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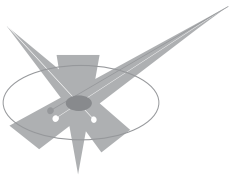

Original Paper

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PSA bounces after brachytherapy HDR and external beam radiation therapy for prostate cancer

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Roman Makarewicz[1ABCDEFG], Krzysztof Roszkowski[2F], Andrzej Lebioda[1C], Joanna Reszke[2F], Ewa Ziółkowska[2BG]

[1] Chair and Clinic of Oncology and Brachytherapy, University of Nicolaus Copernicus in Toruń, Collegium Medicum in Bydgoszcz, Poland
[2] Department of Radiotherapy, Centre of Oncology in Bydgoszcz, Poland

Summary

Background The serum prostate-specific antigen (PSA) test is the most commonly used method for confirming response of prostate cancer after definitive radiation therapy (RT). PSA levels are expected to decrease after radiotherapy but usually remain detectable. Three consecutive PSA rises above the post-treatment nadir have been defined as biochemical failure by the ASTRO consensus panel [1]. Rising serum PSA concentration after RT does not always indicate treatment failure. Some patients have a temporary PSA spike, usually within 12–30 months of radiation therapy [2–4]. Most PSA bounces have a magnitude of 1.0ng/mL or less. This observation was first described by Wallner and colleagues in 1997 [5]. Although this phenomenon is a source of anxiety for both the patient and the physician, its relevance to biochemical failure is controversial.

Aim 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.

Materials/Methods The evaluated population consisted of 71 hormone-naive patients with a minimum of 2 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 ≥0.2ng/mL above the nadir followed by a subsequent 120 decline of ≥0.2ng/mL. Clinical factors evaluated 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. 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 no statistical differences between median nadir among patients who exhibited a PSA bounce and those who did not, but non-bouncers reached PSA nadir earlier than bouncers; median time was 12.1 vs 17.2 months respectively.

Conclusion PSA bouncing occurs in approximately 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

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Author's address: Roman Makarewicz, Chair and Clinic of Oncology and Brachytherapy, University of Nicolaus Copernicus in Toruń, Collegium Medicum in Bydgoszcz, Romanowskiej 2 Str., 85-796 Bydgoszcz, Poland, e-mail: makarewiczr@co.bydgoszcz.pl

Background

The serum prostate-specific antigen (PSA) test is the most commonly used method for confirming response of prostate cancer after definitive radiation therapy (RT). PSA levels are expected to decrease after radiotherapy but usually remain detectable. Three consecutive PSA rises above the post-treatment nadir have been defined as biochemical failure by the ASTRO consensus panel [1]. A rising serum PSA concentration after RT does not always indicate treatment failure. Some patients have a temporary PSA spike, usually within 12–30 months of radiation therapy [2–4]. Most PSA bounces have a magnitude of 1.0ng/mL or less. This observation was first described by Wallner and colleagues in 1997 [5]. Although this phenomenon is a source of anxiety for both the patient and the physician, its relevance to biochemical failure is controversial.

Aim

The purpose of this study was to quantify the frequency of bouncing following brachytherapy HDR and external beam radiation therapy and to identify any relationships that may exist between bouncing activity and clinical and dosimetric factors.

Materials and Methods

Patient selection

The records of 189 patients with T1-T2 NxM0 prostate cancer treated with brachytherapy HDR and external beam radiation therapy between September 2000 and January 2004 were reviewed. This study was limited to the 71 patients with a minimum of 2 years of follow-up meeting the following criteria: all had a pretreatment PSA level, at least 6 post-treatment PSA levels, no neoadjuvant or adjuvant hormonal therapy. Patient characteristics of the study population are shown in Table 1.

Table 1. Patients characteristics (N=71).

Age	
Mean	67
Range	47–78
Pretreatment PSA (ng/mL)	
Mean	12.1
Range	2.7–38.2
<10	28
10–20	21
>20	19
Gleason score	
2–6	43 (60.6%)
7–10	28 (39.4%)
T-stage	
T_1–T_{2a}	50 (70.4%)
T2b	21 (29.6%)
Prostate volume [cm³]	
Mean	28.7
Range	14.2–60.2
iPSA [ng/mL]	
Mean	14.2
Median	17.4
Range	4.2–60.2
PSA nadir [ng/mL]	
Mean	0.84
Median	0.47
Range	0.012–2.17

Treatment

All patients were treated using three-dimensional conformal radiation therapy (3D-CRT) combined with brachytherapy HDR (BT-HDR). Patients underwent simulation and were immobilized using a custom-made immobilization device. This

was followed by a planning CT scan in the treatment position using 5mm slices. The data were transferred to the 3D planning system and the prostate, seminal vesicles, bladder and 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 2.0Gy daily fractions 5d/week to a total dose of 46 Gy. HDR-BT was given in two separate 10Gy 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 a way that CTV was covered by the 10Gy isodose line. The BT was performed under spinal anaesthesia. 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 ERT and HDR-BT was 7–8 weeks.

Follow-up

A bounce was defined as a PSA rise of ≥0.2ng/mL above the nadir followed by a subsequent decline of ≥0.2ng/mL. Bounces were counted if the peak occurred in PSA ranges greater than 0.5ng/mL and less than 4ng/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 χ^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 32 months (range 24–60 months). A PSA bounce was detected in 22 out 71 patients (31%). None of the patients who experienced a PSA bounce had a concurrent urinary tract or prostate infection. Patients' PSA nadir before increase ranged from 0.11ng/mL to 1.55ng/mL (median 0.53ng/mL). There were no statistical differences between median nadir among patients who exhibited a PSA bounce and did not, 0.57ng/mL vs 0.62ng/mL respectively. Non-bouncers reached nadir PSA earlier than bouncers; median time was 12.1 vs 17.2 months respectively. The time from completion of radiation therapy to the start of the spike ranged from 7 to 24 months (median 13.5 months). The neighed increase of PSA ranged from 0.2ng/mL to 0.7ng/mL and was mean 0.28ng/mL.

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 (iPSAmax.), median time to nadir PSA. These factors were confirmed in univariate analysis. Logistic regression 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).

Discussion

The introduction of serum prostate-specific antigen (PSA) determination has changed not only the presentation of prostate cancer worldwide but also is a useful tool in monitoring prostate cancer patients after treatment. PSA level generally falls to undetectable levels after surgery, but for patients treated with radiation therapy 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 in 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 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 reaction leading to prostatitis and elevated PSA concentration. The aetiology for PSA bounce remains unclear, although bacterial and radiation proctitis have been postulated as possible mechanisms [4,7] A PSA bounce can be difficult to distinguish from biochemical failure, leading to significant patient

Table 2. Clinical and dosimetric data for patients with and without PSA bounces.

Factor	No spike (N=49) Mean ±SD	Spike (N=22) Mean ±SD	P
Age [years]	68.5±12.1	62±10.2	**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_{100}	29.4±11.2	34±12.2	**0.041**
V_{150}	11.4±4.2	12.4±3.9	**0.049**
V_{200}	6.2±2.1	8.1±2.3	**0.021**
Follow-up [months]	32.5±7.2	33.1±6.1	0.062
Median nadir PSA [ng/mL]	0.57	0.62	0.072
Nadir PSA [ng/mL]			
≤0.5	23 (58.3%)	10 (45.5%)	0.094
>0.5	26 (41.7%)	12 (54.5%)	
T_{stage}			
T_{1-2a}	35 (71.4%)	14 (63.6%)	0.08
T_{2b}	14 (28.6%)	8 (36.4%)	
Median time to nadir PSA	12.1	17.2	**0.002**

* iPSA max – initial maximal PSA.

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)	0.004	1.82	1.52–4.28	0.003
Gleason score (≤6 vs ≥7)	0.092	–	–	–
Tstage (T_{1-2a} vs T_{2b})	0.421	–	–	–
iPSA max*	0.019	1.21	0.86–1.42	0.002
D_{90}	0.771	–	–	–
D_{100}	0.770	–	–	–
V_{100}	0.022	–	–	–
V_{150}	0.042	–	–	–
V_{200}	0.002	1.22	0.89–1.32	0.002
Median time to nadir (<15 mo vs ≥15mo)	0.039	–	–	–

* iPSA max – initial maximal PSA.

and clinician anxiety with possible unnecessary therapeutic intervention. No universally accepted definitions exist for PSA bounce. PSA increase in the range of 0.1ng/mL [7], 0.2ng/mL [4,17], 0.4ng/mL and ≥15% of the preceding value [18] have been described as a PSA bounce by different authors. Knowledge of the aetiology and predictors of PSA bounces will help to understand and predict this phenomenon and to alleviate patient and clinician anxiety.

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%. 19 patients experienced a single bounce and 3 patients 2 bounces. The rel-

atively high bounce rate in our study may be related to the definition of bounce that we used. As already mentioned, 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 0.4ng/mL increase with any decline below that level and found an association between PSA bounce and biochemical failure [9,10]. According to 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 0.1ng/mL rise with a decline to or below that level, but it seems that fluctuations of 0.1ng/mL were too low because this was within the error of the assay [7,8,19]. In such circumstances we chose a definition of rise of 0.2ng/mL followed by decline as the most reasonable definition. We detected a higher bounce frequency in younger patients. Perhaps younger patients have more androgen production which affects the bounce phenomenon. None of the patients who experienced a PSA increase developed biochemical failure. This association has been confirmed by different authors [2,3,21,22]. On the other hand, Rosser et al. did not find that age has a significant impact on the development, duration or magnitude of PSA bounce [13]. There are also other hypotheses regarding greater sexual activity [17,19] or delayed apoptotic event [20]. The median time to bounce occurred at 15 months after completion of 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 9% of bounces occurred in the first year after RT, 82% in the second year and 9% in the third year or longer time of follow-up. The peak of appearance of bouncing PSA in second year of follow-up may be due to a different reason. According to Merrick benign prostatic elements such as BPH (benign prostate hyperplasia) could respond to radiation with PSA kinetics different to those of malignant cells [22]. It is highly probable 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.

None of our patients who experienced a PSA bounce had biochemical or clinical failure. The present study was limited by the short median time of follow-up. With longer follow-up, more patients may develop biochemical or clinical failure, perhaps including some of the patients now thought to have had a PSA bounce. The relationship of bouncing to bNED (biochemical no evidence of disease) control was investigated by Hanlon et al. [9,10]. According to them bNED rates 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 presence of rising PSA is combined with a histologically positive biopsy in the first year after brachytherapy, it may not mean persistence of viable cancer cells [23,24]. In the other studies bNED control was even better in bouncers [14,25].

In our study we demonstrated the volume of the prostate gland receiving 200% of the prescription dose (V200) predicted for PSA bounce. Merrick et al. found that V150 was a significant predictor of PSA spike [2]. These observations suggest that PSA bounces may be associated with intraprostatic postimplant healthy tissue necrosis or transition from sublethal to lethal cancer cellular damage, in which case patients with PSA bounce should have better prognosis. Such clinical observation was made by Rosser but further pathological studies are needed to prove this hypothesis [14].

Conclusion

Nearly one third of patients after brachytherapy HDR combined with conformal external radiation therapy experienced the PSA bounce effect. As a result, PSA failure could potentially have been overestimated in this group. 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, the detailed history should be known to rule out different reasons connected with elevated PSA level.

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