up is needed.

SABR is also beneficial for the patient and the radiation therapy department. Our group calculated that on average patients saved Cdn$1,928 (range $170–$13,937) out of pocket for travel, parking, accommodation and time off work for a 5-fraction SABR protocol versus a conventional 39 fraction IGRT protocol [38]. For those that would otherwise be treated with standard fractionation IGRT, the 5 treatment hypofractionation technique allows 8–9 times the number of patients to be treated using the same LINAC resources. Despite this increase in treatment capacity, the marginal departmental cost for our 5 treatment technique is actually substantially less than our 39 fraction IGRT technique: Cdn$1470 compared to $6987 (Loblaw D, unpublished data). Note that departmental costs are different from reimbursement received.

This study's biggest limitations are the relatively small sample size, single institutional study and lack of long-term follow-up. Based on our earlier results, [17] our group continues to study the outcomes of localized prostate cancer patients with SABR. We completed a single-institution, prospective, phase 2 study of 40 Gy in 5 fractions for low- and intermediate risk patients. While the follow-up is short, it was reassuring that the protocol was also well tolerated with no grade 3 or higher acute or late GI or GU side effects observed [39]. This gives a biologically equivalent dose to the prostate as our high dose rate (HDR) brachytherapy protocol [40].

Our HDR protocol delivers 15 Gy along with 15 fractions × 2.5 Gy of IGRT. Other centers use HDR monotherapy and the trend is to use fewer treatments – some centers are currently investigating 1 or 2 HDR implants with no IGRT [41,42]. Our clinical experience is that brachytherapy is tolerated best and has less technical limitations for men with smaller prostate volumes and with lower urinary scores at baseline [43] whereas SABR can safely treat patients with larger prostates and worse urinary scores. Further study will be needed to determine the efficacy, tolerability and cost-effectiveness of HDR versus SABR for men with implantable prostates.

We believe that a prospective, phase 3 randomized control trial (RCT) comparing SABR to standard IGRT should be performed using standard linear accelerators. Before this is done, we feel that two technical questions need to be addressed. The first is the optimal duration of treatment. To address this, there is an ongoing multicenter, prospective, phase 2 RCT of treatment duration (11 versus 29 days) for SABR called PATRIOT (clinicaltrials.gov NCT01423474). The second technical question is whether an endorectal balloon improves patient outcomes. To address this question, we are planning to activate a multinational, prospective, phase 2 RCT of SABR +/− endorectal balloon called PROTECT. Other important studies are also ongoing which will help inform this research including RTOG 0938 (phase II RCT of 36.25 Gy/5 fractions vs 52 Gy/12 fractions; clinicaltrials.gov NCT01434290), SPGC7 (phase III RCT of 42 Gy/7 fractions vs 76 Gy/38 fractions, trial number not listed) and Accuray's PACE (phase III RCT of laparoscopic prostatectomy vs SABR (36.25 Gy/5 fractions or 38 Gy in 4 fractions) or SABR vs conventionally fractionated RT, clinicaltrials.gov NCT01584258).

Conclusions

Stereotactic ablative body radiotherapy (SABR) for low-risk localized prostate cancer is feasible, well-tolerated and has excellent efficacy signals up to six years of follow-up. SABR allows safe biological dose escalation of prostate cancer with greater patient convenience, lower out-of-pocket and departmental costs and increased radiation therapy departmental treatment capacity. Further research is needed to refine the optimal SABR technique and machine requirements but ultimately SABR should be compared to conventional or hypofractionated image-guided radiation therapy or brachytherapy in a definitive, phase 3 randomized control trial.

Conflict of interest statement

None of the authors has any conflict of interest with respect to this work.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2013.03.022.

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