A benign elevation in prostate-specific antigen (PSA) values with a subsequent nadir (the lowest PSA reading achieved after prostate cancer treatment) only recently has been identified and reported in the literature as the “PSA bounce.” Men who choose external beam radiation therapy (EBRT) or ultrasound-guided prostate brachytherapy (seed implant) for early-stage prostate cancer may experience this transient rising of PSA values after treatment without disease recurrence. This elevation can be a major source of anxiety for patients and families and create diagnostic challenges for clinicians. Because no standard method exists to define the PSA bounce, more study is needed to explain its occurrence. Clinicians should be aware of this complex phenomenon, observe PSA values, and account for the PSA bounce in post-treatment management of their patients. Patient education and psychosocial support can be helpful for patients and families when PSA values rise after radiation treatment.

Key Words: prostate specific antigen, prostatic neoplasms/blood, tumor markers/biological, external beam radiotherapy

Prostate cancer is the most common cancer in American men. Those who choose external beam radiation therapy or ultrasound-guided prostate brachytherapy (seed implant) as treatment for early-stage prostate cancer may experience a benign rise in prostate-specific antigen (PSA) values after treatment. This phenomenon has been identified in the literature as the “PSA bounce,” which can be mistaken for a rise in PSA resulting from biochemical failure. The PSA bounce can be a major source of anxiety for patients and families and can create diagnostic challenges for clinicians. Additional study is needed to explain its occurrence. Clinicians should be aware of this complex phenomenon, observe PSA values, and account for the PSA bounce in post-treatment management of their patients. Patient education and psychosocial support can be helpful for patients and families when PSA values rise after radiation treatment.

Case Study

P.C., a 66-year-old Caucasian man, had a routine screening PSA drawn at a primary care office in November 1999. Although his PSA had been within normal limits (i.e., 4.0 ng/ml) on previous occasions, this time, it was elevated to 7.1 ng/ml (Morey, 2000). A nodule was palpated in the right zone of the prostate during a digital rectal examination (DRE). A subsequent transrectal ultrasound and biopsy of the prostate revealed a mildly enlarged 31 g prostate, whereas a normal prostate measures 20 g (Grimm et al., 1997). His ultrasound also showed a 1.5 cm hypoechoic nodule in the right transition zone. Final pathology revealed a Gleason grade 3 + 3 adenocarcinoma in the right base and right midgland. Aside from his chronic arthritis, the patient felt healthy and had no urinary symptomatology. He denied weight loss, new bony aches or pains, or bowel problems. When P.C. presented for discussion of treatment options, he had difficulty understanding that he was seriously ill. Although he was cognizant that his prostate cancer had been detected early, he nevertheless was facing treatment decisions for a disease that had caused no symptoms.

P.C. was a good candidate for a radioactive seed implant because he was healthy and had an excellent performance status. His PSA was less than 10, and his Gleason score was 6 (3 + 3) or moderately differentiated. He underwent iodine¹²³ seed implant in early 2000. The implant went well, and he returned to his baseline activities within a week after the procedure. His first post-treatment PSA blood test was drawn one month later and had dropped to 1.4 ng/ml, indicating an excellent response to therapy. Subsequent serial PSA blood tests

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drawn continued to drop, and he had a one-year postimplant nadir of 0.3 ng/ml, which is within normal limits.

P.C. continued to present for regular follow-up in the radiation department. Subsequent PSA levels after his nadir of 0.3 ng/ml began to rise; however, the patient felt fine. He had no symptoms of cystitis, urethritis, or prostatitis. At 16, 18, and 24 months after seed implant, his PSA had risen beyond the previous measurement on each occasion, and at 24 months postimplant, his PSA had reached 1.3 ng/ml, adding to the clinical and psychological dilemma (see Figure 1). The patient became anxious and questioned his treatment decision. He said he wished he had “never had any PSA test in the first place.” Although no clinical evidence of disease existed, the patient and his healthcare team were concerned that they were dealing with locally recurrent disease based on the steady rise of the PSA. Discussion ensued about how to proceed. Should he be restaged with a biopsy and/or radiologic imaging (e.g., bone scan, computed tomography scans of the pelvis)? Should he consider adjuvant hormonal treatment? The mutual decision was to continue to observe his PSA. He returned for a follow-up visit at 36 months postimplant, and his PSA dropped to 0.5 ng/ml. The patient was understandably relieved with this sharp drop in the PSA value, but he understood that regular PSA observation in conjunction with a physical examination was recommended. At 40 months postimplant, P.C. reached his previous nadir of 0.3 ng/ml.

P.C.’s rising PSA was a major source of anxiety. He sought opinions from his radiation oncologist, urologist, and primary care physician during the two-year period from his initial PSA nadir to his PSA bounce and subsequent nadir. Each clinician reviewed P.C.’s situation and believed that ongoing observation was in order. Time proved to be the right treatment for P.C. because his PSA remains very low and the disease is nonexistent.

This case history illustrates the PSA bounce that is experienced by up to a third of the men treated with iodine-125 or palladium-103 prostate brachytherapy at an average of 18–24 months status postimplant (Cavanagh, Blasko, Grimm, & Sylvester, 2000; Critz et al., 2000). For those treated with EBRT, a benign elevation has been reported in approximately 12% of patients on average of nine months status post EBRT (Rosser et al., 2002). Several retrospective analyses are reported in the literature regarding the PSA bounce, which also has been referred to as a PSA spike or bump (see Table 1).

### Prostate-Specific Antigen Background and Significance

Early detection of prostate cancer became possible when the PSA blood test was introduced in the late 1980s (Morey, 2000). Prior to the test’s development, early detection was difficult and many men were diagnosed after the disease was already locally advanced or metastatic (Morey). PSA is a serum tumor marker with high sensitivity and specificity for the prostate gland. This glycoprotein is secreted by normal and malignant cells comprising the prostate gland (Greco & Blank, 1993; Thompson et al., 2000). The sensitivity for PSA is high, yet as many as 20%–30% of prostate cancers are undetected when serum PSA alone is used in screening (Goolsby, 2001; Morey). The patient’s age should be considered prior to interpreting PSA results because prostate size increases with age and PSA rises normally with an increase in prostate volume (Thompson et al.). Clinical practice guidelines now include the use of PSA and DRE as secondary detection tools offered to men (Goolsby; Thompson et al.). However, “Because of the biological variability of prostate cancer and the lack of a completed randomized, controlled trial that proves the benefit of early detection, the use of PSA for prostate cancer early detection remains controversial” (Thompson et al., p. 268).

### Treatment of Early-Stage Prostate Cancer

Patients with elevated PSA and/or abnormal DRE usually are referred for prostate biopsy. Early detection provides patients with more treatment options and a better chance at cure versus control. After positive histologic confirmation is obtained, the Gleason score determines the aggressiveness of the tumor. Gleason grading is a system of evaluating the aggressiveness of prostate cancer cells on a 1–5 scale based on the microscopic appearance of the cells. Well-differentiated tumors are assigned Gleason 1 and 2, moderately well-differentiated tumors are assigned Gleason 2 and 3, and poorly differentiated tumors are assigned Gleason 4 and 5. Pathologists determine the two most prevalent patterns and assign a grade to each pattern. The sum of the grades is the Gleason score. For example, if two patterns are rated as Gleason 3 and 4, the total Gleason score of 7 indicates a biologically aggressive tumor (Ragde, Grado, Nadir, & Elgamal, 2000; Thompson et al., 2000). The use of PSA and DRE as dual screening methods has increased the number of newly diagnosed, localized prostate cancers and affected patients’ treatment options. Patients can make informed decisions regarding treatment with the use of Partin tables, which correlate with PSA level; a Gleason score; and estimated clinical stage. These tables or nomograms, which represent the relationship among a patient’s known prostate cancer staging variables, were developed by urologists Alan Partin and Patrick Walsh to assist in the prediction of prostate cancer stage at presentation (Partin et al., 2003). A nomogram is a “graphic representation of numerical relationships” (Thomas, 1977, p. N-34). The healthcare team uses Partin tables to predict the pathologic stage and select the most appropriate avenue of treatment. Treatment options are determined based on the staging of the prostate cancer as well as the patient’s age, performance status, comorbidities, Gleason score, and PSA (Partin et al.). Patients with early-stage prostate cancer usually are considered candidates for prostatectomy, EBRT,
or seed implant. Patients’ personal treatment decisions often are based on the side effects encountered with these treatments.

External Beam Radiation Therapy

Many men with localized prostate cancer staged as T1 or T2 choose radiation treatment options such as EBRT or seed implant. For treatment of localized, low-risk prostate cancers, EBRT or seed implant has approximately equal cure rates when compared with radical retropubic prostatectomy (Krisch & Koprowski, 2000).

EBRT has been the mainstay of radiation treatment for prostate cancer since the early 1970s and has technically advanced with each decade (Krisch & Koprowski, 2000). Whole pelvis radiation, which included treatment of occult pelvic lymph node metastasis, was a standard therapy into the early 1990s (Krisch & Koprowski). Whole pelvis radiation largely has been replaced with focused beam irradiation with higher doses and smaller pelvic fields such as three-dimensional conformal radiation therapy (3DCRT) and intensity modulated radiation therapy (IMRT). IMRT’s advantage over 3DCRT is its ability to target a high dose of radiation at the prostate while shaping the radiation beam to limit the dosage to the bladder and rectum (Krisch & Koprowski). Treatment regimens range from 35–40 fractions, with a total dose of 6,300–7,200 cGy (Grimm et al., 1997), and administration may take 15–45 minutes daily depending on the radiation treatment software that is used.

Ultrasound-Guided Prostate Brachytherapy (Seed Implant)

Seed implant has become an increasingly popular radiation modality for early-stage prostate cancer; however, not all patients are suitable candidates for this treatment. Patient selection criteria based on the Seattle Prostate Institute’s decision tree include patients with a clinical stage of T1a, T1b, T1c, T2a, T2b, or T2c (Grimm et al., 1997). If a patient has had a transurethral resection of the prostate and has a large surgical defect, he is not considered a good candidate. Gland size of more than 40 g and less than 60 g is optimal, but if the gland is larger than 60 g, it may be downsized with hormonal blockade prior to implant. The best candidates for seed implant theoretically remain those with small volume disease, a PSA of less than 10 ng/ml, and a total Gleason score of less than 7. Other variables also must be considered in decision making. Each patient is evaluated further based on his urinary symptoms, comorbidities, and ability to follow through with radiation safety issues (Grimm et al.). This outpatient procedure allows a very high dose of radiation to be given interstitially based

Table 1. Prostate-Specific Antigen Bounce Literature Review

<table>
<thead>
<tr>
<th>Study</th>
<th>Purpose</th>
<th>N</th>
<th>Sample*</th>
<th>Design</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavanagh et al., 2000</td>
<td>Identify and describe transient benign PSA elevation.</td>
<td>591</td>
<td>Stage T1, T2, and T3 PCA with transient PSA elevation after $^{125}$I or $^{103}$P prostate brachytherapy or brachytherapy with EBRT; median follow-up was 55 months.</td>
<td>Retrospective cohort analysis</td>
<td>About 30% of the sample had transient elevation of PSA with subsequent nadir for as long as three years after prostate brachytherapy. Patients should be managed conservatively. PSA bounce was not associated with subsequent biochemical relapse.</td>
</tr>
<tr>
<td>Critz et al., 2000</td>
<td>Identify and describe transient benign PSA elevation.</td>
<td>779</td>
<td>Stage T1 and T2 PCA treated with $^{125}$I prostate brachytherapy and EBRT; median follow-up was 60 months.</td>
<td>Retrospective cohort analysis</td>
<td>Nearly 30% of the sample had transient elevation of PSA with subsequent nadir 12–24 months after prostate brachytherapy and EBRT. Etiology most likely is radiation prostatitis.</td>
</tr>
<tr>
<td>Das et al., 2002</td>
<td>Identify and describe events that may cause transient benign PSA elevation after MRI-guided prostate brachytherapy.</td>
<td>186</td>
<td>Stage T1c–T2 treated with $^{125}$I prostate brachytherapy or $^{103}$P prostate brachytherapy plus EBRT; median follow-up was 27 months.</td>
<td>Retrospective cohort analysis</td>
<td>About 60% of the sample had one or more bounces occurring at a median of 24–30 months. Patients with PCA treated with radiation can have a temporary rise in PSA without disease recurrence. Etiology may be recent ejaculation, instrumentation, or radiation proctitis.</td>
</tr>
<tr>
<td>Hanlon et al., 2001</td>
<td>Identify and describe transient benign PSA elevation and possible association with biochemical control.</td>
<td>306</td>
<td>Stage T1 and T2 PCA treated with 3D conformal EBRT to a median dose of 74 Gy; median follow-up was 79 months.</td>
<td>Retrospective cohort analysis</td>
<td>Almost 30% of the sample had transient elevation of PSA with subsequent nadir two to five years after treatment. Lower radiation doses and higher pretreatment PSA values were associated with a greater chance of PCA bounce. PSA bounce was related to a subsequent decrease in biochemical control in 50% of the sample.</td>
</tr>
<tr>
<td>Rosser et al., 2002</td>
<td>Describe the temporary benign increase in PSA following EBRT for PCA.</td>
<td>964</td>
<td>Stage T1–T4 PCA treated with four-field or 3D conformal EBRT; median follow-up was 48 months.</td>
<td>Retrospective cohort analysis</td>
<td>PSA bounce occurred in 12% of patients at an average of nine months status post EBRT. PSA bounce was not associated with subsequent biochemical relapse.</td>
</tr>
</tbody>
</table>

* No hormonal therapy was given to any of the patients.

EBRT—external beam radiation therapy; $^{125}$I—iodine$^{125}$; MRI—magnetic resonance imaging; $^{103}$P—palladium$^{103}$; PCA—prostate cancer; PSA—prostate-specific antigen; 3D—three dimensional
on ultrasound guidance. A typical implant dose when used as monotherapy is 16,000 cGy for iodine\textsuperscript{125} and 11,500 cGy for palladium\textsuperscript{103} (Grimm et al.).

**Prostate-Specific Antigen Use in Surveillance After Treatment**

Pre- and post-treatment serial PSA values with clinical follow-up are compared to monitor response to therapy. Currently, no post-treatment PSA value is accepted universally to define treatment success (American Society for Therapeutic Radiology and Oncology [ASTRO] Consensus Panel, 1997; Morey, 2000). The American Urological Association determined that a post-radiation PSA “of less than 0.5 ng/ml (or undetectable levels) is not likely to be associated with disease recurrence within five years of treatment” (Morey, p. 884). However, a hallmark of treatment failure called biochemical failure has been accepted. Three consecutive rises in PSA value without evidence of clinical recurrence are considered biochemical failure. These three consecutive rises are used to distinguish biochemical failure from the benign PSA bounce (ASTRO Consensus Panel).

**Prostate-Specific Antigen Changes After Treatment**

After radical prostatectomy, PSA should fall to undetectable levels as the entirety of the prostate gland is removed. Treatment failure postprostatectomy is defined by a PSA level as low as 1.0 ng/ml (Walsh, 2003). If the PSA is detectable, prostate tissue theoretically must remain in the body (Walsh). Other experts prefer to define treatment success after prostatectomy as a PSA nadir of 0.3 ng/ml or less (ASTRO Consensus Panel, 1997).

Unlike the rapid PSA nadir experienced after radical prostatectomy, the PSA nadir for EBRT and seed implant may take two or more years. PSA measurement to determine treatment success is not as clear or easily understood after EBRT or seed implant. A panel of experts in the radiation treatment of prostate cancer from ASTRO convened in 1996 to develop post-treatment PSA guidelines. Their consensus statement indicated that no single value of post-treatment PSA can measure treatment success. The panel favored a definition that allows an individual’s PSA nadir and subsequent maintenance of that nadir to be that patient’s hallmark of treatment success (ASTRO Consensus Panel, 1997). The panel further recommended that PSA measurements be observed “at three- to four-month intervals for the first two years after the completion of radiation therapy and every six months thereafter” (ASTRO Consensus Panel, p. 1036). Biochemical failure was described as three consecutive increases in PSA after nadir had been achieved. Therefore, the panel chose three consecutive rises in PSA to distinguish biochemical failure from the benign PSA rise and subsequent fall termed PSA bounce (ASTRO Consensus Panel). Although this consensus statement makes sense, its difficulty in clinical applications lies in the complex interpretation of the PSA results. Since the release of the consensus statement, others have attempted to simplify the definition of treatment success after radiation therapy for prostate cancer. Critz et al. (2000) defined treatment success as a post-treatment PSA of less than or equal to 0.2 ng/ml in their seed implant group. Their study reported that after a six-year median follow-up of patients receiving seed implant for early-stage prostate cancer, those with a nadir of more than 1.0 ng/ml went on to have recurrent disease.

**Prostate-Specific Antigen Bounce**

PSA bounce is the temporary benign rise in PSA after seed implant or EBRT. Although PSA spike or bump also has been used interchangeably to describe this phenomenon, “PSA bounce” is used most often in the literature (Wallner, Blasko, & Dattoli, 2001). Since the PSA bounce has been identified, multiple definitions have emerged.

PSA bounce has been defined as a rise in serum PSA of 0.1–0.5 ng/ml or a rise of greater than or equal to 15% of the PSA value above the prebounce level followed by a subsequent decrease below that level (Cavanagh et al., 2000; Critz et al., 2000; Das et al., 2002; Hanlon, Pinover, Horwitz, & Hans, 2001; Rosser et al., 2002; Smathers, Wallner, Sprouse, & True, 2001). None of the patients studied in the literature review had adjuvant hormonal therapy. In patients treated with EBRT alone, 12%–30% were reported to experience a PSA bounce at a median range of 9–60 months. For patients treated with seed implant alone or combination EBRT or seed implant, 30%–60% experienced a PSA bounce (Cavanagh et al.; Critz et al.; Das et al.; Hanlon et al.).

**Etiology**

Many theories exist regarding the etiology of the PSA bounce, and a review of the literature revealed several possible explanations. This literature review is not exhaustive, but it does reflect the most common theories of the etiology of the PSA bounce. The simplest explanation for a change in PSA reading can be related to laboratory error or a variation in laboratory assay. PSA value interpretation can be simplified by asking the patient to use the same laboratory for all PSA series. This will avoid interassay variability because different laboratories may use different methods of measuring PSA and have slightly different ranges for normal values (Critz et al., 2000).

Das et al. (2002) noted an association between PSA bounce and recent ejaculation just prior to PSA measurement, proctitis, and instrumentation such as insertion of a catheter. Das et al. and Critz et al. (2000) noted that delayed bacterial or radiation prostatitis can occur more than 12 months postimplant and may affect PSA levels. Hanlon et al. (2001) found that lower EBRT radiation doses and higher pretreatment PSA values were associated with a greater chance of PSA bounce. In addition, the PSA bounce was associated with a subsequent decrease in biochemical control in 50% of Hanlon et al.’s sample. All other studies noted that patients who experienced a PSA bounce did not have a higher incidence of subsequent cancer recurrence compared to patients who did not experience the PSA bounce. This report may be because Hanlon et al. had a median follow-up that was 19 months longer than any other PSA bounce study reviewed in the literature. Prostate cancer has a slow biologic nature; therefore, recurrence may not be apparent with follow-up data up to 60 months.

Smathers et al. (2001) followed four patients with a PSA bounce who had post-implant biopsies. The patients all experienced a persistent rise in PSA after seed implant and subsequently were biopsied and found to have recurrent disease. All patients were advised to have a salvage radical prostatectomy but declined. Ongoing surveillance revealed that these patients had their PSA drop to a nadir a second time. According to Smathers et al., “Biopsies convert from positive to negative with further follow-up, apparently due to slow cancer involution” (p. 1209). In other benign theoretical etiologies of rising PSA, the residual normal prostate tissue after EBRT or seed implant may be able to manufacture PSA; therefore, an increasing PSA may not be a reliable indicator of recurrent disease (ASTRO Consensus Panel, 1997; Critz et al., 2000).

Stock, Stone, and Cesaretti (2003) found the PSA bounce to be more common in patients younger than 65 compared to those age 65 and older. They also found that those receiving higher implant doses and men with
larger prostate glands were more likely to experience the PSA bounce. Stock et al. suggested that the PSA bounce after brachytherapy may be characterized by a lower rate of bounce, earlier time to bounce, differing effect of dose, and lack of effect on treatment failure compared to PSA bounce after EBRT.

The information from the studies reviewed here is useful to patients and clinicians as they attempt to differentiate between a benign PSA bounce and disease recurrence. Failure to correctly interpret slight changes in PSA can place patients at risk for error, including unnecessary stress and salvage therapy (Wallner et al., 2001). In addition, many patients are keenly aware of their PSA history and are distraught by any elevation (Wallner et al.). As a result, patients who have experienced a rise in PSA after seed implant have developed Web sites to connect with others (Prostate Pointers, 2003).

Implications for Practice

PSA bounce is a common occurrence and can be mistaken for PSA rise because of biochemical failure. It can be a major source of anxiety for patients and families and can create diagnostic challenges for clinicians. Patients with rising PSA levels often fear that their disease has recurred and that further diagnostic imaging and treatment should be done. Slovin (2002) reported that patients in these situations experience stress and anxiety. She also observed that a rising PSA in the absence of clinical evidence of disease recurrence is equally troubling for clinicians. Clinicians should recognize the importance that patients place on the meaning of the PSA level and temper their discussions on the subject with facts. Educating patients about the PSA bounce early in their treatment discussions may prevent subsequent anxiety during their post-treatment surveillance. Patients with a true PSA bounce should be informed that this phenomenon does not seem to be associated with a higher risk of eventual clinical failure (Cavanagh et al., 2000).

The duration of the stress and anxiety created by a rising PSA can challenge patients’ coping skills. The literature abounds with prostate cancer survivor issues related to quality of life (e.g., sexual potency, bowel and bladder symptoms). However, these discussions typically do not address the anxiety of rising PSA levels and methods of coping within the context of the unknown. Psychosocial research on men who received radiation treatment for prostate cancer revealed that those who sought social support and whose main support source was their spouse experienced lower levels of stress (Ptacek, Pierce, & Ptacek, 2002).

Summary

Post-treatment surveillance after EBRT or seed implant for early-stage prostate cancer includes clinical examination and PSA blood testing approximately every four to six months. All patients with prostate cancer are at risk for anxiety arising out of the interpretation of the PSA test. Therefore, patients who experience a rise in their PSA values post-treatment should be educated about the meaning of the PSA trend, as well as the potential benign nature of the PSA bounce. Clinicians should promote long-term observation with repeated PSA testing prior to instituting restaging with radiographs or biopsy. The literature supports educating patients about the PSA bounce early in their treatment and providing psychosocial support for the anticipated anxiety when PSA rises. More study is needed regarding the etiology of the PSA bounce and its implications on the psychosocial well-being of prostate cancer survivors.

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References


Rapid Recap

Prostate Cancer Recurrence Fear: The Prostate-Specific Antigen Bounce

- One-third of men treated with iodine\(^{125}\) or palladium\(^{103}\) prostate seed implant with or without external beam radiation therapy experience a benign elevation in prostate-specific antigen (PSA) at an average of 18–24 months postimplant with a subsequent nadir. This phenomenon is referred to as the PSA bounce.
- Approximately 12%–30% of patients treated with external beam radiation therapy alone for prostate cancer are reported to have a PSA bounce at a median range of 9–60 months with a subsequent nadir.
- Etiology of the PSA bounce remains controversial and may be related to late radiation cystitis, proctitis, prostatitis, recent ejaculation, instrumentation such as catheter insertion, or simply laboratory variability.
- Clinicians should recognize the importance that patients place on the meaning of the PSA level and temper their discussions on the subject with facts.