

Clinical features of prostate-specific antigen bounce after ^{125}I brachytherapy for prostate cancer

Katsumaro Kubo^{1,*}, Koichi Wadasaki¹, Tomoki Kimura², Yuji Murakami², Mitsuru Kajiwara³, Jun Teishima⁴, Akio Matsubara⁴ and Yasushi Nagata²

¹Department of Radiation Oncology, Hiroshima Prefectural Hospital, 1-5-54 Ujinakanda Minami-ku Hiroshima-shi, Hiroshima 734-0004, Japan

²Department of Radiation Oncology, Hiroshima University Hospital, 1-2-3 Kasumi Minami-ku Hiroshima-shi, Hiroshima 734-8553, Japan

³Department of Urology, Hiroshima Prefectural Hospital, 1-5-54 Ujinakanda Minami-ku Hiroshima-shi, Hiroshima 734-0004, Japan

⁴Department of Urology, Hiroshima University Hospital, 1-2-3 Kasumi Minami-ku Hiroshima-shi, Hiroshima 734-8553, Japan

*Corresponding author. Department of Radiation Oncology, Hiroshima Prefectural Hospital, 1-5-54 Ujinakanda Minami-ku Hiroshima-shi, Hiroshima 734-0004, Japan, Tel: +082-254-1818; Fax: +082-253-8274; Email: maro1987@hotmail.co.jp

(Received 1 May 2018; revised 28 May 2018; editorial decision 2 July 2018)

ABSTRACT

The aim of this study was to analyse the clinical features of prostate-specific antigen (PSA) bounce and the difference between biochemical failure and large-magnitude PSA bounce. The cases of 352 patients with prostate cancer who underwent brachytherapy were analysed. PSA bounce was defined as an increase in PSA of ≥ 0.2 ng/ml above an initial PSA nadir, with subsequent decline to or below that initial nadir without treatment. PSA bounce +2 was defined as an increase in PSA of ≥ 2.0 ng/ml above the nadir with subsequent decline to or below that initial nadir without treatment. We analysed the rates, time to onset, and predictive factors for PSA bounce and PSA bounce +2. The median follow-up period at the time of evaluation was 82 months. One hundred and seventeen patients had PSA bounce; of them, 10 had PSA bounce +2. Biochemical failure occurred in 29 patients. The median times to onset of PSA bounce, PSA bounce +2, and biochemical failure were 20, 17.5 and 51 months, respectively. Younger age at implant and larger prostate volume were significant predictive factors for PSA bounce. Age was a significant factor for PSA bounce +2, and PSA bounce +2 patients were significantly younger than biochemical failure patients. The maximum duration from the date of PSA bounce +2 to the date when PSA level decreased was 12 months. Age at implant, time to onset, and 1-year follow-up after an increase in PSA level of ≥ 2 ng/ml above nadir level are useful for distinguishing between biochemical failure and PSA bounce +2.

Keywords: prostate cancer; brachytherapy; prostate-specific antigen; biochemical failure

INTRODUCTION

Brachytherapy (BT) is a well-established standard treatment option for localized prostate cancer [1–3]. Prostate-specific antigen (PSA) is a sensitive indicator of prostate cancer treatment outcomes. Temporary increases in PSA levels after treatment are common, occurring in 15–84% of men receiving ^{125}I BT [4]. This phenomenon is termed PSA bounce, which is defined as a transient increase in PSA, and a subsequent decrease without intervention [5]. However, the PSA threshold value of PSA bounce is variable. A bounce definition of an increase ≥ 0.2 ng/ml has been widely used [6–9]. However, it is clinically important to distinguish between biochemical failure and large-magnitude PSA bounce, because a large-magnitude increase in PSA suggests the possibility of relapse for which salvage treatment may be

considered. Nevertheless, few studies have investigated large-magnitude PSA bounce [10–12], and most were single-centre studies with several limitations; hence, the predictive factors for PSA bounce with large magnitude remain unclear today.

Therefore, here, we aimed to analyse the clinical features of small- or large-magnitude PSA bounce and identify the differences between biochemical failure and large-magnitude PSA bounce.

MATERIALS AND METHODS

Patients

From March 2004 to December 2014, a total of 406 patients with prostate cancer underwent BT at Hiroshima University Hospital or

Hiroshima Prefectural Hospital. The clinical T stage was defined according to Tumor Node Metastasis classification (International Union Against Cancer 7th edition). The risk evaluation was made according to the National Comprehensive Cancer Network (NCCN) risk classification [13] (low risk: T stage \leq 2a, PSA \leq 10 ng/ml, or Gleason score \leq 6; intermediate risk: T stage T2b or T2c, PSA 10–20 ng/ml, or Gleason score 7; high risk: T stage \geq T3a, PSA \geq 20, or Gleason score \geq 8). Patients with a PSA follow-up duration of $<$ 3 years without death were excluded from this study. The study protocol was approved by the Human Ethics Review Committee of Hiroshima Prefectural Hospital, and each subject provided written informed consent.

Treatment

Our implant procedure has previously been described in detail [14]. We implanted ^{125}I sources using a modified peripheral-loading pattern for seed placement, using a treatment planning system (Variseed; Varian Medical Systems, Palo Alto, CA, USA). A pre-plan for the implant was generated from a transrectal ultrasound volume study. A transrectal ultrasound-guided transperineal technique under general and spinal anesthesia was used to deliver the sources. The prescribed dose for an implant was 144 Gy when performed as monotherapy, and 110 Gy when performed before external beam radiotherapy. The prescribed dose of the external beam radiotherapy was 45 Gy, with a daily fraction of 1.8 Gy. External beam radiotherapy was combined in patients with a high risk or a part of intermediate risk. Hormone therapy was indicated in patients with a prostate volume of $>40\text{ cm}^3$ and in patients at high risk. A post-implant dosimetric analysis was performed using a computed tomography (CT) scan performed 30 days post-implant. Thereafter, we calculated dose-volume histograms, including prostate D_{90} (dose to 90% of the gland). Prostate D_{90} is expressed as a percentage of the prescribed dose. PSA measurements after BT were performed every 3 months for the first 3 years, and every 6 months thereafter.

Definitions of PSA bounce

The date of BT was considered to be Day 0 of follow-up. PSA bounce was defined as an increase of $\geq 0.2\text{ ng/ml}$ above the initial PSA nadir, with a subsequent decline to or below that initial nadir without treatment. Date of bounce was the first date that the PSA level reached $\geq 0.2\text{ ng/ml}$ above the nadir. PSA bounce +2 was defined as a PSA increase of $\geq 2.0\text{ ng/ml}$ above the nadir, while the date of PSA bounce +2 was defined as the first date on which the increase occurred. Biochemical failure after BT was determined using the American Society for Therapeutic Radiology and Oncology (ASTRO) Phoenix definition (nadir +2 ng/ml except for PSA bounce +2) [15]. Date of biochemical failure was defined as the first date on which the PSA level was $>2.0\text{ ng/ml}$ above the nadir.

Statistical analysis

Univariate analyses using the Mantel-Haenszel χ^2 test or Student's *t*-test were performed to determine the statistical significance of differences between patients with PSA bounce or PSA bounce +2 and patients without PSA bounce, and between patients with PSA bounce +2 and patients with biochemical failure. Investigated factors included

Table 1. Patient characteristics

	Total <i>n</i> = 352
Age in years at implant, median (range)	69 (49–82)
T stage, <i>n</i> (%)	
T1c	240 (68.2%)
T2a	83 (23.6%)
T2b or T2c	25 (7.1%)
T3a	4 (1.1%)
Pretreatment PSA level, ng/ml, median (range)	6.50 (0.84–52.50)
≤ 10 , <i>n</i> (%)	284 (80.7%)
10–20, <i>n</i> (%)	54 (15.3%)
≥ 20 , <i>n</i> (%)	14 (4.0%)
Gleason score, <i>n</i> (%)	
≤ 6	195 (55.4%)
7	139 (39.5%)
≥ 8	18 (5.1%)
Risk group incidence, <i>n</i> (%)	
Low	166 (47.2%)
Intermediate	155 (44.0%)
High	31 (8.8%)
Pretreatment prostate volume, cm^3 , median (range)	25.4 (7.0–51.0)
Hormone therapy, <i>n</i> (%)	
Yes	129 (36.6%)
No	223 (63.4%)
External beam radiotherapy, <i>n</i> (%)	
Yes	75 (21.3%)
No	277 (78.7%)
Number of implanted seeds, median (range)	65 (34–96)
D_{90} , %, median (range)	114.8 (73.7–175.0)

age at BT, initial PSA, T stage, biopsy Gleason score, pre-implant prostate volume on ultrasound, NCCN risk classification, hormonal therapy, external beam radiotherapy, and prostate D_{90} . A stepwise method and multiple regression analysis were used as multivariate analyses for detecting significant factors. The Kaplan-Meier method was used to calculate the overall survival (OS) and biochemical

relapse-free (bRF) rate. The OS was calculated from the BT start date to the date of the final follow-up or death. The bRF was estimated from the BT start date until the date of biochemical failure. Ekuseru-Toukei 2015 (version 1.02; Social Survey Research Information Co., Ltd, Tokyo, Japan) was used to perform the statistical analyses. Statistical significance was defined as $P < 0.05$.

RESULTS

Patients

Of the 406 patients who underwent BT, 54 were excluded because their PSA follow-up durations were <3 years without death. Therefore, 352 patients were enrolled in this study. The

characteristics of the eligible patients are summarized in Table 1. The median follow-up period at the time of evaluation was 82 months (range, 12–157 months).

Treatment outcomes

Figure 1 shows the OS and bRF rates. The 5- and 7-year OS rates were 96.3% [95% confidence interval (CI), 94.2–98.4% and 93.9% (95% CI, 91.1–96.8%), respectively. During the follow-up period, 26 (7.4%) patients died; five (1.4%) died of prostate cancer and 21 (6%) died of other diseases. The 5- and 7-year bRF rates were 94.2% (95% CI, 91.6–96.7%) and 89.9% (95% CI, 86.2–93.6%),

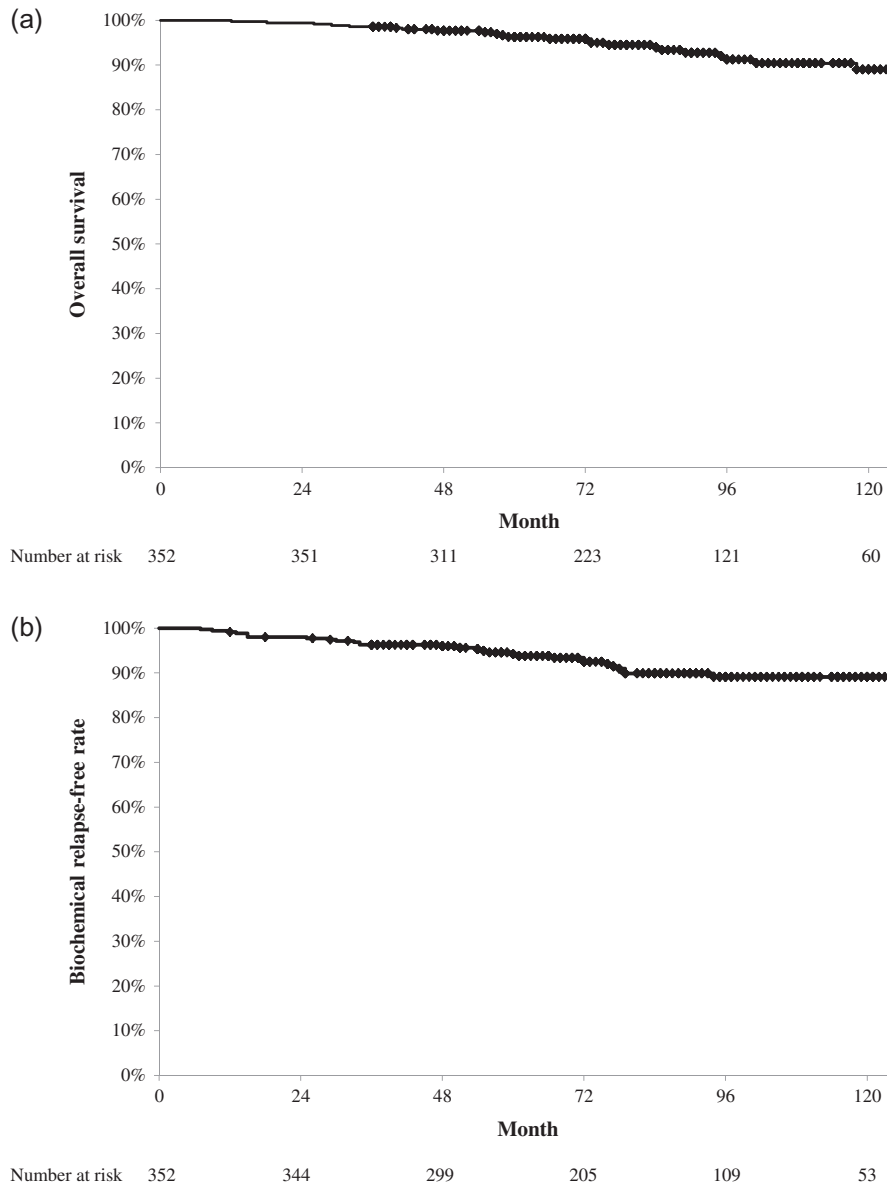


Fig. 1. Treatment results of brachytherapy for prostate cancer. (a) Overall survival rate. The 5- and 7-year overall survival rates were 96.3% and 93.9%, respectively. (b) Biochemical relapse-free survival rate. The 5- and 7-year biochemical relapse-free rates were 94.2% and 89.9%, respectively.

respectively. Biochemical failure was seen in 29 patients (8.2%); of them, 12 (3.4%) had clinically detectable recurrence. One hundred and seventeen (33.2%) had PSA bounce. The median time to PSA bounce onset was 20 months (3–55 months; Fig. 2). More than 90% of those patients experienced PSA bounce within 30 months. The PSA bounce maximum magnitude is shown in Fig. 3. Ten (2.8%) had PSA bounce +2.

Comparison of the whole cohort (excluding PSA bounce) and PSA bounce

Table 2 summarizes the characteristics of the whole cohort and of patients with PSA bounce. Age at implant ($P < 0.001$), T stage ($P = 0.034$), pretreatment PSA level ($P < 0.001$), and pretreatment prostate volume ($P = 0.001$) differed significantly between the whole cohort and patients with PSA bounce on univariate analysis (Table 3), while age at implant ($P < 0.001$) and pretreatment prostate volume ($P = 0.008$) remained significant on multivariate analysis. The median duration from the date of PSA bounce to the date when PSA level decreased was 3 months (2–18 months). Almost 90% of patients with PSA bounce had a decreased PSA level within 6 months (Fig. 4).

Comparison between whole cohort (excluding PSA bounce) and PSA bounce +2

Table 2 summarizes the characteristics of the whole cohort and of patients with PSA bounce +2. Age at implant ($P < 0.001$), T stage ($P < 0.001$), and pretreatment PSA level ($P = 0.020$) differed significantly between the whole cohort and patients with PSA bounce +2 on univariate analysis (Table 3), while age at implant ($P < 0.001$) remained significant on multivariate analysis. In addition, patients with PSA bounce +2 were significantly younger than patients with biochemical failure ($P < 0.001$).

The median time to onset were 51 months (7–94 months) and 17.5 months (12–42 months) in patients with biochemical failure and PSA bounce +2, respectively. The time to onset was significantly earlier in patients with PSA bounce +2 than in patients with biochemical failure ($P = 0.014$). The median duration from the date of PSA bounce +2 to the date when PSA level decreased was 4.5 months (3–12 months) (Fig. 5).

DISCUSSION

PSA bounce was first described in detail by Wallner *et al.* [5]. PSA bounce is observed at a 15–84% incidence after BT. The frequency of PSA bounce depends on the definition. Some studies with definitions similar to ours reported that PSA bounce was observed at a 30.1–37% frequency after BT [6–9], equivalent to our result. The median time to onset was also similar between these studies and our results (median, 14.8–19.2 months). Several studies reported that younger age was the predictive factor for PSA bounce [6, 7, 9]. In this study, younger age at implant was a significant predictive factor for PSA bounce, as in other reports. On the other hand, pretreatment prostate volume was also a significant predictive factor for PSA bounce in our study, but few studies detected pretreatment prostate volume as the predictive factor [16]. However, several studies reported that the

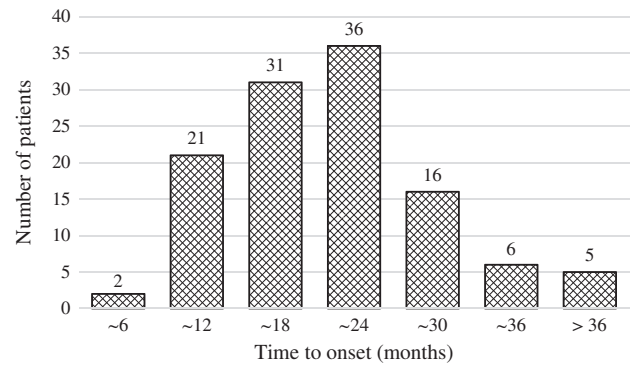


Fig. 2. Distribution of the time from brachytherapy to a prostate-specific antigen increase of ≥ 0.2 ng/ml.

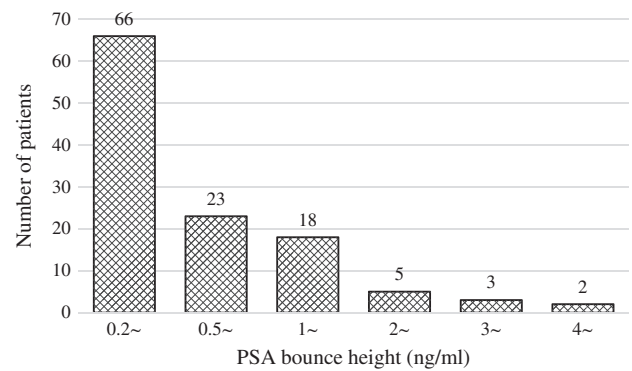


Fig. 3. Distribution of maximum magnitude of prostate-specific antigen bounce.

median pretreatment prostate volume in PSA bounce patients was larger than that in other patients [8, 11]. Therefore, we should carefully follow-up young patients with a high pretreatment prostate volume, looking out for the possibility of PSA bounce.

According to the ASTRO Phoenix definition, biochemical failure after BT is defined as nadir +2 ng/ml [15]. When patients who meet biochemical failure criteria are observed, we must distinguish PSA bounce +2 from biochemical failure to ensure accurate estimates of treatment efficacy and avoid unnecessary salvage treatments. However, few studies have investigated large-magnitude PSA bounce [10–12], and the predictive factors for PSA bounce +2 are unclear. In addition, a sufficient follow-up duration is needed in order to distinguish PSA bounce +2 from biochemical failure. Kanzaki *et al.* investigated the helpful factors for distinguishing biochemical failure from large-magnitude PSA bounce [12]. Nevertheless, they did not identify a significant predictive factor. We think one of the reasons for this is the small sample size due to the single-centre design. In this two-institution study, age at implant was a significant predictive factor for PSA bounce +2. Thompson *et al.* mentioned that PSA bounce +2 patients were significantly younger than those with biochemical failure, as we also found [10]. Therefore, as mentioned above, younger age is a predictive factor for PSA bounce and PSA bounce +2.

Table 2. Comparison of the whole cohort (excluding PSA bounce) with PSA bounce or PSA bounce +2

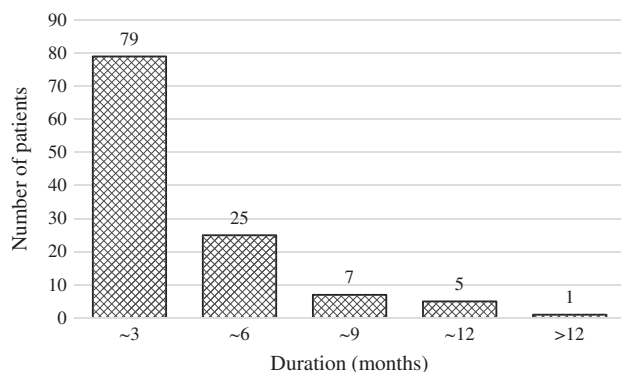
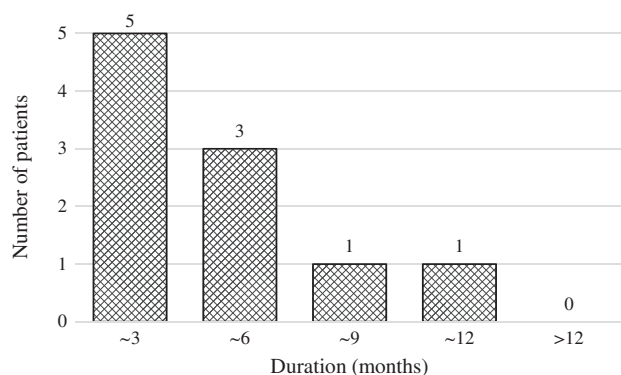
	Whole cohort <i>n</i> = 235	PSA bounce <i>n</i> = 117	PSA bounce +2 <i>n</i> = 10
Age at implant, years, median (range)	71 (52–80)	65 (49–82)	61 (57–67)
T stage, <i>n</i> (%)			
T1c	151 (64.3%)	89 (76.1%)	10 (100%)
T2a	61 (26.0%)	22 (18.8%)	0
T2b or T2c	19 (8.0%)	6 (5.1%)	0
T3a	4 (1.7%)	0	0
Pretreatment PSA level, ng/ml, median (range)	7.3 (0.84–52.50)	5.90 (3.5–29)	5.51 (4–7.12)
≤10, <i>n</i> (%)	181 (77.0%)	103 (88.0%)	10 (100%)
10–20, <i>n</i> (%)	42 (17.9%)	12 (10.3%)	0
≥20, <i>n</i> (%)	12 (5.1%)	2 (1.7%)	0
Gleason score, <i>n</i> (%)			
≤6	129 (54.9%)	66 (56.4%)	7 (70.0%)
7	90 (38.3%)	49 (41.9%)	3 (30.0%)
≥8	16 (6.8%)	2 (1.7%)	0
Risk group incidence, <i>n</i> (%)			
Low	106 (45.1%)	60 (51.3%)	7 (70.0%)
Intermediate	102 (43.4%)	53 (45.3%)	3 (30.0%)
High	27 (11.5%)	4 (3.4%)	0
Pretreatment prostate volume, cm ³ , median (range)	23.9 (7.0–51.0)	26.9 (11.3–45.8)	28.3 (21.0–36.9)
Hormone therapy, <i>n</i> (%)			
Yes	93 (39.6%)	36 (30.8%)	3 (30.0%)
No	142 (60.4%)	81 (69.2%)	7 (70.0%)
External beam radiotherapy, <i>n</i> (%)			
Yes	54 (23.0%)	21 (17.9%)	0
No	181 (77.0%)	96 (82.1%)	10 (100%)
Number of implanted seeds, median (range)	65 (34–95)	66 (42–96)	69 (60–83)
D ₉₀ , %, median (range)	114.6 (79.3–175.0)	115.4 (73.7–159.8)	113.2 (92.9–124.3)

Several guidelines for follow-up after BT for prostate cancer have been described [17, 18]. However, these studies do not mention the factors that distinguish biochemical failure from PSA bounce. When we observe a PSA level of ≥2 ng/ml above the nadir, we check for the presence or absence of recurrence lesions by imaging diagnostic methods, including CT and bone scan. If the increase in PSA levels continues without detectable recurrence

lesions, we discuss whether we are observing biochemical failure or PSA bounce, and whether salvage treatment is needed. In this study, the median duration from the date of PSA bounce +2 to the date when the PSA level decreased was 4.5 months, while the maximum duration was 1 year. Sagalovich *et al.* evaluated the impact of timing of androgen deprivation therapy on survival in a cohort of patients with biochemical failure after BT for prostate cancer [19], but

Table 3. Predictive factors; univariate and multivariate analysis

	Whole cohort vs PSA bounce		Whole cohort vs PSA bounce +2	
	Univariate analysis P value	Multivariate analysis P value	Univariate analysis P value	Multivariate analysis P value
Age at implant	<0.001	<0.001	<0.001	<0.001
T stage (T1c vs \geq T2a)	0.034	0.352	0.020	0.371
Pretreatment PSA level	<0.001	0.057	<0.001	0.211
Gleason score (\leq 6 vs \geq 7)	0.876		0.347	
Risk group incidence (Low vs Intermediate or High)	0.327		0.122	
Pretreatment prostate volume	0.001	0.008	0.070	
Hormone therapy (Yes or No)	0.134		0.544	
External beam radiotherapy (Yes or No)	0.074		0.086	
D ₉₀	0.953		0.654	

**Fig. 4. Duration from the date of PSA bounce to the date when PSA level decreased.****Fig. 5. Duration from the date of PSA bounce +2 to the date when PSA level decreased.**

identified no significant difference in survival between immediate and delayed salvage hormonal therapy. The median delay till salvage androgen deprivation therapy in their study was 19 months. We

found that a 1-year follow-up after increasing PSA level of \geq 2 ng/ml above the nadir with no evidence of proven recurrence did not affect the prognosis of prostate cancer patients. In addition, the time to onset was significantly earlier in PSA bounce +2 than in biochemical failure, as mentioned in other reports mentioned [10–12]. Therefore, 1 year of additional follow-up was useful for distinguishing between biochemical failure and PSA bounce in cases of an increasing PSA level to \geq 2 ng/ml above the nadir in patients who were young, had a short time to onset and no evidence of proven recurrence.

This study had several limitations, including its retrospective design, which introduced potential biases, and its small sample size. Biochemical failure was not always pathologically proven, and 17 patients were diagnosed with recurrence only on the basis of an increasing PSA level. Despite these limitations, we were able to distinguish between biochemical failure and PSA bounce +2.

In conclusion, age at implant was the significant predictive factor for PSA bounce and PSA bounce +2. Early onset and 1 year of follow-up after an increasing PSA level of \geq 2 ng/ml above the nadir were useful for distinguishing between biochemical failure and PSA bounce +2.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

FUNDING

None.

REFERENCES

- Cesaretti JA, Stone NN, Skouteris VM et al. Brachytherapy for the treatment of prostate cancer. *Cancer J* 2007;13:302–12.
- Potters L, Morgenstern C, Calugaru E et al. 12-year outcomes following permanent prostate brachytherapy in patients with clinically localized prostate cancer. *J Urol* 2005;173:1562–6.

3. Grimm PD, Blasko JC, Sylvester JE et al. 10-year biochemical (prostate-specific antigen) control of prostate cancer with ^{125}I brachytherapy. *Int J Radiat Oncol Biol Phys* 2001;51:31–40.
4. Caloglu M, Ciezki J. Prostate-specific antigen bounce after prostate brachytherapy: review of a confusing phenomenon. *Urology* 2009;74:1183–90.
5. Wallner KE, Blasko J, Dattoli MG. *Prostate Brachytherapy Made Complicated*. Seattle: SmartMedicine Press, 1997, 14.11–14.15.
6. Caloglu M, Ciezki JP, Reddy CA et al. PSA bounce and biochemical failure after brachytherapy for prostate cancer: a study of 820 patients with a minimum of 3 years of follow-up. *Int J Radiat Oncol Biol Phys* 2011;80:735–41.
7. Mitchell DM, Swindell R, Elliott T et al. Analysis of prostate-specific antigen bounce after ^{125}I permanent seed implant for localised prostate cancer. *Radiother Oncol* 2008;88:102–7.
8. Hinnen KA, Monninkhof EM, Battermann JJ et al. Prostate specific antigen bounce is related to overall survival in prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2012;82:883–8.
9. Mazeron R, Bajard A, Montbarbon X et al. Permanent ^{125}I -seed prostate brachytherapy: early prostate specific antigen value as a predictor of PSA bounce occurrence. *Radiat Oncol* 2012;7:46.
10. Thompson A, Keyes M, Pickles T et al. Evaluating the phoenix definition of biochemical failure after ^{125}I prostate brachytherapy: can PSA kinetics distinguish PSA failures from PSA bounce? *Int J Radiat Oncol Biol Phys* 2010;78:415–21.
11. Hackett C, Ghosh S, Slobona R et al. Distinguishing prostate-specific antigen bounces from biochemical failure after low-dose-rate prostate brachytherapy. *J Contemp Brachytherapy* 2014;6:247–53.
12. Kanzaki H, Kataoka M, Nishikawa A et al. Kinetics differences between PSA bounce and biochemical failure in patients treated with ^{125}I prostate brachytherapy. *Jpn J Clin Oncol* 2015;45:688–94.
13. National Comprehensive Cancer Network. *NCCN Practice Guidelines for Prostate Cancer, Version 3*, 2016. <http://www.nccn.org> (29 March 2018, date last accessed).
14. Wadasaki K, Seidou M, Morimoto K et al. The experiences of brachytherapy for 100 cases with prostate cancer. *Med J Hiroshima Pref Hosp* 2011;43:9–15.
15. Roach M, Hanks G, Thames H et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix consensus conference. *Int J Radiat Oncol Biol Phys* 2006;65:965–74.
16. 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.
17. Heidenreich A, Bellmunt J, Bolla M et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localized disease. *Eur Urol* 2011;59:61–71.
18. Horwich A, Parker C, Bangma C et al. Prostate cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21:129–33.
19. Sagalovich D, Leapman M, Sfakianos J et al. The impact of timing of salvage hormonal therapy on survival after brachytherapy for prostate cancer. *Brachytherapy* 2016;15:730–5.