

# Prostate-specific Antigen Bounce After Prostate Brachytherapy: Review of a Confusing Phenomenon

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Prostate brachytherapy is a commonly used modality for the treatment of prostate cancer. After prostate brachytherapy, the prostate-specific antigen (PSA) level may fluctuate and increase temporarily without a clear reason in 30-40% of successfully treated men. This phenomenon is called "PSA bounce" and engenders anxiety on the part of the patient and physician. Having reviewed the literature we found 19 articles and summarized in the current review to delineate the facts of this relatively common and ambiguous phenomenon. Although several patient and treatment related factors were assessed by studies, only age remained as the most consistent predictor. *UROLOGY* 74: 1183-1190, 2009. © 2009 Elsevier Inc.

Prostate brachytherapy is a commonly used treatment modality of prostate cancer. Its efficacy has been shown to be comparable to either prostatectomy or external beam radiotherapy (EBRT).<sup>1,2</sup> It is estimated that >60 000 patients are treated every year in United States.<sup>3</sup> It was shown that even elderly patients, >75 years old, prefer this treatment rather than undergoing hormonal therapy or follow-up with watchful waiting.<sup>4</sup>

Prostate-specific antigen (PSA) is a sensitive measure of treatment outcome after RT for prostate cancer. Although in radical prostatectomy, an undetectable PSA level is expected within a few weeks after surgical removal of the prostate, it takes 2-5 years to achieve an eventual nadir in PSA with either EBRT or permanent seed brachytherapy owing to the slower process of tumor cell kill, resulting in a gradual decrease of PSA.<sup>5</sup> After prostate brachytherapy, the PSA level might fluctuate and increase temporarily without a clear reason. This phenomenon is called a "PSA bounce" and engenders anxiety on the part of the patient and physician.<sup>6</sup> It was first described in 1997 by Wallner et al.,<sup>7</sup> who noted it occurring most often between 12 and 30 months after implantation. Since that date, it has been studied in several studies, but neither its definition nor etiology has been defined in detail.

We reviewed the published data to obtain original reports of the PSA bounce phenomenon. Consequently, 19 articles, of which 2 studies reported the high-dose-rate

brachytherapy results, were found and summarized in the present review to delineate the facts of this relatively common and ambiguous phenomenon.

## WHAT IS BOUNCE?

A bounce or "spike" is a benign temporary increase in PSA level of varying magnitude that spontaneously decreases without therapeutic intervention to a level at, or less than, the prebounce PSA reading. Although the PSA bounce was first identified in implant patients, this phenomena is not unique to this treatment modality and instead appears related to RT in general.<sup>8,9</sup> However, it has not been reported after other treatments such as cryosurgery or high-intensity focused ultrasonography.

Several definitions have been suggested for the bounce<sup>10</sup> (Table 1). The PSA bounce has previously been defined as an increase of  $\geq 0.1$  ng/mL, followed by a subsequent decrease to less than that level<sup>6</sup>; as an increase of  $\geq 0.2$  ng/mL, followed by a decline<sup>11,12</sup>; a minimal increase of 0.4 ng/mL<sup>13</sup> during a 6-month period, followed by a decrease of any magnitude; as an increase of 0.5 ng/mL<sup>14</sup>; or even as an increase of any magnitude.<sup>15</sup> The PSA bounce was also defined as a  $\geq 15\%$ <sup>16</sup> and  $\geq 20\%$ <sup>17</sup> elevation in PSA compared with the most recent value, followed by a decline to a level at or less than the prebounce value or  $>35\%$ .<sup>13</sup>

It is important to have a definition that minimizes the "noise" due to laboratory testing error. Pruthi<sup>18</sup> emphasized that the minor fluctuations in PSA are not unique to patients undergoing brachytherapy but can simply be explained by the normal, expected, and already well-described variability of serum PSA determinations. Prestigiacomo and Stamey<sup>19</sup> demonstrated that the overall PSA variability is 35% in patients without prostatic disease and is composed of physiologic (24%) and assay (11%) variation. The PSA bounce, or any PSA change

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**Table 1.** Previously published brachytherapy studies reporting bounce phenomenon

Study	Stage	Treatment	Hormonal Therapy	Definition	Frequency of Bounce (n)	Time to Occurrence (Median)	Duration	Magnitude of PSA Increase	Factors Predicting Bounce	Failure	Bounce-Failure Relationship or Conclusion
Critz et al., <sup>6</sup> 2000 (n = 779)	T1-T2	EBRT + brachytherapy	NA	0.1 ng/mL	273 (35%)	18 mo (range NA) 92% in 36 mo	174 (64%) decreased within 6 mo	0.4 ng/mL (range 0.1-15.8)	T2 > T1	158 median 30 mo	Median time of onset is different. bounce is not a prognostic factor for failure
Cavanagh et al., <sup>11</sup> 2000 (n = 534)	NA	Brachytherapy/ EBRT + brachytherapy	No	0.2 ng/mL	191/534 (35.8%) or 178/474 (free of disease) (37.5%)	20.4 mo for 178 patients	NA	1.1 ng/mL (median peak PSA value)	No factor was determined	60/534 (11.2%)	bounce is not associated with clinical failure
Das et al., <sup>16</sup> 2002 (n = 186)	T1-T2	Brachytherapy/ EBRT + brachytherapy	No	15%	115 (61.8%)	2.2-2.6 y	1 y (range 0.38-2)	Idiopathic: 0.6ng/mL Other: 1.4-2.2 ng/mL	NA	6 (biopsy proven)	Median PSA rise bounce < failure
Critz et al., <sup>36</sup> 2002 (n = 539)	T1c-T2c	Brachytherapy + EBRT	No	0.1 ng/mL	185	NA	NA	NA	NA	NA	PSA must decrease to nadir within 60 mo. bounce delayed the time to nadir
Merrick et al., <sup>33</sup> 2002 (n = 218)	T1b-T3a	Brachytherapy/ brachytherapy + EBRT	No	0.2 ng/mL	52 (23.9%)	16.3 mo (range 6.5-59.9)	16 mo (range 9-45)	Median PSA 0.90 ng/mL (range 0.3-3.0; not magnitude/ increase)	Younger age (mean 63.9 vs 67.3), stage, first postimplant PSA level, V <sub>150</sub>	No	NA
Merrick et al., <sup>29</sup> 2003 (n = 218)	T1b-T3a	Brachytherapy/EBRT + brachytherapy	No	0.2 ng/mL	52 (23.9%)	16.3 mo			Transition zone index, age; preimplant PSA velocity and first postimplant PSA	No	NA
Stock et al., <sup>13</sup> 2003 (n = 373)	T1a-T2c	Brachytherapy	No	0.1 ng/mL 0.4 ng/mL 35%	31% 17% 20%	19.5 mo 19.5 mo 20.5 mo	NA	NA	Younger age (≤65 y), greater dose (>160 Gy) Prostate volume (>35 cm <sup>3</sup> )	NA	Definition 1, bounce has less failure Bounce does not predict failure
Cesaretti et al., <sup>37</sup> 2003 (n = 172)	T1b-T3a	Brachytherapy	52 (32.6%) 3 mo+3 mo	0.1 ng/mL	44%	NA	NA	NA	NA	NA	NA
Critz et al., <sup>31</sup> 2003 (n = 1011)	T1a-T2c	EBRT + brachytherapy	No	0.1 ng/mL	Age ≤60 y: 57%; age 61-70 y: 41%; age ≥71 y: 26% (P = .000)	Age ≤60 y: 19 mo; age61-70 y: 20mo; age ≥71 y: 25mo (average) (P = .002)	Age ≤60 y: 11 mo; Age 61-70 y: 8 mo; age ≥71 y: 8 mo (average) (P < .000)	Age 60: 1.0ng/mL (Av ht); Age 61-70 y: 0.5 ng/mL; Age ≥71 y: 0.8 ng/mL (P < .000)	younger age (61-70 vs ≥71 y)	150	DFS with bounce greater than without Younger men had greater frequency, earlier onset, and longer bounce duration
Reed et al., <sup>15</sup> 2003 (n = NA)	NA	Brachytherapy	No	Any increase? NA	8	13 mo (range 9-24)	NA	Median PSA 3.1 ng/mL (range 2.6-8.4) (not magnitude of increase)	NA	No	All patients were biopsy proven free of disease
Patel et al., <sup>32</sup> 2004 (n = 295)	T1a-2c	Brachytherapy	184 (62.4%) NHT 6 mo	0.2 ng/mL	82 (28%)	19.4 mo (range 8-40.8)	NA	0.5 ng/mL (0.2-4.1)	Younger age (≤65 vs >65 y)	17	bFRS: patients with bounce 100% vs without bounce 92% (P = .018)
Ciezki et al., <sup>12</sup> 2006 (n = 162)	Localized PCa	Brachytherapy	62 (38.3%)	0.2 ng/mL	75 (46.3%)	15.1 mo (2.1-57.3)	NA	NA	younger age (median 67 vs 69 y)	5 y bFRS bF3: 87% bF2: 96%	Bounce had better bFRS (regardless of definition) median time of onset is different

Continued

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Study	Stage	Treatment	Hormonal Therapy	Definition	Frequency of Bounce (n)	Time to Occurrence (Median)	Duration	Magnitude of PSA Increase	Factors Predicting Bounce	Failure	Bounce-Failure Relationship or Conclusion
Pickles, <sup>28</sup> 2006* (n = 449)	Localized PCa	Brachytherapy	315 (70.2%) 3 mo+ 3 mo	Any rise	84%	13 mo (range NA)	12.1 mo (range NA)	median 0.32 ng/mL (range NA)	bounce more common with ADT	NA	NA
Toledano et al., <sup>14</sup> 2006 (n = 295)	T1c-T2c	Brachytherapy	125 (42.4%) 4 mo NHT	0.1, 0.2, 0.3, 0.4, 0.5, and 1 ng/mL	0.1: 161 (55%) 0.2: 145 (49%) 0.4: 93 (32%) 1: 43 (15%)	Mean 19 mo (95% within 3 y)		Mean 0.8 ng/mL	Age <70 and D <sub>90</sub> >200 Gy for 0.4 ng/mL	32 (11%) 18/32 showed normalization without treatment	No relationship
Singh et al., <sup>17</sup> 2006 (n = 9)	≥T2b	HDR Brachytherapy + EBRT	4 (44%) NHT + concurrent	20%	5 (56%)	2 patients 6 mo, 3 patients 12mo	NA	NA	NA	NA	NA
Makarewicz et al., <sup>26</sup> 2006 (n = 71)	T1-T2b	EBRT +HDR brachytherapy	No	0.2 ng/mL	22 (31%)	13.5 mo (range 7-24)	NA	Mean 0.28 ng/mL	Younger age (mean 62 vs 68.5 y), iPSA and V <sub>200</sub>	NA (no failure in bounce patients)	No failure in bounce patients
Bostancic et al., <sup>34</sup> 2007 (n = 164)	T1c-T2b	Brachytherapy	61 (37.2%) 3 mo NHT	0.2 ng/mL	44 (26.9%)	Median time 18.9mo (range NA) HT(-), <sup>125</sup> I: 22.6 mo; <sup>103</sup> Pd: 18.7 mo (mean) HT(+), <sup>125</sup> I: 18.9; <sup>103</sup> Pd: 6 mo (mean)	Median time 8.7 mo (range NA) HT(-), <sup>125</sup> I: 8.1 mo; <sup>103</sup> Pd: 8.8 mo (mean) HT(+), <sup>125</sup> I: 11; <sup>103</sup> Pd: 7.1 mo (mean)	0.47 ng/mL (range NA)	Younger age (65 vs ≥65 y), isotope used (HT, with I, spike 3 times more likely than those with Pd)	NA	NA
Crook et al., <sup>5</sup> 2007 (n = 275)	T1-T2	Brachytherapy	No	0.2 ng/mL	109 (40%)	15.2 mo (range 3-29)	6.8 mo (range 3-50)	0.76 ng/mL (range 0.21-11.79)	Younger age (median 59 vs 66 y)	8 median 30.9 mo	Median time of onset different Bounce does not predict failure
Mitchell et al., <sup>20</sup> 2008 (n = 205)	T1c-T2b	Brachytherapy	No	0.2 ng/mL	79 (37)	14.9 (range 1.7-40.6)	11.3 mo (range 2.3-32.5)	0.91 ng/mL (range 0.2-5.8)	Younger age (mean 60 vs 64 y)	23 (11%) 20.8 mo	Bounce had less failure PSA velocity of bounce < failure Timing of bounce and failure different

EBRT = external beam radiotherapy; NA = not available; PSA = prostate-specific antigen; V<sub>150</sub> = percentage of volume receiving 150% of prescribed minimal peripheral dose; DFS = disease-free survival; HDR = high dose rate; NHT = neoadjuvant hormonal therapy; HT = hormonal therapy; bRFS = biochemical relapse-free survival; iPSA = initial PSA.

\* Pickles reported the results of 2030 patients treated with external radiotherapy or brachytherapy. In the table only the results of brachytherapy patients were summarized.

deemed significant, should be defined as a percentile change of >35% from baseline, thereby accounting and controlling for the expected physiologic and assay variability.<sup>18</sup> Additionally, it is known that 1 standard deviation of error in the PSA level in most clinical pathology laboratories is 0.1 ng/mL.<sup>19</sup> Thus, it is important to have the PSA bounce be  $\geq 2$  standard deviations, or 0.2 ng/mL, greater than the nadir, with a subsequent decrease to, or less than, the initial nadir, to have a greater probability of observing a bounce rather than a laboratory error.<sup>12</sup>

However, efforts to reduce the effect of daily physiologic and laboratory variation using alternate bounce definitions have not helped to differentiate between treatment failure and PSA bounce.<sup>13,20</sup> Post-treatment prostate biopsy to differentiate recurrence from bounce could produce misleading information. Previous studies of prostate biopsies after EBRT have documented a slow resolution of histologic evidence of prostate cancer that can require  $\geq 30$  months of follow-up.<sup>21,22</sup> Thus, prostate biopsies 12-24 months after implantation, the peak time for a PSA bounce, might be unreliable and can show false-positive histologic results because the cancer cells have not had time to disintegrate. These observations could be especially pertinent relative to <sup>125</sup>I seed implantation, because 98% of the dose is not produced until 12 months after implant owing to the 60-day half-life.<sup>6</sup>

## ETIOLOGY

Knowledge of the etiology and predictors of PSA bounce will help to understand and predict this phenomenon and to lessen patient and physician anxiety. The etiology of this phenomenon is unknown; however, it has been hypothesized to be the result of prostate cell membrane instability, bacterial and radiation prostatitis,<sup>6</sup> or microvascular fibrosis leading to prostate infarction. Its timing is in keeping with that of a late radiation effect.<sup>20</sup> Critz et al.,<sup>6</sup> reported that a PSA bounce was uncommon when a PSA nadir of  $\leq 0.2$  ng/mL was achieved, a level that reflects little or no existing benign epithelium that could become inflamed as additional support of this association. However, in that study, most men with a PSA bounce were asymptomatic. They also emphasized that laboratory error could be another cause of PSA bounce, especially in some men who have had a single PSA increase, or the prebounce PSA level could have been measured in error. A PSA bounce could also be caused by using different laboratories with different assay techniques. Laboratory error could be especially true if the prebounce PSA nadir was  $\leq 0.2$  ng/mL. Previous studies have also shown that transient elevations in PSA can arise from recent ejaculation, instrumentation, proctitis, and bicycle riding.<sup>23-25</sup>

In most studies, the frequency of PSA bounce seems to be greater after brachytherapy than after EBRT.<sup>26-28</sup> The insertions of needles or seeds might cause an inflammatory reaction, leading to prostatitis and an elevated PSA

concentration.<sup>26</sup> Makarewicz et al.,<sup>26</sup> proposed that PSA bounces might be associated with intraprostatic postimplant healthy tissue necrosis or transition from sublethal to lethal cancer cellular damage, in which case patients with a PSA bounce should have a better prognosis. However, additional pathologic studies are needed to prove this hypothesis.<sup>26</sup>

According to Merrick et al.,<sup>29</sup> benign prostatic elements such as benign prostatic hyperplasia (BPH) might respond to RT with PSA kinetics different from those of malignant cells. It is highly probable that areas of necrosis identified in BPH nodules might have resulted in PSA bounces, with the suggestion that radiation-induced cell death in BPH elements might occur at a later interval than that of malignant cells.

## FREQUENCY

In general, after prostate brachytherapy, 30%-40% of successfully treated men will experience a benign PSA increase or a "bounce." The range has been varied from 15% to 84% (Table 1). This wide range of incidence is partially because several definitions have been used to describe this occurrence.<sup>30</sup> In the study by Stock et al.,<sup>13</sup> the incidence was 31%, 17%, and 20% using a bounce definition of 0.1 ng/mL, 0.4 ng/mL, and 35% increase, respectively. Toledano et al.<sup>14</sup> stated the incidence was as low as 15% when the bounce was defined as a 1-ng/mL increase. They also reported a frequency of 55%, 49%, and 32% using a definition of 0.1 ng/mL, 0.2 ng/mL, and 0.4 ng/mL, respectively. However, when any increase was accepted as a bounce, such as was done in the study by Pickles et al.,<sup>28</sup> the incidence increased  $\leq 84\%$ . According to the widely accepted definition of 0.2 ng/mL, the frequency has varied from 23.9% to 49%. Although the incidence of PSA bounce clearly depends on the definition used, the occurrence is certainly evident. Therefore, the development of a standardized definition of this phenomenon is imperative to allow for a better comparison of the incidence among studies.<sup>30</sup> It is also true, from a basic mathematical standpoint, that the frequency of post-treatment PSA blood tests will correlate directly with the PSA bounce frequency. None of the aforementioned data addressed this confounding variable.

## FACTORS PREDICTING BOUNCE

Although several factors, such as age, T stage, prostate volume, prostate transitional zone volume, isotope used, implant dose, hormonal therapy, baseline PSA level, and PSA nadir, were assessed by the previously cited studies, only age remained as the most consistent predictor.

### Age

The effect of age on the PSA bounce phenomenon has been widely emphasized in previous studies. Younger patients, usually <65 years old, have experienced a PSA bounce more often than their older counterparts. In the

study by Stock et al.,<sup>13</sup> patients who were <65 years old had a bounce rate of 38% compared with a rate of 24% for older patients ( $P = .009$ ) at 5 years. Critz et al.,<sup>31</sup> stated that patients who were  $\leq 60$  years old experienced a PSA bounce 2 times more often than did the patients  $\geq 71$  years old (57% vs 26%,  $P < .000$ ). In contrast, Das et al.<sup>16</sup> did not report an association between idiopathic PSA bounce and age, but they excluded men who had reported recent ejaculation at the time of their PSA bounce.

Although several hypotheses have been proposed, the exact mechanism behind the age and bounce relationship has not been clearly explained. One of the probable reasons might be that younger patients having more androgen production and more reactive epithelial cells, which could affect the bounce phenomenon.<sup>13</sup> However, because the glandular component of the prostate increases with age, intuitively one might have expected the opposite result.<sup>31</sup> Alternately, a completely separate phenomenon might account for the bounce (eg, a delayed apoptotic event or greater sexual activity) that simply is more common in younger individuals.<sup>32</sup> Because ejaculation can cause a PSA increase and younger men are more apt to be sexually active, sexual function might have some role in this observed relationship of age and bounce.<sup>31</sup> However, the attempt to link sexual activity to the occurrence of the PSA bounce has not shown any difference between the bounce and nonbounce groups.<sup>20</sup> In a study by Crook et al.,<sup>5</sup> although potency was a significant determinant of a PSA bounce on univariate analysis, only age was independently associated with a PSA bounce on multivariate analysis.

Age also influenced the interval to the occurrence and duration significantly. In the study by Critz et al.,<sup>31</sup> young men treated with brachytherapy not only had a significantly greater incidence, but also an earlier onset, a greater bounce increase, a lower nadir before the bounce, more multiple PSA bounces, and a longer duration of PSA bounce than did the older men.<sup>31</sup>

## T STAGE

In the study by Critz et al.<sup>6</sup> in 2000, patients who had Stage T2 disease experienced a PSA bounce more often than did patients with Stage T1 on univariate analysis (66% vs 34%,  $P = .04$ ). Merrick et al.<sup>33</sup> found clinical stage to be a predictive factor for a PSA bounce on multivariate analysis; however, it was not clear whether an advanced disease stage was more associated with a PSA bounce or not.

## Prostate Volume and Transitional Zone Volume

In general, it has been accepted that a larger prostate volume results in more frequent PSA bounces. However, only 2 studies have emphasized its significance to date. Stock et al.,<sup>13</sup> reported that patients with larger glands had a 23% increased risk of bounce at 5 years. In a study by Merrick et al.,<sup>29</sup> the transition zone volume, but not

the prostate volume, was a predictive factor for a PSA bounce. The investigators stated that the increased risk of bounce might be related to the possibility that benign prostatic elements, such as BPH, could respond to RT with differing PSA kinetics than those of malignant cells.

## Isotope

In most of the studies, <sup>125</sup>I radioactive implant was used as the brachytherapy source. However, <sup>103</sup>Pd was used in 5 studies with <sup>125</sup>I, in which only 1 report<sup>33</sup> emphasized the importance of the isotope used.<sup>11,13,29,33,34</sup> Merrick et al.<sup>33</sup> reported that <sup>125</sup>I resulted in twice the likelihood of a spike (33% vs 17%) compared with <sup>103</sup>Pd in a retrospective evaluation of hormone-naïve patients. The investigators, in another publication, reported that hormone-naïve <sup>125</sup>I patients were more than 3 times as likely as hormone-naïve <sup>103</sup>Pd patients to develop a PSA spike (45.7% vs 14.0%).<sup>34</sup> They stated that the reason for the greater bounce rate with <sup>125</sup>I was unknown but might be related to the dose rate delivery.

## Implant Dose

The importance of a given dose has been stressed in many studies. In the study by Stock et al.,<sup>13</sup> it was revealed that a greater implant dose ( $>160$  Gy for <sup>125</sup>I) was associated with a significantly increased incidence of PSA bounce (38% vs 24% at 5 years). The investigators stated that the increased rate of bounce seen with the greater doses might be related to a greater likelihood of a radiation-induced inflammatory reaction. Similarly, Toledano et al.<sup>14</sup> showed that a minimal dose received by 90% of target volume of  $>200$  Gy was significantly associated with a PSA bounce ( $P < .003$ ). However, contradictory results have also been reported. Merrick et al.<sup>33</sup> reported that the dosimetric parameters were predictive of a PSA bounce (percentage of volume receiving 150% of prescribed minimal peripheral dose and minimal dose received by 90% of target volume in the absence of the former), suggesting that greater radiation doses might obliterate malignant and benign prostatic tissue, with a resultant lower probability of a bounce. The investigators stated that their dosimetric findings were consistent with the observations by Hanlon et al.<sup>35</sup> that bounces were more common with lower EBRT doses. However, it should be remembered that a PSA bounce after EBRT might be different and have different implications than the bounce seen after brachytherapy.

## Hormonal Therapy

Although the phenomenon of PSA bounces in hormone-naïve brachytherapy patients has been well documented, little information is available regarding the PSA kinetics in androgen deprivation therapy (ADT) patients undergoing brachytherapy.<sup>14</sup> In the scenario of neoadjuvant hormonal therapy, the temporary increase in PSA level seen a few months after therapy had been attributed to

the effect of testosterone recovery on residual PSA-producing tissue.<sup>5,28</sup>

Pickles<sup>28</sup> reported an analysis of 2030 men treated for prostate cancer with EBRT (1581 patients) or brachytherapy (449 patients) with or without adjuvant ADT. Pickles reported that bounces were more common with ADT (89% vs 71%,  $P = .001$ ) in the brachytherapy patients and PSA bounces during EBRT were less common in those who had received ADT (55% vs 66%,  $P < .001$ ). He also reported that bounces occurred sooner in those treated with ADT (13 vs 20 months) for the whole group.

Patel et al.<sup>32</sup> reported that the use of ADT unexpectedly did not affect the occurrence of the PSA bounce nor did it blunt the magnitude of the PSA increase during a bounce. Similarly, in the study by Ciezki et al.<sup>12</sup> (an update of the Patel et al. data), the bounce occurred in 30 of 62 (48.4%) hormone-naive patients and in 45 of 100 (45%) hormone-given patients ( $P = .67$ ).

Toledano et al.<sup>14</sup> stated that neoadjuvant hormonal therapy was not found a significant factor on multivariate analysis for a PSA bounce. Moreover, hormonal therapy did not have an effect on the bounce rate, PSA increase, or bounce duration. Finally, Bostancic et al.<sup>34</sup> reported that in ADT patients, a minimal difference was found in the spike rates, regardless of which isotope had been used.

#### **PSA Nadir, Initial Maximal PSA, First Postimplant PSA Level, and Preimplant PSA Velocity**

In published data, a few other prognostic factors have been reported that were relatively less emphasized for PSA bounce. In the study by Merrick et al.,<sup>33</sup> when the variables only determinable after the occurrence of the PSA spike were included in the multivariate analysis, the nadir PSA was 1 of several significant predictors. The investigators reported that when stratified into 3 nadir PSA groups, patients with a nadir PSA  $<0.2$  ng/mL were significantly less likely to develop a PSA spike than those patients with a PSA nadir of  $>0.2$  but  $<0.5$  ng/mL or  $>0.5$  but  $\leq 1.0$  ng/mL (20%, 50%, and 80%, respectively;  $P < .001$ ).

In another study reported by Makarewicz et al.,<sup>26</sup> the maximal initial pretreatment PSA value was a predictive factor for bounce. The investigators reported that patients who experienced a bounce had a greater mean maximal initial pretreatment PSA value than those who did not (16.7 ng/mL vs 14.7 ng/mL,  $P = .045$ ). Merrick et al.<sup>33</sup> found that the first postimplant PSA value was a predictive factor for a PSA bounce. They reported that patients who experienced a bounce had a greater mean first postimplant PSA value than did those who did not experience a PSA bounce (1.24 ng/mL vs 0.72 ng/mL,  $P < .001$ ). In a subsequent study by the same investigators, this finding was also confirmed. In that study, it was also reported that a lower preimplant PSA velocity was a significant predictor for PSA bounce.<sup>29</sup> The investigators emphasized that although the biologic basis of this finding remained unclear, it might be of significant utility.

## **TIME OF OCCURRENCE**

In general, a transient elevation or “bounce” in PSA level has been widely accepted to occur at 12-24 months after implant in up to one third of patients<sup>20</sup> (Table 1). In the published data, it has been reported that the range for the median interval of occurrence varies from 13 months to 2.6 years. Critz et al.<sup>6</sup> stated that 92% of 779 patients experienced such a transient elevation in a 36-month period. They also stated that a PSA bounce was not observed after 60 months of follow-up. Toledano et al.<sup>14</sup> reported that 95% of 295 patients experienced the bounce phenomenon within 3 years. However, it must be taken into account that this time might protract over 5 years, even it is valid for a few cases.<sup>13</sup> In contrast, the time of occurrence can vary by age, hormonal therapy status, and radioisotope used. Critz et al.<sup>31</sup> reported that the average time was 19 or 20 months for those  $<70$  years old and was 25 months for those  $>71$  years old ( $P = .002$ ). In the study by Bostancic et al.,<sup>34</sup> the mean time to the bounce was comparable between the hormone-naive patients and the hormone-given patients who had received <sup>125</sup>I but occurred significantly earlier in the hormone-given patients who had received <sup>103</sup>Pd.

## **DURATION OF PSA BOUNCE**

In more than one half of the studies, the duration of PSA bounce was not reported. Although the median and/or mean have varied from 6 to 16 months in the published studies, usually a PSA spike decreases to the nadir or to less than the prebounce value within 12 months. Critz et al.<sup>31</sup> reported that the average PSA duration varied in relation to patient age. In that study, the average duration was 11 months in the patients  $<60$  years old and was 8 months in the patients  $>61$  years old. This interval can also vary depending on the radioactive source used and the use of ADT. In a study by Bostancic et al.,<sup>34</sup> the mean duration of the bounce was 8.1 and 8.8 months in hormone-naive patients treated with <sup>125</sup>I and <sup>103</sup>Pd, respectively, and was 11 and 7.1 months in hormone-given patients, respectively. The mean duration was comparable for all cohorts, except for the hormone-given patients who had received <sup>125</sup>I, who had a PSA bounce duration 3-4 months longer than that of the other 3 cohorts.

## **MAGNITUDE OF INCREASE**

In the published data, the mean and median PSA increases were both given. The peak value of the PSA level instead of the increase was also reported in a few studies. In general, the median and mean magnitude of the PSA increase varied from 0.4 ng/mL to 1 ng/mL (Table 1). This value was found to be different between bounce and failure merely in 1 study,<sup>16</sup> the details of which are given in the next section.

## BOUNCE AND FAILURE

The clinical importance of the PSA bounce comes from the possibility that it is an indication of treatment failure. Several bounce studies also reported the failure rates of their patients who were examined because of a PSA bounce. Critz et al.<sup>6</sup> first mentioned bounce and failure, but they stated that the PSA bounce had no prognostic significance relative to recurrence. Almost at the same time, Cavanagh et al.<sup>11</sup> achieved the same result. Stock et al.<sup>13</sup> reported that the PSA bounce did not predict for future PSA failure in a study in which they used 3 different definitions for bounce. Critz et al.<sup>31</sup> stated that an increase in PSA due to recurrence will mask a bounce, especially during the first 3 years after implant, when bounces commonly occur. Toledano et al.<sup>14</sup> also reported that bounce was not significantly associated with subsequent true biochemical failure, as defined by continued increases in PSA, in their series. Finally, Crook et al.<sup>5</sup> also reported that the PSA bounce did not predict for subsequent failure.

In contrast, a few studies have implied the patients who experienced a PSA bounce were less likely to experience biochemical failure. Patel et al.<sup>32</sup> reported that the overall biochemical relapse-free survival rate of the patients experiencing a PSA bounce was 100% compared with 92% for those who did not have a PSA bounce ( $P = .018$ ). The investigators concluded that a PSA bounce might be associated with improved biochemical relapse-free survival because the range of time to PSA failure and the median follow-up time overlapped. The same group subsequently reported a similar finding more emphatically. Ciezki et al.<sup>12</sup> stated that regardless of which biochemical failure definition was used, patients who experienced a PSA bounce had superior biochemical relapse-free survival compared with patients who did not experience a PSA bounce. Recently, Mitchell et al.<sup>20</sup> also reported that a PSA bounce was a common finding in their population and was associated with a lower rate of subsequent biochemical failure.

Most efforts have focused on the distinction of bounce from failure. For this purpose, different clinical features have been examined as predictors. The difference between the median time of the onset of a bounce and failure has been the most common factor mentioned. Critz et al.<sup>6</sup> found that the median time to cancer recurrence was 30 months, significantly greater than the median time to a PSA bounce of 18 months. They reported that although the overlap was considerable, the only distinguishing characteristics between PSA bounce and cancer recurrence was the interval to occurrence. Ciezki et al.<sup>12</sup> first emphasized the importance of the interval to the first increase in PSA. They reported that the interval to the first increase in PSA after brachytherapy was an excellent discriminator between a PSA bounce and treatment failure because a PSA bounce usually occurred much earlier than did failure. This important observation was also stated in 2 additional studies.<sup>5,20</sup> Crook et al.<sup>5,20</sup>

reported that the only distinguishing factor between patients undergoing a benign PSA bounce and recurrence was the interval to the onset of the increasing PSA level. However, they noted that a considerable overlap was present between bounce and failure.

Finally, a few less common factors related to bounce and failure have been reported. In a study by Das et al.,<sup>16</sup> the median PSA elevation in patients with biopsy-proven local recurrence was significantly greater than in those patients with an idiopathic PSA bounce. Nevertheless, this finding was not confirmed by subsequent studies. Ciezki et al.<sup>2,12</sup> reported that the PSA velocity before a PSA bounce and that before biochemical failure was identical. They concluded that the PSA velocity is a poor discriminator between the 2 events. In a recent study by Mitchell et al.,<sup>20</sup> the median PSA velocity during the bounce was significantly lower than the median velocity before Phoenix-defined biochemical failure ( $P = .0005$ ).

## CONCLUSIONS

A PSA bounce after prostate brachytherapy causes anxiety in the patient because of the fear of treatment failure and anxiety in the physician owing to uncertainty about the patient's disease status and the possible need for additional therapy. Physicians should inform the patient about the possibility of a PSA elevation after brachytherapy that is most likely a temporary situation, before initiating treatment, to ensure awareness and decrease anxiety. It is important to treat patients conservatively, with continued close observation, eliminating unnecessary salvage therapy, and possibly avoiding other unnecessary and expensive imaging studies when the physician has determined that the elevation is a PSA bounce.<sup>30</sup> Additional studies, focused on understanding the etiology and pathogenesis of this phenomenon, are strongly needed.

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