High Postprostatectomy Prostate-specific Antigen Level Prior to Salvage Radiation Therapy Is Not Always a Bad Sign

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Although radical prostatectomy is a popular treatment modality for clinically localized prostate cancer, 10-year biochemical recurrence can reach 28%. Before salvage radiation therapy (SRT), prostate-specific antigen (PSA) values alone should be used cautiously in predicting SRT eligibility. A long, slow PSA rise may suggest locally confined disease still amenable to SRT; corresponding imaging to identify potential gross recurrence is useful. Patients with local disease may safely benefit from higher doses of radiation.

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KEY WORDS

Salvage radiation therapy • Prostate-specific antigen • Radical prostatectomy

Although radical prostatectomy is a popular treatment modality for clinically localized prostate cancer, 10-year biochemical recurrence can reach 28%.[1] Before salvage radiation therapy (SRT), prostate-specific antigen (PSA) values alone should be used cautiously in predicting SRT eligibility. A long, slow postprostatectomy PSA rise should be evaluated with magnetic resonance imaging (MRI) to identify potential gross local recurrence, which may respond to SRT. Radiographically identified gross recurrence may benefit from higher than standard radiation doses.

The key to successful SRT following radical prostatectomy (RP) is distinguishing between local and distant recurrence. Unfortunately, no diagnostic test can accurately distinguish local from distant recurrence at low PSA levels when biochemical recurrence is first observed. Most clinicians use clinical correlates to prognosticate the effectiveness of SRT. Among other factors, a high PSA level prior to SRT has been correlated with poor control.[2] However, a long, slow PSA rise, despite a high PSA value, may independently predict local recurrence and good biochemical control following SRT.[3] A high PSA value may also be associated with clinically detectable gross disease within the prostate fossa. Patients with gross recurrent disease have been reported to have

poorer outcomes following standard SRT doses when compared with their biochemical progression-only counterparts.[4]

Here we present two patients with biochemical recurrence after RP. Both present with high PSA values (some practitioners choose to forego referral for SRT with PSA values this high). Both patients had MRI demonstrating evidence of gross disease in the prostatic fossa and were treated with an integrated boost, as standard doses were thought to be insufficient.

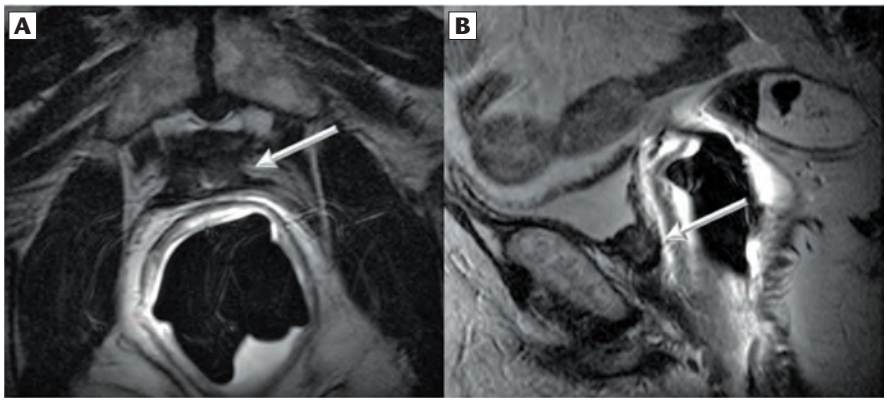
Our case report emphasizes three key points. First, a high pre-SRT PSA value does not automatically equate with a poor SRT outcome. Second, patients with a long, slow PSA rise should be evaluated with MRI to identify potential gross recurrence. And third, radiographically identified recurrence may benefit from higher radiation doses.

Presentation

Patient 1 is a 59-year-old white man with post-RP pathology showing a margin-negative, pT2c, Gleason score 3 + 4 = 7. His preoperative PSA level was 7.1 ng/mL. His post-RP PSA level was 0.1 ng/mL, which rose over 11 years to a pre-SRT level of 1.59 ng/mL. Pre-SRT MRI showed a small soft-tissue lesion, measuring 1.7 × 0.7 × 1.2 cm, within the surgical bed at the level of the vesicoureteral anastomosis (Figure 1). The patient was treated with rotational arc-based intensity-modulated radiation therapy (IMRT) using 6 MV photons. Dose to the prostate fossa was 66.6 Gy in 37 fractions, and an integrated boost treated the nodule to 74 Gy in 37 fractions (Figure 2). The patient did not receive any hormone therapy.

Patient 2 is a 79-year-old Hispanic man with post-RP pathology showing bilateral seminal vesicle invasion, right capsule extension, positive margin, and Gleason score 3 + 4 = 7. His preoperative PSA level was 7.8 ng/mL. His post-RP PSA was 0.1 ng/mL, which then rose over 11 years, due to the patient declining workup, to a pre-SRT level of 6.5 ng/mL. Pre-SRT MRI showed a small soft-tissue lesion anterior to the rectum and posterior to the bladder anastomosis within the operative bed, measuring 1.0 × 0.6 × 0.6 cm (Figure 3). The patient was treated with rotational arc-based IMRT using 6 MV photons. Dose to the prostate fossa was 68.4 Gy in 38 fractions, and an integrated boost treated the nodule to 76 Gy in 38 fractions (Figure 4). This patient refused hormone therapy.

Figure 1. Patient 1, a 59-year-old man with biochemical recurrence after radical retropubic prostatectomy. Transaxial **(A)** and sagittal **(B)** T2-weighted magnetic resonance images without fat saturation. A soft-tissue signal-intensity nodule (*arrows*) measuring 1.7 × 0.7 × 1.2 cm was detected in the prostatectomy bed involving the neck of the urinary bladder.



Following completion of SRT, both patients had their PSA values fall to an undetectable level (Figure 5). Neither patient had any late toxicity other than erectile dysfunction, which was present prior to the start of SRT. Patient 2 developed a separate epidermal growth factor receptor-mutated non–small-cell lung cancer and died of that disease.

Discussion

Post-RP PSA levels should remain suppressed and undetectable. A detectable PSA level may be attributed to local recurrence at the prostatic fossa, metastasis, residual benign prostatic tissue, or some combination thereof. Although RP

Figure 2. Patient 1 **(A)** dosimetry (saggital) and corresponding **(B)** dose volume histogram showing gross tumor volume (*red*) treated to 74 Gy. Gross disease planning tumor volume is displayed in *green* and standard prostate fossa planning tumor volume is shown in *yellow*.

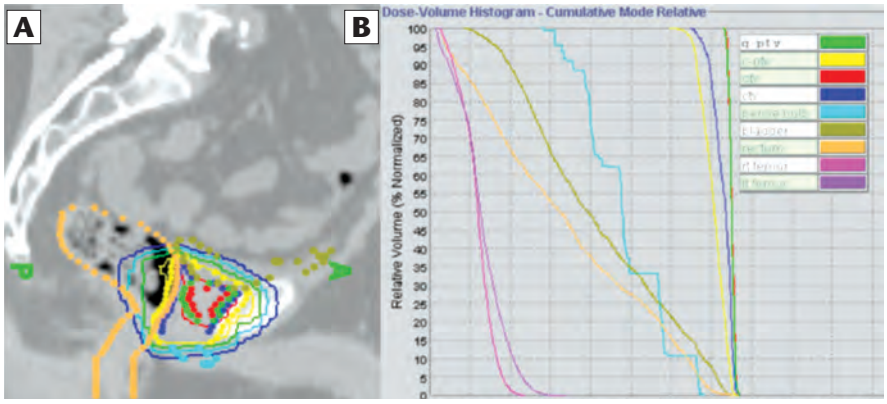
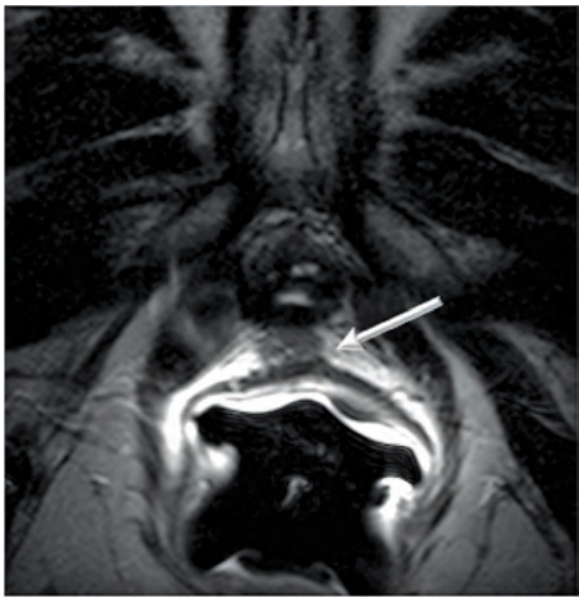


Figure 3. Patient 2, a 79-year-old man with biochemical recurrence after radical prostatectomy. Transaxial T2-weighted magnetic resonance image without fat saturation. A soft-tissue signal-intensity nodule (*arrow*) measuring 1.0 × 0.6 × 0.6 cm was detected in the prostatectomy bed between the rectum and the neck of the urinary bladder.



is a popular modality, 10-year biochemical recurrences of up to 28% are reported.[1]

Without SRT, the median time from PSA recurrence to metastasis is 8 years.[5] SRT reduces prostate cancer-specific mortality compared with observation alone,[3] and delays time to hormone administration and systemic progression.[6] SRT can be curative in patients with biochemical recurrence following RP[7]; however, less than half of patients who receive a post-RP secondary therapy of some sort will receive SRT.[8] It is important to note that all men may not benefit from SRT, particularly those with findings suggestive of systemic disease. In this setting, balancing potential benefits against therapeutic toxicities and underlying comorbidities can be challenging and significant differences in practice between urologist and radiation oncologist recommendations for post-RP radiotherapy exist.[9]

SRT reduces prostate cancer-specific mortality compared with observation alone, and delays time to hormone administration and systemic progression.

SRT does not address subclinical disease outside of the prostate fossa, and efforts to identify subclinical systemic disease are challenging. Post-RP factors predictive of local or metastatic disease include PSA velocity, Gleason score, and pathologic stage.[2] A short time to postoperative PSA failure, short PSA doubling time, and elevated PSA velocity prior to RP have all been associated with presumed subclinical metastatic disease.[10,11] Frequently, clinicians weigh presenting post-RP PSA level heavily as part of this determination; our case report illustrates why this should be done with caution.

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The ideal SRT dose to the prostatic fossa is still debated, along with the role of neoadjuvant androgen deprivation therapy. Technologic development has facilitated dose escalation, and doses have slowly been rising. Modest doses of 64 to 65 Gy may be insufficient for durable biochemical control.[12,13] Doses above 65 Gy correlate with improved disease-free survival.[14] Dose escalations to 70 Gy, versus 60 Gy, demonstrate improved 5-year biochemical control.[15] Guidelines endorse a minimum of 64 to 65 Gy,[16] but patients with gross disease probably require significantly higher doses, as displayed by the sustained biochemical response in our report.

Endorectal coil MR has the potential to capture a high proportion of suspected local recurrence after RP.[17] Although no minimum PSA threshold for initiating MRI has been established, many clinicians will use PSA kinetics and value at presentation to guide decision making. Interestingly, Sella and colleagues[17]

Figure 4. Patient 2, **(A)** dosimetry (axial) and corresponding **(B)** dose volume histogram showing gross tumor volume (*red*) treated to 76 Gy. Gross disease planning tumor volume is displayed in *green* and standard prostate fossa planning tumor volume is shown in *blue*. Hot-spot of 81.3 Gy.

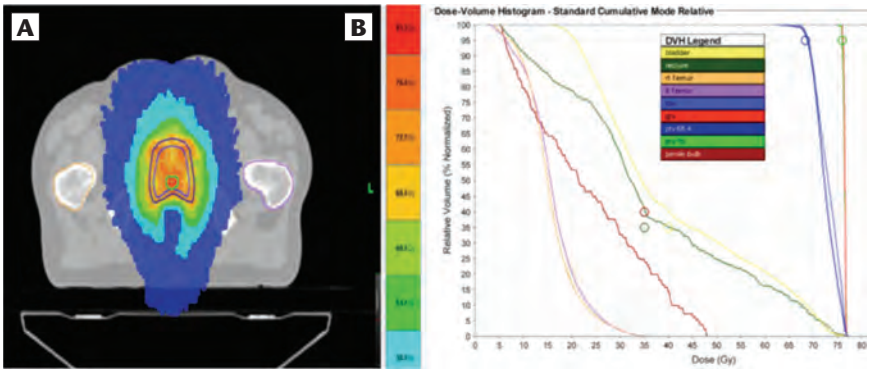
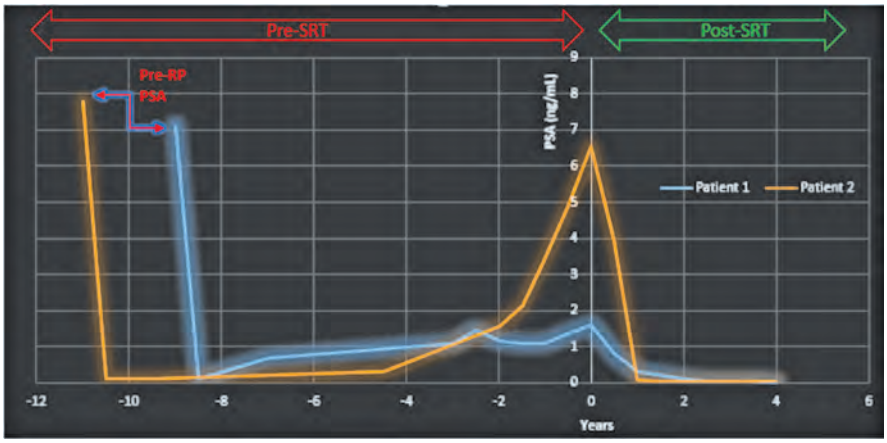


Figure 5. Post-SRT PSA history. The last PSA value before radical prostatectomy is labeled. Subsequent pre-SRT values are in years before SRT. PSA values at "time = 0" represent the last recorded pre-SRT value. Each value that follows is the corresponding PSA for the specified post-SRT year. Both pre-SRT values, 1.59 ng/mL (Patient 1) and 6.5 ng/mL (Patient 2), approach 0 after SRT. PSA, prostate-specific antigen; RP, radical prostatectomy; SRT, salvage radiation therapy.



reported that post-RP endorectal coil MRI confirmed local recurrence in 38% of their cohort when PSA levels were lower than 0.4 ng/mL at the time of imaging. Dynamic contrast-enhanced (DCE) MRI is used in combination with diffusion-weighted imaging for local detection after radiation therapy,[18] whereas DCE-MRI alone can effectively increase detection utility in the post-RP setting.[18] The radiographic confirmation of local disease by MRI here allowed for treatment with an additional integrated radiotherapy boost. Despite the escalated dose—higher than most published studies—neither patient demonstrated late urinary or rectal symptoms. Studies on dose escalation have shown similar results.[19]

Dynamic contrast-enhanced (DCE) MRI is used in combination with diffusion-weighted imaging for local detection after radiation therapy, whereas DCE-MRI alone can effectively increase detection utility in the post-RP setting.

Post-RP hormone therapy with SRT has been shown to improve overall survival.[20] Of note, both treated patients did not receive hormone therapy. Our study suggests that pre-SRT PSA values alone should be used cautiously in predicting SRT eligibility. Instead, we advocate incorporating the pattern of PSA rise. A long, slow PSA rise may suggest locally confined disease still amenable to SRT; corresponding imaging to identify potential gross recurrence is useful. Patients with local disease may safely benefit from higher doses, here treated with an integrated boost up to 76 Gy. ■

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MAIN POINTS

- Before salvage radiation therapy (SRT), prostate-specific antigen (PSA) values should be used cautiously in predicting SRT eligibility. Incorporating the pattern of PSA rise is recommended. A long, slow PSA rise may suggest locally confined disease still amenable to SRT.
- Postprostatectomy PSA rise should be evaluated with magnetic resonance imaging (MRI) to identify potential gross local recurrence, which may respond to SRT. Although no minimum PSA threshold for initiating MRI has been established, many clinicians will use PSA kinetics and value at presentation to guide decision making.
- Radiographically identified gross recurrence may benefit from higher than standard radiation doses.

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