Relationship between sexual function and prostate-specific antigen bounce after ^{125}I permanent implant brachytherapy for localized prostate cancer

Short title: Sexual function and PSA bounce

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List of abbreviations: PSA, prostate-specific antigen; EBRT, external-beam radiotherapy; ASTRO, the American Society for Therapeutic Radiology and Oncology; GS, Gleason score; IPSS, International Prostate Symptom Score; UCLA-PCI, University of California Los Angeles-Prostate Cancer Index; QOL, quality of life; D90, the minimal dose received by 90% of the prostate; V100, volume of prostate receiving 100% of the prescribed dose; UD10, the minimal dose received by 10% of the urethra

ABSTRACT

Objective:

Clinical and dosimetric factors involved in prostate-specific antigen (PSA) bounce were analyzed in patients who underwent permanent implant brachytherapy for localized prostate cancer; the relationships among PSA bounce, age, and sexual function were also analyzed.

Methods:

Between March 2007 and April 2012, 116 patients with localized prostate cancer underwent permanent implant, ^{125}I brachytherapy. Patients receiving external-beam radiotherapy or who used phosphodiesterase-5 inhibitor pre- or post-treatment were excluded. PSA bounce was defined as an increase of ≥0.2 ng/mL and ≥0.4 ng/mL above an initial PSA nadir followed by a subsequent decline to or below the initial nadir without treatment. Clinical and dosimetric factors involved in PSA bounce were analyzed using multivariate logistic regression analysis with the forced entry method.

Results:

The median age was 66 (51–80) years, and PSA bounce on a PSA rise of ≥0.2 ng/mL occurred in 47 of the 116 subjects (40.5%). The median period before the PSA bounce was 17.5 (8–36) months. Patients with PSA bounce were younger and had higher sexual function before treatment ($p = 0.003$) than those who not show PSA bounce. Regression analysis results showed that young age and a high level of pretreatment sexual function were significant predictive factors for PSA bounce ($p = 0.028$ and $p = 0.048$).

Conclusion:

Sexual function was associated with a PSA bounce and might be preserved after treatment if it was highly maintained before treatment. Highly maintained sexual function after treatment might influence PSA bounce.

Key words: ejaculation, brachytherapy, prostate cancer, prostate-specific antigen, radiotherapy

INTRODUCTION

Permanent implant brachytherapy is a highly useful and safe method for treating localized prostate cancer.[1] In Japan, it began being covered by health insurance in September 2003 and has been established as a treatment option for localized prostate cancer.[1]

Measurement of prostate-specific antigen (PSA) is an important method for evaluating the therapeutic effect and patient condition after radical treatment, as PSA levels decline rapidly after radical prostatectomy. However, following radiation therapy with brachytherapy or external-beam radiotherapy (EBRT), the decline in PSA level is gradual, taking 2–5 years to reach the nadir.[2-6] During that time, PSA values, which decline, often temporarily rise and then decrease again (called a PSA bounce). PSA bounce is said to occur with all forms of radiation therapy.[7] Although its definition differs, PSA bounce occurs at a high frequency (20–40% of cases) after brachytherapy.[2,3,7,8] Moreover, its cause is not yet clear, and many reports have indicated a strong correlation with younger age.[3,9-12] However, the basis for why PSA bounce occurs more frequently in younger people has not been clarified. A relationship with sexual function is one factor that could explain the correlation with younger men. Therefore, in this study, we analyzed PSA bounce in patients undergoing brachytherapy at our hospital and examined the relationship with age and sexual function.

SUBJECTS AND METHODS

The subjects were selected from among 135 patients who underwent ^{125}I brachytherapy at our hospital following a diagnosis of localized prostate cancer between March 2007 and April 2012. Data on 127 patients who were observed for at least 18 months were included. PSA bounce was evaluated using data from 116 patients for whom preimplant sexual function evaluation was possible; patients were excluded if they received EBRT or used a phosphodiesterase-5 inhibitor during the pre- or post-treatment phase. In addition, 64 patients were assessed after determining their sexual function for at least 6 months after the implantation. This retrospective study involved only patients who provided informed consent.

The criteria for brachytherapy were based on the recommendations of the National

Comprehensive Cancer Network. Using pretreatment PSA values, clinical stage (TNM stage), and pathological diagnostic findings (Gleason score, GS), the subjects were divided into a low risk group (all of the following applied: stage, ≤T2a; GS, ≤3 + 3 = 6; PSA < 10 ng/mL) and an intermediate risk group (only 1 of the following applied: stage, T2b–T2c; GS, 7; PSA, 10–20 ng/mL). A patient with a GS of 4 + 3 = 7 in the intermediate risk group received brachytherapy combined with EBRT. All pathological diagnoses involved a repeat diagnosis by a pathology specialist at our hospital.

Treatment began with a therapeutic plan that was based on a transrectal ultrasound conducted several weeks before treatment. Patients with a prostate volume ≥40 mL and pubic bone interference underwent initial androgen deprivation therapy for 3–6 months using a luteinizing hormone-releasing agonist and bicalutamide to shrink the prostate volume. None of the patients received androgen deprivation therapy after brachytherapy. The prescribed dose was 145 Gy for brachytherapy alone and 110 Gy for combination therapy with a subsequent boost of 45 Gy EBRT. Postimplant dosimetric analysis was conducted by computed tomography 1 month after treatment. Dose-volume histograms for the prostate and urethra were constructed to determine the minimal dose received by 90% of the prostate (D90), the volume of the prostate receiving 100% of the prescribed dose (V100), and the minimal dose received by 10% of the urethra (UD10). Post-brachytherapy observations were performed by measuring PSA levels every 3 months for the first 2 years and then at 6-month intervals.

Two different PSA values were used to define a PSA bounce: a PSA rise of ≥0.2 ng/mL (definition A) and ≥0.4 ng/mL (definition B). A PSA bounce was defined as a rise in PSA values above an initial PSA nadir followed by a subsequent decline to or below the initial nadir, without treatment. In cases involving androgen deprivation therapy, the lowest PSA value measured at least 12 months after treatment was considered the nadir due to the influence of androgen deprivation during the first 12 months after treatment. Biochemical failure after brachytherapy was defined according to the American Society for Therapeutic Radiology and Oncology (ASTRO) Phoenix definition (+2 ng/mL rise of PSA values above the nadir).

The dosimetric factors that were analyzed were D90, V100, and UD10. The analyzed clinical factors that contributed to PSA bounce included age at diagnosis, body mass index at diagnosis,

pretreatment PSA value, risk classification, GS, preimplant prostate volume, requirement for preimplant androgen deprivation therapy, preimplant International Prostate Symptom Score (IPSS), and preimplant sexual function and sexual bother levels measured with the Japanese version of the University of California Los Angeles-Prostate Cancer Index (UCLA-PCI), version 1.2.[13]

Student's *t*-tests and chi-square tests were used to assess the differences among PSA bounce, clinical, and dosimetric data and to evaluate preimplant and postimplant sexual functions. The Kaplan-Meier method was used to determine the biochemical PSA relapse-free rates. In addition, univariate and multivariate logistic regression analyses were used to assess the impact of age, preimplant sexual function, preimplant IPSS, requirements for preimplant androgen deprivation therapy, D90, UD10, and PSA bounce using the forced entry method. Differences were deemed significant when $p < 0.05$. Statistical analyses were conducted using SPSS Statistics 20 (SPSS, Chicago, IL, USA).

The sex evaluation items in the UCLA-PCI consisted of 8 items pertaining to sexual function and 1 item pertaining to sexual bother (i.e., so-called satisfaction with one's own sexual function). The questions related to sexual conduct included those pertaining to sexual desire, orgasm, erectility, and insertion; higher scores indicated that sexual function was highly maintained. In addition, higher scores were considered to reflect more sexual activity and a higher personal satisfaction with one's own sexual function. There are other disease-specific quality of life (QOL) questionnaires for patients who have been treated for localized prostate cancer, such as the Expanded Prostate Cancer Index Composite[14] and Functional Assessment of Cancer Therapy-Prostate.[15] However, the UCLA-PCI has been used previously at our hospital for evaluating the QOL of localized prostate cancer patients, because its usefulness is fully understood, its 20 questions do not place a major burden on patients, and it can sufficiently evaluate sexual function. Sexual function and sexual bother were evaluated by providing grades of 100 and 0 points to the most favorable and worst conditions, respectively. Pretreatment evaluations of sexual function and IPSS were assessed approximately two weeks before implantation.

RESULTS

The patient backgrounds of the 127 patients are shown in Table 1. The median patient age was 66 (range, 51–80) years, and the median period of observation was 42 (range, 18–77) months. The median pretreatment PSA value was 6.7 (range, 3.52–26.11) ng/mL, with only 2 cases being over 20 ng/mL; 27 of the 127 patients (21%) received androgen deprivation therapy before brachytherapy. Brachytherapy only was administered to 121 of 127 patients (95%); 6 patients (5%) underwent brachytherapy combined with EBRT. Three patients were treated with a phosphodiesterase-5 inhibitor, 1 patient at pretreatment and 2 at post-treatment. On the basis of the Phoenix definition, the 5-year biochemical PSA relapse-free rate was 87%; 9 patients (7%) had biochemical failure, and 3 of those (33%) were diagnosed as only biochemical failure, whereas 2 patients (22%) also diagnosed as distant disease and 4 (45%) also diagnosed as PSA bounce (Figure 1). PSA bounce was noted in 47 patients (40.5%) according to definition A and in 30 patients (25.9%) using definition B. The median time to bounce was 17.5 (range, 8–36) months using definition A, and it was 17.5 (range, 7–31) using definition B. and the PSA bounce occurred within 24 months in 40 patients (83.3%) according to definition A and in 26 patients (86.7%) according to definition B. By either definition, PSA bounce was not observed at 36 months or later after the start of treatment. The median increase during the PSA bounce was 0.49 (range, 0.21–5.67) ng/mL using definition A and 0.67 (range, 0.40–5.67) ng/mL using definition B.

Comparing the PSA bounce and non-bounce groups showed that the PSA bounce group was significantly younger and had statistically higher levels of pretreatment sexual function (definition A, $p = 0.03$ and $p = 0.03$; definition B, $p < 0.001$ and $p = 0.006$, respectively) (Table 2). Similar results were obtained in the univariate analysis, where higher levels of pretreatment sexual function accompanied significant occurrences of PSA bounce (definition A, $p = 0.04$; definition B, $p = 0.07$). In the multivariate logistic regression analysis, younger age was significantly related to PSA bounce (definition A, $p = 0.028$; definition B, $p = 0.003$). In the analyses performed here, high levels of preimplant sexual function were also shown to significantly predict PSA bounce (definition A, $p = 0.048$) (Tables 3 and 4).

A complete evaluation of sexual function was conducted in 64 patients whose sexual function was followed for at least 6 months after the implantation; in these patients, a PSA bounce was

defined according to definition A. These patients were observed for a median of 24 (range, 6–60) months, and 29 of the 64 (45%) patients exhibited a PSA bounce. The mean preimplant sexual function score was 40.7 ± 26.0, and the postimplant sexual function score was 37.4 ± 21.9; the difference between these scores was not significant ($p = 0.475$). For 35 of 64 patients (55%) who did not exhibit a PSA bounce, the preimplant sexual function score was 25.4 ± 19.7, and the postimplant score was 26.0 ± 21.1 ($p = 0.833$). The PSA bounce group was observed to have maintained higher sexual function after treatment.

DISCUSSION

In addition to obtaining a complete cure, raising a patient's post-treatment QOL has become an important part of modern cancer treatment, even for those with localized prostate cancer. Although a complete cure can definitely be obtained with surgery, post-therapeutic urinary incontinence and sexual dysfunction cannot be avoided.[16,17] On the other hand, brachytherapy provides a high complete cure rate with fewer post-treatment complications than surgery, making it a superior therapy.[6,16,17] As the number of prostate cancer patients in Japan is expected to rise, there will likely be a further increase in the number of patients for whom this therapy is indicated. However, unlike surgery, the therapeutic effect for brachytherapy appears gradually, taking 2–5 years for PSA levels to reach a nadir.[2-6] During that period, PSA values often temporarily rise. This phenomenon, called PSA bounce, was first reported by Critz et al.[18] Patients in whom this was observed experienced severe anxiety over a possible recurrence, and doctors found it challenging to determine if this phenomenon was, in fact, due to recurrence.

The definition of a PSA bounce is not uniform with reports containing various definitions such as a rise of ≥0.1 ng/mL,[7,11,18] ≥0.2 ng/mL,[2,3,8,10,12] ≥0.4 ng/mL,[2,7,9,19] ≥0.5 ng/mL,[20] and ≥35%.[7] increases in PSA values relative to the nadir. Thus, this study defined PSA bounce as a temporary rise in PSA levels of ≥0.2 ng/mL and ≥0.4 ng/mL, the most widely used bounce thresholds reported in the literature.

Although PSA bounces are generally considered benign temporary increases in PSA levels, its cause is unclear. Many studies have reported that PSA bounce occurs more often in younger men.[3,9-

[12] The relationship between PSA bounce and younger age has been investigated, but the details are not yet fully understood. Sexual function could be an underlying factor for this correlation with a younger age. Young people generally have better sexual function than elderly people, and they also tend to engage in more sexual activity.[3] Ejaculation has been suggested to cause PSA increases. Tchetgen et al.[21] reported higher PSA levels 48 h after ejaculation than baseline values before ejaculation.[22] However, although a relationship between sexual function and PSA bounce is expected, a clear correlation has yet to be shown.[3,12,19]

Merrick et al.,[23] in an investigation of conserved sexual function following brachytherapy, reported that the radiation dose has an effect on the crus corporis cavernosi penis. However, this and other reports showed that higher levels of pretreatment sexual function increased the likelihood that sexual function would be conserved after treatment.[23-25] Further, high blood pressure, diabetes, a history of smoking, and a history of pretreatment androgen deprivation therapy have not been shown to influence post-brachytherapy sexual function.[23,24]

Studies have reported regarding short-term preservation of sexual function 2–3 years after brachytherapy, as well as long-term preservation after treatment.[4,26] However, sexual function also gradually declines after brachytherapy.[17] PSA bounces occur within 3 years of treatment, with nearly all cases occurring within the first 2 years.[3,7,8,19] In this study as well, the median period from treatment to PSA bounce was 17.5 months, with about 85% occurring within approximately 2 years. As both the period before the PSA bounce and the post-treatment period, during which sexual function is maintained are during the early post-treatment stages, sexual activity may influence the incidence of PSA bounce. Further, the incidence of PSA bounce is reportedly higher following brachytherapy than after EBRT.[20] As sexual function is preserved at a higher rate with brachytherapy than with EBRT, sexual activity influences the PSA bounce.[4,16,17] The multivariate logistic regression analysis performed in this study demonstrated that a younger age was predictive of PSA bounce, with high levels of preimplant sexual function exhibiting a significant difference as a predictive factor for PSA bounce (definition A, $p = 0.048$). Other reports have shown that the more that sexual function is maintained before treatment, the more it might be preserved after treatment. In this study, the PSA bounce group had highly maintained sexual function after treatment as well as before

treatment. Conventionally, a younger age was considered as a predictor of PSA bounce, but a highly maintained sexual function after treatment (more likely in younger men) may influence PSA bounce, as suggested by the results of this study.

Several reports have stated that PSA bounce can cause a biochemical failure or improve the overall survival rate.[2,8,10,20] In an analysis of 975 cases over a median observation period of 6 years, Hinnen et al.[8] reported better results in patients who experienced a PSA bounce than those who did not. The PSA bounce group had a 10-year non-recurrence rate of 90%, a disease-specific survival rate of 99%, and an overall survival rate of 88%; the non-bounce group demonstrated rates of 70%, 93%, and 82%, respectively. Rosser et al.[20] proposed that the PSA bounce is not due to the growth of prostate cancer, but to a large die-off of prostate cancer cells as the radiation-induced cellular damage moves from sublethal to lethal, raising the level of free PSA in the serum and thus, temporarily increasing PSA levels. This hypothesis supports the observation that the PSA bounce is linked to better treatment results. However, a relationship between PSA bounce and age was not found in this study. In our analysis, D90 was evaluated as an index of the curative effect and did not show a significant difference between the groups (definition A, $p = 0.431$; definition B, $p = 0.831$).

Increased PSA levels may also accompany a rise in testosterone levels after the cessation of pretreatment, short-term androgen deprivation therapy, thereby having an effect on the incidence of PSA bounce. In 50–80% of cases, testosterone levels normalize or recover from post-treatment levels 6–12 months after cessation of short-term androgen deprivation therapy, and an accompanying increase in PSA levels has been reported.[27,28] Testosterone levels were not recorded in this study, but the 116 patients examined in this study included 25 (21.6%) who also underwent preimplant androgen deprivation therapy. This group included patients in whom PSA levels increased gradually after androgen deprivation therapy was completed, but only 7 of the 25 patients (28%) experienced a PSA bounce according to definition A and 4 of the 25 patients (16%) according to definition B. In our analyses, a significant difference in PSA bounce was not observed due to androgen deprivation therapy (definition A, $p = 0.871$; definition B, $p = 0.744$). Further, urinary disorders due to post-radiation therapy prostate inflammation have been reported to influence the incidence of PSA bounce. In this study, preimplant IPSS, which can effect post-therapeutic urinary disorders, and

UD10 were not associated with significant differences in the incidence of PSA bounce (definition A, $p = 0.902$ and $p = 0.369$; definition B, $p = 0.343$ and $p = 0.126$, respectively).[7,18]

In conclusion, in this study, we found a relationship between PSA bounce and sexual function. PSA bounces often occur in young people, and these results suggest that abundant post-treatment sexual activity influences PSA bounce. Most reports on PSA bounce do not discuss the relationship with cancer progression, but rather indicate that PSA bounce as a benign and temporary rise in PSA levels. Doctors should have a good understanding of the PSA bounce associated with brachytherapy to avoid causing undue anxiety to patients; however, differentiation of this phenomenon from recurrence is necessary.

CONFLICT OF INTEREST

None declared.

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Figure Legends:

Figure 1. Biochemical prostate-specific antigen relapse-free rate.

Table 1. Baseline patient characteristics

Factor	
Patients (n)	127
Age (year)	65.9 ± 6.4
BMI (kg/m^2)	24.4 ± 2.9
PSA (ng/mL)	7.4 ± 3.3
Risk classification	
Low	76 (59.8)
Intermediate	51 (40.2)
Gleason score	
≤ 6	83 (65.4)
7 (3 + 4)	38 (29.9)
7 (4 + 3)	6 (5.7)
Prostate volume (cm^3)	27.4 ± 7.1
Androgen deprivation therapy	
Yes	27 (21.3)
No	100 (78.7)
Recurrence	
Yes	5 (3.9)
No	122 (96.1)
EBRT combination	
Yes	6 (4.7)
No	121 (95.3)
D90 (Gy)	169 ± 20.4
V100 (%)	95.5 ± 3.3
UD10 (Gy)	215.7 ± 29.8
follow up (months)	41.9 ± 16.8

Data are presented as mean ± standard deviation or number (percentage).
BMI, body mass index; PSA, prostate-specific antigen; EBRT, external beam radiotherapy; D90, minimal dose received by 90% of the prostate; V100, the prostate receiving 100% of the prescribed dose; UD10, the minimal dose received by 10% of the urethra

Table 2. Analysis of patient characteristics in men experiencing a prostate-specific antigen (PSA) bounce of ≥0.2 ng/mL (definition A)

	Total	No bounce	Bounce	*p* value
Patients (n)	116	69	47	
Age (year)	65.8 ± 6.5	67.2 ± 5.8	63.6 ± 7.0	0.003*
BMI (kg/m^2)	24.6 ± 2.9	24.5 ± 3.0	24.7 ± 2.7	0.787
PSA (ng/mL)	7.3 ± 3.0	7.2 ± 2.2	7.5 ± 3.9	0.642
Risk classification†				
Low	73 (62.9)	45 (65.2)	28 (59.6)	0.537
Intermediate	43 (37.1)	24 (34.8)	19 (40.4)	
Gleason score†				
≤ 6	80 (69.0)	50 (72.5)	30 (63.8)	0.324
7 (3 + 4)	36 (31.0)	19 (27.5)	17 (36.2)	

Prostate volume (cm^3)	27.4 ± 7.1	27.6 ± 7.4	26.8 ± 6.1	0.587
Androgen deprivation therapy†				
Yes	25 (21.6)	18 (26.1)	7 (14.9)	0.15
No	91 (78.4)	51 (73.9)	40 (85.1)	
IPSS	7.4 ± 6.5	7.6 ± 6.4	7.1 ± 6.5	0.713
UCLA-PCI				
Sexual function	32.2 ± 23.6	26.9 ± 21.1	40.1 ± 25.1	0.003*
Sexual bother	79.7 ± 25.9	77.9 ± 29.3	82.5 ± 20.1	0.356
D90 (Gy)	171.8 ± 18.2	171.9 ± 18.9	171.7 ± 17.2	0.962
V100 (%)	95.7 ± 3.3	95.7 ± 3.2	95.6 ± 3.4	0.82
UD10 (Gy)	218.7 ± 27.4	216.9 ± 28.1	221.3 ± 26.4	0.392
follow up (months)	42.5 ± 16.9	40.7 ± 17.4	45.1 ± 15.9	0.174

Data are presented as mean ± standard deviation or number (percentage).

* Age and Sexual function were statistically significant ($p<0.001$, unpaired *t* test).

† These were calculated by chi-square test.

BMI, body mass index; PSA, prostate-specific antigen; EBRT, external beam radiotherapy; D90, minimal dose received by 90% of the prostate; V100, the prostate receiving 100% of the prescribed dose; UD10, the minimal dose received by 10% of the urethra; IPSS, International Prostate Symptom Score; UCLA-PCI, University of California Los Angeles-Prostate Cancer Index

Table 3. Univariate and multivariate logistic regression analysis of factors affecting prostate-specific antigen (PSA) bounce of ≥0.2 ng/mL (definition A)

	Univariate *p* value	Multivariate *p* value	OR	95%CI
Age (year)	0.004*	0.028*	0.928	0.869–0.992
D90 (Gy)	0.961			
UD10 (Gy)	0.389			
IPSS	0.71			
Androgen deprivation therapy	0.155			
Sexual function	0.004*	0.048*	1.02	1.000–1.041

Data were presented as odds ratio and 95% confidence interval.

* Statistically significant ($p < 0.05$, Forced entry method).

D90, minimal dose received by 90% of the prostate; UD10, the minimal dose received by 10% of the urethra; IPSS, International Prostate Symptom Score

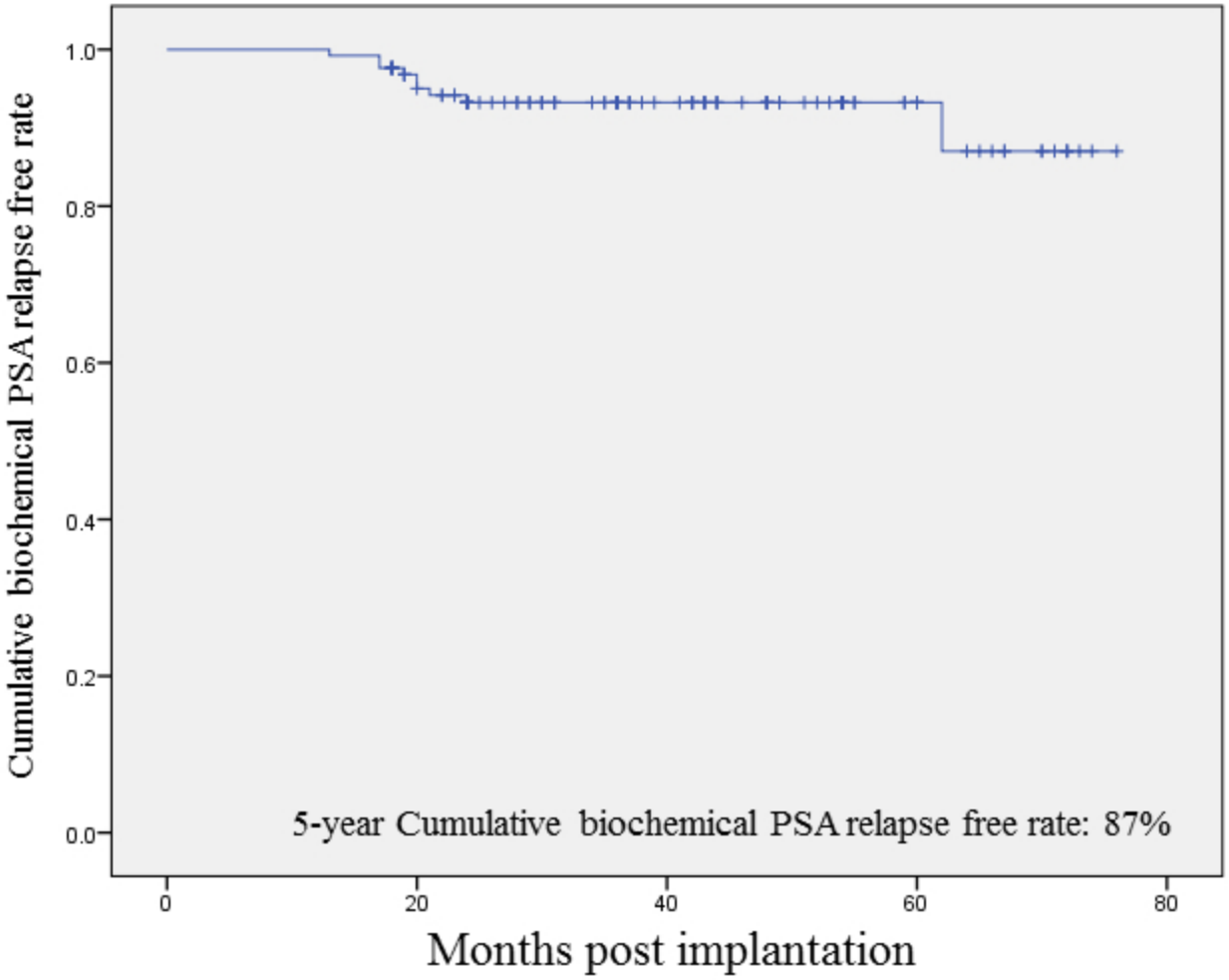
Table 4. Univariate and multivariate logistic regression analysis of factors affecting prostate-specific antigen bounce of ≥0.4 ng/mL (definition B)

	Univariate *p* value	Multivariate *p* value	OR	95%CI
Age (year)	0.001*	0.003*	0.888	0.821-0.961
D90 (Gy)	0.43			
UD10 (Gy)	0.123			
IPSS	0.642			
Androgen deprivation therapy	0.211			
Sexual function	0.007*	0.108	1.019	0.996-1.042

Data were presented as odds ratio and 95% confidence interval.

* Statistically significant ($p < 0.05$, Forced entry method).
D90, minimal dose received by 90% of the prostate; UD10, the minimal dose received by 10% of the urethra;
IPSS, International Prostate Symptom Score

Fig.1


Cumulative biochemical PSA relapse free rate
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
Months post implantation
5-year Cumulative biochemical PSA relapse free rate: 87%