Predictive factors for PSA bounce in $^{125}$I brachytherapy for prostate cancer – A literature review

V. Mădan¹, A. Aungurenci¹, A. Rădulescu¹, T. Constantin², C.D. Badiu³, D. Mischianu¹
¹Urology Clinic, Central Military Emergency Hospital “Dr. Carol Davila”, Bucharest
²Urology Clinic, Clinical Urology Hospital “Prof. Dr. Th. Burghele”, Bucharest
³General Surgery Clinic, Clinical Emergency Hospital “Bagdasar-Arseni”, Bucharest

Abstract

Introduction and objectives: The purpose of the article is to provide a review of key publications about PSA bounce, by which we could identify the predictive factors and their correlation with the clinical course of patients receiving brachytherapy for prostate cancer.

Materials and methods: The criteria for study inclusion in the meta-analysis were: prospective studies based on large numbers of patients diagnosed with non-metastatic prostate cancer treated with brachytherapy, where it was discovered and pursued a PSA bounce. The main information extracted included data on tumor stage, follow-up time, other treatments, PSA bounce definition, rate of occurrence, time to install, PSA value recorded during persistence and analysis of predictive factors.

Results: We included in the meta-analysis 5 studies which counted a total of 3565 patients with localized prostate cancer (T1a-T2c) under $^{125}$I brachytherapy, on which it was found PSA bounce. Among the predictive factors analyzed, age had the strongest correlation with the occurrence of PSA bounce. Other analyzed factors (T stage prostate cancer, prostate volume, radioactive source, the implanted dose, hormonal therapy, pretreatment PSA and PSA nadir) had a weak correlation or insufficiently investigated in order to be considered predictors of PSA bounce.

Conclusion: Although PSA bounce is met with a frequency of 30% its occurrence can cause concerns for both patients and physicians. The importance of these factors derives from the need to make the distinction between a PSA bounce and a biochemical failure in order to avoid unnecessary investigations or to administrate wrong complementary treatments.

Key words: localised prostate cancer, brachytherapy, PSA bounce, predictive factors.
Introduction and objectives
Brachytherapy is currently a commonly used therapeutic alternative in the treatment of localized prostate cancer. Brachytherapy results are comparable to those of radical prostatectomy or external beam radiation therapy, and because of the advantages related to simplicity, invasiveness and potential complications of the procedure it becomes a therapeutic method often preferable for patients diagnosed with prostate cancer. [1]

The therapeutic efficiency of brachytherapy is followed by determination of prostate specific antigen (PSA), which, due to the slow process of tumour cells apoptosis it shows a gradual decrease to a minimal stable value. This value is called PSA nadir and can be detected after a median time of 2 years from treatment initiation, during which fluctuations in PSA may occur [1].

After PSA nadir is established transient increases in PSA may still occur, which, depending on amplitude and duration, can be interpreted as biochemical failure or PSA bounce. About PSA bounce or PSA spike is known to be a temporary benign increase of variable intensity in PSA levels, which subsequently decreases spontaneously to PSA nadir value, or a value lower than this. In 1997 the American Society for Therapeutic Radiology and Oncology (ASTRO) proposed a definition of treatment failure as three consecutive increases in PSA levels after PSA nadir setting [1,2]. For PSA bounce phenomenon over the past years many definitions have been proposed, but none has been universally accepted [1-3].

Although this phenomenon was first identified in patients with brachytherapy, it can be found in patients receiving external bean radiotherapy [1]. On the other hand PSA bounce was not reported after other treatments such as cryotherapy or HIFU (high-intensity focused ultrasonography), which means that the phenomenon is specific for radiotherapy treatments [1-3].

The predictive value of PSA bounce was also a highly debated topic in medical literature. Most reference studies on this topic declares that PSA bounce can be considered a predictive factor of treatment success, but the distinction between it and biochemical failure should be done very carefully, based on well-established criteria [2, 3].

The purpose of our article is to provide a review of key publications in medical literature about PSA bounce the predictive factors and their correlation with clinical evolution of patients receiving brachytherapy for prostate cancer.

Materials and method
In order to create a database that contains the desired information, we included a series of studies accessed via search engines like Pub Med, Science Direct and Mendeley. The inclusion criteria were: prospective studies made on groups of patients diagnosed with localized prostate cancer that benefited of brachytherapy, as basic therapeutic method, on which it was discovered and pursued a post-procedural PSA bounce.

The main information extracted from those studies included data on patient’s prostate cancer stage, follow-up duration, alternative treatments followed prior to brachytherapy, the definition of PSA bounce used, rate of occurrence, time to onset, amplitude and duration of PSA bounce, and analysis of predictive factors.

Results
Following the selection process conducted, a series of 24 published articles within the last 14 years were included in the meta-analysis, having as main theme the research of PSA bounce phenomenon in patients with brachytherapy for prostate cancer. Among those publications we excluded the articles that had patients treated with external bean radiotherapy, because the brachytherapy results may be influenced by radiation therapy previously made. Out of the 24 articles originally evaluated we selected 18. Then we evaluated the definition of PSA bounce used and included only the studies in which it was used the ASTRO consensus definition (PSA Nadir = PSA bounce + 0.2 ng/ml), thus keeping only 14 articles. Since hormone therapy administered prior to brachytherapy could influence the results of brachytherapy, the studies in which patients were treated with hormone therapy prior to brachytherapy were separated and their results were analysed comparatively with the articles in which PSA bounce appeared only after brachytherapy, as described above.

The meta-analysis according to the criteria described above, was carried out based on the information extracted from 5 articles on this subject, in which the PSA bounce occurred in 3565 patients to whom brachytherapy was performed, without having other treatments before this procedure. The clinical stage in patients who had been diagnosed with prostate cancer was localized (T1a-T2c), who subscribe to low or intermediate D’Amico risk criteria. The average age of patients in each study ranged from 61.8 years to 67 years with a mean age of 64.22 years per study [2,4-7].
In 3 out of 5 studies the average PSA per study before treatment ranged from 5.9 to 10.5 ng/ml, with a mean PSA of 7.8 ng/ml [2,6,7]. The main radioactive substance inserted during brachytherapy was $^{125}$I, and the prescribed radioactive dose was 145 Gy in two studies [6,7], and 160 Gy in only one study [2]. The median follow-up ranged between 44 and 64 months, averaging 55.2 months per study. Regarding the characteristics of PSA bounce, median time to onset was 15.68 months, with a median persistence period of 11.62 months. The median PSA recorded during the bounce period was 0.73 ng/ml [2, 4-7].

Table 1. PSA bounce characteristics in the main literature studies

<table>
<thead>
<tr>
<th>Author's Name</th>
<th>Number of Patients</th>
<th>Clinical Stage</th>
<th>Mean Age</th>
<th>PSA mean value before treatment (ng/ml)</th>
<th>Hormonal Therapy</th>
<th>Brachytherapy modality</th>
<th>Prescribed dose of radioactive substance (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crook [4]</td>
<td>275</td>
<td>T1-T2c</td>
<td>66</td>
<td>-</td>
<td>Nu</td>
<td>$^{125}$I</td>
<td>-</td>
</tr>
<tr>
<td>Kuban [5]</td>
<td>2693</td>
<td>T1a-T2b</td>
<td>-</td>
<td>-</td>
<td>Nu</td>
<td>$^{125}$I</td>
<td>-</td>
</tr>
<tr>
<td>Mitchell [6]</td>
<td>205</td>
<td>T1c-T2b</td>
<td>62.1</td>
<td>7</td>
<td>Nu</td>
<td>$^{125}$I</td>
<td>145</td>
</tr>
<tr>
<td>Mazeron [2]</td>
<td>198</td>
<td>T1-T2b</td>
<td>67</td>
<td>10.5</td>
<td>Nu</td>
<td>$^{125}$I</td>
<td>160</td>
</tr>
<tr>
<td>Zwahlen [7]</td>
<td>194</td>
<td>T1a-T2c</td>
<td>61.8</td>
<td>5.9</td>
<td>Nu</td>
<td>$^{125}$I</td>
<td>145</td>
</tr>
</tbody>
</table>

Table 1. PSA bounce characteristics in the main literature studies (continue)

<table>
<thead>
<tr>
<th>Author's Name</th>
<th>Mean follow-up (months)</th>
<th>PSA bounce definition used (ng/ml)</th>
<th>Rate (%)</th>
<th>Mean time of occurrence (months)</th>
<th>Mean PSA bounce value (ng/ml)</th>
<th>PSA bounce duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crook [4]</td>
<td>44</td>
<td>PSA Nadir + 0.2</td>
<td>40</td>
<td>15.6</td>
<td>0.76</td>
<td>6.8</td>
</tr>
<tr>
<td>Kuban [5]</td>
<td>63</td>
<td>PSA Nadir + 0.2</td>
<td>17</td>
<td>17</td>
<td>0.9</td>
<td>14</td>
</tr>
<tr>
<td>Mitchell [6]</td>
<td>45</td>
<td>PSA Nadir + 0.2</td>
<td>37</td>
<td>14.8</td>
<td>0.91</td>
<td>11.3</td>
</tr>
<tr>
<td>Mazeron [2]</td>
<td>64</td>
<td>PSA Nadir + 0.2</td>
<td>35.9</td>
<td>17</td>
<td>0.6</td>
<td>14</td>
</tr>
<tr>
<td>Zwahlen [7]</td>
<td>60</td>
<td>PSA Nadir + 0.2</td>
<td>50</td>
<td>14</td>
<td>0.5</td>
<td>12</td>
</tr>
</tbody>
</table>

Although PSA bounce phenomenon is known since 1997, when it was first described by Wallner, and it has been extensively studied since, many information known until now are ambiguous or have no direct clinical correlation.

So far several definitions have been proposed to determine the value of PSA nadir growth so that it could be interpreted as a PSA bounce [1]. These include:
- PSA nadir increase ≥ 0.1 ng / ml, followed by a subsequent decline below the initial level;
- PSA nadir increase ≥ 0.2 ng / ml, followed by a decrease;
- PSA nadir increase ≥ 0.4 ng / ml over a period of 6 months, followed by a decrease;
- PSA nadir increase of 0.5 ng / ml;
- PSA nadir increase of ≥ 15% or ≥ 20 ng / ml compared with the most recent value, followed by a decrease in the PSA nadir, or even to a lower level [1].

In 2006 ASTRO proposed a definition for PSA bounce, which today is considered to be the closest to reality: benign transient increase in PSA of 0.2 ng / ml above PSA nadir value, which then spontaneously returns to the same value or to a lower value than PSA nadir.

In the studies included in our meta-analysis, the average PSA bounce was 35.8%. The highest rate of PSA bounce, calculated using the ASTRO definition, was recorded by Zwahlen et al. - 50% [7], while the minimum rate of PSA bounce was found by Kuban et al. - 17% [5]. Regarding these major differences we can say that a major role is held by the harvest conditions and data interpretation. Thus the need for a universally accepted definition derives from the necessity to avoid misinterpretation of physiological fluctuations of PSA and laboratory errors.

Age is a predictive factor recognised by all reviewed studies. It is known the fact that patients under 65 years, were confronted with PSA bounce phenomenon more often than those aged over 65 years. However Mazeron et al. and Crook et al. stated that the average age of occurrence of PSA bounce was 67 years [2], respectively 66 [4].

These data are supported by other similar publications. In the study of Stock et al., 13 patients with age under 65 years had a PSA bounce rate of 38% at 5 years follow-up, compared with a rate of 24% seen in patients younger than 65 years [8]. Critz et al., stated that in patients younger than 60 years, PSA bounce was met 2 times more often than in those aged over 71 years.
Although so far several hypotheses have been proposed, the correlation between age and PSA bounce was not clearly explained. One hypothesis supports androgen theory, that younger patients have a higher secretion of androgens and more reactive epithelial cells, that could influence PSA bounce [1,8]. Another hypothesis supports the emergence of PSA bounce based on sexual activity that would occur due to transient increase in PSA after ejaculation. A study by Mitchell et al., who tries to prove a link between sexual activity and the emergence of PSA bounce, showed no difference between groups of patients with PSA bounce and other non-bounce groups [6]. Crook et al. states that although on univariate analysis sexual activity had a decisive role in the emergence of PSA bounce, on multivariate analysis only age was an independent predictive factor correlated with PSA bounce [4].

Including other characteristics of PSA bounce, Critz et al. alleged that younger patients who received brachytherapy had a significantly higher incidence of PSA bounce and an earlier onset of it. In the same study the younger patients who had a PSA bounce, also had a lower nadir value and a longer persistence of PSA bounce than older patients aged over 65 years [9].

The initial pretreatment PSA value was a minor predictive value for PSA bounce. In the studies reviewed by us, a clear correlation between initial PSA and PSA bounce could not be detected. Makarewicz et al. found a positive correlation between pretreatment PSA and the occurrence of PSA bounce (16.7 ng/ml vs 14.7 ng/ml) [10]. Merrick et al. found that the first post-implant PSA value was a predictive factor for PSA bounce and patients on which PSA bounce was detected had an average post-implant PSA higher than those at which PSA bounce was not detected (1.24 ng/ml vs 0.72 ng/ml) [11]. In the same study, among the variables included in the multivariate analysis, PSA nadir was one of the significant predictive factors. The likelihood of developing a PSA bounce was significantly smaller in patients whose PSA nadir was lower than 0.2 ng/ml, than in patients with PSA nadir between 0.2 and 0.5 ng/ml, or between 0.5 and 1 ng/ml (20%, 50%, 80%) [11].

The tumour stage was not a significant predictor. In the studies included in our meta-analysis, patients diagnosed with T2 stage prostate cancer on univariate analysis, PSA bounce was more common than in patients with T1 stage. Although on multivariate analysis clinical stage was a predictive factor for PSA bounce, there was not enough evidence to demonstrate an association between disease stage and PSA bounce [2,4-7].

The theory that a larger prostate volume may be associated with the risk of PSA bounce had not enough level of evidence in the 5 studies included in our analysis. So far in literature only two studies have highlighted the importance of this association: Stock et al. reported that patients with large prostate volume were associated with a 23% risk of developing PSA bounce at 5 years [8], while Merrick et al., says that the volume of transitional zone, but not the total prostate volume could be a predictive factor for PSA bounce [11]. Some authors have pointed out that increased risk of PSA bounce could be linked to the possibility of benign prostate diseases, such as prostate adenoma, to play a subsequent change in PSA kinetics [11].

Radioactive source and the prescribed radiation dose were considered factors that could have an influence in PSA bounce emergence. In our 5 trials, the 125I radioactive isotopes are used as a source for brachytherapy. In the studies of Mitchell et al. and Zwahlen et al. was prescribed a dose of 145 Gy while Mazeron et al. prescribed a dose of 160 Gy. Although a direct correlation between these data and the occurrence of PSA bounce was not shown by the studies cited above, Merrick et al. pledged that the use of 103Pd seeds can lead to a 50% decrease of PSA bounce occurrence risk [11]. Bostancic et al. reported that hormone-naïve patients, to which 125I was used, had a 3 time higher susceptibility to develop a PSA bounce than in patients who used 103Pd (45.7% vs 14.0%) [12]. Some authors have argued that the reason for these high rates of PSA bounce at patients who were implanted with 125I seeds could be related to prescribed radiation dose [12].

The importance of emitted radiation dose of implanted seeds was highlighted in the study of Stock et al., who demonstrated that a higher implant dose of 160 Gy for 125I, was associated with a significantly increased incidence of PSA bounce (38%) [8]. Similar results were obtained by Mazeron et al. (35.9%) [2]. The authors stated that the high rate of PSA bounce discovered after taking these high doses of radiotherapy may be related to an inflammatory reaction of local radiation. Similarly, Toledano, et al. have shown that the administration of a 200 Gy dose was significantly associated with the development of PSA bounce [13], while McGrath et al. reported that PSA bounce rates were similar between LDR brachytherapy (low-dose rate) and HDR (high-dose rate) (34%, 36%) [14]. Although literature data may be plausible to achieve a correlation between radiation dose and PSA bounce, the results...
published to date are contradictory.

The occurrence of PSA bounce phenomenon in patients who received brachytherapy has been well documented, but the available information on PSA kinetics in these patients are relatively few. In patients with neoadjuvant hormone therapy, temporary increase in PSA levels observed several months after therapy has been assigned to testosterone recovery effect, produced by the end of hormonal therapy [1,2]. To avoid biased results, studies taken in our meta-analysis included patients who did not receive hormonal therapy.

The trial of Pickles et al. stated based on an analysis of 2030 patients, that PSA bounce sites were more common in patients who received hormone therapy (89% vs 71%) [15]. Also, the same authors reported that PSA bounce appeared earlier in the whole group of patients who received hormone therapy (13 months vs 20 months) [15]. In contrast to this, Patel et al. reported that the use of hormone therapy neither influenced the occurrence of PSA bounce, nor decreased the value of PSA during the bounce [16]. Similarly, in the study conducted by Ciezki et al., PSA bounce occurred in almost half of the hormone-naive patients (48.4%) and similarly in patients receiving hormonal therapy (45%) [17]. Tolecano, et al. concluded in their study that neoadjuvant hormone therapy was not a significant factor in the multivariate analysis of PSA bounce community. In addition, hormonal treatment had no significant effect on the biochemical failure, increased PSA or PSA bounce duration [13]. Bostancic et al. stated that in patients with adjuvant hormone therapy, a minimal difference in bounce rates was discovered, no matter what kind of isotope contained the implanted seeds [12].

Conclusions

Although the phenomenon of PSA bounce is met with an average frequency situated around 30% in the [125I] seeds, its appearance causes anxiety both for patients and physicians, which may be related to the possibility of biochemical failure. Such misinterpretation of a PSA bounce may lead to unnecessary investigations at the time of brachytherapy and flawed administration of complementary treatments. Until now research conducted on PSA bounce highlighted a number of predictive factors with direct involvement in the occurrence of this phenomenon. Out of these predictive factors that had a direct statistically significant correlation with the emergence of this phenomenon, the age under 65 years was the most prominent. Other factors such as tumour stage, prostate volume, radioactive source used, implanted dose, hormone therapy, PSA and PSA nadir pre-brachytherapy appear to be involved in the occurrence of PSA bounce, but did not reach a statistically significant level of evidence in trials evaluated.

The importance of these factors derives from the need to differentiate PSA bounce from biochemical failure, in order to continue monitoring these patients. Additionally some studies suggested that PSA bounce can be a potential prognostic factor for positive therapeutic success, but on this issue there are still ongoing researches.

References:

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