Original Contribution Kitasato Med J 2023; 53: 76–85

Prostate-specific antigen bounce after permanent Iodine-125 implant brachytherapy in Japanese men: a nationwide J-POPS multi-institutional prospective cohort study

Takefumi Satoh,[1,2] Hiromichi Ishiyama,[3] Manabu Aoki,[4] Norihisa Katayama,[5] Nobumichi Tanaka,[6] Seiji Naito,[7] Kazuto Ito,[8] Atsunori Yorozu,[9] Takashi Kikuchi,[10] Takushi Dokiya,[11] Shiro Saito[12]

[1] Satoh Takefumi Prostate Clinic, Tokyo
[2] Department of Urology, Kitasato University Hospital, Kanagawa
[3] Department of Radiation Oncology, Kitasato University School of Medicine, Kanagawa
[4] Department of Radiation Oncology, Jikei University School of Medicine, Tokyo
[5] Department of Radiology, Okayama University School of Medicine, Okayama
[6] Department of Urology, Nara Medical University, Nara
[7] Department of Urology, Harasanshin Hospital, Fukuoka
[8] Institute of Preventive Medicine, Kurosawa Hospital, Gunma
[9] Department of Radiation Oncology, National Hospital Organization Tokyo Medical Center, Tokyo
[10] Translational Research Informatics Center, Hyogo
[11] Department of Radiation Oncology, Saitama Medical College, Saitama
[12] Department of Urology, National Hospital Organization Tokyo Medical Center, Tokyo

Objective: To evaluate the incidence of benign prostate-specific antigen (PSA) bounce and biochemical recurrence-free survival between PSA bounce and non-bounce patients treated with permanent prostate brachytherapy (BT).

Methods: A total of 991 patients underwent BT without hormonal therapy or external beam radiotherapy. Three definitions of bounce were used: A, rise >35% over the previous value; B, rise ≥0.2 ng/mL; and C, rise ≥0.4 ng/mL, followed by a subsequent fall.

Results: The likelihood of experiencing a PSA bounce was 46.5% for definition A, 42.9% for definition B, and 26.8% for definition C, with a median follow-up time of 60 months. Among the pre- and posttreatment factors, younger age predicted a PSA bounce on multivariate analysis using all definitions (A, $P < 0.0001$; B, $P < 0.0001$; C, $P < 0.0001$). The 5-year biochemical recurrence-free survival rate was 94.6%. Patients with a PSA bounce had better biochemical recurrence-free survival (98.1% with bounce vs. 91.7% without bounce, $P < 0.0001$ [definition A]).

Conclusion: PSA bounce may possibly be a beneficial phenomenon following prostate BT and must be excluded before implementing salvage interventions.

Keywords: prostate cancer, brachytherapy, prostate-specific antigen bounce, outcomes, prospective cohort study

Introduction

Prostate-specific antigen (PSA) is a sensitive measure of treatment outcome after definitive treatment of prostate cancer. The kinetics of PSA after radiation treatment (RT) and radical prostatectomy significantly differ.[1,2] After RT, unlike after radical prostatectomy, the PSA level consecutively decreases slowly and may temporarily increase over several months, which does not reflect disease recurrence. This phenomenon is known as benign PSA bounce.[3,4] We have previously reported that benign PSA bounce occurred at a rate of 20%–50% in patients who underwent permanent prostate brachytherapy (BT), and the median time to PSA

Received 23 May 2023, accepted 19 July 2023
Correspondence to: Takefumi Satoh, Satoh Takefumi Prostate Clinic, Lifix Bld. 2F, 4-14-14, Haramachida, Machida, Tokyo 194-0013, Japan
E-mail: tsatoh@kitasato-u.ac.jp

bounce was 12–18 months after BT, depending on the definition.[2] Multivariate Cox proportional-hazards regression analysis revealed predictors for PSA bounces with each clinical parameter. The only predictor of a PSA bounce after BT was younger age.

However, previous studies had several limitations. They were retrospective studies with small sample sizes and relatively short follow-up periods. Furthermore, the correlation between PSA bounce and recurrence-free survival remains unclear.

The present study aimed to evaluate the incidence and timing of PSA bounce and correlate that with clinical and dosimetric factors after BT. The present study also examined the correlation between PSA bounce and biochemical recurrence-free survival after BT alone, with no hormonal therapy or external beam radiotherapy, based on the world's largest prospective cohort study.

Materials and Methods

Study cohort

A nationwide prospective cohort study titled Japanese Prostate Cancer Outcome Study of Permanent Iodine-125 (I-125) Seed Implantation (J-POPS) was started in July 2005.[5] Overall, 6,927 patients were enrolled by the end of 2010, and approximately 40% of all patients were treated around the country. Of the 2,354 patients enrolled in cohort 1 from 46 facilities between July 2005 and June 2007, 991 patients were included, and 2 duplicate enrollments, 12 previously treated patients, 70 ineligible patients, 1,147 hormonal treated patients, and 132 patients, whose treatment had been combined with external beam radiotherapy, were excluded. Eligible patients for the study had to have a minimum of a 1-year follow-up and at least 3 posttreatment PSA measurements.

This study was approved by the foundation for Biochemical Research and Innovation, by the ethical review committee of the Translational Research Informatics Center, and by the institutional review boards of all participating facilities.[5]

Implant procedures

The prescribed dose to the periphery of the prostate was 145 to 160 grays (Gy) using the previously described prostate implant technique.[6–8] In both the preplan and postimplant analyses, a radiotherapy planning system dedicated for transperineal interstitial BT was used, and all doses were defined using the TG43 criteria. I-125 seeds were loose seeds, and OncoSeed (Nihon Medi-Physics, Tokyo, Japan) or Brachy source (Medicon, Osaka, Japan) was used and implanted using a Mick applicator (Mick TP 200 & TPV Mick Radio-Nuclear Instruments, Mount Vernon, NY, USA) in all patients.[9] Approximately 1 month after implant, computed tomography-based dosimetric analysis was conducted. Postimplant dosimetry data were available for all patients. To analyze the effect of the dose on the PSA bounce, dose was defined as the dose delivered to 90% of the gland on the 1-month postimplant dose–volume histogram (D90).

Definition of PSA bounce and biochemical failure

PSA bounce was defined as an initial elevation of the PSA level (excluding the 1-month PSA value) from the previous value with a subsequent decrease to pre-bounce baseline PSA levels. Three definitions of PSA bounce were used: A, rise >35% over the previous value[2,4]; B, rise ≥0.2 ng/mL[2–4]; and C, rise ≥0.4 ng/mL.[2,4] We have previously reported using these definitions in multi-institutional pooled analyses. We therefore used the same definitions for the present study.[2]

Follow-up

The date of BT was considered day 0 of follow-up. The PSA value was determined 1 month after implant, at 3-month follow-up intervals for 2 years after implant, and continuing at 6-month follow-up intervals thereafter.

Statistical analyses

All intervals were calculated from the date of BT. The Chi-squared test, Mann–Whitney two-sample test, and Cox proportional-hazards regression analysis were conducted for univariate analysis, as appropriate. Cox proportional-hazards regression analysis was employed in the multivariate models. The significance level was set at 0.05. For these analyses, we excluded patients who exhibited a PSA bounce after a PSA biochemical failure. Therefore, the sample sizes for these analyses varied depending on the definition of PSA bounce. All statistical analyses were conducted using the SAS statistical software (version 9.3; SAS Institute Inc., Cary, NC, USA) at the Translational Research Informatics Center.[5]

The J-POPS study was funded by the Foundation for Biomedical Research and Innovation (Kobe) and approved by the ethics review committee of the Translational Research Informatics Center (Translational Research Informatics Center, Kobe, Japan) of the Foundation for Biochemical Research and Innovation (approval no. 05-01, 195; May 6, 2005) and the individual institutional review boards of all participating facilities (TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00534196).

Results

The patients' clinical disease characteristics and dosimetric variables are presented in Table 1. Among the patients, 585 (59.0%), 380 (38.3%), and 7 (0.7%) had low-, intermediate-, and high-risk diseases, respectively. The median age at diagnosis was 68 years. Furthermore, the median percentage of the prostate volume receiving a minimum of 100% of the prescribed dose (V_{100}) was 95.1%, and the median minimum dose in Gy receiving 90% of the prostate volume (D_{90}) was 161.8 Gy. The median follow-up for the entire group was 60 months (range, 12–85 months).

The actuarial likelihood of experiencing a PSA bounce was 46.5% for definition A, 42.9% for definition B, and 26.8% for definition C. Figure 1 presents the histogram of the time to develop a PSA bounce based on definition A. The median times to a bounce were 24.1, 18.3, and 19.3 months for definitions A, B, and C, respectively.

The effects of patient age, initial PSA, Gleason score, clinical T stage, prostate volume, PSA density, D_{90}, V_{100}, and V_{150} on developing a PSA bounce were tested via univariate analysis using each of the 3 definitions (Table 2). Using definition A, patient age, initial PSA, Gleason score, and D_{90} (Gy) significantly affected the incidence of bounce ($P < 0.001$, $P = 0.0034$, $P = 0.0036$, and $P = 0.0496$, respectively). Using definition B, patient age, clinical T stage, Gleason score, and V_{150} (%) significantly affected the incidence of bounce ($P < 0.001$, $P < 0.001$, $P = 0.0495$, and $P = 0.0394$, respectively). Using definition C, patient age, clinical T stage, and Gleason score significantly affected the incidence of bounce ($P < 0.001$, $P = 0.0129$, and $P = 0.0215$, respectively). The multivariate Cox proportional-hazards regression analysis determined the predictors for PSA bounces (Table 3). On multivariate analysis using definition A, patient age, initial PSA, and Gleason score predicted a PSA bounce ($P < 0.001$, $P = 0.012$, and $P = 0.023$, respectively). On multivariate analysis using definition B, patient age, Gleason score, and V_{150} (%) predicted a PSA bounce ($P < 0.001$, $P = 0.001$, and $P = 0.044$, respectively). On multivariate analysis using definition C, patient age, clinical T stage, and Gleason score predicted a PSA bounce ($P < 0.001$, $P = 0.043$, and $P = 0.048$, respectively).

After a median follow-up of 60.0 months (range, 12–85 months), 49 (5.4%) and 65 (7.0%) of the patients had a PSA failure based on the Phoenix (Figure 2A) and ASTRO (Figure 2B) definitions, respectively.

Figure 3 presents the biochemical recurrence-free survival for patients with or without a PSA bounce

Table 1. Patients' characteristics before treatment and dosimetric variables after treatment

Factors	Values
N	991
Age (years)	
Median	68
Range	49–89
Initial PSA (ng/ml)	
Median	6.02
Range	1.60–22.12
Clinical T stage (n)	
T1a–b	2
T1c	771
T2a	163
T2b	35
≤T2c	15
Missing	5
Gleason score (n)	
≤6	682
7	302
≥8	4
Missing	3
Prostate volume (cm^3)	
Median	27.3
Range	9.6–71.0
Risk classification (n)	
Low	585
Intermediate	380
High	7
Unclassified	19
BMI	
Median	23.4
Range	15.5–32.8
Number of needle inserts	
Median	22
Range	10–41
V_{100} (%)	
Median	95.1
Range	56.3–100.0
V_{150} (%)	
Median	65.8
Range	18.4–98.1
D_{90} (Gy)	
Median	161.8
Range	57.8–223.7
BED	
Median	173.1
Range	59.0–252.8

PSA, prostate-specific antigen; V_{100}, volume of prostate receiving 100% of prescribed dose; V_{150}, volume of prostate receiving 150% of prescribed dose; D_{90}, dose received by 90% of prostate; BMI, body mass index; Gy, gray; BED, biological equivalent dose

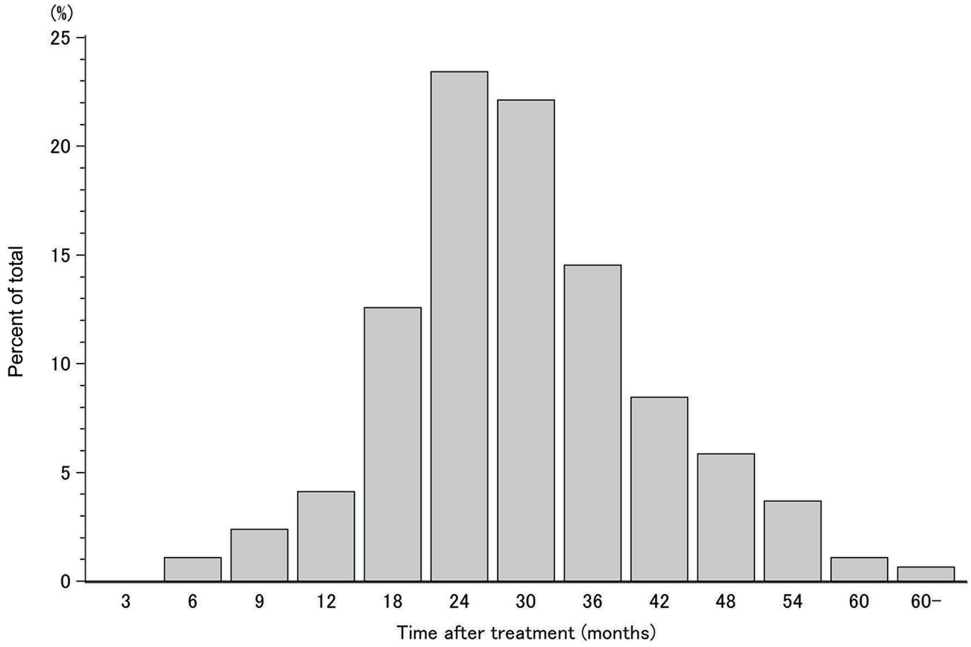

Figure 1. Histogram of the time to develop PSA bounce (in months) after BT (definition A). PSA, prostate-specific antigen; BT, brachytherapy

according to definition A. PSA bounce proved to be a significant factor for biochemical control after 5 years. Patients with a PSA bounce had better biochemical recurrence-free survival than did those without (Figure 3A: Phoenix definition, 98.1% with bounce vs. 91.7% without bounce, $P < 0.0001$; Figure 3B: ASTRO definition, 97.4% with bounce vs. 89.8% without bounce, $P < 0.0001$).

Discussion

PSA was discovered by Flocks M.D. as "species-specific prostate antigens" in 1960, Hara M.D. reported it as a "unique antigen in the semen" in 1964, and Ablin M.D. reported it as a "prostate-specific antigen" in 1970.[10] Since then, PSA has been established as a tumor marker and has come to its current clinical use.[11] Although PSA is not specific for prostate cancer and various limitations have been pointed out, it continues to be the most useful tumor marker after radical treatment of prostate cancer. However, the kinetics of PSA after RT are significantly different than those after radical prostatectomy.

The phenomenon of temporary spikes of PSA after radiation therapy is commonly referred to as "benign PSA bounce." This phenomenon can agitate both attending physicians and patients alike. While PSA bounce was frequently observed in relatively young patients in previous studies, no conclusion was drawn regarding its clinical significance. Regarding the relationship between PSA bounce and the outcome, several studies reported that patients with bounce were less likely to experience PSA recurrence,[12–14] whereas others reported that PSA bounce was not correlated with PSA recurrence.[15,16] Based on retrospective examinations, the clinical significance of PSA bounce is unknown. The present study has demonstrated that patients with a PSA bounce have significantly less PSA recurrence based on this prospective cohort study of prostate BT.

The next question that warrants further investigation is why patients with PSA bounce have less PSA recurrence.

The relationship between PSA bounce and high D_{90}, V_{100}, and the biological equivalent dose has been reported in previous studies[4,17,18] is an indicator of implant quality. Stock et al.[4] reported that patients receiving an implant dose of $D_{90} > 160$ Gy had a PSA bounce rate of 38% at 5 years compared with 24% for those receiving an implant dose of $D_{90} \leq 160$ Gy. Meanwhile, Merrick et al.[19] found the opposite association with the dose. In the present study, a low correlation was observed between PSA bounce and D_{90}, V_{100}, and the biological equivalent dose. To date, the correlation between PSA bounce, radiation dose, and dosimetry remains unclear, and further case accumulation and additional analyses are required.

Another hypothesis involves the possibility of tumor immunity induction in radiation therapy, i.e., the "abscopal effect," in which tumor immunity is induced after RT, whereby regression of distant tumors occurs after local irradiation.[20] Yamamoto et al. reported that their minimal model captures the dynamics of the tumor after therapy and suggest that a strong antitumor immune

Table 2. Univariate analysis of factors potentially affecting PSA bounce

Factors	Values	Definition A					Definition B					Definition C				
		Bounce		Univariate analysis			Bounce		Univariate analysis			Bounce		Univariate analysis		
		No	Yes	P value	OR	(95% CI)	No	Yes	P value	OR	95% CI	No	Yes	P value	OR	(95% CI)
Age (years)	≥65	401	264				438	227				540	125			
	≤65	129	197	<0.0001	2.32	(1.769, 3.041)	128	198	<0.0001	2.985	(2.269, 3.926)	185	141	<0.0001	3.293	(2.456, 4.414)
Prostate volume (cc)	<30	343	288				379	252				482	149			
	30–<40	150	140	0.6607	1.112	(0.841, 1.469)	151	139	0.3852	1.384	(1.046, 1.832)	199	91	0.7124	1.479	(1.086, 2.014)
	≥40	37	33	0.9764	1.062	(0.648, 1.742)	36	34	0.4506	1.42	(0.866, 2.330)	44	26	0.0814	1.912	(1.139, 3.211)
PSA (ng/ml)	<6	233	250				262	221				346	137			
	6–<10	228	178	0.5392	0.728	(0.558, 0.948)	237	169	0.612	0.845	(0.648, 1.103)	302	104	0.7855	0.87	(0.646, 1.172)
	≥10	66	31	0.0034	0.438	(0.276, 0.695)	64	33	0.0694	0.611	(0.387, 0.965)	73	24	0.6385	0.83	(0.503, 1.371)
Clinical T stage	T1	407	366				428	345				552	221			
	T2/T3	119	94	0.4049	0.878	(0.647, 1.192)	134	79	0.0495	0.731	(0.535, 0.999)	169	44	0.0215	0.65	(0.451, 0.938)
Gleason score	<7	344	338				361	321				483	199			
	≥7	185	121	0.0036	0.666	(0.506, 0.875)	203	103	<0.0001	0.571	(0.431, 0.756)	240	66	0.0129	0.668	(0.485, 0.918)
V_{100} (%)	<90	90	73				88	75				119	44			
	90–<95	172	142	0.7632	1.018	(0.696, 1.489)	181	133	0.6338	0.862	(0.589, 1.262)	226	88	0.6535	1.053	(0.689, 1.610)
	≥95	265	243	0.3871	1.13	(0.793, 1.611)	294	214	0.5275	0.854	(0.599, 1.218)	375	133	0.6484	0.959	(0.644, 1.429)
V_{150} (%)	<50	72	63				71	64				97	38			
	50–<70	256	230	0.6947	1.027	(0.701, 1.505)	269	217	0.6274	0.895	(0.611, 1.312)	344	142	0.2399	1.054	(0.690, 1.608)
	≥70	199	165	0.6407	0.948	(0.638, 1.408)	223	141	0.0394	0.701	(0.471, 1.045)	279	85	0.0911	0.778	(0.497, 1.216)
D_{90} (Gy)	<140	92	51				89	54				112	31			
	140–<180	328	301	0.1179	1.655	(1.136, 2.412)	354	275	0.3613	1.28	(0.882, 1.859)	449	180	0.0853	1.448	(0.939, 2.235)
	≥180	107	106	0.0496	1.787	(1.157, 2.761)	120	93	0.47	1.277	(0.828, 1.970)	159	54	0.9201	1.227	(0.742, 2.030)
BED	<180	320	281				333	268				433	168			
	≥180	207	177	0.8391	0.974	(0.753, 1.259)	230	154	0.1652	0.832	(0.642, 1.079)	287	97	0.3528	0.871	(0.651, 1.165)
BMI	<18.5	14	11				16	9				22	3			
	18.5–<25.0	334	313	0.3387	1.193	(0.533, 2.667)	363	284	0.4022	1.391	(0.606, 3.194)	466	181	0.0724	2.848	(0.842, 9.631)
	≥25.0	146	106	0.4893	0.924	(0.404, 2.116)	145	107	0.6669	1.312	(0.558, 3.082)	188	64	0.2536	2.496	(0.723, 8.618)

PSA, prostate-specific antigen; OR, odds ratio; CI, confidence interval; V_{100}, volume of prostate receiving 100% of prescribed dose; V_{150}, volume of prostate receiving 150% of prescribed dose; D_{90}, dose received by 90% of prostate; BMI, body mass index; Gy, gray; BED, biological equivalent dose

Table 3. Multivariate analysis of factors potentially affecting PSA bounce

Factors	Values	Definition A					Definition B					Definition C				
		Bounce		Multivariate analysis			Bounce		Multivariate analysis			Bounce		Multivariate analysis		
		No	Yes	P value	OR	(95% CI)	No	Yes	P value	OR	95% CI	No	Yes	P value	OR	(95% CI)
Age	≥65	396	261				433	225				537	125			
	<65	127	195	<0.0001	2.199	(1.668, 2.900)	125	197	<0.0001	3.01	(2.277, 3.980)	183	140	<0.0001	3.222	(2.398, 4.330)
PSA (ng/ml)	<6	231	248				–	–	–	–	–	–	–	–	–	–
	6–<10	226	177	0.5808	0.761	(0.579, 1.000)	–	–	–	–	–	–	–	–	–	–
	≥10	66	31	0.012	0.486	(0.303, 0.780)	–	–	–	–	–	–	–	–	–	–
Clinical T stage	T1	–	–	–	–	–	426	345				552	221			
	T2/T3	–	–	–	–	–	132	77	0.0804	0.746	(0.538, 1.036)	168	44	0.0429	0.676	(0.463, 0.988)
Gleason score	<7	341	335				357	319				480	199			
	≥7	182	121	0.0223	0.719	(0.542, 0.954)	201	103	0.001	0.613	(0.457, 0.821)	240	66	0.0482	0.717	(0.516, 0.997)
V_{150} (%)	<50	–	–	–	–	–	71	64				–	–	–	–	–
	50–<70	–	–	–	–	–	268	217	0.763	0.863	(0.580, 1.286)	–	–	–	–	–
	≥70	–	–	–	–	–	219	141	0.0437	0.684	(0.451, 1.036)	–	–	–	–	–
D_{90} (Gy)	<140	92	51				–	–	–	–	–	–	–	–	–	–
	140–<180	326	299	0.166	1.597	(1.086, 2.350)	–	–	–	–	–	–	–	–	–	–
	≥180	105	106	0.0695	1.728	(1.105, 2.701)	–	–	–	–	–	–	–	–	–	–

PSA, prostate-specific antigen; OR, odds ratio; CI, confidence interval; V_{150}, volume of prostate receiving 150% of prescribed dose; D_{90}, dose received by 90% of prostate; Gy, gray

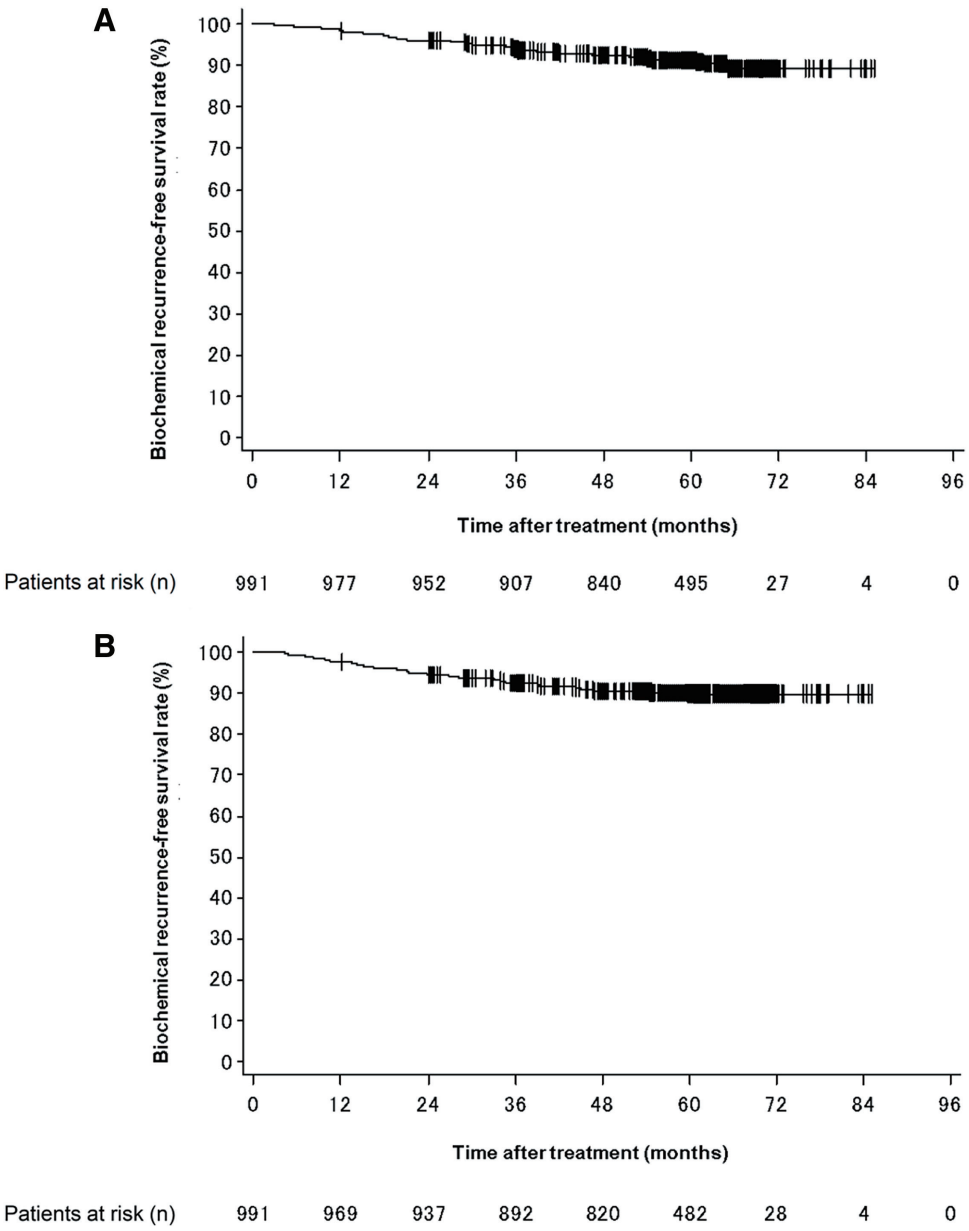

Figure 2. Biochemical recurrence-free survival according to each definition: (**A**) the phoenix definition and (**B**) the ASTRO definition

response coupled with the therapeutic effect of radiation on the tumor is responsible for the PSA bounce. Patients who experience a PSA bounce have a higher density of CD3 and CD8 cells within the tumor, which likely contribute to the PSA bounce and overall better outcomes observed.[21] They suggested that the strength of the immune response decreases with age, which can explain the increased PSA bounce rates particularly in younger patients.

The present study also confirmed a correlation between Gleason scores of <7 and early clinical T stage and PSA bounce. Particularly, it was first confirmed that the Gleason score correlated with all PSA bounce definitions. This may suggest a hypothesis that more differentiated tumors are likely to induce tumor immunity. We previously reported that the proportion of activated T cells (CD3+HLA-DR+, CD4+HLA-DR+, and CD8+HLA-DR+) in peripheral blood exhibited a gradual and bimodal increase following BT, whereas memory CD8+ T cells had a bimodal decrease after treatment.[22] The ratios of activated and regulatory T cells gradually increased after the treatment. This increase of activated T cells may facilitate the maintenance of remission and reduction of relapse rates. However, the correlation between PSA bounce and the ratios of activated and regulatory T cells has not yet been elucidated. Therefore, further studies are warranted.

It is also unclear why PSA bounce tends to be more common among younger patients. One hypothesis

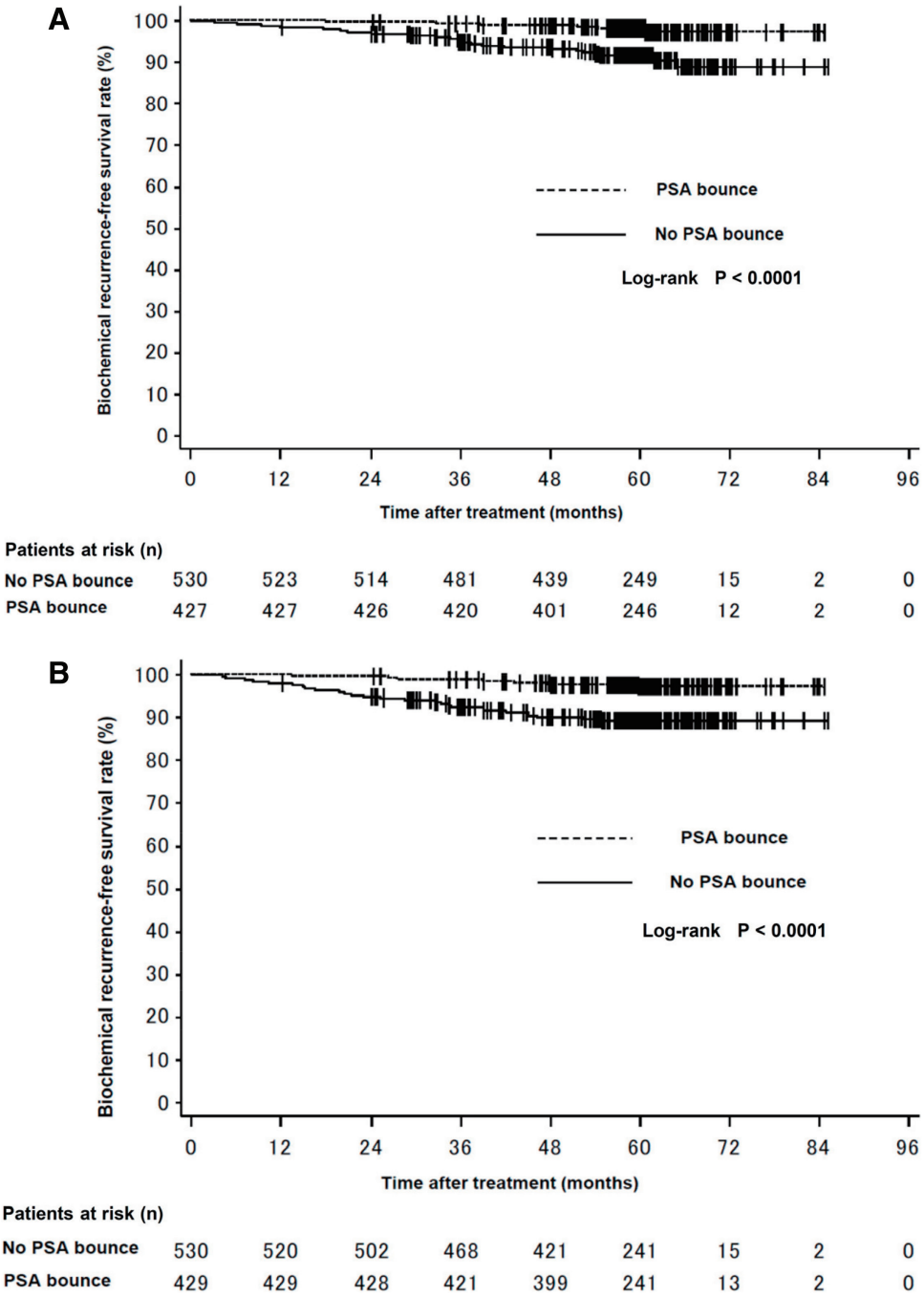

Figure 3. Biochemical recurrence-free survival for patients with or without a PSA bounce according to definition A: (**A**) the phoenix definition and (**B**) the ASTRO definition

involves the influence of ejaculation on PSA bounce. Crook et al.[23] reported that potency before implantation was a significant predictor of PSA bounce. Furthermore, Tchetgen et al.[24] reported that ejaculation significantly increases the serum PSA concentration in men aged 49–79 years, which may persist for up to 48 hours. This change appears to correlate with age and baseline PSA levels, and men are recommended to abstain from ejaculation for 48 hours before having a serum PSA determination. However, sexual function correlated with age is usual, and whether a correlation exists between the influence of ejaculation and the timing of PSA bounce (median time to PSA bounce, 18.3–24.1 months) remains unclear. The other hypothesis that it results from late damage to healthy prostatic tissue,[25] the presence of residual epithelial tissue susceptible to a higher baseline testosterone level in younger patients may explain the association between bounce and younger age.[26] According to Yamamoto et al.,[21] the additional hypothesis that the relationship between strength of the immune response and age has already been described. This seems to be a consistent result.

This study had limitations. First, because the studies were based on different prescribed doses, it is necessary to consider the bias. Second, 3 PSA bounce definitions were used in this analysis, according to our previous study.[21] However, the official definition of PSA bounce remains to be established. Thus, it is necessary to examine the validity and consistency of the cases according to the definition. Furthermore, the follow-up period, at a median of 60 months, was relatively short. Therefore, a longer follow-up period is warranted to determine the radiological progression-free survival and overall survival after BT in prostate cancer.

Conclusions

PSA bounce is a common phenomenon after prostate BT and occurs at a rate of 27%–47% depending on the definition used. In addition, patients who experienced a benign PSA bounce were found to have an improved biochemical recurrence-free survival based on the world's largest prospective cohort study. PSA bounce may possibly be a beneficial phenomenon after prostate BT and must be excluded before implementing salvage interventions.

Acknowledgments

We thank all of the investigators who contributed to cohort 1 in the J-POPS. We also thank Satoshi Higashide and Masanori Fukushima, Translational Research Informatics Center, Hyogo, for the statistical analyses, Robert E. Brandt for the English language review.

Funding

This research was supported by the Foundation for Biomedical Research and Innovation (Kobe, Japan; http://www.ibri-kobe.org/english/foundation.html) and in part by a Health and Labour Sciences Research Grant from the Japanese Ministry of Health, Labour and Welfare (H29-ICT-Ippan-002).

Conflicts of Interest

Nobumichi Tanaka reported nonfinancial interests, endowed chair by Nihon Medio-Physics Co., Ltd., and honoraria for presentations from Sanofi S.A. Takefumi Satoh, Hiromichi Ishiyama, Manabu Aoki, Norihisa Katayama, Seiji Naito, Kazuto Ito, Atsunori Yorozu, Takashi Kikuchi, Takushi Dokiya, and Shiro Saito have nothing to disclose.

References

1. Lazarev S, Thompson MR, Stone NN, et al. Low-dose-rate brachytherapy for prostate cancer: outcomes at >10 years of follow-up. *BJU Int* 2018; 121: 781–90.
2. Satoh T, Ishiyama H, Matsumoto K, et al. Prostate-specific antigen 'bounce' after permanent 125I-implant brachytherapy in Japanese men: a multi-institutional pooled analysis. *BJU Int* 2009; 103: 1064–8.
3. Critz FA, Williams WH, Benton JB, et al. Prostate specific antigen bounce after radioactive seed implantation followed by external beam radiation for prostate cancer. *J Urol* 2000; 163: 1085–9.
4. Stock RG, Stone NN, Cesaretti JA. Prostate-specific antigen bounce after prostate seed implantation for localized prostate cancer: descriptions and implications. *Int J Radiat Oncol Biol Phys* 2003; 56: 448–53.
5. Saito S, Ito K, Yorozu A, et al. Nationwide Japanese prostate cancer outcome study of permanent iodine-125 seed implantation (J-POPS). *Int J Clin Oncol* 2015; 20: 375–85.
6. Ohashi T, Yorozu A, Saito S, et al. Urinary and rectal toxicity profiles after permanent iodine-125 implant brachytherapy in Japanese men: nationwide J-POPS multi-institutional prospective cohort study. *Int J Radiat Oncol Biol Phys* 2015; 93: 141–9.
7. Katayama N, Yorozu A, Maruo S, et al. Predictive factors of rectal toxicity after permanent iodine-125 seed implantation: prospective cohort study in 2339 patients. *Brachytherapy* 2016; 15: 736–45.
8. Ito K, Saito S, Yorozu A, et al. J-POPS Investigators. Nationwide Japanese Prostate Cancer Outcome Study of Permanent Iodine-125 Seed Implantation (J-POPS): first analysis on survival. *Int J Clin Oncol* 2018; 23: 1148–59.
9. Nakano M, Yorozu A, Saito S, et al. Seed migration after transperineal interstitial prostate BT by using loose seeds: J-POPS multi-institutional cohort study. *Radiat Oncol* 2015; 10: 228.
10. Morris DS, Tomlins SA, Montie JE, et al. The discovery and application of gene fusions in prostate cancer. *BJU Int* 2008; 102: 276–82.
11. Rao AR, Motiwala HG, Karim OM. The discovery of prostate-specific antigen. *BJU Int* 2008; 101: 5–10.
12. Åström L, Sandin F, Holmberg L. Good prognosis following a PSA bounce after high dose rate brachytherapy and external radiotherapy in prostate cancer. *Radiother Oncol* 2018; 129: 561–6.
13. Freiberger C, Berneking V, Vögeli TA, et al. Long-term prognostic significance of rising PSA levels following radiotherapy for localized prostate cancer - focus on overall survival. *Radiat Oncol* 2017; 12: 98.

14. Bernstein MB, Ohri N, Hodge JW, et al. Prostate-specific antigen bounce predicts for a favorable prognosis following brachytherapy: a meta-analysis. *J Contemp Brachytherapy* 2013; 5: 210–4.
15. Charret J, Baumann AS, Eschwege P, et al. Prostate-specific antigen bounce in patients treated before 60 years old by iodine 125 brachytherapy for prostate cancer is frequent and not a prognostic factor. *Brachytherapy* 2018; 17: 888–94.
16. Paoluzzi M, Losa A, Cerboneschi V, et al. Prostate-specific antigen percentage: an early predictive tool after iodine-125 interstitial brachytherapy for prostate cancer. *Brachytherapy* 2017; 16: 1000–6.
17. Tanaka N, Asakawa I, Fujimoto K, et al. Minimal percentage of dose received by 90% of the urethra (%UD90) is the most significant predictor of PSA bounce in patients who underwent low-dose-rate brachytherapy (LDR-brachytherapy) for prostate cancer. *BMC Urol* 2012; 12: 28.
18. Kanai K, Nakashima J, Sugawara A, et al. Prediction of PSA bounce after permanent prostate brachytherapy for localized prostate cancer. *Int J Clin Oncol* 2009; 14: 502–6.
19. Merrick GS, Butler WM, Wallner KE, et al. Prostate-specific antigen (PSA) velocity and benign prostate hypertrophy predict for PSA spikes following prostate brachytherapy. *Brachytherapy* 2003; 2: 181–8.
20. Twyman-Saint Victor C, Rech AJ, Maity A, et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. *Nature* 2015; 520: 373–7.
21. Yamamoto Y, Offord CP, Kimura G, et al. Tumour and immune cell dynamics explain the PSA bounce after prostate cancer brachytherapy. *Br J Cancer* 2016; 115: 195–202.
22. Kubo M, Satoh T, Ishiyama H, et al. Enhanced activated T cell subsets in prostate cancer patients receiving iodine-125 low-dose-rate prostate brachytherapy. *Oncol Rep* 2018; 39: 417–24.
23. Crook J, Gillan C, Yeung I, et al. PSA kinetics and PSA bounce following permanent seed prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2007; 69: 426–33.
24. Tchetgen MB, Song JT, Strawderman M, et al. Ejaculation increases the serum prostate-specific antigen concentration. *Urology* 1996; 47: 511–6.
25. Waters A, Delouya G, Donath D, et al. Risk factors for PSA bounce following radiotherapy: outcomes from a multi-modal therapy analysis. *Can J Urol* 2014; 21: 7548–53.
26. Hackett C, Ghosh S, Sloboda R, et al. Distinguishing prostate-specific antigen bounces from biochemical failure after low-dose-rate prostate brachytherapy. *J Contemp Brachytherapy* 2014; 6: 247–53.