Radiotherapy and Oncology 140 (2019) 105–109

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Two versus five stereotactic ablative radiotherapy treatments for localized prostate cancer: A quality of life analysis of two prospective clinical trials

Yasir Alayed [a,b,c], Harvey Quon [d], Patrick Cheung [a,b], William Chu [a,b], Hans T. Chung [a,b], Danny Vesprini [a,b], Aldrich Ong [e], Amit Chowdhury [e], Dilip Panjwani [f], Joelle Helou [g], Geordi Pang [a,b], Renee Korol [a,b], Melanie Davidson [a,b], Ananth Ravi [a,b], Boyd McCurdy [e], Liying Zhang [a], Alexandre Mamedov [a], Andrea Deabreu [a], Angela Commisso [a], Kristina Commisso [h], Andrew Loblaw [a,b,*]

[a] Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto; [b] Department of Radiation Oncology, University of Toronto, Canada; [c] Division of Radiation Oncology, College of Medicine, King Saud University, Riyadh, Saudi Arabia; [d] Department of Radiation Oncology, Tom Baker Cancer Centre, Calgary; [e] CancerCare Manitoba, Winnipeg, Canada; [f] Compassionate Cancer Centers, India; [g] Department of Radiation Oncology, University of Toronto, Princess Margaret Cancer Centre; and [h] University Health Network, Toronto, Canada

ARTICLE INFO

Article history:
Received 29 April 2019
Received in revised form 11 June 2019
Accepted 12 June 2019
Available online 29 June 2019

Keywords:
Prostate cancer
Stereotactic body radiotherapy
SABR
QOL

ABSTRACT

Purpose: Stereotactic ablative radiotherapy (SABR) is appealing for prostate cancer (PCa) due to low α/β, and increasing the dose per fraction could improve the therapeutic index and lead to a better quality of life (QOL). Here we report the outcomes of a QOL comparison between two phase II clinical trials: two vs. five fraction prostate SABR.

Methods: Patients had low or intermediate risk PCa. The doses prescribed were 26 Gy/2 and 40 Gy/5. Expanded prostate cancer index composite was collected. Urinary, bowel and sexual domains were analyzed. Minimal clinically important change (MCIC) was defined as >0.5 standard deviation.

Results: 30 and 152 patients were treated with 2-fraction and 5-fraction SABR. Median follow-up was 55 and 62 months. Five-year biochemical failure rate was 3.3% and 4.6%. The 2-fraction cohort had a significantly better mean QOL over time in the bowel domain ($p = 0.0004$), without a significant difference in the urinary or sexual domains. The 2-fraction cohort had a significantly lower rate of bowel MCIC (17.8% vs 42.3%, $p = 0.01$), but there was no difference in urinary (24.1% vs 35.7%) or sexual (15.3% vs 29.2%) MCIC. For MCIC x2 (moderate QOL change), the 2-fraction trial had significantly lower MCIC rates in both the bowel (7.1% vs 24%, $p = 0.04$) and sexual (0 vs 17.6%, $p = 0.01$) domains.

Conclusions: 2-Fraction SABR is feasible to deliver and well tolerated, with significant signals of improved bowel and sexual QOL. A randomized trial of two vs. five fractions for prostate SABR is needed to confirm the promising findings of this study.

Stereotactic ablative radiotherapy (SABR) offers an effective treatment option for clinically localized prostate cancer (PCa) [1,2]. SABR has been tested extensively in low- and intermediate-risk PCa, and our group previously reported the long-term outcomes of SABR trials in that patient population [3]. The majority of reported SABR trials used a 5-fraction treatment protocol [4–7]. We recently reported the outcomes of a phase II clinical trial using a novel 2-fraction treatment protocol (2STAR) [8]. Considering that the α/β of PCa is lower than the surrounding normal tissues, using a higher dose per fraction could improve the therapeutic ratio [9]. 2STAR showed that a 2-fraction protocol was safe and feasible with a minimal change in quality of life (QOL) and a low rate of late grade 3–4 toxicity. Delivering prostate SABR over fewer fractions is more convenient to the patient and less costly to the radiotherapy department, patient and system [10,11]. Given the favorable QOL outcomes seen in 2STAR, the next logical step would be to statistically compare those results with the results from our previous 5-fraction randomized clinical trial (PATRIOT) [12]. Here we report the outcomes of a QOL comparison between the clinical trials 2STAR (2-fraction) and PATRIOT (5-fraction).

Patients and methods

Both trials were approved by the Sunnybrook research ethics board and registered on clinical trials.gov (NCT02031328 and

* Corresponding author at: Rm T2-161, 2075 Bayview Avenue, Sunnybrook Health Sciences Center, Toronto, ON M4N 3M5, Canada.
E-mail address: andrew.loblaw@sunnybrook.ca (A. Loblaw).

https://doi.org/10.1016/j.radonc.2019.06.018
0167-8140/

NCT01423474). Written, informed consent was obtained from all participants.

Patient selection and treatment details

Between January 2012 and November 2013, 152 men with low and intermediate risk prostate cancer (clinical stage T1-2b, Gleason Score ≤ 7, and PSA ≤ 20 ng/mL) were enrolled to PATRIOT, a randomized phase II trial comparing 40 Gy in 5 fractions delivered weekly versus every other day. Three gold-fiducial markers were implanted transperineally into the prostate under trans-rectal ultrasound guidance, and then 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 uniform 5 mm expansion on the CTV. Planning objectives included the volume of CTV receiving 40 Gy (CTV V40 Gy) > 99%, PTV V38 Gy > 99%, PTV V42 Gy < 1 cc, and PTV maximum dose (Dmax) $\leq$ 42.8 Gy. Normal tissue constraints were rectum V28 Gy $\leq$ 20%, V32 Gy $\leq$ 15%, bladder V28 Gy $\leq$ 20%, V32 Gy $\leq$ 15%, and femoral head V28 $\leq$ 5%. Treatment was delivered with image-guided, intensity-modulated radiotherapy. Daily orthogonal images (kV or MV) or cone beam CT was used to identify the implanted fiducials to calculate patient shifts to ensure proper positioning. Short-term androgen deprivation therapy (ADT) use for <6 months was allowed at the discretion of the treating physician.

Following the completed accrual in PATRIOT, thirty patients with low and intermediate risk prostate cancer (clinical stage T1-2b, Gleason's Score ≤ 7, and PSA ≤ 20 ng/mL) were accrued in 2014 to a phase II prospective 2-fraction SABR study (2STAR) at the Odette Cancer Centre, Sunnybrook Health Sciences Centre. Three gold fiducial markers were implanted transperineally into the prostate, and a planning CT was performed with patients 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 an endorectal immobilization system [13]. The dose prescribed to D99 CTV was 26 Gy in 2 weekly fractions (PTV V22 Gy > 99%), with an EQD2 of 110 $Gy_{1.4}$ that is similar to our 40 Gy in 5 fractions SABR protocol [3]. OAR constraints for the rectum were V20.8 Gy < 1 cc, V17.6 Gy < 4 cc and V13 Gy < 7 cc. Constraints for the bladder were V20.8 Gy < 5 cc and V14.6 Gy < 15 cc, and femoral heads V14 Gy $\leq$ 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.

Study endpoints and follow-up

Patients were assessed at baseline, during SABR, and at 3 and 6 months. In the late period (>6 months), patients were followed up every 6 months for 5 years. Biochemical and toxicity outcomes of both trials were reported previously [8,12]. QOL data were collected using expanded prostate cancer index composite (EPIC) questionnaires at baseline and during each subsequent follow up [14]. The primary endpoint of this analysis was QOL using the EPIC questionnaire.

Statistical analysis

Demographic and tumor characteristics were summarized for patients in 2STAR and PATRIOT using mean, standard deviation (SD), median and range for continuous variables, and proportions for categorical variables. Wilcoxon's rank-sum test or Fisher's exact test was applied for comparing continuous or categorical variables between two trials. Three domains of EPIC scores and sub-scores were analyzed: urinary (function/bother), bowel (function/bother) and sexual (function/bother). For patients with a missing baseline QOL score, the 6-month score was used as a baseline if there was no significant difference between the baseline and 6-month time-points in patients with complete QOL data [15]. For PATRIOT, both arms (weekly vs. every other day treatment) were combined for the purpose of this analysis given that there was no significant long-term difference in QOL between the two [12]. The patient responses to questions were transformed to a scale from 0 to 100, with higher scales indicating better function and less bother. To compare EPIC score and sub-score at baseline and compare the average score during follow-up period between the two treatment groups, Wilcoxon's rank-sum test was also performed. A minimally clinical important change (MCIC) was scored if the average EPIC QOL score (months 6–60) was >0.5 standard deviation (SD) of baseline scores for each domain score or sub-score in all patients. We believe this corresponds to "mild QOL change". MCIC x2 (moderate QOL change) was also calculated. In addition, an analysis of specific items in each domain of the questionnaire was done after transforming the item scores into a 5-point Likert scale (0: big problem, 1: moderate problem, 2: small problem, 3: very small, 4: no problem). The proportion of patients who started with no to small problems at baseline and who subsequently developed a moderate to big problem on average over follow-up was calculated. Fisher's exact test was used to compare the percentage of patients with moderate to big problem in the two treatment groups. All analyses were conducted using Statistical Analysis Software (SAS version 9.4 for Windows, Cary, NC) and R package (version 3.4.2). *P*-values <0.05 were considered statistically significant.

Results

The demographics are summarized in Table 1. There was no significant difference in T-stage, baseline PSA, Gleason's score, risk group, prostate volume or baseline IPSS between the two trials.

Table 1
Demographics and baseline characteristics. Numbers are expressed as median (inter-quartile-range) or number (%) as appropriate.

	2-Fraction trial (n = 30)	5-Fraction trial (n = 152)	p-value
Age [years]	67 (62–71)	70 (65–75)	**0.024**
T-Stage			0.1
T1c	20 (66.6%)	98 (64.47%)	
T2a	6 (20%)	36 (23.68%)	
T2b	3 (10%)	15 (9.87%)	
T2c	1 (3.33%)	0	
Unknown	0	3 (1.97%)	
Baseline PSA [ng/mL]	8.6 (5.6–11.4)	8 (5.8–12.4)	0.95
Gleason Score			0.13
6	4 (13.33%)	30 (19.74%)	
7	26 (86.67%)	121 (79.61%)	
Unknown	0	1 (0.66%)	
Risk Group (NCCN)			0.47
Low	3 (10%)	20 (13.1%)	
Favorable intermediate	10 (33.3%)	39 (25.66%)	
Unfavorable intermediate	17 (56.6%)	92 (60.5%)	
Unknown	0	1 (0.66%)	
Prostate Volume (cc)	36 (27, 42)	36 (28, 50)	0.44
IPSS Score at Baseline	5.0 (3.0, 11.0)	5.0 (3.0, 11.0)	0.81
Androgen deprivation Therapy			0.09
Yes	5 (16%)	11 (7%)	
No	25 (84%)	141 (93%)	

PSA-Prostate Specific Antigen; IPSS-International Prostate Symptom Score.
p-values < 0.05 are considered statistically significant.

The median follow-up was 55 months (IQR 52–56) in the 2-fraction trial and 62 months (IQR 60–69) in the 5-fraction trial. The five-year biochemical failure rate was 3.3% and 4.6%, respectively. The PSA nadir was 0.2 ng/ml (IQR 0.1–0.4) in the 2-fraction trial and 0.1 ng/ml (IQR 0–0.2) in the 5-fraction trial ($p = 0.01$), and the time to PSA nadir was 50 months (IQR 35–55) and 54 months (IQR 43–60), respectively ($p = 0.007$). The overall survival was 100% and 94.7%, and the prostate cancer-specific survival was 100% and 98.9%, respectively ($p = 0.3$). Further details on biochemical and toxicity outcomes of both trials were reported previously [8,12].

Adequate baseline and follow-up QOL data were available for most patients. Urinary, bowel, and sexual QOL scores at baseline and during follow-up are reported in Table 2. There was no significant difference in QOL domain scores at baseline between the two treatment groups. When comparing the average score of QOL during follow-up period, patients in the 2-fraction treatment group had a significantly better QOL in the bowel domain ($p = 0.0004$), but there was no significant difference in the urinary or sexual domains (Fig. 1). The thresholds (0.5 SD) for MCIC were 5.98 for the urinary domain, 5.45 for the bowel domain, and 13.56 for the sexual domain. The 2-fraction trial had a significantly lower number of patients reporting a bowel MCIC (17.8% vs 42.3%, $p = 0.01$), but there was no difference in urinary (24.1% vs 35.7%, $p = 0.28$) or sexual (15.3% vs 29.2%, $p = 0.22$) MCIC between the two trials (Table 3). For MCIC x2 (moderate QOL change), the 2-fraction trial had a significantly lower MCIC rates in both the bowel (7.1% vs 24%, $p = 0.04$) and sexual (0 vs 17.6%, $p = 0.01$) domains (Table 3).

For specific items in the EPIC QOL questionnaire, the proportion of patients who had no problems at baseline and who subsequently developed a moderate to big problem on average over follow-up was calculated, and no significant difference between the two trials was shown (Table 4).

Table 2
Urinary, bowel and sexual QOL scores at baseline and during follow-up for the two trials.

QOL Domain	At baseline			Average score during follow-up		
	2-Fraction	5-Fraction	*p*-value	2-Fraction	5-Fraction	*p*-value
Urinary			0.58			0.32
n	29	144		29	140	
Median (IQR)	91 (79, 96)	90 (81, 98)		90 (79, 94)	88 (75, 94)	
Bowel			0.07			**0.0004**
n	29	144		28	140	
Median (IQR)	98 (95, 100)	95 (89, 98)		96 (93, 99)	91 (82, 96)	
Sexual			0.71			0.32
n	26	139		27	134	
Median (IQR)	48 (24, 67)	49 (28, 69)		44 (22, 66)	36 (19, 55)	

p-values < 0.05 are considered statistically significant.

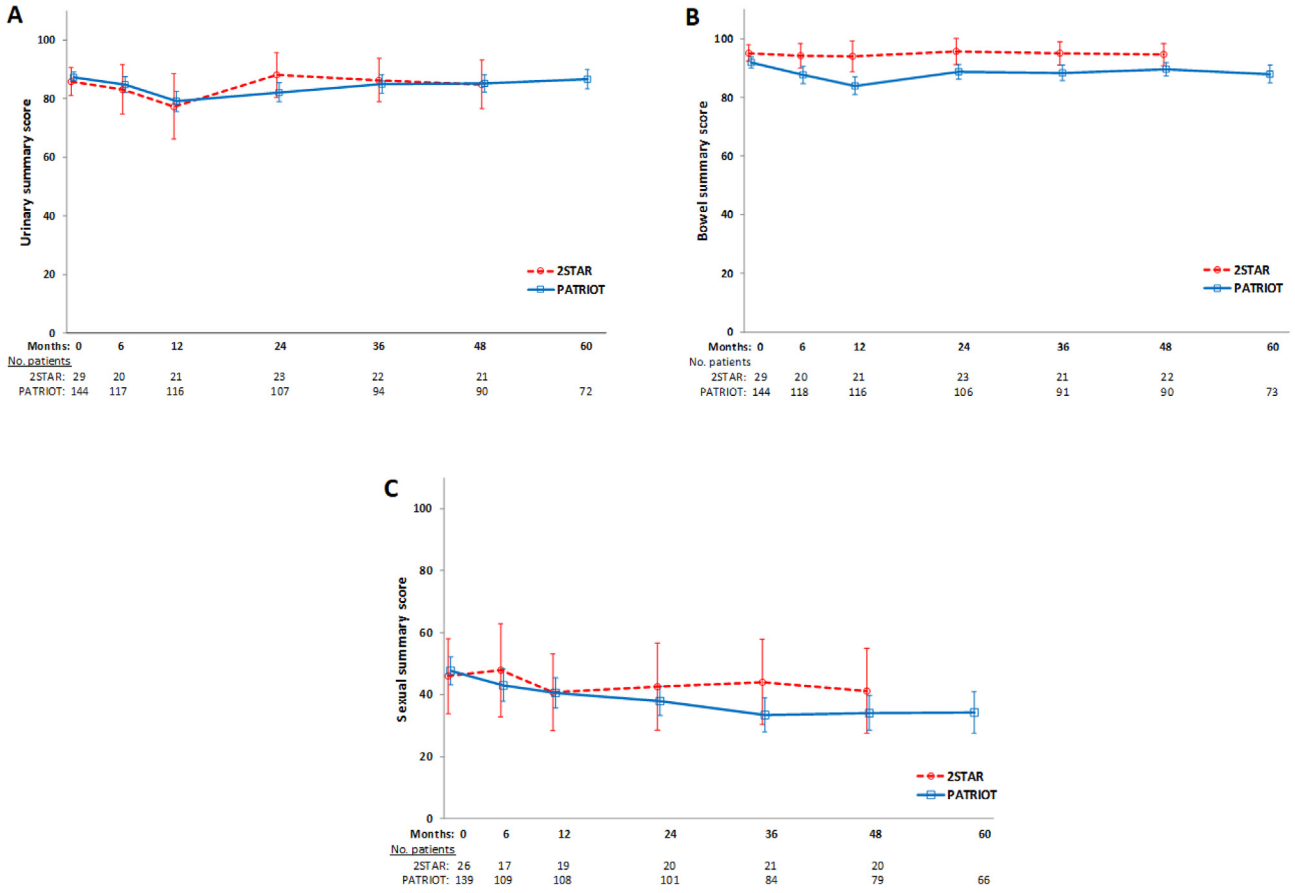

Fig. 1. Mean (+/- standard deviation) quality of life over time.

Table 3
Minimal clinically important change (MCIC) in the urinary, bowel and sexual domains in both trials.

	Small QOL Change (>0.5 SD)			Moderate QOL Change (>1 SD)		
EPIC QOL	2-Fraction	5-Fraction	*p*-value	2-Fraction	5-Fraction	*p*-value
Urinary			0.28			0.6
No MCIC	22 (75.8%)	88 (64.2%)		25 (86.2%)	110 (80.2%)	
MCIC	7 (24.1%)	49 (35.7%)		4 (13.7%)	27 (19.7%)	
Bowel			0.01			0.04
No MCIC	23 (82.1%)	79 (57.6%)		26 (92.8%)	104 (75.9%)	
MCIC	5 (17.8%)	58 (42.3%)		2 (7.1%)	33 (24%)	
Sexual			0.22			0.01
No MCIC	22 (84.6%)	92 (70.7%)		26 (100%)	107 (82.3%)	
MCIC	4 (15.3%)	38 (29.2%)		0 (0%)	23 (17.6%)	

Table 4
Quality of life changes for specific questions in EPIC.

	2-Fraction	5-Fraction	*p*-value
Among patients with "no to small problem" at baseline, How big a problem on follow up was:			
URINARY			
Dripping or leaking			0.47
"no" to "small" problem	28 (96.55%)	122 (98.39%)	
"moderate" to "big" problem	1 (3.45%)	2 (1.61%)	
Urinary function			0.56
"no" to "small" problem	26 (96.30%)	115 (97.46%)	
"moderate" to "big" problem	1 (3.70%)	3 (2.54%)	
BOWEL			
Urgency to have a bowel movement			0.49
"no" to "small" problem	29 (100%)	125 (98.43%)	
"moderate" to "big" problem	0 (0%)	2 (1.57%)	
Bloody stools			0.64
"no" to "small" problem	28 (100%)	130 (99.24%)	
"moderate" to "big" problem	0 (0%)	1 (0.76%)	
Bowel habits			0.59
"no" to "small" problem	25 (100%)	121 (96.03%)	
"moderate" to "big" problem	0 (0%)	5 (3.97%)	
SEXUAL			
Ability to have an erection			0.65
"no" to "small" problem	8 (80%)	77 (84.62%)	
"moderate" to "big" problem	2 (20%)	14 (15.38%)	
Overall Sexual function			0.42
"no" to "small" problem	8 (72.73%)	76 (82.61%)	
"moderate" to "big" problem	3 (27.27%)	16 (17.39%)	
Among patients with fairly good erections at baseline:			
Ability to have an erection on follow up			0.86
"fair" to "very good"	9 (75.00%)	53 (72.60%)	
"poor" to "not existent"	3 (25.00%)	20 (27.40%)	

Discussion

Hypofractionation was shown to be non-inferior to conventional fractionation in PCa in multiple randomized trials [16–19], with one randomized trial showing non-inferiority of ultrahypofractionation [20]. Multiple phase II trials showed that SABR is safe in PCa with excellent long-term outcomes [3–6]. A recent pooled analysis of individual patient data of 2142 men with PCa treated with SABR showed that the 7-year incidence of biochemical recurrence was 4.5% for those with low-risk disease and 10.2% for those with intermediate-risk disease [7]. The 7-year cumulative incidence of late grade 3 or higher GU toxicity was 2.4% and of late grade 3 or higher GI toxicity was 0.4%. The doses of SABR in that pooled analysis ranged from 33.5 to 40 Gy in 4 to 5 fractions, with 1885 of 2142 patients (88%) receiving 5 fractions.

We recently reported the results of a phase II trial (2STAR) that explored a novel SABR protocol of 26 Gy in 2 weekly fractions [8]. To our knowledge, no other trials exploring a 2-fraction protocol in PCa were reported in the literature. It was hypothesized that increasing the fraction size would take advantage of the low PCa α/β ratio to further enhance the therapeutic ratio, potentially leading to less long-term toxicity and improved QOL. At 5 years, this 2-fraction protocol had biochemical control rates and PSA nadirs that are comparable to previously published 5-fraction SABR protocols. In addition, the rates of acute and late CTCAE toxicities were comparable or slightly better compared to our 5-fraction SABR protocols [21,22]. More interestingly, the impact on bowel and sexual QOL seemed slightly more favorable compared to 5-fraction SABR. The improvement in QOL is likely due to the dose-fractionation, smaller PTV margin, and the use of an endorectal immobilization system. Given the favorable QOL outcomes seen in 2STAR, the next logical step was to statistically compare those results with the results from our previous 5-fraction randomized clinical trial (PATRIOT) [12].

The methodology of this current QOL comparison between 2STAR and PATRIOT was similar to our previous paper comparing SABR to HDR brachytherapy boost [15]. Both 2-fraction and 5-fraction SABR were associated with excellent biochemical control rates and low toxicity rates [8,12]. In this current analysis, there were no significant differences between the two patient

populations in key characteristics or baseline QOL. Both SABR cohorts appeared to have similar or lower MCICs than with HDR boost (urinary 58%, bowel 44%, sexual 55%). Patients that received the 2-fraction treatment had a significantly better mean bowel domain scores during follow-up compared to the 5-fraction treatment, with no difference in mean urinary or sexual domain scores. Patients that received the 2-fraction treatment also had a lower rate of mild QOL change (>0.5 SD) in the bowel domain, and a lower rate of moderate QOL change (>1 SD) in both sexual and bowel domains.

In conclusion, 2-fraction SABR is feasible to deliver and well tolerated with encouraging early signals of efficacy. Upon comparing this protocol with standard 5-fraction SABR, there were significant signals of improved bowel and sexual QOL with 2 fractions. The 2-fraction protocol is more convenient for the patient and less costly to the radiotherapy department, patient and system. Although this analysis compares two prospective phase II trials, the main limitation of this analysis is its post-hoc nature. A well conducted randomized trial of two vs. five fractions for prostate SABR is needed to confirm the promising findings of this study.

Declaration of Competing Interest

None.

Acknowledgments

Peer-reviewed grants gratefully acknowledged from Abbvie CARO Urological Research Award (Canada), Ride For Dad Huronia Chapter (Canada) and Prostate Cancer Canada.

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