Distinguishing prostate-specific antigen bounces from biochemical failure after low-dose-rate prostate brachytherapy

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Abstract

Purpose: The purpose of this study was to characterize benign prostate-specific antigen (PSA) bounces of at least 2.0 ng/mL and biochemical failure as defined by the Phoenix definition after prostate brachytherapy at our institution, and to investigate distinguishing features between three outcome groups: patients experiencing a benign PSA bounce, biochemical failure, or neither.

Material and methods: Five hundred and thirty consecutive men treated with low-dose-rate brachytherapy with follow-up of at least 3 years were divided into outcome groups experiencing bounce, failure, or neither. A benign bounce was defined as a rise of at least 2.0 ng/mL over the pre-rise nadir followed by a decline to 0.5 ng/mL or below, without intervention. Patient and tumor characteristics, treatment variables, and PSA kinetics were analyzed between groups.

Results: Thirty-two (6.0%) men experienced benign bounces and 47 (8.9%) men experienced failure. Men experiencing a bounce were younger ($p = 0.01$), had a higher 6-month PSA level ($p = 0.03$), and took longer to reach a final nadir ($p < 0.01$). Compared to the failure group, men with bounce had a lower pre-treatment PSA level ($p = 0.01$) and experienced a rise of at least 2.0 ng/mL that occurred sooner after the implant ($p < 0.01$) with a faster PSA doubling time ($p = 0.01$). Only time to PSA rise independently differentiated between bounce and failure ($p < 0.01$), with a benign bounce not being seen after 36 months post-treatment. Prostate-specific antigen levels during a bounce reached levels as high as 12.6 ng/mL in this cohort, and in some cases took over 5 years to decline to below 0.5 ng/mL.

Conclusions: Although there is substantial overlap between the features of benign PSA bounces and failure, physicians may find it useful to evaluate the timing, absolute PSA level, initial response to treatment, and rate of rise when contemplating management for a PSA rise after low-dose-rate brachytherapy.

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erable anxiety when faced with a rise in PSA level great enough to satisfy the Phoenix definition of biochemical failure. The objectives of this study were to characterize the features of benign PSA bounces of at least 2.0 ng/mL and biochemical failures as defined by the Phoenix definition at our institution, and to investigate associations between pre-treatment, treatment, and post-treatment variables and patients experiencing a benign PSA bounce, biochemical failure, or neither.

Material and methods

Study population

From September 1998 to August 2009, 710 consecutive men were treated with 125I brachytherapy at the Cross Cancer Institute. Men with indolent disease (clinical stage < T2b, PSA level < 10 ng/mL, Gleason score < 7, and < 3 positive biopsy cores with a minimum sample of 6 cores), low-risk disease (clinical stage < T2b, PSA level < 10 ng/mL, and Gleason score < 7), and low-tier intermediate-risk disease (one intermediate risk feature: either clinical stage of T2b or T2c, Gleason score ≥ 7 or PSA of 10-20 ng/mL) were eligible for brachytherapy. Patients with a PSA follow-up time of less than 3 years and those receiving external beam radiation therapy (15) were excluded, for a study population of 530 patients. No patient died of prostate cancer within 3 years of implant.

Treatment

Patients were treated with 125I sources (model 6711; Oncura, Arlington Heights, IL and model MED3631-AM; North American Scientific, Chatsworth, CA, USA) using an implant technique that our group has previously described [20]. Briefly, a pre-operative planning ultrasound was utilized to create a modified peripheral loading pattern delivering a minimum peripheral dose of 145 Gy to the PTV. A transrectal ultrasound-guided transperineal technique under general or spinal anesthesia was used to deliver the sources. Post-operative dosimetry was assessed one month after the implant with computed tomography using the Variseed treatment planning system (Varian Medical Systems, Palo Alto, CA, USA). The Cross Cancer Institute switched from low (0.4 U) to intermediate (0.5 U) activity sources in 2002. One hundred and four (19.6%) patients received neoadjuvant hormone therapy (NHT), for a median time of 4.73 months (range 1.0–18.5 months).

Follow-up and data collection

The follow-up care of these patients consisted of assessments at four weeks followed by semi-annual assessments for two years and then annually thereafter. Pre-treatment, treatment, and post-treatment variables were retrospectively entered into a database, last updated in August 2012. At our institution, a large proportion of patients travel significant distances for their treatment and are discharged with guidelines provided to local family physicians for follow-up including physical examinations, toxicity, and PSA assessments. In the province of Alberta, patients’ electronic medical records contain all PSA measurements performed within the province, allowing this data to be captured retrospectively in the database.

Definitions and outcome groups

A PSA rise was defined as an increase of at least 2.0 ng/mL in PSA level over a pre-rise nadir, the minimum PSA level between implant and a PSA rise. If the PSA rise was followed by a decrease to ≤ 0.5 ng/mL without intervention, it was considered a benign bounce. Duration was calculated from the first increase over the pre-rise nadir to the time at which the PSA level was ≤ 0.5 ng/mL. The time to peak PSA was calculated from this first increase to the peak PSA level. Patients were considered to have failure if they experienced a PSA rise that was not a benign bounce, or received salvage treatment for a rising PSA. For these patients, the final nadir was defined as the lowest post-implant PSA level before failure.

Prostate-specific antigen rate of decline was calculated, excluding patients with a final nadir greater than or equal to the pre-treatment PSA level as well as all patients who received NHT, in patients without a PSA rise as the velocity from the pre-treatment PSA level to the final nadir, and in patients with a PSA rise, from the pre-treatment PSA level to the pre-rise nadir. Prostate-specific antigen doubling time was calculated assuming an exponential growth model, as ln (2) * (a1 – b1)/(ln(a2) – ln(b2)), and PSA velocity was calculated as a mean velocity, (a1 – b1)/(a2 – b2), where a1 and a2 represent the time and PSA level of the nadir ±2.0 ng/mL measurement, and b1 and b2 represent the time and PSA level of the last measurement before a PSA rise equal to the pre-rise nadir. Prostate-specific antigen doubling time and PSA velocity were also calculated using the peak PSA level rather than the nadir ±2.0 ng/mL measurement.

Statistical analysis

Three outcome groups were analyzed: those with benign bounce, those with failure, and those with neither a benign bounce nor failure. Descriptive statistics were used to present the study variables. Median and range were used for continuous variables; frequency and percentages were used for categorical variables. Binary logistic regression was used to determine the pre-treatment, treatment, and post-treatment factors associated with bounce vs. failure, as well as bounce vs. neither failure nor bounce. Univariate analysis was conducted to determine the factors associated with the outcome variable, and the factors significant at p < 0.10 level were considered significant for inclusion in the multivariate model. The final model was chosen with only significant variables. Since we had multiple hypotheses, a p-value of 0.03 was chosen for significance level. SAS (SAS Institute Inc., Cary, NC USA version 9.3) was used to conduct all statistical analysis.

Results

Patient characteristics of the entire study cohort are shown in Table 1. Thirty two (6.0%) patients experienced a benign bounce, and 47 (8.9%) patients experienced failure. Table 2 shows the variables compared between all
three outcome groups. On univariate analysis comparing the bounce group to the group with neither bounce nor failure, bounce patients were younger ($p = 0.0144$), had a higher 6-month PSA level ($p = 0.0345$), a faster PSA rate of decline ($p < 0.0001$), more post-treatment PSA measurements ($p = 0.0124$), and took longer to reach a final nadir ($p < 0.0001$). A trend towards a greater $V_{200}$ in the bounce group approached statistical significance ($p = 0.0604$). After excluding the number of PSA measurements from the model, differences in the 6-month PSA level ($p = 0.0065$), the PSA rate of decline ($p < 0.0001$), and time to final nadir ($p < 0.0001$) remained significant on multivariate analysis.

Comparing bounce and failure groups, the bounce patients had a lower pre-treatment PSA level ($p = 0.0132$), a lower final nadir ($p = 0.0009$), a longer time to final nadir ($p = 0.001$), a shorter time to pre-rise nadir ($p = 0.0066$), a shorter time to PSA rise ($p = 0.007$), a faster PSA doubling time ($p = 0.0114$ and $p = 0.0143$ for the two definitions used), and more post-treatment PSA measurements ($p = 0.0114$). Prostate-specific antigen kinetics exclusive to patients experiencing a PSA rise are shown for bounce and failure groups in Table 3. Excluding the number of PSA measurements from the model, on multivariate analysis, only time to PSA rise independently differentiated between bounce and failure groups ($p = 0.0007$).

The median times to PSA rise were 19.5 months and 48 months for the bounce and failure groups, respectively, as shown in Figure 1. Characteristics of bounces are shown in Figures 2 and 3. The median duration of bounce, from the first increase to the time when the PSA level was less than 0.5 ng/mL, was 34 months (range 19-126 months). The median peak PSA level during bounce was 4.45 ng/mL (range 3.1-12.6 ng/mL). The two largest PSA bounces reached peaks of 12.4 ng/mL and 12.6 ng/mL, magnitudes of 11.5 and 9.9 ng/mL above pre-rise nadirs, respectively. The median time from implant to the peak PSA was 22 months (range 11-36 months).

**Discussion**

Benign bounces of various magnitudes are common after prostate brachytherapy, and the frequency of bounce can depend on the study population and most importantly, the bounce definition used. In this population with a median follow-up time of 83 months, the frequency of a bounce of at least 2.0 ng/mL was 6.0%, falling within the range of previously published frequencies of 2.5-9.8% in Table 4. Bounce frequency and kinetics are affected by the frequency of PSA measurement and the length of minimum follow-up [13,21]. Given the reported timing of bounces of at least 2.0 ng/mL, a minimum follow-up of 3 years should capture most, if not all bounces. However, in this study, some patients experienced a benign bounce 60 months after their PSA levels dropped below 0.5 ng/mL, even after ignoring those with large gaps in follow-up. Therefore, it remains important to exercise caution to avoid misclassification of a benign bounce as biochemical failure during retrospective analysis.

Younger age is the factor most consistently found to predict for bounce (Table 4) [10,11,13]. In this study, it may have been related to another variable such as the 6-month PSA level or PSA rate of decline, given its significance on univariate, but not multivariate analysis. Though post-implant PSA levels do not correspond to sexual activity or testosterone levels [22-24], the presence of residual epithelial tissue susceptible to a higher baseline testosterone level in younger patients may explain both the association between bounce and younger age, and a higher pre-rise PSA nadir before bounce compared to failure [10].

The most likely etiologies of benign bounce are late radiation-induced effects on PSA-producing epithelium, either prostatitis, tissue necrosis or both [10,25,26]. Associations between large prostate volumes and bounce rates [18,25] might support these etiologies, but are not supported by this study, nor other investigations of bounces [19,20,25]. Size effects unrelated to dosimetry may not effect bounce, but in this study, a trend towards greater $V_{200}$ in bounce patients compared to those experiencing neither bounce nor failure was close to statistical significance ($p = 0.0604$), whereas a similar large cohort study has previously found a similar trend between bounce patients and failure patients [10]. This association may become clearer in larger cohort or multi-institutional studies. Along with a recent study showing diffuse prostatic activity in MRI scans during benign

| Table 1. Patient characteristics. Data are represented as median (range), unless otherwise specified |
|-----------------------------------------------|
| **Characteristic**                           | **All patients (n = 530)** |
| Age at implant (years)                        | 64.1 (48.1-79.4) |
| Risk group incidence (%)                      |                           |
| Indolent                                      | 200 (37.7) |
| Low                                           | 206 (38.9) |
| Low-tier intermediate                         | 124 (23.4) |
| Percentage positive biopsy cores (%)          | 33.3 (6.7-100.0) |
| Bilateral disease incidence (%)               |                           |
| Yes                                           | 176 (33.2) |
| No                                            | 335 (63.2) |
| Unknown                                       | 81 (15.3) |
| Pre-treatment PSA level (ng/mL)               | 6.1 (0.28-17.3) |
| Prostate volume on TRUS (cc)                  | 42.9 (15.8-83.7) |
| Hormone therapy incidence (%)                 |                           |
| Yes                                           | 104 (19.6) |
| No                                            | 425 (80.2) |
| Unknown                                       | 1 (0.2) |
| Source strength (U) incidence (%)             |                           |
| ≤ 0.445                                       | 158 (29.8) |
| > 0.445                                       | 372 (70.2) |
| $D_{90}$ (Gy)                                 | 152.38 (57.0-274.2) |
| $V_{100}$ (%)                                 | 92.8 (25.5-100) |
| $V_{150}$ (%)                                 | 51.5 (8.9-97.4) |
| $V_{200}$ (%)                                 | 22.8 (3.7-86.8) |
| PSA follow-up (months)                        | 83 (36-179) |
| Number of PSA measurements                    | 9 (1-42) |
Table 2. Pre-treatment, treatment and post-treatment characteristics compared between all three outcome groups. Data are represented as median (range), unless otherwise specified.

| Characteristic                          | Bounce (n = 32) | Failure (n = 47) | Neither bounce nor failure (n = 451) |
|----------------------------------------|-----------------|-----------------|-----------------------------------|
| Age at implant (years)                 | 62.0 (48.2-73.8) | 62.7 (51.9-75.9) | 64.9 (48.1-79.4)                  |
| Risk group incidence (%)               |                 |                 |                                   |
| Indolent                               | 11 (33.3)       | 18 (38.4)       | 171 (38.4)                        |
| Low                                    | 15 (48.5)       | 16 (38.2)       | 175 (38.2)                        |
| Low-tier intermediate                  | 6 (18.2)        | 13 (23.5)       | 105 (23.5)                        |
| Percentage positive biopsy cores (%)   | 30.8 (7.7-100.0) | 29.3 (7.7-100.0) | 33.3 (6.7-100.0)                 |
| Bilateral disease incidence (%)        |                 |                 |                                   |
| Yes                                    | 12 (39.4)       | 14 (32.7)       | 150 (32.7)                        |
| No                                     | 19 (57.6)       | 31 (63.7)       | 285 (63.7)                        |
| Unknown                                | 1 (3.0)         | 2 (3.7)         | 16 (3.7)                          |
| Pre-treatment PSA level (ng/mL)        | 5.75 (1.8-12.1) | 7.3 (0.28-13)   | 6 (0.28-17.3)                     |
| Prostate volume on TRUS (cc)           | 43.6 (27.0-74.4) | 41.1 (19.4-62.1) | 42.9 (15.8-83.7)                 |
| Hormone therapy incidence (%)          |                 |                 |                                   |
| Yes                                    | 4 (12.1)        | 9 (20.2)        | 91 (20.2)                         |
| No                                     | 28 (87.9)       | 38 (79.6)       | 359 (79.6)                        |
| Unknown                                | 0 (0.0)         | 0 (0.0)         | 1 (0.2)                           |
| Source strength (U) incidence (%)      |                 |                 |                                   |
| ≤ 0.445                                | 11 (36.4)       | 23 (48.9)       | 124 (29.6)                        |
| > 0.445                                | 21 (63.6)       | 24 (51.1)       | 327 (70.4)                        |
| D90                                    | 154.1 (117.4-195.6) | 151.9 (57.0-207.2) | 152.4 (79.2-274.2)               |
| V100                                   | 93.4 (78.2-99.5) | 93.2 (58.6-99.8) | 92.8 (25.5-100.0)                |
| V150                                   | 60.8 (29.4-79.2) | 50.2 (26.3-86.9) | 51.5 (8.9-97.4)                  |
| V200                                   | 31.0 (11.4-46.7) | 23.5 (11.3-54.3) | 22.3 (3.7-86.8)                  |
| PSA follow-up (months)                 | 75 (40-158)     | 102 (36-160)    | 82 (36-179)                       |
| Number of PSA measurements             | 12 (4-20)       | 16 (6-42)       | 9 (1-27)                          |
| 6-month PSA level (ng/mL)              | 1.6 (1.1-3.5)   | 1.5 (0.57-12)   | 0.87 (0.1-5.9)                    |
| PSA rate of decline (ng/mL/month)      | 0.231 (0.012-1.045) | 0.385 (0.068-2.300) | 0.131 (0.008-2.533)              |
| Final nadir, PSA level                 | 0.1 (0.1-0.5)   | 0.92 (0.1-11.8) | 0.1 (0.1-1.7)                     |
| Time to final PSA nadir (months)       | 64 (40-138)     | 11 (3-60)       | 45 (2-159)                        |

1Significant on univariate logistic regression analysis between bounce and failure groups
2Significant on univariate logistic regression analysis between bounce and neither groups
3Significant on multivariate analysis between bounce and failure groups

Table 3. Post-treatment characteristics, bounce and failure groups. Data are represented as median (range), unless otherwise specified.

| Characteristic                          | Bounce (n = 32) | Failure (n = 47) |
|----------------------------------------|-----------------|-----------------|
| Pre-rise nadir, PSA level (ng/mL)      | 1.2 (0.1-2.7)   | 0.97 (0.1-11.8) |
| Time to pre-rise nadir (months)        | 6.5 (3-19)      | 11 (3-60)       |
| Time from implant to nadir +2.0 ng/mL (months) | 19.5 (11-36)     | 48 (7-144)      |
| Doubling time, pre-rise nadir to nadir +2.0 ng/mL (months) | 6.3 (2.9-23.7) | 10.8 (1.7-45.2) |
| Doubling time, pre-rise nadir to peak PSA level (months) | 7.1 (2.9-23.7) | 11.3 (1.9-38.3) |
| PSA velocity, pre-rise nadir to nadir +2.0 ng/mL (ng/mL/month) | 0.25 (0.09-1.05) | 0.12 (0.02-5.17) |
| PSA velocity, pre-rise nadir to peak PSA level (ng/mL/month) | 0.22 (0.09-1.05) | 0.22 (0.04-15.30) |

1Significant on univariate logistic regression analysis between bounce and failure groups
2Significant on univariate logistic regression analysis between bounce and neither groups
3Significant on multivariate analysis between bounce and failure groups
bounce compared with focal activity during recurrence [27], this may provide evidence for PSA hyperproduction or release from heavily irradiated areas. Though there was no significant difference between the means, the low D90 of some failed implants (range 57.0-207.2, Table 2) compared to the bounce group (range 117.4-195.6, Table 2) may be explained by D90 as a previously published predictive factor for biochemical failure [28].

Although the patient groups experiencing bounce and neither bounce nor failure had similar pre-treatment PSA levels, a higher 6-month PSA level as an independent predictor of bounce may be attributed to a slower initial response to treatment, leaving residual PSA-producing epithelium accounting for PSA bounce. The time to trigger the definition of biochemical failure remains the most distinguishing feature of a benign bounce (Table 4).

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**Table 4.** Reported results from studies of PSA bounces of at least 2.0 ng/mL after prostate brachytherapy

| Authors, year | Patients | Frequency of bounce of 2.0 ng/mL | Time to occurrence, median in months (range) | Median magnitude, ng/mL (range) | Factors predicting bounce | Failure rate | Factors differentiating failure from bounce |
|--------------|---------|---------------------------------|---------------------------------------------|---------------------------------|---------------------------|-------------|--------------------------------------------|
| Crook et al., 2007 [13] | 292 | 5.8% | 15.2 (3-29) | 0.76 (0.21-11.79) | Younger age¹ | 2.9%, median follow-up 44 months | Time to occurrence¹ |
| Bachand et al., 2009 [8] | 153² | 9.8% | NA | 3.21 (NA) | NA | 6.4%, median follow-up 44 months | NA |
| McGrath et al., 2010 [6] | 691² | 3.0% | NA | 2.6 (NA) | NA | NA, median follow-up 48 months | NA |
| Thompson et al., 2010 [10] | 1006 | 2.5% | 20 (6-36) | 3.1 (NA-9) | Younger age | 3.2%, median follow-up 54 months | Younger age, time to occurrence |
| Mazeron et al., 2012 [11] | 198 | 4.5% | 17.9 (3.6-24.2) | 2.5 (2.1-5.1) | Younger age, higher PSA value at 6 weeks | 7.1%, median follow-up 64 months | None |
| Hackett et al. – this study | 530 | 6.0% | 19.5 (11-36) | 3.0 (2.1-11.5) | 6-month PSA level, PSA rate of decline, time to final nadir | 8.9%, median follow-up 83 months | Time to occurrence |

¹Included bounce magnitudes under 2.0 ng/mL
²Included HDR brachytherapy patients and HDR brachytherapy with EBRT
NA – Not available
Although most (62.7%) PSA rises of at least 2.0 ng/mL occurring at 36 months or less after brachytherapy were benign bounces in our cohort, there remains substantial overlap in the timing of bounce and failure. With this degree of uncertainty in any PSA rise of at least 2.0 ng/mL in the three years following brachytherapy, most clinicians will monitor the patient and use PSA kinetics to guide treatment decisions, given the low sensitivity of bone scans and feasibility of MR imaging for bone metastases [29], as well as the inaccuracy of prostate biopsy after brachytherapy [8,30]. In our population, most patients with a benign bounce experienced an increase of less than 4.0 ng/mL over the pre-rise nadir, but the magnitude of the largest benign bounce was 11.5 ng/mL, close to the maximum magnitude previously reported [13]. Treatment before a PSA increase of this magnitude may subject a patient to unnecessary side effects and risks, whereas delaying treatment in patients with true failure allows time for disease progression. Faced with an increasing PSA level, patients and physicians may find it useful to understand the duration of a benign bounce. The duration of bounce from the first increase over a pre-rise nadir to the time when the PSA level was ≤ 0.5 ng/mL was 34 months, although most patients reached a peak PSA level within a year from the first increase. In fact, the time from implant to the peak PSA level, 22 months, is similar to the time to bounce, 19.5 months, and the bounce duration is largely a result of a lengthy decline to a PSA ≤ 0.5 ng/mL. McGrath et al. found that hormone therapy increased the duration of a benign bounce [6]. The effect of NHT on bounce duration was difficult to analyze in our study, with only four patients who experienced bounce having received NHT, and having similar bounce durations to the hormone-naïve patients. Additionally, the use of NHT was not significantly different in the bounce group compared to the failure group and compared to the group experiencing neither bounce nor failure. In addition to characterizing PSA rises in terms of timing, magnitude, and duration, it may be useful to calculate a rate of increase. In our study, two different methods of calculating doubling time were used, both of which yielded statistically significantly shorter PSA doubling times for patients experiencing benign bounce than for patients experiencing failure. Although this result agrees with the comparison made by Thompson et al. [10], the doubling time is longer for both outcome groups and is instead similar to that reported by Mazeron et al. [11]. Despite this difference, a greater range of rates of increase is found among patients experiencing failure, and extremely high rates of increase are only found in failure. After finding a maximum PSA velocity of 0.98 ng/mL/month during bounces of at least 0.2 ng/mL, Mitchell et al. concluded that all patients with a velocity over 1.0 ng/mL/month are likely failures [22], which is supported by our maximum PSA velocity during bounce of 1.045 ng/mL/month.

Conclusions

In this study’s cohort of 530 patients receiving low-dose-rate prostate brachytherapy, 6.0% experienced a benign bounce of at least 2.0 ng/mL that fulfilled the Phoenix definition of biochemical failure, and 8.9% experienced true failure. Although the etiology of bounce after brachytherapy remains unknown, patients with a bounce were younger, had higher PSA levels 6 months post-treatment, and took longer to reach a final nadir than patients with neither bounce nor failure. Prostate-specific antigen kinetics during bounce in our patient population matched those published by others. Bounce patients experienced a PSA rise much earlier and one that rose faster than most failure patients, although no bounce was found after 36 months post-implant, none exceeded a PSA level of 12.6 ng/mL, and none rose faster than 1.045 ng/mL/month in our cohort. These results support an approach that combines continued monitoring with evaluation of timing, magnitude and rate of rise when faced with a PSA increase after prostate brachytherapy.

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Disclosure

Authors report no conflict of interest.

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