PSA bouncing after brachytherapy HDR and external beam radiation therapy: a study of 121 patients with minimum 5-years follow-up

Roman Makarewicz, MD, PhD, Prof., Andrzej Lebioda, MD, PhD, Joanna Terlikiewicz, MD, PhD, Marta Biedka, MD, PhD, Tomasz Wiśniewski, MD, PhD

The Chair and Clinic of Oncology and Brachytherapy, University of Nicolaus Copernicus in Toruń, Collegium Medicum in Bydgoszcz

Abstract

**Purpose:** To determine the clinical and dosimetric factors that predict prostate-specific antigen (PSA) bouncing following brachytherapy HDR and three-dimensional conformal radiation therapy (3D-CRT) for prostate cancer patients.

**Material and methods:** The evaluated population consisted of 121 prostate cancer patients with a minimum of 5 years of follow-up and at least 6 post-treatment PSA levels. All patients were treated using 3D-CRT combined with brachytherapy HDR. A bounce was defined as a PSA rise of $\geq 0.2$ ng/ml above the nadir followed by a subsequent 120 decline of $\geq 0.2$ ng/ml. The evaluated clinical factors included: patient age, Gleason score, maximum initial pretreatment PSA value (iPSAmax), clinical stage, prostate volume, median time to PSA nadir, median PSA nadir value and patient follow-up in months. The dosimetric factors evaluated included the percentage of the prostate volume receiving 100% (V100), 150% (V150) and 200% (V200) of the prescribed minimal peripheral dose.

**Results:** Statistically significant predictive factors for PSA bounce were age, V100, V150, V200, iPSAmax and median time to PSA nadir. Logistic regression model for multivariate analysis revealed that only age, iPSAmax and V200 were statistically significant predictors for PSA bounce. There were not statistical differences between median nadir among patients who exhibited a PSA bounce and did not but non-bouncer reached PSA nadir earlier than bouncer, respectively median time was 12.1 vs. 17.2 months.

**Conclusions:** PSA bouncing occurs in approximately a one third (1/3) of patients treated with 3D-CRT and brachytherapy HDR. Bouncing is associated with age, higher pretreatment PSA level and increased V200 factor.

**Key words:** prostate cancer, PSA bounces, brachytherapy.
an analysis. After this, the study was limited to the 121 patients with a minimum of 5 years of follow-up met the following criteria: all had a pretreatment PSA level, at least 6 post-treatment PSA levels, no adjuvant hormonal therapy. Forty-two from 121 patients (34.7%) were treated with neoadjuvant hormonal therapy for a mean 3-6 months, mainly to decrease the prostate volume. Patients characteristics of the study population are shown in Table 1.

**Treatment**

All patients were treated using three-dimensional conformal radiation therapy (3D-CRT) combined with brachytherapy HDR (BT-HDR). Patients were underwent simulation and were immobilized using a custom-form immobilization device. This was followed by a planning CT scan in the treatment position using 5-mm slices. The data were transferred to the 3D planning system and the prostate, seminal vesicles, bladder, rectum were contoured on each image by the physician. Dose was reported as the ICRU reference dose. Treatment plans were acceptable if the planning target volume was encompassed by the 95% isodose surface. Treatment was delivered at 2.0 Gy daily fractions 5d/week to a total dose 46 Gy. HDR-BT was given in two separate 10 Gy fractions before and after external beam radiation therapy. A dose plan was constructed based on ultrasound images. The HDR-BT PTV was equal to the CTV and was defined as the prostate gland. The number of needles and their position were defined in such way that CTV was covered by the 10 Gy isodose line. The BT was performed under spinal anesthesia. Seven to eighteen needles were inserted transperineally guided by transrectal ultrasound. A remote afterloading technique was used with an HDR Ir 192 source (Nucletron). The total treatment time of 3D-CRT and HDR-BT was 7-8 weeks.

**Follow-up**

A bounce was defined as a PSA rise of \( \geq 0.2 \) ng/ml above the nadir followed by a subsequent decline of \( \geq 0.2 \) ng/ml. Bounces were counted if the peak occurred in PSA ranges greater than 0.5 ng/ml and less than 4 ng/ml. Patients were followed with serum PSA measurement and DRE (digital rectal examination) every 3 months after completion of radiotherapy for the first two years and every 6 months thereafter. Serum PSA determinations were by the Abbot assay (normal 0-4 ng/ml) and all blood was drawn before DRE. PSA failure was defined according to the ASTRO Consensus Panel definition [1].

**Statistical analysis**

Differences in percentages for categorical variables according to bouncing were evaluated using the \( \chi^2 \) test. Mann-Whitney U test was used for the comparison of differences between the means of continuous variables. Logistic regression analysis was performed to assess the independent predictive factors for PSA bounce. Statistical significance was assigned to \( p \) values of 0.05 or less.

**Results**

The median follow-up time was 81 months (range 60-106 months). A PSA bounce was detected 38 out of 121 patients (31%). None of the patients who experienced a PSA bounce had a concurrent urinary tract or prostate infection. PSA nadir ranged from 0.11 ng/ml to 2.17 ng/ml (median 0.57 ng/ml). There were no statistical differences between median nadir among patients who exhibited a PSA bounce and did not, respectively 0.53 ng/ml vs. 0.60 ng/ml. Non-bouncer reached nadir PSA earlier than bouncer respectively median time was 12.1 vs. 17.2 months. The time from completion radiation therapy to the start of the spike ranged from 7 to 26 months (median 14.5 months). The highest increase of PSA ranged from 0.2 ng/ml to 0.7 ng/ml and was mean 0.28 ng/ml. Biochemical failure was observed in 19 patients from 121 (15.7%). The frequency of biochemical failures among non-bouncer and bouncer group was respectively 7/38 and 12/83 (18.4% vs. 14.5%).

Relationships between clinical and dosimetric data for patients with and without PSA bounces are given in Table 2. Statistically significant predictive factors for PSA bounce were age, V100, V150, V200, maximum initial pretreatment PSA value (iPSA max.), median time to nadir PSA. These factors were confirmed in univariate analysis. Logistic regression model for multivariate analysis was performed with significant parameters in univariate analysis and revealed that only age, maximum initial PSA level and V200 were statistically significant predictors for PSA bounce (Table 3).

| Table 1. Patients characteristics (N = 121) |
|---|---|
| **Age** | mean 68 range 47-78 |
| **Pretreatment PSA (ng/ml)** | mean 12.8 range 2.7-38.2 |
| **Gleason score** | \( 2-6 \) median 70 (57.8%) \( 7-9 \) median 51 (42.2%) |
| **T-stage** | \( T_1-T_2a \) median 82 (67.8%) \( T_2b \) median 39 (32.2%) |
| **Prostate volume [cm^3]** | mean 31.7 range 14.2-60.2 |
| **iPSA [ng/ml]** | mean 13.8 median 17.7 range 4.2-60.2 |
| **PSA nadir [ng/ml]** | mean 0.84 median 0.57 range 0.011-2.17 |
### Table 2. Clinical and dosimetric data for patients with and without PSA bounces

| Factor                        | No spike (N = 83) | Spike (N = 38) | P     |
|-------------------------------|-------------------|----------------|-------|
| Age [years]                   | 67.5 ±12.4        | 61 ±10.3       | 0.001 |
| Gleason score                 | 5.2 ±1.2          | 5.9 ±1.3       | 0.842 |
| Prostate volume               | 27.7 ±11.3        | 28.4 ±12.1     | 0.741 |
| iPSA max*                     | 14.7 ±12.1        | 16.7 ±10.2     | 0.045 |
| V<sub>100</sub>               | 29.6 ±11.3        | 34.3 ±12.6     | 0.041 |
| V<sub>150</sub>               | 11.8 ±4.2         | 12.8 ±3.9      | 0.049 |
| V<sub>200</sub>               | 6.1 ±2.1          | 8.1 ±2.2       | 0.021 |
| Median nadir PSA [ng/mL]      | 0.53              | 0.60           | 0.072 |
| Nadir PSA [ng/mL] ≤ 0.5       | 39 (47%)          | 16 (42.1%)     | 0.088 |
| Nadir PSA [ng/mL] > 0.5       | 44 (53%)          | 22 (57.9%)     |       |
| T<sub>stage</sub>             | 58 (69.8%)        | 24 (63.2%)     | 0.077 |
| T<sub>1,2a</sub>              | 25 (30.1%)        | 14 (36.8%)     |       |
| Median time to nadir PSA      | 12.1              | 17.2           | 0.002 |

*IPSA max – initial maximal PSA

### Discussion

The introduction of serum prostate-specific antigen (PSA) determination has changed not only the presentation of prostate cancer worldwide but also is useful tool in monitoring prostate cancer patients after treatment. The PSA level generally falls to undetectable levels after surgery but for patients treated with radiation therapy, the PSA level often decreases slowly and steadily [6]. Some of them can experience a temporary elevation in serum PSA without biochemical or clinical failure. This phenomenon called a PSA bounce or PSA spike, occurs up to 35% of patients undergoing brachytherapy [2, 4, 6-8] and 12% to 54% of men undergoing external beam radiation therapy [9-16]. In the most papers the frequency of PSA bounce seems to be higher after brachytherapy than after EBRT. Insertions of needles or seeds might cause an inflammatory reactions leading to prostatitis and elevated PSA concentration. The etiology for PSA bounce remains unclear, although bacterial and radiation proctitis have been postulated as a possible mechanisms [4, 7]. A PSA bounce can be difficult to distinguish from biochemical failure, leading to significant patient and clinicians anxiety with possible unnecessary therapeutic intervention. No universally accepted definitions exists for PSA bounce. PSA increase in the range of 0.1 ng/ml [7], 0.2 ng/ml [4,17], 0.4 ng/ml and ≥ 15% of the preceding value [18] have been described as PSA bounce by different authors. Knowledge of the etiology and predictors of PSA bounces will help to understand and predict this phenomenon and to alleviate patients and clinicians anxiety.

The bounce frequencies using different definitions are reported to be in the range of 12-54% [4, 8-10, 13, 14, 18, 19]. The bounce rate observed in our study was 31%. Nineteen patients experienced a single bounce and 3 patients 2 bounces. The relatively high bounce rate in our study may really be an erratic pathway toward PSA failure [20]. There are several studies that have detected a higher bounce frequency in younger patients. Effects of age on PSA bounce may be related to the definition bounce which we used. As was mention before the definition of PSA bounce varies widely in published reports and every choice of definition may be problematic. Hanlon et al. used a definition of at least a 0.4 ng/ml with any decline below that level and found association between PSA bounce and biochemical failure [9, 10]. According Patel et al. this value is too high and may reflect a meandering PSA after treatment that may really be an erratic pathway toward PSA failure [20]. Critz et al. used a definition of at least a 0.1 ng/ml rise with a decline to or below that level but it seems that fluctuations of 0.1 ng/ml were to low because this was within the error of the assay [7, 8, 19]. In such circumstances we chose a definition of rise of 0.2 ng/ml followed by decline as the most reasonable definition. We have detected a higher bounce frequency in younger patients. Perhaps younger patients have more androgen

### Table 3. Analysis of factors predicting PSA bounce

| Factor                        | Univariate analysis | Multivariate analysis |
|-------------------------------|---------------------|----------------------|
|                               | p-value             | Relative risk | 95% CI | p-value |
| Age (≤ 65 vs. > 65)           | 0.005               | 1.81            | 1.52-4.28 | 0.003 |
| Gleason score (≤ 6 vs. > 7)   | 0.092               | –              | –       | – |
| T<sub>stage</sub> (T<sub>1,2a</sub> vs. T<sub>2b</sub>) | 0.421               | –              | –       | – |
| iPSA max*                     | 0.019               | 1.21            | 0.86-1.42 | 0.002 |
| D<sub>90</sub>                | 0.771               | –              | –       | – |
| D<sub>100</sub>               | 0.770               | –              | –       | – |
| V<sub>100</sub>               | 0.022               | –              | –       | – |
| V<sub>150</sub>               | 0.042               | –              | –       | – |
| V<sub>200</sub>               | 0.002               | 1.22            | 0.89-1.32 | 0.002 |
| Median time to nadir (< 15 mo vs. ≥ 15 mo) | 0.039               | –              | –       | – |

*IPSA max – initial maximal PSA
production that affects the bounce phenomenon. None of patients who experienced PSA increase developed biochemical failure. This association was confirmed by different authors [2, 3, 21, 22]. On the other hand Rosser et al. did not find that age have a significant impact on the development, duration or magnitude of PSA bounce [13]. There are also other hypothesis regarding greater sexual activity [17, 19] or delayed apoptotic event [20]. The median time to bounce occurred at 15 months after completion radiation therapy. Our observed median time to bounce is consistent with the range of values reported in studies of patients treated with EBRT alone and brachytherapy ranged from 1.5 to 2.6 years [9, 10, 13, 16, 18, 21]. In our study 8% of bounces occurred in first year after RT, 69% in second year and 23% in third year or longer time of follow-up. The peak of appearance of bouncing PSA in second year of follow-up may be caused by different reason. According Merrick benign prostatic elements such as BPH (benign prostate hyperplasia) could respond to radiation with PSA kinetics different than that of malignant cells [22]. It is highly probably that areas of necrosis identified in BPH nodules could have resulted in PSA bounces with the suggestion that radiation-induced cell death in BPH elements may occur at a later time interval than malignant cells.

Among patients who experienced a PSA bounce, the risk of biochemical failure was slightly greater than in group without spikes. The relationship of bouncing to bNED (biochemical no evidence of disease) control was investigated by Hanlon et al. [9, 10]. Accoring Merrick benign prostatic rate were for bouncers and non-bouncers 52% and 69%, respectively. This observation was not confirmed by other authors [3, 4, 8, 15, 18]. Even when the PSA peak was over 30% of nadir, it is highly likely that the bounce phenomenon is responsible for this phenomenon. When a prostate cancer patient treated with radiation therapy presents an elevation in PSA, a detailed history should be known to rule out different reasons connected with elevated PSA level. Very important also is physician and preradiotherapy patient education regarding PSA fluctuation after therapy. These steps would minimize patient’s anxiety and result in avoiding inappropriate initiation of salvage intervention.

To minimize this problem clinicians should be aware of this phenomenon. When a prostate cancer patient treated with radiation therapy presents an elevation in PSA, a detailed history should be known to rule out different reasons connected with elevated PSA level. Very important also is physician and preradiotherapy patient education regarding PSA fluctuation after therapy. These steps would minimize patient’s anxiety and result in avoiding inappropriate initiation of salvage intervention.

**References**

1. Consensus Statement: guidelines for PSA following radiation therapy. American Society for Therapeutic Radiology and Oncology Consensus Panel. *Int J Radiat Oncol Biol Phys* 1997; 37: 1035-1041.
2. Merrick GS, Butler WM, Wallner KE et al. Prostate-specific antigen spikes after permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2002; 54: 450-456.
3. Akylol F, OzeyIGHT G, Selcek U. PSA bouncing after short term androgen deprivation and 3D-conformal radiotherapy for localized prostate adenocarcinoma and the relationship with the kinetics of testosterone. *Eur Urol* 2005; 48: 40-45.
4. Cavanagh W, Blasko JC, Grimm PD et al. Transient elevation of serum prostate-specific antigen following (125) I/(103) Pd brachytherapy for localized prostate cancer. *Semin Urol Oncol* 2000; 18: 160-165.
5. Wallner KE, Blasko J, Dattoli MJ. Evaluating cancer status. In: Wallner KE, Blasko J, Dattoli MJ (editors). Prostate brachytherapy made complicated. *Smart Medicine Press, Seattle* 1997: 1415.
6. D’Amico A, Tempary CM, Sultan D et al. Comparing PSA outcome after radical prostatectomy or magnetic resonance imaging-guided partial prostatic irradiation in select patients with clinically localized adenocarcinoma of the prostate. *Urology* 2003; 62: 1063-1067.
7. Critz FA, Williams WH, Benton JB et al. Prostate specific antigen bounce after radioactive seed implantation followed by external beam radiation for prostate cancer. *J Urol* 2000; 163: 1085-1089.
8. Critz FA, Williams WH, Holladay CT et al. PSA normalization following radiotherapy of prostate cancer: an analysis of PSA in 649 disease free men. *Int J Radiat Oncol Biol Phys* 2000; 48: 313-319.
9. Hanlon AL, Pinover WH, Horwitz EM et al. Patterns and fate of PSA bouncing following 3D-CRT. *Int J Radiat Oncol Biol Phys* 2001; 50: 845-849.
10. Hanlon AL, Pinover WH, Horwitz EM et al. Patterns and fate of PSA bouncing following 3D-CRT. *Int J Radiat Oncol Biol Phys* 2000; 48: 207-211.
11. Horwitz EM, Levy LB, Kuban DA et al. The biochemical and clinical significance of the post-treatment PSA bounce for prostate cancer patients treated with external beam radiation therapy alone: a multi-institutional pooled analysis. *Int J Radiat Oncol Biol Phys* 2004; 60: 235-241.
12. Kamar AM, Rosser ChJ, Levy LB et al. Rise in serum PSA of 1.5 ng/ml above 24-month nadir after external beam radiotherapy is predictive of biochemical failure. *Urology* 2004; 63: 1132-1137.
13. Rosser ChJ, Kamar AM, Wang X et al. Is patient age a factor in the occurrence of prostate-specific antigen bounce phenomenon after external beam radiotherapy for prostate cancer? *Urology* 2005; 66: 327-331.
14. Rosser ChJ, Kuban DA, Levy LB et al. The prostate specific antigen bounce phenomenon after external beam radiation for clinically localized prostate cancer. *J Urol* 2002; 168: 2001-2005.
15. Sengoz M, Abacioglu U, Cetin I et al. PSA bouncing after external beam radiation for prostate cancer with or without hormonal treatment. *Eur Urol* 2003; 43: 473-477.

16. Zietman AL, Christodoulou JS, Shipley WU. PSA bounces after neoadjuvant androgen deprivation and external beam radiation: Impact of definitions of failure. *Int J Radiat Oncol Biol Phys* 2005; 62: 714-718.

17. Patel C, Elshaikh MA, Angermeier K et al. Erratic PSA behavior (PSA bounce) following permanent I-125 implantation of the prostate. *Int J Radiat Oncol Biol Phys* 2001; 51 (Suppl 1): 277 [abstract].

18. Das P, Chen MH, Valentine K et al. Using the magnitude of PSA bounce after MRI-guided prostate brachytherapy to distinguish recurrence benign precipitating factors, and idiopathic bounce. *Int J Radiat Oncol Biol Phys* 2002; 54: 698-702.

19. Critz FA, Williams WH, Levinson AK et al. Prostate specific antigen bounce after simultaneous irradiation for prostate cancer: the relationship to patient age. *J Urol* 2003; 170: 1864-1867.

20. Patel C, Elshaikh MA, Angermeier K et al. PSA bounce predicts early success in patients with permanent iodine-125 prostate implant. *Urology* 2004; 63: 110-113.

21. 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: 448-453.

22. Merrick GS, Butler WM, Wallner KE et al. Prostate-specific antigen (PSA) velocity and benign prostate hypertrophy predict for PSA spikes following prostate brachytherapy. *Brachytherapy* 2003; 2: 181-188.

23. Smathers S, Wallner K, Sprouse J et al. Temporary PSA rises and repeat prostate biopsies after brachytherapy. *Int J Radiat Oncol Biol Phys* 2001; 50: 1207-1211.

24. Reed D, Wallner K, Merrick G et al. Clinical correlates to PSA spikes and positive repeat biopsies after prostate brachytherapy. *Urology* 2003; 62: 683-688.

25. Ciezki JP, Reddy ChA, Garcia J et al. PSA kinetics prostate brachytherapy: PSA bounce phenomenon and its implications for PSA doubling time. *Int J Radiat Oncol Biol Phys* 2006; 64: 512-517.

26. Merrick GC, Butler WM, Wallner KD et al. Temporal effect of neoadjuvant androgen deprivation therapy on PSA kinetics following permanent prostate brachytherapy with or without supplemental external beam radiation. *Brachytherapy* 2004; 3: 141-146.