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Original Article

Two StereoTactic ablative radiotherapy treatments for localized prostate cancer (2STAR): Results from a prospective clinical trial

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ABSTRACT

Purpose: Ultrahypofractionation is appealing for prostate cancer (PCa) due to low α/β, and increasing the dose per fraction could improve the therapeutic index. Here we report the outcomes of a phase II prostate SABR trial using two fractions.
Methods: Patients had low or intermediate risk prostate cancer. Three gold fiducials were implanted for image guidance. The clinical target volume (CTV) included the prostate only, and the planning target volume (PTV) was a 3 mm expansion enabled through the use of a rectal immobilization device. The dose prescribed was 26 Gy in 2 weekly fractions (EQD2 110 $Gy_{1.4}$). The primary endpoint was quality of life using EPIC, and minimal clinically important change (MCIC) was defined as an EPIC QOL decrease >0.5 SD.
Results: 30 patients were accrued with a median follow-up of 49.3 months. 10% had low-risk, 33% had favourable intermediate-risk and 57% had unfavourable intermediate-risk PCa. Five patients received a short course of ADT. Median nPSA was 0.2 ng/ml. One patient had BF and is being observed. 56.6% of patients had a 4yPSARR. Six (20.7%) patients had a MCIC in the urinary domain, 6 (21.4%) had a MCIC in the bowel domain, and 3 (20%) had a MCIC in the sexual domain.
Conclusions: Two-fraction SABR in prostate cancer is safe and feasible, with a minimal change in QOL and a low rate of late grade 3–4 toxicity. The PSA kinetics and biochemical control rates are encouraging given that the majority had unfavourable intermediate-risk disease, although longer follow-up is required.

There is now clear evidence of improved biochemical disease free survival (bDFS) with radiotherapy dose-escalation in all prostate cancer (PCa) risk groups [1,2]. Stereotactic ablative radiotherapy (SABR) seems to offer an effective treatment option for clinically localized PCa [3,4]. SABR has been tested widely in low- and intermediate-risk PCa, and our group formerly reported the long-term outcomes of SABR trials in that patient population [5]. A spectrum of total doses and fraction sizes are reported in the SABR literature, all of which used a fraction size of 10 Gy or less [6]. Only one phase II SABR trial reported as an abstract looked at fraction sizes more than 10 Gy, randomizing between 45 Gy in 5 fractions and 24 Gy in 1 fraction [7]. Delivering prostate SABR over fewer fractions can be more convenient to the patient and less costly to the radiotherapy department, patient and system [8,9]. Given that the α/β of PCa is lower than the surrounding normal tissues, using a higher dose per fraction can improve the therapeutic ratio [10]. Here we report the outcomes of a prospective phase II trial in prostate SABR using a novel two-fraction protocol.

Patients and methods

The trial was approved by the Sunnybrook research ethics board and registered on clinical trials.gov (NCT02031328). Written, informed consent was obtained in all participants.

Patient selection and treatment details

In 2014, thirty patients with low and intermediate risk prostate cancer (clinical stage T1-2b, Gleason's Score $\leq$7, and PSA $\leq$20 ng/ml) were accrued to a phase II prospective SABR study (2STAR) at the Odette Cancer Centre, Sunnybrook Health Sciences Centre. Patients were excluded if they had prior pelvic radiation therapy, bleeding diathesis, presence of hip prosthesis, prostate size >90 cm^3, or inflammatory bowel disease. Three gold fiducial mark-

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ers were implanted transperineally into the prostate, and a planning CT was performed with patients immobilized with a custom vacuum lock bag in the supine position with a comfortably full bladder and empty rectum. The clinical target volume (CTV) included the prostate only, and the planning target volume (PTV) was a 3 mm expansion on the CTV, enabled through the use of a rectal immobilization device [11]. The dose prescribed to D99 CTV was 26 Gy in 2 weekly fractions, with an EQD2 of 110 $Gy_{1.4}$ that is similar to our 40 Gy in 5 fractions of SABR protocol [5]. OAR constraints for the rectum were V20.8 Gy < 1 cc, V17.6 Gy < 4 cc and V13Gy < 7 cc. Constraints for the bladder were V20.8 Gy < 5 cc and V14.6 Gy < 15 cc, and femoral heads V14Gy $\leq$ 10 cc. Daily image guidance with CBCT was used pre- and post-treatment. Short-term ADT use (<6 months) was allowed at the discretion of the treating physician and was recommended for all unfavorable intermediate risk patients.

Study endpoints and follow-up

Patients were assessed at baseline, weeks 1 and 4, and at 3 and 6 months. In the late period (>6 months), patients were followed every 6 months for 5 years and subsequently every year. Acute toxicities, late toxicities and quality of life (QOL) data were collected using Common Terminology Criteria for adverse events version 4.0 (CTCAE v4.0) and expanded prostate cancer index composite (EPIC) questionnaires, respectively up to 5 years [12,13]. The primary endpoint was QOL using the EPIC questionnaire, and the minimal clinically important change (MCIC) was defined as an EPIC QOL decrease >0.5 SD of the baseline score for each domain or subscore. Secondary endpoints included acute and late toxicity, biochemical disease-free survival, and the rate of salvage therapy (ADT, surgery or brachytherapy). Biochemical failure (BF) was defined as per the American Society for Therapeutic Radiology and Oncology Phoenix definition (nadir + 2.0 ng/ml) [14]. Four-year PSA response rate (4yPSARR) was defined as <0.4 ng/ml.

Statistical analysis

Demographic and tumour characteristics were summarized using mean, standard deviation (SD), median and range for continuous variables, and proportions for categorical variables. For each domain and subscore, QOL scores were transformed to a 0–100 point scale with higher score representing better QOL. BF was calculated from the time of first radiation treatment to failure. The cumulative incidence of BF was estimated using the Nelson–Aalen curves. PSA nadir was set to be the lowest PSA value following treatment completion. The PSA response rate at 4 years (4yPSARR) was evaluated. Overall survival was estimated using the Kaplan–Meier curve. All analyses were conducted using Statistical Analysis Software (SAS version 9.4 for Windows) and R package (version 3.4.2). P-values <0.05 were considered statistically significant.

Sample size calculation

The objective for this phase I/II study was to determine whether a 2-fraction adaptive SABR technique (2STAR) can be delivered and tolerated well (at least as good as our current 5-fraction SABR technique) [5] as determined by QOL MCIC. QOL was chosen as the primary outcome as it has been shown that QOL is more sensitive to change than the CTC toxicity scales for hypofractionated studies. Thirty patients completed our pHART6 study, receiving SABR 40 Gy in 5 fractions [5]. There were 23% (7/30) of patients who reported a significant change in QOL within 3 months of starting treatment. We used the same 30 patient sample design for 2STAR that we have used for many of our other SABR studies. If 12 or more of 30 patients had a significant decrement in QOL, we can conclude that the 2STAR protocol is too toxic compared to our 5-fraction SABR protocol. This tests the hypothesis that acute toxicity is greater than 25% (alpha = 0.05, power = 80%, one-sided, H0: $p = .23$, HA = $p = .40$). Exact 95% confidence limits (with no continuity correction) for 12/30 = 40% are (24.6, 57.7), F distribution method, (23.2, 59.3 with continuity correction). It is recognized that the 95% confidence intervals are fairly wide given the relatively small number of patients. If trial is successful (i.e., 12 or less of the 30 patients have significant decrement in acute QOL), funding for a larger sample of patients will be sought to further refine the point estimates.

Results

Demographic factors and basic tumour characteristics are summarized in Table 1. The median follow-up was 49.3 months. 10% had low-risk, 33% had favourable intermediate-risk and 57% had unfavourable intermediate-risk PCa (defined as a primary Gleason pattern of 4, percentage of positive biopsy cores $\geq$50%, or multiple intermediate-risk factors [15]). Short-term ADT was recommended to all patients with unfavourable intermediate-risk PCa, however only five patients (17%) agreed to receive ADT.

One patient, who had unfavourable intermediate-risk PCa and did not receive ADT, had BF and is under observation. The cumulative BF probability was 5.2% at 54 months (Fig. 1). By the last follow-up, 17 (56.6%) patients had achieved a 4yPSARR. The median PSA nadir was 0.2 ng/ml, with a median time to nadir of 40.9 months (Fig. 2). No patient died from any cause or developed metastatic disease.

No acute grade $\geq$3 GU or GI toxicity was reported. In the late period, there was one grade 3 GU toxicity (urinary retention in a patient who had TURP with complications prior to starting SABR),

Table 1
Demographic and tumour characteristics.

	Total (N = 30)	
Median age (range)	67.3 (53.2, 83.2)	
Clinical stage		
T1a	1	(3.33%)
T1c	19	(63.33%)
T2a	6	(20.00%)
T2b	3	(10.00%)
T2c	1	(3.33%)
Gleason's score		
6	4	(13.33%)
7	26	(86.66%)
Gleason's score categories		
3 + 3	4 (13.3%)	
3 + 4	23 (76.6%)	
4 + 3	3 (10%)	
Risk groups		
Low risk	3 (10%)	
Favourable intermediate risk	10 (33%)	
Unfavourable intermediate risk	17 (57%)	
PSA at baseline (ng/ml)		
Median (range)	8.59 (2.19, 18.6)	
PSA categories at baseline (ng/ml)		
<4	3	(10.00%)
4–10	17	(56.67%)
>10–15	7	(23.33%)
>15	3	(10.00%)
Prostate volume (ml)		
Median (range)	36.4 (20.4, 89)	
IPSS Score at baseline		
Median (range)	5 (0, 26)	

PSA, Prostate Specific Antigen; IPSS, International Prostate Symptom Score.

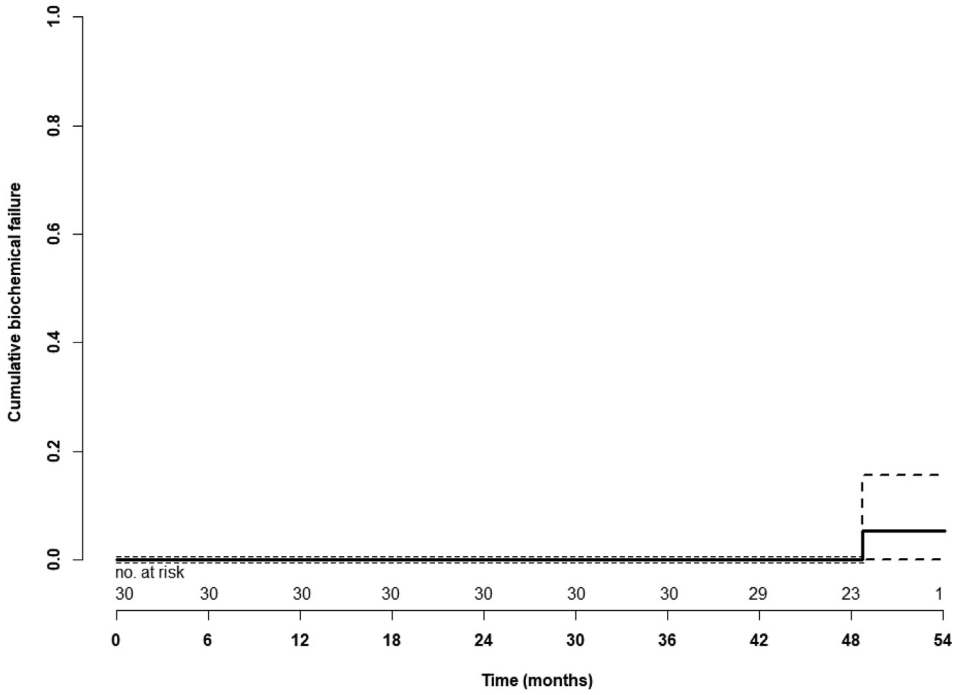

Fig. 1. Nelson–Aalen's cumulative biochemical failure probability curve.

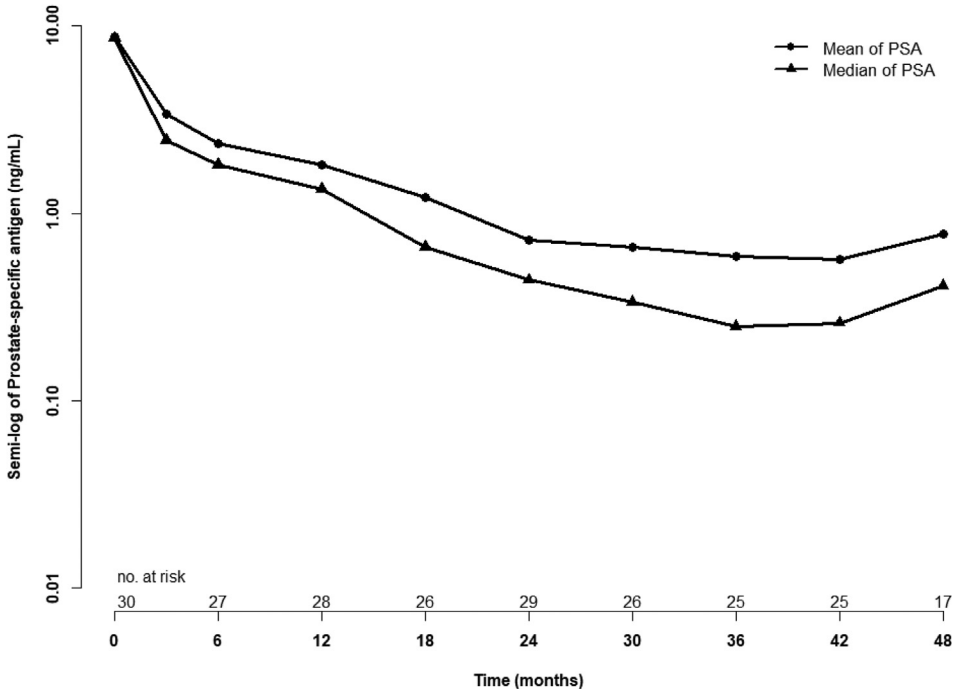

Fig. 2. Mean and median PSA over time.

one grade 3 GI toxicity (haemorrhoids), and 2 patients with grade 3 sexual toxicity (erectile dysfunction). The cumulative worst acute and late toxicity rates are summarized in Table 2.

The mean EPIC QOL change from baseline (average score during the late period – baseline score) was −1.1 for the urinary domain, −1.0 for the bowel domain, and −3.8 for the sexual domain (Fig. 3). With regard to the proportion of patients that had a MCIC, 6 (20.7%) patients had a MCIC in the urinary domain, 6 (21.4%) had a MCIC in the bowel domain, and 3 (20%) had a MCIC in the sexual domain. (Table 3).

Discussion

Four RCTs have shown moderate hypofractionation to be non-inferior to conventionally fractionated RT [16–19]. More recently, the results of an RCT testing whether ultrahypofractionated RT is

Table 2
Cumulative worst acute and late CTCAE toxicities.

Cumulative worst toxicity	CTCAE toxicity grade			
	0	1	2	3
Acute period (N = 30)				
GI	21 (70%)	8 (26.67%)	1 (3.33%)	0 (0%)
GU	4 (13.33%)	14 (46.67%)	12 (40%)	0 (0%)
Sexual	16 (53.33%)	12 (40%)	1 (3.33%)	1 (3.33%)
Late period (N = 30)				
GI	19 (63.33%)	7 (23.33%)	3 (10%)	1 (3.33%)
GU	4 (13.33%)	13 (43.33%)	12 (40%)	1 (3.33%)
Sexual	7 (23.33%)	8 (26.67%)	13 (43.33%)	2 (6.67%)

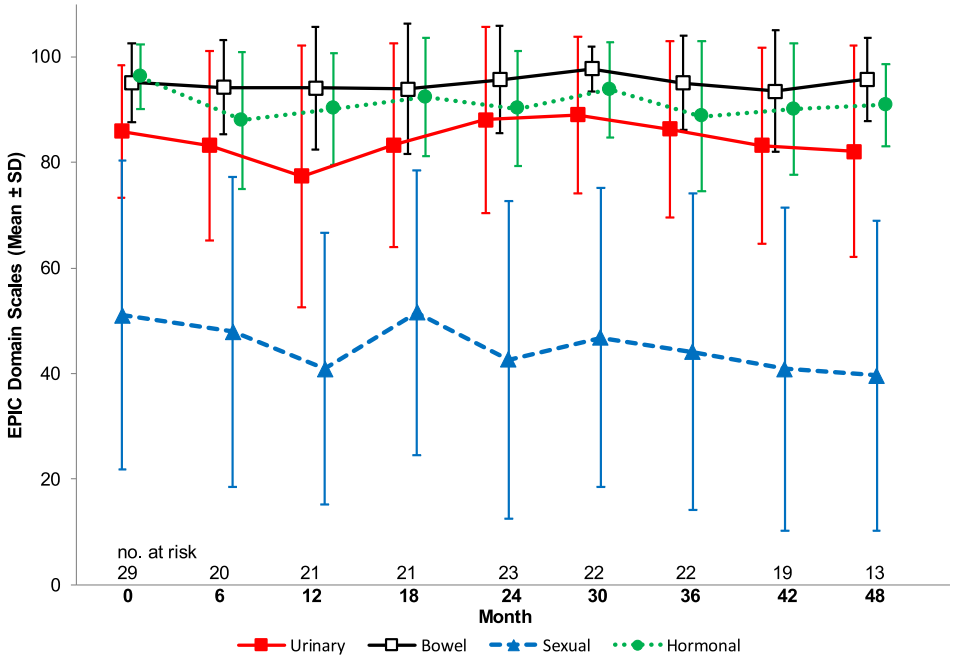

Fig. 3. EPIC QOL change from baseline in the urinary, bowel, sexual and hormonal domains.

Table 3
Minimally clinically important differences between 2-fraction and 5-fraction SABR at our centre.

MCIC	2-Fraction SABR [this series]	5-Fraction SABR (Quon et al. [26])
Bladder	6/26 (20.7%)	7/29 (24%)
Bowel	6/26 (21.4%)	12/29 (41%)
Sexual	3/15 (20%)	10/26 (39%)

non-inferior to conventional RT were presented as an abstract showing non-inferiority [20]. SABR has been tested widely in low- and intermediate-risk PCa, and our group previously reported the long-term outcomes of SABR trials in that patient population [5]. Mature prostate SABR studies were summarized in a previous publication [21]. King et al. performed a combined analysis of 1100 SABR patients, with a 5-year bRFS of 95% and 84% for low and intermediate-risk patients [22]. Katz et al. reported a similar 10-year bRFS of 93% in low and low-tier intermediate risk patients receiving SABR dose of 35 Gy or 36.25 Gy in 5 daily fractions [23]. However, these different studies all looked at fraction sizes $\leq$10 Gy, with only one phase II trial reported as an abstract that delivered 24 Gy in 1 fraction [7].

This phase II trial explored a novel SABR protocol of 26 Gy in 2 weekly fractions, taking advantage of the low PCa α/β ratio to further enhance the therapeutic ratio. At a median follow-up of 49.3 months, this treatment was associated with biochemical control rates and PSA nadirs that are comparable to previously published 5-fraction SABR protocols [5,22,23]. The 4yPSARR was previously shown to be a predictor of long-term biochemical control in SABR and LDR brachytherapy [5,24], and in this trial 57% of patients achieved that cutoff. Although the 4yPSARR is lower than what was reported in our previous 40 Gy in 5 fractions trial (pHART6), the 97% of patients in pHART6 had low-risk or favourable intermediate-risk PCa [5] which may explain the higher 4yPSARR (80%) in that study.

Despite the CTV volumes being the same (prostate only) and CTV-PTV margins being very similar (3 mm for this protocol and 4 mm for our 5-fraction protocol) the rates of acute and late CTCAE toxicities were comparable or slightly better compared to our 5-fraction SABR protocols [25,26]. The rate of late grade 3–4 toxicity remained low with 2-fraction SABR and is comparable to other SABR trials. QOL remained very close to baseline in the bowel and urinary domains during follow up, and the impact on sexual QOL seemed slightly more favourable compared to 5-fraction SABR. The percentage of patients with MCIC was also comparable in the bladder domain but appeared better in the bowel and sexual domains for the 2-fraction programme compared with the 5-fraction programme [26].

In conclusion, 2-fraction SABR is feasible to deliver and well tolerated. Early signals of efficacy (4yPSARR, PSA nadir and bDFS) are

encouraging but longer follow-up is needed to confirm the late efficacy of the protocol. This novel protocol is more convenient for the patient and less costly to the radiotherapy department, patient and system. However, the main potential advantage of this programme would be the better QOL, particularly in the bowel and sexual domains. Well conducted randomized trials are needed to compare this treatment protocol to standard of care radiotherapy options.

Conflict of interest

Yasir Alayed, Patrick Cheung, William Chu, Hans Chung, Melanie Davidson, Ananth Ravi, Joelle Helou, Liying Zhang, Alexandre Mamedov, Angela Commisso, Kristina Commisso: None.

Andrew Loblaw: Honoraria – Abbvie; Amgen; Astellas Pharma; AstraZeneca; Bayer; Janssen; Sanofi; TerSera; Grant – AstraZeneca, Sanofi, TerSera; Patents, Royalties, Other Intellectual Property – Prostate immobilization device (GU-Lok); Travel, Accommodations, Expenses – Amgen; Astellas; Janssen; TerSera.

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