PSA Spike after Brachytherapy
For Localized Prostate Cancer

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Prostate brachytherapy, radical prostatectomy, and external beam radiation therapy are standard treatments for patients with low, intermediate, and high-grade prostate cancer. Following definitive treatment, prostate-specific antigen (PSA) levels are monitored closely to determine cure or recurrence. In some cases, the PSA may fluctuate after radiation treatment for no apparent reason, causing anxiety for both the patient and his health care providers. Knowing the factors that may contribute to an elevation in PSA can help providers and patients be more confident in assessing whether the elevation is due to recurrent disease or a benign condition.

PSA is a protein produced by the lining of the prostate gland. In a normal healthy male, a small amount of this protein (0-2.5 ng/ml) is typically found in the bloodstream (Gretzer & Partin, 2003). PSA is elevated in men with prostate cancer and is used as a tumor marker for this disease (Partin et al., 1997). PSA rise after treatment is associated with both local and distant recurrence.

The PSA level, usually drawn every 6 months after completion of treatment, is monitored closely to determine cure. Following radical prostatectomy, PSA levels decline rapidly and should be undetectable as the prostate gland has been completely removed. After external beam radiation therapy (EBRT) and prostate brachytherapy, the PSA level drops, but may fluctuate with no apparent cause.

This phenomenon of PSA spike, also known as a PSA bounce, occurs when PSA temporarily increases followed by a durable decline without disease recurrence. The rise in PSA is thought to be due to a result of compromised cell membrane integrity in PSA-producing epithe-
lium in the prostate, as is commonly caused with radiation-induced prostatitis (Cavanagh, Blasko, Grimm, & Sylvester, 2000; Critz et al., 2000). A PSA profile of a patient with a benign PSA spike demonstrates a PSA that dropped considerably following prostate brachytherapy, but suddenly rose 2 to 3 years following treatment, followed by a steady decline to an undetectable level, with no intervention (see Figure 1).

Assessment of PSA Spike

PSA spike was first described by Wallner, Blasko, and Datolli in 1997, who noted it occurring most often between 12 to 30 months following prostate brachytherapy. Though rare, PSA spikes have been reported as late as 5 to 6 years following treatment (Stock, Stone, & Cesaretti, 2003), and patients can also experience multiple PSA spikes (Merrick, Butler, Wallner, Galbreath, & Anderson, 2002). In a recent study at Schiffer Cancer Center, the overall incidence of PSA spike was 24% (33% of those patients received I-125 as the isotope, 17% received Pd-103). No patients received androgen deprivation therapy. This study showed the median time to spike was 16.3 months (range 6.5-30 months), with 83% having the spike within 30 months. The average duration for the spike was 16 months (ranging 9-45 months) (Merrick et al., 2002).

Following brachytherapy, PSA spikes occur in 17% to 84% of patients (Critz et al., 2000; Stock et al., 2003). This wide range of incidence is partially due to the fact that several definitions exist to describe this occurrence. Das and colleagues (2002) described PSA spike as 15% or more elevation in serum PSA when compared with the most recent value, followed by any decrease or return to pre-spike value. It also has been described as a rise of 0.1 ng/ml after treatment, or a temporary increase of 0.2% or more, or a rise of more than 35% from the baseline PSA value (Stock et al., 2003). Merrick and colleagues (2004) defined PSA spike as a rise of 0.2 ng/ml or more followed by a durable decline to pre-spike levels. Cavanagh et al. (2000) described it as “any rise” in PSA value that was then followed by a drop of any magnitude. Toledano et al. (2006) described the PSA spike as an increase of 0.1 ng/ml or more followed by subsequent decrease. The incidence of PSA spike according to definition is listed, with the median PSA increase, median time to onset, and median duration in a summary table (see Table 1). While the incidence of PSA spike clearly depends on the definition used, the occurrence is certainly evident. Therefore, the development of a standardized definition of PSA spike is imperative to allow better comparison of incidence between studies.

The phenomenon of PSA spike is also complicated by the fact that PSA can vary normally in the general population. PSA variability can be as high as 35% in patients without prostate cancer (Prestiagiacomo & Stamey, 1996). This variability, due to both physiologic and assay variations, reflects varying results in the same patient. Physiologic variations (normal variations of PSA within an individual) and

**Figure 1.**
PSA profile for a 53 year-old male diagnosed with Gleason Score 7 (3+4) prostate cancer. Three of 12 biopsies were positive with perineural invasion, and a pre-treatment PSA of 6.3 ng/ml was reported. The patient was treated with 125Gy Pd without EBRT or ADT.
assay variations (which compare the immunoassay method used by the laboratory) contribute to variations as high as 30% in the same individual. This is particularly true of men with low PSA. For example, the value in a man with a PSA of 4.0 ng/ml can be as high as 5.2 ng/ml when tested 2 to 3 weeks later (Prestigiacomo & Stamey, 1996).

Factors Affecting PSA Spike

Many factors are associated with predicting PSA spike: patient age, isotope, baseline PSA, time to PSA nadir, size of the prostate, and implant dose. Other factors with less of an impact include clinical stage, pre-implant PSA, Gleason score, and external beam radiation therapy. Ejaculation, rectal instrumentation, prostatitis, and bicycle riding can also cause an elevated PSA (Das et al., 2002).

Patient age and isotope. Men aged 62 years and younger and those implanted with I-125 have a greater chance of PSA spike (Critz et al., 2000; Das et al., 2002; Merrick et al., 2002; Stock et al., 2003). Bostancic et al. (in press) reported that patients treated with I-125 are three times more likely to develop a PSA bounce.

Baseline PSA. The baseline PSA is the first post-implant PSA, drawn approximately 3 months after the completion of treatment. Patients who have a baseline PSA of 1.0 ng/ml or greater have a higher likelihood of PSA spike (Merrick et al., 2002; Merrick et al., 2003).

PSA nadir. The PSA nadir following brachytherapy is a predictor for subsequent PSA spike. The nadir is the lowest measurable PSA before a spike would occur. Patients with a nadir of 0.2 ng/ml or less are less likely to develop a PSA spike (Merrick et al., 2002). The median time to achieve nadir is 27 months. When nadir occurs within this time frame, it indicates that there is little to no viable prostate epithelium present; hence, the absence of residual malignancy. A PSA spike, therefore, is uncommon after a nadir of less than 0.2 ng/ml is reached.

Prostate size. The larger the prostate, the more likely the patient will experience PSA spike. Stock and colleagues (2003) found that patients with larger glands have a 23% increased risk of PSA spike within 5 years. Merrick et al. (2003) found that patients with large prostates (those with a large volume of benign cells) may have an increased risk of PSA spike due to the belief that benign prostatic elements, such as BPH, may respond to radiation differently than cancer cells. Radiation-induced cell death occurs at a later time interval in patients with BPH, hence causing a delayed PSA spike (Merrick et al., 2003).

Implant dose. The dose of radiation that the prostate receives also predicts the possibility of PSA spike. Dosimetric evaluations, determined by CT scan immediately following brachytherapy, suggest that higher radiation doses kill both malignant and benign prostate tissue, allowing less probability of PSA spike (Merrick et al., 2002).

Androgen deprivation therapy. Androgen deprivation therapy (ADT) is commonly used to “shrink” the size of the prostate. This cytoreduction is an adjuvant therapy that affects PSA spikes. Pickles et al. (2006) showed that

<table>
<thead>
<tr>
<th>Lead Author</th>
<th>Definition: PSA Increase (ng/mL)</th>
<th>Incidence (%)</th>
<th>Number of Patients</th>
<th>ADT (%)</th>
<th>Median PSA Increase (ng/mL)</th>
<th>Median Time to Onset (months)</th>
<th>Median Duration (months)</th>
</tr>
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<tr>
<td>Critz</td>
<td>≥ 0.1</td>
<td>35</td>
<td>1011</td>
<td>0</td>
<td>0.8</td>
<td>18</td>
<td>9</td>
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<tr>
<td>Cavanaugh</td>
<td>≥ 0.2</td>
<td>36</td>
<td>591</td>
<td>0</td>
<td>0.6</td>
<td>20.4</td>
<td>–</td>
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<td>Merrick</td>
<td>≥ 0.2</td>
<td>24</td>
<td>218</td>
<td>0</td>
<td>0.4</td>
<td>16.3</td>
<td>16</td>
</tr>
<tr>
<td>Ciezki</td>
<td>≥ 0.2</td>
<td>46</td>
<td>162</td>
<td>38</td>
<td>0.5</td>
<td>15.1</td>
<td>–</td>
</tr>
<tr>
<td>Toledano</td>
<td>≥ 0.4</td>
<td>32</td>
<td>295</td>
<td>42</td>
<td>0.8</td>
<td>19 (mean)</td>
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</tr>
<tr>
<td>Pickles</td>
<td>Any rise</td>
<td>84</td>
<td>449</td>
<td>70</td>
<td>–</td>
<td>13</td>
<td>–</td>
</tr>
<tr>
<td>Stock</td>
<td>≥ 0.1</td>
<td>31</td>
<td>373</td>
<td>0</td>
<td>–</td>
<td>19.5</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>≥ 0.4</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
<td>19.5</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>&gt; 35% previous PSA</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td>20.5</td>
<td>–</td>
</tr>
<tr>
<td>Das</td>
<td>&gt; 15% previous PSA</td>
<td>186</td>
<td>0</td>
<td>0.6</td>
<td>18.9</td>
<td>8.7</td>
<td>–</td>
</tr>
<tr>
<td>Bostancic</td>
<td>≥ 0.2</td>
<td>164</td>
<td>37</td>
<td>0.5</td>
<td></td>
<td>19.9</td>
<td>8.7</td>
</tr>
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</table>
ADT with brachytherapy has an 88.9% chance of PSA spike, while brachytherapy without ADT has a 71.4% chance of spike. They also stated that EBRT with ADT has a 55.3% chance of spike, while EBRT without ADT has 66.4% chance of spike. In Ciezki et al.’s (2006) series, 40% of those treated with ADT and brachytherapy had a spike, while 60% of brachytherapy patients without ADT showed a spike. Merrick et al. (2004) showed that when ADT and brachytherapy are combined, PSA spikes occur at 15 to 21 months after brachytherapy, lasting an average of 4 months, with an average rise of 0.1 ng/ml. In a current prospective randomized trial, Bostancic et al. (in press) noted that minimal spike difference is noted in ADT patients regardless of which isotope is used. These varying results suggest that the use of ADT does not predict PSA spike.

Interpretation of PSA Spike

While many definitions exist for describing a PSA spike and while many studies prove the frequency of PSA spike, all these studies determined that the PSA spike does not predict biochemical failure following prostate brachytherapy. While the occurrence is demonstrated repeatedly in the literature, so is the fact that all PSA spikes return to nadir at approximately 66 months, with a median nadir of less than 0.1 ng/ml, with no intervention (Akyol, Ozyigit, Selek, & Karabulut, 2003; Cavanagh et al., 2000; Critz et al., 2000; Merrick et al., 2003; Stock et al., 2003; Toledoano et al., 2006). A biopsy of the prostate may seem to be a logical determination of recurrence. However, when patients with elevated PSAs have a positive prostate biopsy within 12 to 30 months after brachytherapy, all patients subsequently had PSA normalization with no intervention (Reed, Wallner, Merrick, Buskirk, & True, 2003). Also, other studies suggest that the pathological changes have such slow resolution that it may take up to 3 years for accurate biopsy result (Prestidge et al., 1997). Hence, re-biopsy within 3 years of treatment is likely to be misleading.

False PSA elevation can also complicate followup care, requiring the need to distinguish PSA spike from recurrent disease. This is important in order to avoid unnecessary salvage therapy. Benign PSA spikes can be a potential source for substantial inappropriate use of unnecessary diagnostic and/or therapeutic interventions, such as CT scans, MRIs, bone scans, prostactinct scans, and re-biopsy. Consequently this could result in unnecessary health care dollar expenditures.

Conclusions

The PSA spike dilemma causes extreme anxiety for both the patient and his health care providers, with the elevation suggesting that their prostate cancer is not cured. Physicians and nurses should discuss the possibility of PSA spike with the patient prior to initiating treatment, to ensure awareness and decrease anxiety should a PSA spike occur. Following treatment, nurses are often designated to counsel patients, answer questions, and allay concerns. Relaying an elevated PSA result can be devastating to a patient. A confident, well-informed nurse can allay fears, decrease anxiety, and reassure patients that the PSA elevation following brachytherapy is most likely a temporary situation. Knowing when a true spike exists helps clinicians to manage patients conservatively, with continued close observation, eliminating unnecessary salvage therapy, and possibly avoiding other unnecessary and expensive imaging.

References


