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Original Article

Prostate-specific Antigen Bounce After Stereotactic Body Radiotherapy for Prostate Cancer: A Pooled Analysis of Four Prospective Trials

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Abstract

Aims: We conducted a pooled analysis of four prospective stereotactic body radiotherapy (SBRT) trials of low- and intermediate-risk prostate cancer to evaluate the incidence of prostate-specific antigen (PSA) bounce and its correlation with the time–dose–fraction schedule. The correlation between bounce with PSA response at 4 years (nadir PSA < 0.4 ng/ml) and biochemical failure-free survival (BFFS) was also explored.
Materials and methods: The study included four treatment groups: 35 Gy/five fractions once per week (QW) (TG-1; $n = 84$); 40 Gy/five fractions QW (TG-2; $n = 100$); 40 Gy/five fractions every other day (TG-3; $n = 73$); and 26 Gy/two fractions QW (TG-4; $n = 30$). PSA bounce was defined as a rise in PSA by 0.2 ng/ml (nadir + 0.2) or 2 ng/ml (nadir + 2.0) above nadir followed by a decrease back to nadir. Patients with fewer than three follow-up PSA tests were excluded from the pooled analysis.
Results: In total, 287 patients were included, with a median follow-up of 5.0 years. The pooled 5-year cumulative incidence of bounce by nadir + 2.0 was 8%. The 2-year cumulative incidences of PSA bounce by nadir + 0.2 were 28.9, 21, 19.6 and 16.7% ($P = 0.12$) and by nadir + 2.0 were 7.2, 8, 2.7 and 6.7% ($P = 0.32$) for TG-1 to TG-4, respectively. Multivariable analysis revealed that for nadir + 2.0, pre-treatment PSA (odds ratio 0.49; 95% confidence interval 0.26–0.97) correlated with PSA bounce. Although PSA bounce by nadir + 0.2 (odds ratio 0.10; 95% confidence interval 0.04–0.24) and nadir + 2.0 (odds ratio 0.29; 95% confidence interval 0.09–0.93) was associated with a lower probability of PSA response at 4 years, there was no association between bounce by nadir + 0.2 (hazard ratio 0.36; 95% confidence interval 0.08–1.74) or nadir + 2 (hazard ratio 1.77; 95% confidence interval 0.28–11.07) with BFFS.
Conclusion: The incidence of PSA bounce was independent of time–dose–fraction schedule for prostate SBRT. One in 13 patients experienced a bounce high enough to be misinterpreted as biochemical failure, and clinicians should avoid early salvage interventions in these patients. There was no association between PSA bounce and BFFS.

Key words: Prostate cancer; PSA bounce; stereotactic body radiotherapy; time–dose fractionation

Introduction

Radiotherapy is an effective treatment for organ-confined prostate cancer [1]. Studies have proven the efficacy of higher biological equivalent dose of external beam radiotherapy (EBRT) in attaining superior long-term biochemical control and distant metastasis-free survival in these patients [2–4]. Stereotactic body radiotherapy (SBRT) delivers a high dose per fraction in a limited number of fractions, resulting in a higher biological equivalent dose without an increase in the overall treatment time [5]. Randomised data have shown that 42.7 Gy in seven fractions is non-inferior to 78 Gy in 39 fractions in terms of biochemical control [6].

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Prostate-specific antigen (PSA) is used to monitor the treatment response after radiotherapy for prostate cancer [7]. Analysis of PSA kinetics after treatment potentially reflects clinical outcome. However, one of the challenges of a PSA-based response assessment is the occurrence of benign PSA fluctuations, known as 'PSA bounces', which can be misinterpreted as biochemical failure [8]. A number of studies have described PSA bounces after SBRT for prostate cancer [9–15]. However, the limitations of these studies include their retrospective nature, modest sample size, heterogeneous patient population or radiotherapy treatment, and short follow-up. Also, most studies used a low threshold for defining a PSA bounce. The literature is sparse regarding the impact of the time–dose–fraction (TDF) schedule on PSA bounce or the association of bounce with biochemical outcome after prostate SBRT. Therefore, we conducted a pooled analysis of four prospective clinical trials of SBRT for low-risk and intermediate-risk prostate cancer to evaluate the incidence of PSA bounce and correlation with the TDF scheme. We also analysed the influence of bounce on biochemical outcome.

Materials and Methods

We pooled data from four prospective clinical trials of SBRT for patients with prostate cancer: pHART3 (NCT01578902), pHART6 (NCT01146340), PATRIOT (NCT01423474) and 2-STAR (NCT02031328). PATRIOT was a multi-institutional, randomised phase II trial; the other three studies were single-institution phase II single-arm studies. All studies were approved by the institutional research ethics board of each participating centre. These studies were overseen by an independent data safety and monitoring committee. All patients provided written informed consent.

The details of the four studies have been previously published [16–19] but are summarised here. In pHART3, patients with cT1-T2b, Gleason sum $\leq$6 and PSA $\leq$10 ng/ml prostate cancer received 35 Gy in five fractions delivered once per week (QW) over 29 days [16]. pHART6 included patients with cT1-T2b, Gleason sum $\leq$6 and PSA $\leq$15 ng/ml; or cT1-T2b, Gleason sum 7 and PSA $\leq$10 ng/ml. Patients received 40 Gy/five fractions QW over 29 days [17]. In PATRIOT, patients with cT1-T2b, Gleason sum $\leq$7 and PSA $<$20 ng/ml were randomised to one of two treatment arms: 40 Gy/five fractions QW (overall treatment time 29 days) or 40 Gy/five fractions delivered every other day (EOD) (overall treatment time 9–12 days) [18]. 2-STAR was a phase II single-arm study of patients with cT1-T2b, Gleason sum $\leq$7 and PSA $<$20 ng/ml prostate cancer treated with a total dose of 26 Gy/two fractions QW [19].

Day 0 was defined as the start of radiotherapy. In all studies, PSA was assessed at baseline, months 3 and 6, and every 6 months thereafter. In PATRIOT and 2-STAR, PSA was also assessed at week 6. Follow-up for all end points was continued for at least 5 years. Patients with few than three follow-up PSA tests were excluded from the pooled analysis.

The objectives of this study were to evaluate the correlation of different TDF schedules with PSA bounce and to explore the correlation of bounce with PSA response at 4 years and biochemical failure-free survival (BFFS). Biochemical failure was defined as any PSA of nadir + 2 ng/ml without a further decrease back to or below the nadir [20]. PSA response was defined as a post-treatment PSA nadir $<$0.4 ng/ml at 4 years [21,22]. The treatment groups were defined as: TG-1 35 Gy/five fractions QW; TG-2 40 Gy/five fractions QW; TG-3 40 Gy/five fractions EOD; and TG-4 26 Gy/two fractions QW. Using a PSA bounce definition of nadir + 0.2 or nadir + 2.0, the time to first bounce was calculated from day 0 to the first PSA bounce (peak) if a patient had a bounce or to the date of last follow-up or death if a patient did not have a bounce. Patients without a bounce were censored. The cumulative incidences of bounce by both definitions were compared among the treatment groups.

Statistical Analysis

PSA bounce was identified using two definitions: an increase in PSA of either 0.2 ng/ml (nadir + 0.2) or 2 ng/ml above nadir (nadir + 2.0) followed by a decrease back to or below nadir. Peak PSA for a bounce was defined as the highest PSA level attained during that event of bounce. Bounce magnitude was calculated as the difference between the peak PSA and the immediate pre-bounce nadir PSA. The duration of bounce was measured from the pre-bounce nadir to the time when the PSA returned to or dropped below the pre-bounce nadir. BFFS was calculated from the date of first radiotherapy to biochemical relapse if a patient had a failure; or to the last date of follow-up or death if a patient had no failure.

Descriptive statistics were used to report patient characteristics and were summarised as median with interquartile range (IQR) for continuous variables and proportions for categorical variables. The Kruskal–Wallis non-parametric test and Fisher's exact test were applied to compare continuous and categorical variables.

Univariable (UVA) and multivariable (MVA) logistic regression analyses were conducted to identify predictors of PSA bounce and PSA response; covariates included age, tumour stage, prostate volume, Gleason categories, baseline International Prostate Symptom Score, pre-treatment PSA and treatment groups. Natural log-transformation was applied to pre-treatment PSA to normalise the distribution. Backward stepwise selection of variables was used in MVA. Odds ratios and 95% confidence intervals were calculated for each predictive factor. The cumulative incidence of biochemical failure was estimated using the Nelson–Aalen method. Cox proportional hazard models were used to explore the association of bounce with BFFS adjusted for covariates, as mentioned above. Hazard ratios with 95% confidence intervals and P values were reported.

All variables with $P < 0.10$ obtained from UVA were included in the MVA. $P < 0.05$ was considered to be statistically significant. All statistical analyses were carried out using SAS statistical software (version 9.4) [23].

Results

In total, 296 patients were treated in the four trials. Nine patients were excluded as they had fewer than three follow-up PSA measurements. Therefore, 287 patients were included in the bounce analysis. The median follow-up was 5.0 years (IQR 3.9–8.9) and the median number of follow-up PSA measurements was 10 (IQR 8–13). Patient characteristics are summarised in Table 1. The median age of the study population was 69 years (IQR 64–74). The median pre-treatment PSA was 6.78 ng/ml (IQR 4.71–9.4). The median prostate volume was 37 cm^3 (IQR 28–51). About 75% ($n = 215$) of patients had cT1c tumours; cT2 tumours were noted in 24% ($n = 68$) of patients. Gleason 3 + 3 adenocarcinoma was found in 47% ($n = 135$), 3 + 4 in 40% ($n = 116$) and 4 + 3 in 13% ($n = 36$) of patients. Overall, 2% ($n = 6$) of patients had short-term neoadjuvant androgen deprivation therapy (ADT) with gonadotropin-releasing hormone analogue for ≤6 months.

Prostate-specific Antigen Bounce Characteristics

The cumulative incidence of PSA bounce by nadir + 0.2 was 22.5 and 31.1% at 2 and 5 years, respectively (Figure 1A). There was no difference in the cumulative incidence of bounce by nadir + 0.2 among the four treatment groups ($P = 0.12$), with 2-year cumulative incidences of 28.9, 21, 19.6 and 16.7%, respectively (Figure 1B). At 2 and 5 years the cumulative incidences of bounce by nadir + 2.0 were 6.3 and 8%, respectively (Figure 2A). There was no significant difference in bounce incidence among the four treatment groups ($P = 0.32$), with 2-year cumulative incidences of 7.2, 8, 2.7 and 6.7%, respectively (Figure 2B).

Using a definition of nadir + 0.2, 31.4% ($n = 90$) of patients had at least one PSA bounce, whereas 10.1% ($n = 29$) and 2.8% ($n = 8$) had at least two and three bounces, respectively. The median time to first bounce in all patients was 17.8 months (IQR 11.8–25.1) and for the four treatment groups were 18.2, 17.7, 17 and 11.5 months, respectively ($P = 0.157$). The pooled median bounce magnitude was 0.60 ng/ml (IQR 0.35–1.61) and the bounce magnitude was not significantly different among the treatment groups (0.55 versus 0.59 versus 0.65 versus 1.53 ng/ml, respectively; $P = 0.281$). The median duration of bounce was 17.3 months (IQR 11.9–23.9). The duration of bounce was significantly different among the four treatment groups (18.2 versus 15.0 versus 12.8 versus 11.9 months, respectively; $P = 0.005$). PSA bounce characteristics are summarised in Table 2.

Using a definition of nadir + 2.0, 8.4% ($n = 24$) of patients had at least one PSA bounce. Only one patient experienced two bounces. As shown in Table 2, the median time to first bounce was 16.7 months for all patients (IQR 11.8–23.8), with no significant difference among the four treatment groups (18.2 versus 15.7 versus 10 versus 14 months, respectively; $P = 0.095$). The pooled median bounce duration and magnitude were 17.1 months (IQR 12.2–20.4) and 2.94 ng/ml (IQR 2.21–4.02), respectively, with no significant difference in duration ($P = 0.694$) or magnitude ($P = 0.178$) among the four treatment groups (Table 2).

UVA showed that for PSA bounce defined by nadir + 0.2, older age, cT2 tumours, higher pre-treatment PSA and Gleason score 4 + 3 were associated with a lower incidence of bounce, whereas TG-1 was associated with a higher incidence of bounce (Table 3). On MVA, older patients (odds ratio 0.95; 95% confidence interval 0.91–0.98) and those with cT2 tumours (odds ratio 0.43; 95% confidence interval 0.21–0.84) were noted to have a lower incidence of bounce. For bounce by nadir + 2.0, higher pre-treatment PSA was found to be the lone factor associated with a lower incidence of bounce (odds ratio 0.49; 95% confidence interval 0.26–0.97) (Table 3).

Biochemical Response

At 4 years, 148/233 (63.5%) patients had a PSA nadir < 0.4 ng/ml. There was a significant difference in PSA response at 4 years among treatment groups: 23/76 (30.3%); 73/87 (83.9%); 47/60 (78.3%) and 5/10 (50.0%) in TG-1 to TG-4, respectively ($P < 0.0001$). The median PSA nadir at 4 years was 0.53 ng/ml (IQR 0.36–1.04), 0.14 ng/ml (IQR 0.05–0.31), 0.16 ng/ml (IQR 0.08–0.29) and 0.39 ng/ml (IQR 0.2–1.4) in the four treatment groups ($P < 0.001$). The MVA determined that patients with a PSA bounce defined as nadir + 0.2 (odds ratio 0.10; 95% confidence interval 0.04–0.24; $P < 0.0001$) and nadir + 2.0 (odds ratio 0.29; 95% confidence interval 0.09–0.93; $P < 0.047$) were less likely to achieve a PSA nadir < 0.4 ng/ml at 4 years.

Only 10 patients developed a biochemical failure. The cumulative incidence of biochemical failure was 0% for patients with a 4-year PSA nadir <0.4 ng/ml compared with 4 and 12% at 5 and 10 years, respectively, for those with a PSA nadir ≥0.4 ng/ml ($P = 0.007$). Despite the correlation between PSA bounce and response, there was no significant association between bounce by nadir + 0.2 (hazard ratio 0.36; 95% confidence interval 0.08–1.74; $P = 0.204$) or nadir + 2.0 (hazard ratio 1.77; 95% confidence interval 0.28–11.07; $P = 0.539$) and BFFS (Supplementary Table S1).

Discussion

To the best of our knowledge, this is the first report highlighting the post-SBRT 'false call' phenomenon of high-rising PSA bounces (nadir + 2 ng/ml) that occur in about one in 13 patients and can be misinterpreted as biochemical failure. We found that the incidence of PSA bounce was independent of the TDF schedule of prostate SBRT. Although PSA bounce significantly correlated with PSA response at 4 years, it had no association with BFFS. Compared with existing studies of PSA bounce, the current pooled analysis of prospective studies had a number of strengths, including uniform radiation treatment protocols, predefined follow-up policies and longer follow-up duration.

The most common threshold for defining a PSA bounce in the SBRT literature is 0.2 ng/ml [9,11,12,14]. None of the existing SBRT studies described PSA bounce using the nadir + 2.0 definition, which is especially pertinent given the

Table 1
Patient characteristics

	Total $n = 287$		35 Gy/5 fractions QW (TG-1; $n = 84$)	40 Gy/5 fractions QW (TG-2; $n = 100$)	40 Gy/5 fractions EOD (TG-3; $n = 73$)	26 Gy/2 fractions QW (TG-4; $n = 30$)	*P* value
Age (years)							0.002
Median (IQR)	69 (64, 74)		67 (61, 71)	70 (65, 75)	71 (66, 75)	67 (62, 71)	
Prostate volume							0.799
Median (IQR)	37 (28, 51)		37 (29, 55)	38 (28, 51)	36 (28, 53)	36 (27, 42)	
IPSS							0.177
Median (IQR)	5 (3, 10)		5 (3, 9)	6 (3, 12)	4 (2, 8)	5 (3, 11)	
Pre-treatment PSA							<0.0001
Median (IQR)	6.78 (4.71, 9.40)		5.31 (4.21, 7.30)	6.44 (4.59, 9.37)	8.25 (6.24, 12.60)	8.59 (5.56, 11.40)	
Total number of PSA measurements							<0.0001
Median (IQR)	10 (8, 13)		15 (13, 17)	10 (8, 11)	9 (8, 10)	7 (6, 7)	
Gleason score categories							<0.0001
3 + 3	135	(47.04%)	84 (100%)	29 (29.00%)	18 (24.66%)	4 (13.33%)	
3 + 4	116	(40.42%)	0 (0%)	54 (54.00%)	39 (53.42%)	23 (76.67%)	
4 + 3	36	(12.54%)	0 (0%)	17 (17.00%)	16 (21.92%)	3 (10.00%)	
Clinical T-stage							0.0003
T1a	2	(0.70%)	1 (1.19%)	0 (0%)	0 (0%)	1 (3.33%)	
T1c	215	(74.91%)	77 (91.67%)	72 (72.00%)	47 (64.38%)	19 (63.33%)	
T2a	49	(17.07%)	6 (7.14%)	22 (22.00%)	15 (20.55%)	6 (20.00%)	
T2b	18	(6.27%)	0 (0%)	6 (6.00%)	9 (12.33%)	3 (10.00%)	
T2c	1	(0.35%)	0 (0%)	0 (0%)	0 (0%)	1 (3.33%)	
Unknown	2	(0.70%)	0 (0%)	0 (0%)	2 (2.74%)	0 (0%)	
Duration of follow-up (years)							<0.0001
Median (IQR)	5.01 (3.85, 8.85)		9.60 (9.04, 10.12)	4.74 (4.06, 6.58)	4.43 (3.67, 4.96)	3.20 (3.09, 3.51)	

EOD, every other day; IPSS, International Prostate Symptom Score; IQR, interquartile range; PSA, prostate-specific antigen; QW, once per week; TG, treatment group.

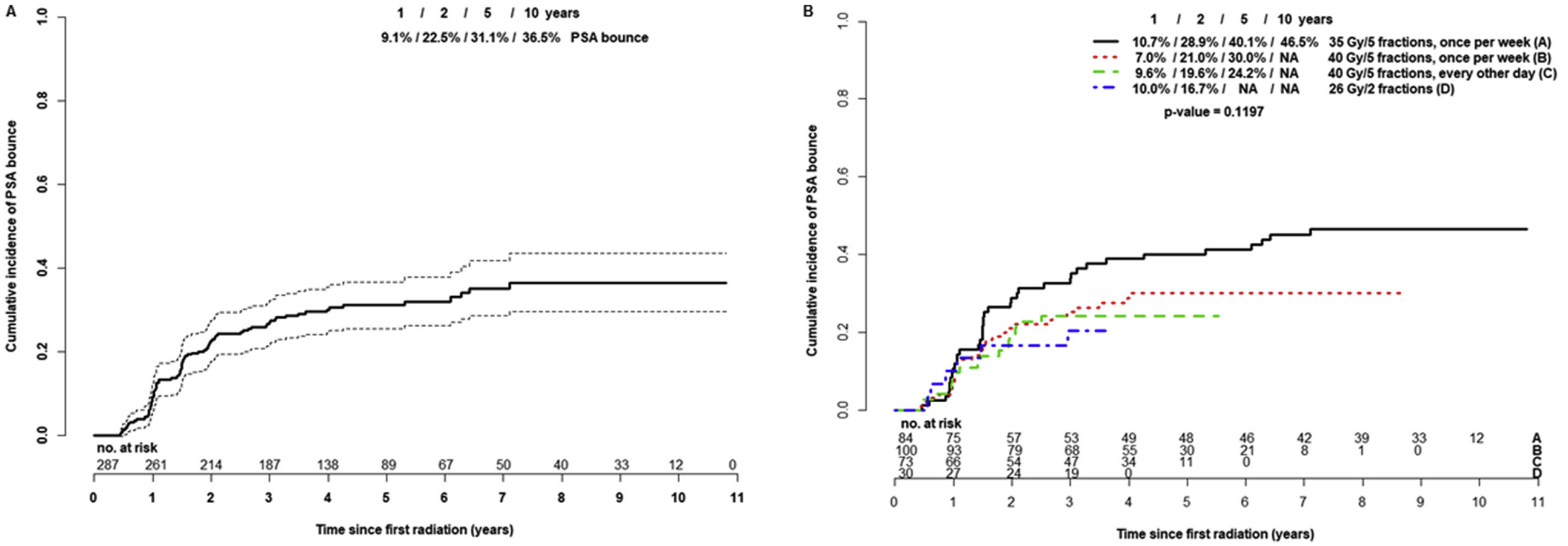

Fig 1. Cumulative incidence of prostate-specific antigen (PSA) bounce (nadir + 0.2 ng/ml) in (A) all patients and (B) the four treatment groups.

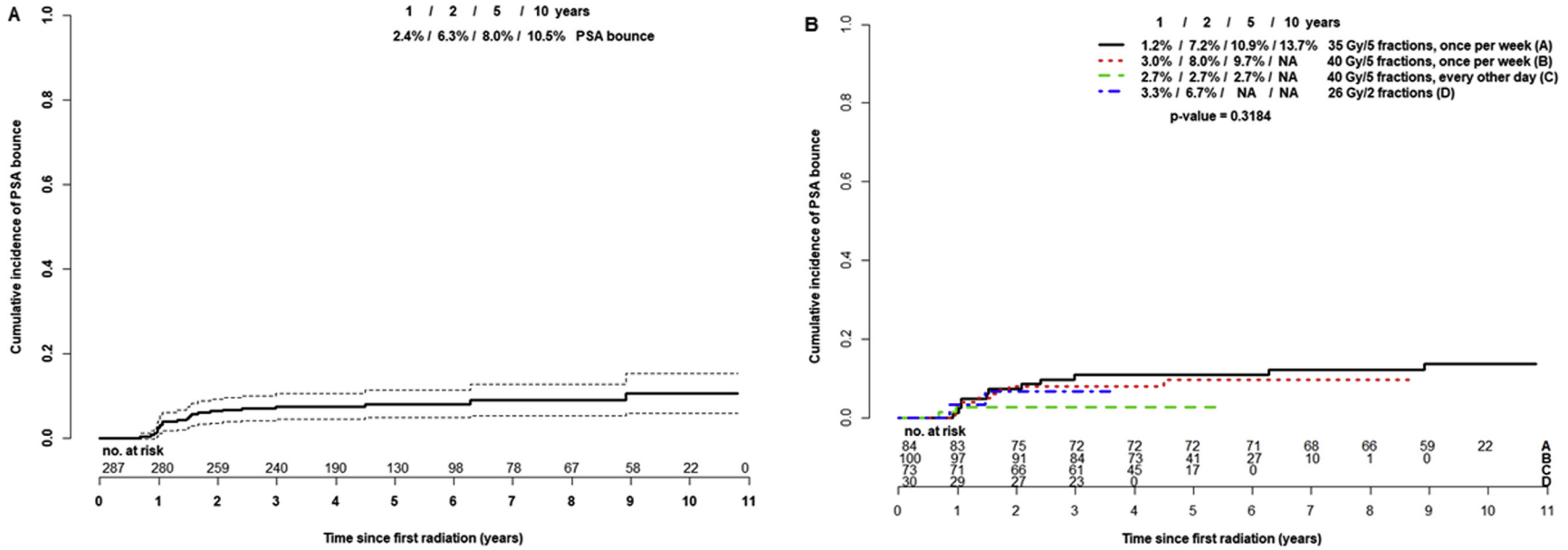

Fig 2. Cumulative incidence of prostate-specific antigen (PSA) bounce (nadir + 2.0 ng/ml) in (A) all patients and (B) the four treatment groups.

Table 2
Prostate-specific antigen (PSA) bounce characteristics ($n = 287$)

	35 Gy/5 fractions QW (TG-1; $n = 84$)	40 Gy/5 fractions QW (TG-2; $n = 100$)	40 Gy/5 fractions EOD (TG-3; $n = 73$)	26 Gy/2 fractions QW (TG-4; $n = 30$)	*P* value
PSA bounce by nadir + 0.2 ng/ml					
No. PSA bounces					0.177
Patients with ≥1 bounce	38 (45.2%)	29 (29%)	17 (23.3%)	6 (20%)	
Patients with ≥2 bounces	20 (23.8%)	6 (6%)	3 (4.1%)	0 (0.00%)	
Patients with ≥3 bounces	6 (7.1%)	2 (2%)	0 (0.0%)	0 (0.0%)	
PSA bounce magnitude *					0.281
n	64	37	20	6	
Median (IQR)	0.55 (0.33, 1.57)	0.59 (0.40, 1.98)	0.65 (0.38, 1.36)	1.53 (0.95, 2.20)	
Duration of PSA bounces (months) *					0.005
n	64	37	20	6	
Median (IQR)	18.2 (12.2, 26.4)	15 (12, 19.6)	12.8 (11.8, 18.3)	11.9 (9.3, 12.02)	
Time to first PSA bounce (months)					0.157
Median (IQR)	18.2 (12.3, 36.1)	17.7 (12.2, 24.2)	17 (11.5, 23.4)	11.5 (7.4, 17.7)	
PSA bounce by nadir + 2 ng/ml					
No. PSA bounces					0.770
Patients with ≥1 bounce	11 (13.1%)	9 (9%)	2 (6.2%)	2 (6.7%)	
Patients with ≥2 bounces	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.00%)	
PSA bounce magnitude *					0.178
n	12	9	2	2	
Median (IQR)	2.68 (2.14, 4.22)	3.87 (2.94, 4.60)	2.20 (2.19, 2.21)	3.07 (2.20, 3.93)	
Duration of PSA bounces (months) *					0.694
n	12	9	2	2	
Median (IQR)	16.5 (12.1, 40.02)	20.4 (15, 21)	13.7 (13.1, 14.3)	14.6 (11.9, 17.3)	
Time to first PSA bounce (months)					0.095
Median (IQR)	18.2 (12.7, 35.8)	15.7 (11.8, 20.01)	10 (8.3, 11.7)	14 (10.4, 17.7)	

EOD, every other day; IPSS, International Prostate Symptom Score; IQR, interquartile range; QW, once per week; TG, treatment group.
* All bounces (including multiple bounces from the same patient) were included.

potential for misdiagnosis of a biochemical failure ('false call'), which can lead to both patient and physician anxiety and may result in inappropriate management. Pickles [8] reported a false call rate (FCR) of 2% in their prostate cancer cohort treated with EBRT or brachytherapy with or without ADT. Merrick *et al.* [24] reported a FCR of 0.6% after a median follow-up of 56 months in patients treated with short-term ADT and brachytherapy. Our observation of 8% FCR is compatible with brachytherapy studies that have reported FCR ranging from 2.5 to 15% [25–29].

The duration of PSA bounce is also clinically important, particularly in younger patients, as they have a higher probability of experiencing bounces [9,27,30,31]. With a longer duration of bounce, there is a greater concern of biochemical relapse, with the potential for unnecessary salvage treatment for an early rising PSA that might just be a benign oscillation. With the nadir + 2.0 definition our study reported a median bounce duration of 17 months, with no significant difference across the treatment groups. This is shorter than contemporary brachytherapy studies that have reported bounce durations in the range of 19–29 months [26–28].

The reports on the influence of radiation dose on bounce are contradictory. Romesser *et al.* [32] found that higher radiotherapy dose was associated with bounce after EBRT, whereas Stock *et al.* [33] had similar findings with higher doses (>160 Gy) after brachytherapy. On the contrary, Merrick *et al.* [24] reported that a higher radiation dose was associated with a lower incidence of bounce. We did not find any correlation of bounce with the dose–fraction regimens used in these four SBRT studies.

Our study noted that patients with PSA bounces were less likely to achieve a PSA response at 4 years, which is in agreement with other studies. Kole *et al.* [13] found that patients with post-SBRT PSA bounces had a higher PSA nadir after a median follow-up of 3 years. However, the literature describing the correlation of bounce and BFFS is conflicting. In a meta-analysis of 3011 patients, Bernstein *et al.* [34] determined PSA bounce to be a predictor of superior biochemical outcome after brachytherapy. Romesser *et al.* [32] also showed that in patients treated with dose-escalated EBRT (≥75 Gy), post-treatment bounce (nadir + 0.2) was associated with improved BFFS. By contrast, a pooled analysis of 4839 men treated with EBRT found that PSA bounce (an increase ≥ 0.4 ng/ml) was an independent predictor of biochemical failure [35]. In the current study, we did not observe any association between post-SBRT PSA bounce and BFFS.

The limitations of our study are acknowledged. The four prospective studies included in this analysis differ with respect to follow-up duration and sample size. As PSA kinetics are a function of time, study results should be

Table 3
Factors associated with prostate-specific antigen (PSA) bounce

PSA bounce by nadir + 0.2	Odds ratio (95% confidence interval)	P value
Univariable analysis		
Age	0.94 (0.91–0.98)	0.002
T stage (T2 versus T1)	0.39 (0.19–0.75)	0.007
Prostate volume	1.01 (0.99–1.02)	0.394
IPSS score (log)	0.78 (0.56–1.09)	0.146
Gleason score		0.01
3 + 4 versus 3 + 3	0.66 (0.39–1.12)	0.256
4 + 3 versus 3 + 3	0.2 (0.06–0.54)	0.01
4 + 3 versus 3 + 4	0.3 (0.01–0.92)	0.035
Pre-treatment PSA (log)	0.65 (0.42–0.99)	0.048
Treatment		0.01
35 Gy/5 fractions QW versus 26 Gy/2 fractions QW	3.3 (1.29–9.67)	0.001
40 Gy/5 fractions QW versus 26 Gy/2 fractions QW	1.63 (0.64–4.78)	0.924
40 Gy/5 fractions EOD versus 26 Gy/2 fractions QW	1.21 (0.44–3.7)	0.269
35 Gy/5 fractions QW versus 40 Gy/5 fractions QW	2.02 (1.11–3.72)	0.024
35 Gy/5 fractions QW versus 40 Gy/5 fractions EOD	2.72 (1.36–5.44)	0.005
40 Gy/5 fractions QW versus 40 Gy/5 fractions EOD	1.35 (0.67–2.69)	0.402
Multivariable analysis		
Age	0.95 (0.91–0.98)	0.006
T-stage (T2 versus T1)	0.43 (0.21–0.84)	0.018
PSA bounce by nadir + 2.0		
Univariable analysis		
Age	0.95 (0.9–1.01)	0.105
T stage (T2 versus T1)	0.62 (0.17–1.7)	0.392
Prostate volume	0.99 (0.97–1.02)	0.511
IPSS score (log)	0.72 (0.41–1.26)	0.243
Gleason score		0.455
3 + 4 versus 3 + 3	0.74 (0.3–1.73)	0.696
4 + 3 versus 3 + 3	0.35 (0.04–1.52)	0.309
4 + 3 versus 3 + 4	0.48 (0.08–2.85)	0.418
Pre-treatment PSA (log)	0.49 (0.26–0.97)	0.035
Treatment		0.213
35 Gy/5 fractions QW versus 26 Gy/2 fractions QW	1.78 (0.49–9.61)	0.071
40 Gy/5 fractions QW versus 26 Gy/2 fractions QW	1.18 (0.31–6.46)	0.552
40 Gy/5 fractions EOD versus 26 Gy/2 fractions QW	0.4 (0.06–2.7)	0.096
35 Gy/5 fractions QW versus 40 Gy/5 fractions QW	1.51 (0.6–3.77)	0.381
35 Gy/5 fractions QW versus 40 Gy/5 fractions EOD	4.47 (1.09–18.42)	0.038
40 Gy/5 fractions QW versus 40 Gy/5 fractions EOD	2.97 (0.71–12.48)	0.138
Multivariable analysis		
Pre-treatment PSA (log)	0.49 (0.26–0.97)	0.035

EOD, every other day; IPSS, International Prostate Symptom Score; QW, once per week.

interpreted accordingly. The number of patients in TG-4 was comparatively modest compared with the other groups, which may limit the power to detect significant differences. Moreover, 2% of our study population had short-term neoadjuvant ADT. Only a small number of patients experienced biochemical failure and, therefore, our analysis of an association of bounce with BFFS may be underpowered.

In conclusion, this pooled analysis highlights that the incidence of PSA bounce is independent of TDF schema of SBRT. One in 13 patients experiences a PSA bounce high enough to mimic biochemical failure. Therefore, clinicians should be cautious when considering further management, including necessary investigations and salvage interventions, during the first 2 years after prostate SBRT. There was no association between PSA bounce and BFFS.

Conflict of Interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2019.05.001.

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