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Prostate specific antigen bounce after intensity-modulated radiation therapy in an Asian population

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Abstract *Objective:* Serum prostate specific antigen (PSA) is commonly used to evaluate treatment response after definitive radiation therapy (RT). However, PSA levels can temporarily rise without a clear reason, termed "PSA bounce", and often engender great anxiety for both patients and physicians. The present study aimed to determine the prevalence and factors that predict "PSA bounce" after intensity-modulated radiation therapy (IMRT), and the relevance to biochemical failure and cancer recurrence in an Asian population.
Methods: We retrospectively reviewed 206 patients who received IMRT for prostate cancer from 2004 to 2012 in the National Cancer Centre Singapore. These patients were followed up with regular PSA monitoring. We defined "PSA bounce" as a rise of 0.1 ng/mL, followed by two consecutive falls. Patients with biochemical failure (PSA nadir + 2 ng/mL) were further evaluated for cancer recurrence.
Results: Sixty-one patients (29.6%) experienced "PSA bounce", at a median time of 16 months and lasted for 12 months. Age remained the most consistent predictor of the incidence, duration and extent of "PSA bounce". Other contributory factors included baseline PSA, Gleason score and PSA nadir. Hormonal therapy and prostate volume did not affect this phenomenon. Sixteen patients (7.8%) developed biochemical recurrence, at median time of 32 months, of which 11 were confirmed to have metastatic disease. The median follow-up time was 71 months.

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Conclusion: A younger age predicts PSA bounce incidence, duration and magnitude. The extent of bounce appears to be lower in Asian population. The interval to occurrence and extent of PSA elevation separates PSA bounce from disease recurrence.

1. Introduction

Serum prostate specific antigen (PSA) is a sensitive measure of treatment outcome for prostate cancer [1]. Although undetectable levels can be expected after a few weeks for patients undergoing radical prostatectomy, it can take 2–5 years to achieve a nadir PSA level with radiation therapy (RT), owing to the slower process of tumor-cell killing [2]. More importantly, it is not uncommon for the PSA levels to rise temporarily, a phenomenon known as "PSA bounce" [3,4], first described by Wallner and colleagues in 1997 [5]. While the exact etiology remains unknown, it is hypothesized to be the result of prostate cell membrane instability, bacterial and radiation prostatitis [6]. Although the relevance to biochemical failure remains controversial, these fluctuations can engender much anxiety amongst the physicians and patients.

The present study is the first to examine PSA bounce after intensity modulated radiation therapy (IMRT) in an Asian population. In particular, we reviewed the factors associated with this phenomenon, in order to stratify the patient profile that will most likely present with a PSA bounce. We also looked at the relevance to biochemical failure and synthesized an approach to help physicians differentiate between the two entities.

2. Patients and methods

We retrospectively reviewed 206 consecutive patients that received IMRT for prostate cancer from 2004 to 2012 at the National Cancer Centre Singapore. Data were obtained from review of casenotes, cancer registry and electronic records with IRB approval from the Singhealth Ethics Committee. None of the patients had nodal or metastatic spread prior to treatment. A variety of factors were recorded, including the patients profile, cancer staging and risk group, the concomitant use of androgen deprivation, the onset, magnitude and duration of PSA bounce and the time to biochemical failure. External radiotherapy was delivered via IMRT, planning for at least 90% of the planning target volume to receive the prescribed dose (of 70 to 74 Gy).

Given the retrospective nature of this study, follow-ups were not consistently standardized. However, in our institution's follow-up protocol, we recommended quarterly for the first 2 years post-operatively, semiannually for the subsequent 3 years and yearly follow-ups onwards. PSA level and digital rectal examination were done routinely at follow-ups. We defined PSA bounce as a rise of 0.1 ng/mL, followed by two consecutive falls. Biochemical failure was defined according to the Phoenix criteria, a rise of 2 ng/mL above nadir.

Patients with biochemical failure were all further evaluated with imaging and bone scan to detect any disease recurrence.

Statistical analyses were performed using SPSS statistics version 21.0 (IBM, New York, USA). Uni- and multi-variate Cox proportional hazard and linear/logistics regression models were used to stratify and evaluate individual factor's contribution. The clinical significance of the results is taken as p value of <0.05, corresponding to $>95\%$ confidence interval.

3. Results

The patient profile and disease characteristics are summarized in Table 1. A total of 206 patients were recruited, with the median age of 68.5 years old (range: 48.0–85.0 years). Median prostate volume was 31.0 mL (range 10.0–97.0 mL). Transrectal ultrasound biopsy was the most common method of diagnosis. Risk stratification was based on the D'Amico classification: 25 patients (12.1%) low risk, 69 (33.5%) intermediate risk, and 112 (54.4%) high risk.

All patients received IMRT ranging from 70 to 74 Gy. One hundred and eight-five patients (89.8%) received concomitant hormonal therapy. The median time to PSA nadir was 7 months and the median PSA nadir value was 0.03 ng/mL, partly due to the significant proportion of patients who had adjuvant hormonal therapy in our study group.

Sixty-one patients (29.6%) experienced the PSA bounce phenomenon, at a median time of 16 months (range 6–36 months), with a median magnitude of 0.35 ng/mL (range 0.1–4.2 ng/mL) and for a median duration of 12 months (range 5–38 months) (Table 2). Age was a significant consistent predictor of PSA bounce. When stratified, younger patients (aged <65 years) were associated with 3 times higher likelihood to experience bounce ($p = 0.001$), for a longer duration ($p = 0.022$) and with greater magnitude, although not statistically significant ($p = 0.113$).

Table 1 Patient demographics.

Parameter	Value
Age (year), median (range)	68.5 (48.0–85.0)
Risk stratification, *n* (%) [D' Amico Classification]	
Low	25 (12.1)
Intermediate	69 (33.5)
High	112 (54.4)
Prostate volume (mL), median (range)	31.0 (10.0–97.0)
Adjuvant hormonal therapy, *n* (%)	
Yes	185 (89.8)
No	21 (10.2)

Table 2 PSA bounce prevalence and statstics.

Parameter	Value
PSA bounce, *n* (%)	
Yes	61 (29.6)
No	145 (70.4)
Time to occurrence (month), median (range)	16 (6–36)
Duration of bounce (month), median (range)	12 (5–38)
Magnitude of bounce (ng/mL), median (range)	0.35 (0.1–4.2)
Follow-up time (month), median (range)	71 (32–116)
Biochemical failure, *n* (%)	
Yes	16 (7.8)
No	190 (92.2)
Disease recurrence, *n*	
Yes	11
No	5
Time to biochemical failure (month), median (range)	32 (12–59)
Time to disease recurrence (month), median (range)	36 (16–63)

PSA, prostate specific antigen.

Other significant factors associated with PSA bounce included a lower baseline PSA ($p = 0.010$), lower Gleason score ($p = 0.010$), low risk prostate cancer ($p = 0.01$) and higher nadir PSA levels post-treatment ($p = 0.020$), after adjusting for confounders on multivariate analysis (Table 3). On the other hand, hormonal therapy and pre-treatment prostate volume did not affect the occurrence of PSA bounce.

The median follow-up time was 71 months (range 32–116 months). Sixteen (7.8%) patients developed biochemical recurrence, at a median time of 32 months post-radiation (range 12–59 months), of which 11 (5.3%) were subsequently confirmed to have clinical disease recurrence, at a median time of 36 months (range 16–63 months) (Table 2). Of these, nine had systemic metastatic and two had local recurrences. Four of these 16 patients had previous PSA bounce. PSA bounce did not seem to predict a biochemical recurrence or clinical disease recurrence.

Table 3 Factors associated with PSA bounce.

Factor	*p*-Value
Age <65 years	0.001
Duration of bounce	0.022
Magnitude of bounce	0.113
Higher PSA nadir	0.020
Lower PSA at diagnosis	0.010
Lower Gleason score	0.010
Hormonal therapy	0.161
Prostate volume	0.972

PSA, prostate specific antigen.

4. Discussion

The PSA bounce phenomenon had been known for some time [7]. Caloglu and Ciezki [1], in their review article of 11 large case series, detailed that 30%–40% of successfully treated men would experience a benign PSA bounce, although the exact range could vary from 15%–84%, attributed to the several definitions used to describe this occurrence [8]. The PSA bounces were previously defined as an increase in ≥0.1 ng/mL, followed by a subsequent decrease [6]; an increase of ≥0.2 ng/mL, followed by a decline [9,10]; minimal increase of 0.4 ng/mL over a 6-month period; and a rise of ≥35% over the previous value [7]. Similarly, in our study, the PSA bounce was observed in 29.6% of our patients. We adopted a lower threshold of PSA rise of ≥0.1 ng/mL, followed by two subsequent falls, as we believed that any small increment would nonetheless create much anxiety for our patients. Fig. 1 shows the extent of PSA bounce in our study.

Our median time to a transient elevation of PSA of 16 months and a median duration lasting 12 months were consistent with the literature [11,12]. However, the median magnitude of PSA bounce of 0.35 ng/mL appeared to be much lower compared to our Western counterparts, which typically ranged from 0.1 to 1.0 ng/mL [1]. This concurred with the observation by Satoh et al. [13], in their multi-institutional pooled analysis of 388 Japanese patients, which they attributed the lower magnitude to the limited follow-up duration. Given the long follow-up period in our study, we believe that there maybe a different mechanism explaining the difference in PSA bounces between the Asian and Western population, which required further exploration and studies.

Amongst the various factors (Table 3), age remained the single most consistent predictor of PSA bounce. Similarly, in our study, patients aged <65 years old were thrice more likely to develop a PSA bounce ($p = 0.001$). Stock et al. [7] also reflected 1.5 times more likelihood in the younger patients.

While the exact mechanisms between age and PSA bounce remained unknown, several hypotheses had been discussed. Firstly, younger patients would have more reactive epithelial cells that would affect this phenomenon [7]. These patients would be more susceptible to post-radiation prostatitis and cell membrane instability [6]. Similarly, we also identified a higher nadir in patients with PSA bounce (0.22 *vs.* 0.08 mL, $p = 0.02$) on multivariate analysis, which may suggest a greater number of post-treatment epithelial cells corresponding to a greater degree of inflammation, resulting in a PSA elevation, as

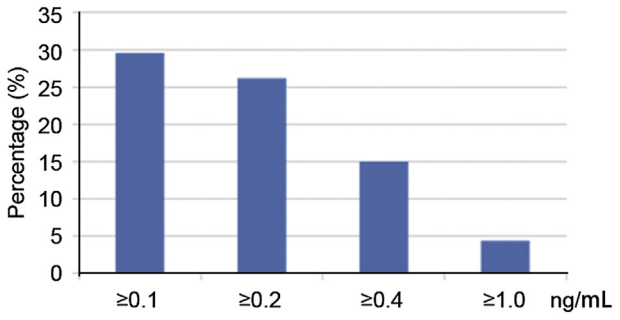

Figure 1 Extent of PSA bounce. PSA, prostate specific antigen.

concurred by Merrick et al. [14]. Although pre-treatment prostate volume did not seem to correspond with this event, we believed that a post-radiation prostate volume would have given us a better understanding of the relationship with PSA bounce.

Secondly, younger patients have more androgen production, which may stimulate a PSA rise. In the same vein, we would have expected concomitant hormonal therapy to influence the bounce phenomenon. Discussion regarding PSA kinetics in androgen deprivation therapy (ADT) patients undergoing radiotherapy remained divided [15]. Pickles [16] commented that the effects of ADT could delay the onset and lower the magnitude of PSA bounce, but these findings was not replicated in our study and other large series [17,18]. Neither was hormonal therapy confounding other factors in predicting PSA bounce on multivariate analyses.

More importantly, age also influenced the duration and magnitude of PSA bounce, as previously observed by Critz et al. [12]. Younger patients not only had a significantly greater incidence of PSA bounce, but also a longer duration (14.5 *vs.* 10.6 months, $p = 0.022$) and higher magnitude (0.66 *vs.* 0.39 ng/mL) of the phenomenon, although the latter was not of statistical significance ($p = 0.113$).

Cancer grading and staging appeared to influence on the PSA bounce phenomenon. Patients who experienced the transient elevation of PSA tended to have a lower Gleason score (35.5% of patients with Gleason 6—7 compared to 17.9% of patients with Gleason 8—10, $p = 0.01$) and lower initial PSA levels (16.49 *vs.* 34.17 ng/mL, $p = 0.01$). As such, the stratified low risk group (D'Amico classification) was most susceptible to the bounce ($p = 0.01$). The higher propensity for low risk prostate cancer group to develop PSA bounce was similarly reflected in several larger studies [19,20].

Sixteen patients (7.8%) developed biochemical recurrence, defined according to the Phoenix criteria. The relationship between PSA bounce and biochemical recurrence remained undefined. Some studies had suggested a protective effect of PSA bounce on subsequent biochemical recurrence [10,11,17] while others [2,6,7,9] did not reveal any prognostic relevance.

More importantly, the main concern was the likelihood that the PSA bounce could be an early indicator of disease recurrence. Under-investigation would risk disease progression, while over-investigation could engender unnecessary anxiety and strain healthcare resources. Given the low recurrence rate in our population, there were limited data to evaluate the prognostic effect of PSA bounce on disease recurrence. However, the interval to the onset of PSA rise remained the single most distinguishing factor that separated the two entities. In our study, the median time to PSA bounce was 16 months (range 6—36 months), which was significantly shorter than the time to disease recurrence of 36 months (range 16—63 months) (Fig. 2). By the end of 24 months, 86.9% of PSA bounce phenomenon would have occurred. This observation was reflected in several articles [2,6,10,11], which re-emphasized the discriminatory intervals to onset of PSA elevation. Critz et al. [12] commented on a similar distinction that the median time to cancer recurrence was 30 months compared to PSA bounce of 18 months. However, there remains a considerable overlap between the two observations, with three patients developing disease recurrence within 2 years of IMRT treatment.

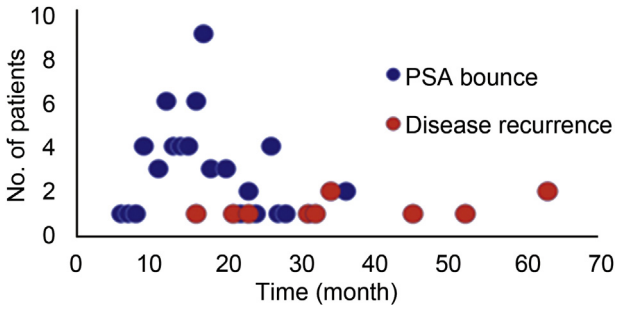

Figure 2 Time to PSA bounce and disease recurrence. PSA, prostate specific antigen.

Apart from the interval to occurrence, we identified the magnitude of PSA elevation as another possible discriminatory characteristic. The median PSA rise in the bounce group was 0.35, compared to 5.3 in those with disease recurrence. Given the magnitude of PSA bounce is much lower in an Asian population than the Western counterparts, we find greater reason to stick to the Phoenix criteria, and continue watchful waiting until significant rise (nadir + 2 ng/mL) warrants further investigations.

Lastly, we revisited our cancer registry database and briefly evaluated patients who underwent brachytherapy (BT) during the time period of this study. All 77 patients, except one patient, who underwent ^{125}I prostate brachytherapy, had low risk prostate cancer, compared to the 12.1% who underwent IMRT in our study. Following BT, there was a higher proportion of patient (65%) who experienced PSA bounce, at a shorter median time of 9 months, and higher median magnitude of 0.50 ng/mL. Pinkawa et al. [21] also noted similar findings of greater proportion and higher magnitude of PSA bounce after BT compared to external beam radiation therapy. He postulated that BT could have induced a greater local inflammatory response that explained the differences.

5. Conclusion

To conclude, we believe that PSA bounce remains a significant phenomenon in the Asian population, although the magnitude of bounce appears to be much lower. Age remains the single most consistent predictor of PSA bounce, its duration and magnitude. Lastly, there remains a clear distinction between PSA bounce and subsequent biochemical failure or disease recurrence. The interval to occurrence and extent of PSA elevation separates these entities.

Conflicts of interest

The authors declare no conflict of interest.

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