

# When PSA levels rise following surgery or radiation therapy

Anthony V. D'Amico, MD, PhD

Dana-Farber/Brigham and Women's Cancer Center and Harvard Medical School, Boston, MA

What do you do with a patient who has had some form of local therapy for prostate cancer, whether surgery or radiation therapy, and then his prostate-specific antigen level rises? This is a unique situation, unlike any encountered in managing other solid tumors.

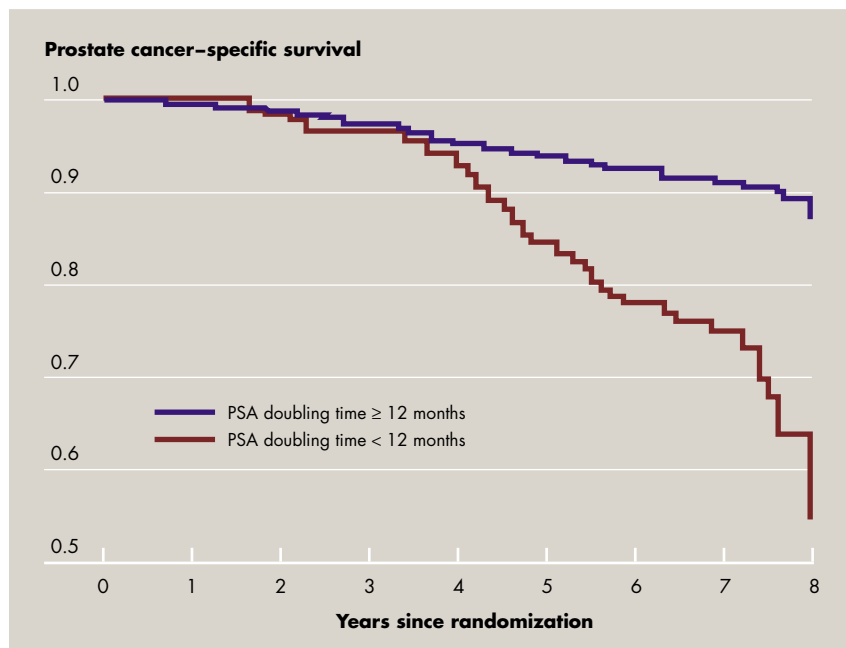
Prostate cancer has a specific biochemical marker, prostate-specific antigen (PSA), that provides some insight into what the future holds. With other malignancies—breast, colorectal, lung—imaging studies can pinpoint a recurrence or a metastasis to a distant organ. In following patients who have undergone surgery or radiotherapy for other solid tumors, it is relatively easy to monitor the progression of their disease radiographically. But in prostate cancer, radiographic studies often are misleading or of no use at all.

Knowing a patient's PSA value post-operatively or post radiation therapy both helps and hurts. It helps in the sense that it can tell us what is likely to happen down the road, but it hurts in the sense that sometimes overtreatment is prescribed for men who have a PSA recurrence and don't really need anything more than observation. So, when does a rising PSA level in a prostate cancer patient who has had surgery or radiation treatment warrant medical attention? What kind of treatment do these patients need? And, do they need treatment at all?

## PSA rise: how quickly?

Outcomes data from both multicenter and single institutional studies all come to the same conclusion: "PSA failure" or biochemical recurrence (the detection of a rising PSA level following local therapy of prostate cancer) by itself is unimportant. What is important is how long ago the patient underwent "definitive" local treatment for prostate cancer and, even more so, how quickly his PSA level is rising.

At the 2005 annual meeting of the American Society of Clinical Oncology, Valicenti and colleagues presented survival data from Radiation Therapy Oncology Group protocol 9202, which compared hormonal blockade plus external-beam radiation therapy with radiation therapy alone in men with localized prostate cancer (stage T2c–T4) and a pretreatment PSA level < 150 ng/mL.<sup>1</sup> Figure 1 shows the prostate cancer-specific survival of the cohort of patients in the trial who received short- or long-term hormonal therapy combined



**FIGURE 1** Prostate cancer-specific survival by rate of rise in PSA level post surgery or radiotherapy. Adapted from Valicenti et al.<sup>1</sup>

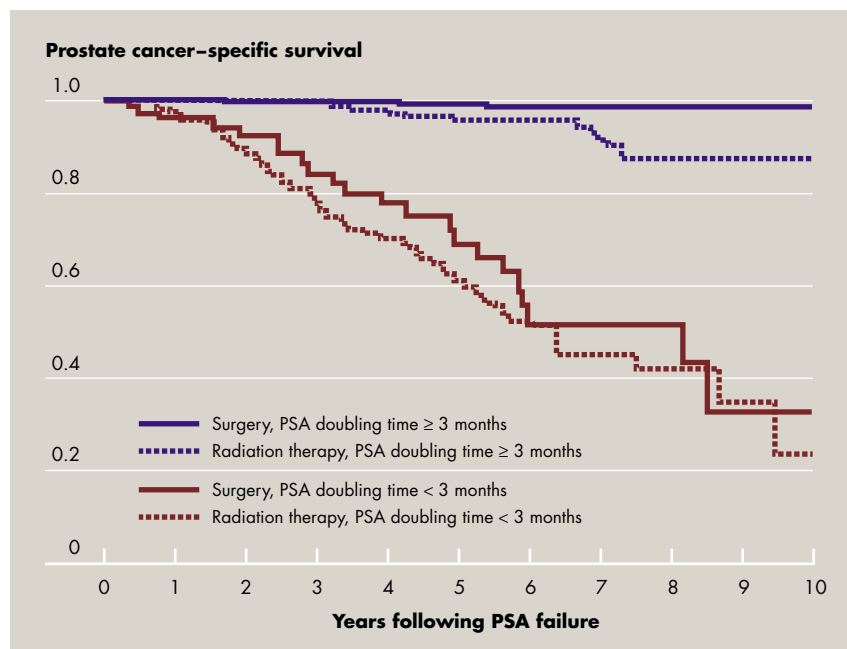
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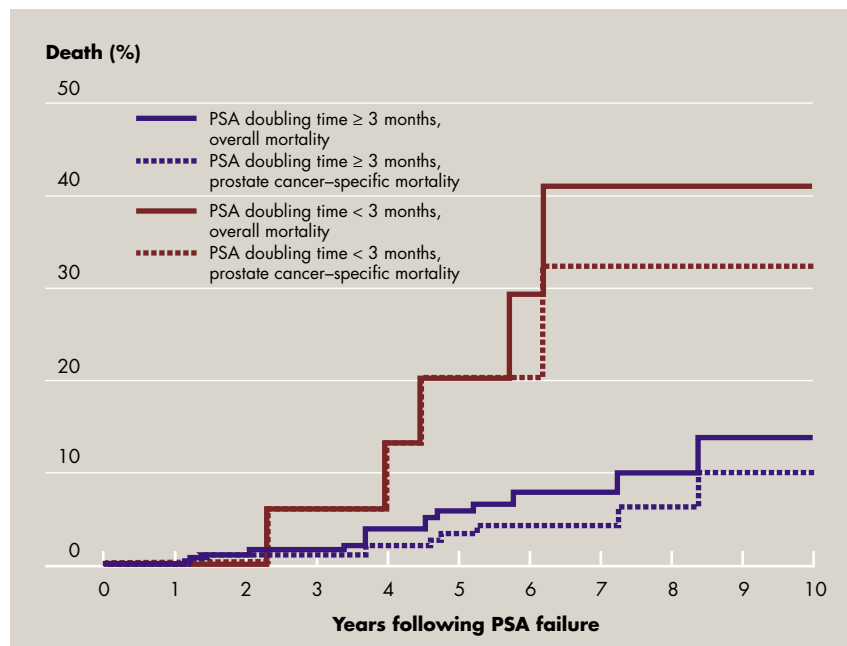
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Correspondence to: Anthony V. D'Amico, MD, PhD, Department of Radiation Oncology, Dana-Farber Cancer Institute, 44 Binney Street, Tower L2, Boston, MA 02115; telephone: 617-732-7936; fax: 617-732-7347; e-mail: adamico@lroc.harvard.edu.

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**FIGURE 2** Prostate cancer-specific survival following surgery or radiation therapy among patients with short (< 3 months) PSA doubling times compared with patients having more slowly rising PSA levels. Adapted from Moul et al<sup>2</sup> and D’Amico et al.<sup>3</sup>



**FIGURE 3** Overall and prostate cancer-specific mortality among patients with short (< 3 months) PSA doubling times compared with patients having more slowly rising PSA levels. Adapted from D’Amico et al.<sup>4</sup>

with radiation treatment (n = 1,514). Median follow-up was 5.9 years (range, 0.5–8.9 years). The results are stratified by whether the patients’ posttreat-

ment PSA level doubled in less than 12 months or rose more slowly. The difference in prostate cancer-specific survival between men with a PSA doubling time

< 12 months and those with a PSA doubling time ≥ 12 months, which shows an obvious separation around 4 years after the subjects were randomized to treatment, is highly statistically significant ( $P < 0.0001$ ).

### Community-based studies

Figure 2 presents pooled data acquired from two large community-based databases: the Department of Defense’s Center for Prostate Disease Research (CPDR)<sup>2</sup> and CaPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor).<sup>3</sup> What these data show is that if the posttreatment PSA level is rising rapidly, doubling more frequently than every 3 months, then median prostate cancer-specific survival is about 6 years, whereas if the PSA level rises more slowly, doubling at intervals of 3 months or more, then the risk of dying from prostate cancer is small for at least a decade. In fact, 98% of the men who underwent surgery and more than 90% of those who received radiation therapy and had a postoperative PSA doubling time ≥ 3 months were still alive 10 years later.

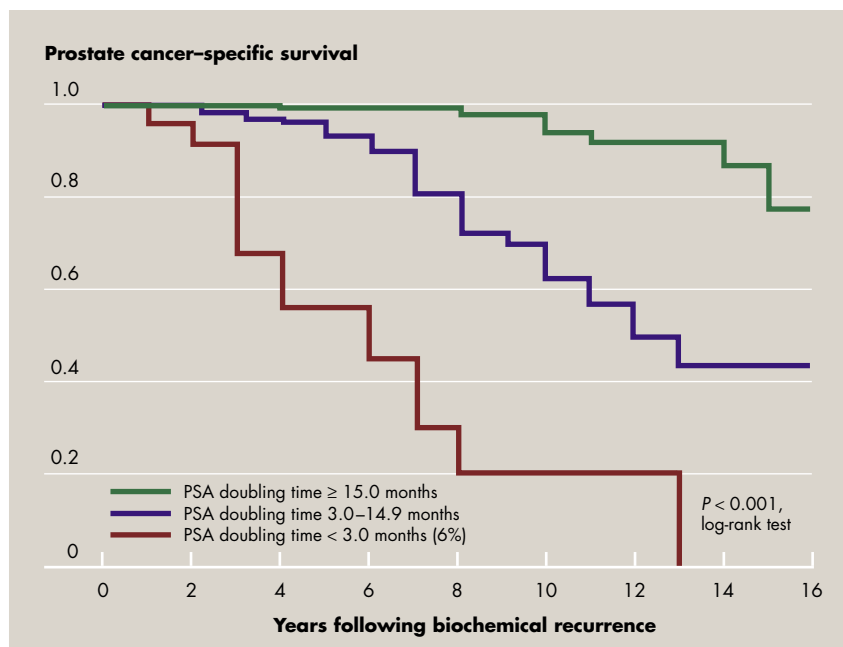
Figure 3 looks at the same sort of comparison but from the opposite perspective: how many patients died after a biochemical recurrence of their prostate cancer was detected. The data were drawn from a population of 1,011 men who underwent a radical prostatectomy at Barnes-Jewish Hospital in St. Louis, Missouri, for localized prostate cancer.<sup>4</sup> Of this group, 341 patients had a PSA failure. Once again, a significantly higher percentage of men with a PSA doubling time < 3 months died within the first decade post failure, compared with men who had a more slowly rising PSA level. Interestingly, within the first 5½ years after a rapid rise in PSA level was noticed, all-cause mortality and prostate cancer-related mortality were virtually superimposable; in other words, almost all of the deaths that occurred during this period in the group with a PSA doubling

time < 3 months were due to prostate cancer, whereas among the group of men with a PSA doubling time  $\geq 3$  months, only about half of the deaths were cancer related throughout the 10-year period of observation.

#### Single-institution studies

Another demonstration of the prognostic importance of the PSA doubling time comes from the Brady Urological Institute at Johns Hopkins.<sup>5</sup> Freedland and coworkers retrospectively analyzed the clinical course of 379 men who had undergone a radical prostatectomy for localized cancer and then suffered a relapse. The team stratified these patients into three groups: those with a PSA doubling time of < 3 months, those with a PSA doubling time  $\geq 15$  months, and those with a PSA doubling time in between. Figure 4 clearly shows a continuum of prostate cancer-specific survival that is inversely proportional to the rate of rise in PSA post surgery. For those patients with a PSA doubling time of < 3 months in this single-institution study, median survival was 6 years after PSA failure—the same value derived from the two community-based registries.

The obvious conclusion is that a PSA doubling time < 3 months is a surrogate for micrometastatic disease in the pelvis and elsewhere. It may even be a surrogate for hormone-refractory micrometastatic disease, as there does not appear to be much we can do to change the outcome of these patients once their PSA value is rising this rapidly. One other interesting conclusion comes out of these studies when you compare the two community-based databases with the two single-institution studies described above: In the CPDR and CaPSURE registries, 15% of the postsurgical patients and 20% of the postradiation patients had a PSA doubling time < 3 months and, therefore, were in the worst prognostic group. In contrast, only 7% of the Barnes-Jewish Hospital cohort and 6% of the Brady Urological Institute population were in this same group. This difference could suggest stage migration.



**FIGURE 4** Variation in prostate cancer-specific survival among men with a rising PSA level depending upon PSA doubling time. Adapted from Freedland et al.<sup>5</sup>

### Managing PSA rise

As mentioned at the outset, bone scans and other radiographic imaging studies are of little or no help in following prostate cancer patients who have undergone a radical prostatectomy and/or radiation therapy and may have suffered a recurrence of their disease. ProstaScint monoclonal antibody scanning, as well as endorectal magnetic resonance imaging (MRI), has so far not been shown to be of much value in this setting. To improve the detection of lymph-node metastases, Weissleder and colleagues<sup>6</sup> injected highly lymphotropic superparamagnetic nanoparticles into 80 presurgical patients with stage T1–T3 prostate cancer and then examined them by MRI. The technique correctly identified all patients with nodal metastases. There is some promise that with such sophisticated techniques we might be able to visualize pelvic lymph node disease on the order of 5 mm or less, whereas currently a diseased node has to be a minimum of 1 cm to show up on an MRI scan. Even so, no imaging study available today allows us to vi-

sualize microscopic metastases. Consequently, we have come to rely on PSA kinetics to guide decisions about whether to proceed with salvage therapy and what form that therapy should take.

#### Patients with short PSA doubling times

For the group of men who have short PSA doubling times (< 3 months), starting hormonal salvage therapy early is probably justified, even though their metastases may not show up on a bone scan for a year or a year and a half. Hormonal therapy will delay the time to symptomatic disease progression, but it will not prolong their survival. Even so, if a patient has an expected survival of 6 years and 4½ of those years can be spent relatively symptom free from bone metastases, albeit not free of the potential side effects of hormonal therapy, that trade-off might be worthwhile compared with having 2 years of symptom-free survival, breaking a bone, and then going on hormonal therapy to catch up.

This is also a setting where immediate versus delayed chemotherapy, in the form of docetaxel (Taxotere), in

conjunction with primary hormonal therapy is being studied.

### *Patients with long PSA doubling times*

For patients whose PSA level is creeping up slowly (ie, PSA doubling times > 12 months), postoperative irradiation of the prostatic bed probably makes the most sense—or even doing nothing at all. For example, no more than continued follow-up is necessary for patients with low-risk disease who have had benign prostatic hypertrophy, a slowly rising PSA level before diagnosis of their cancer, removal of a large prostate gland, and a postoperative PSA velocity of  $\leq 0.5$  ng/mL per year. The persistent elevated PSA value may simply be the result of some benign prostatic epithelial cells being left behind following resection. Approximately 2% of patients in the Barnes-Jewish Hospital database fell into this category.

What about the rest whose PSA level slowly creeps up after surgery or radiation therapy? If the rise occurs post irradiation, the decision on how to proceed is difficult because salvage local therapies all have significant sequelae. Colostomy and urostomy are realities for 10% of patients who undergo salvage treatment, and the rates of urinary incontinence after surgery and of rectal injury after brachytherapy or cryotherapy are high.

At Dana-Farber/Brigham and Women's Cancer Center, we have been using MRI-guided brachytherapy in the salvage setting for a select number of patients (only 20 patients with locally recurrent prostate cancer have been accrued over 4 years). The technique uses three-dimensional imaging to help position high-dose brachytherapy seeds in the area of the tumor while sparing surrounding tissues and organs; only a handful of centers around the world are currently using this technique to reduce the incidence of urinary incontinence and other urologic problems associated with brachytherapy. Yet even with this sophisticated form of

therapy, severe (grade 3/4) complications can happen. Within the first year after treatment, among 20 patients, there were 3 instances of rectal bleeding requiring a temporary diversion (ie, a colostomy) and treatment of the patient with hyperbaric oxygen. Although a complication rate of 15% doesn't seem that bad, we have never seen an instance of rectal fistula following the use of MRI-guided brachytherapy in patients with newly diagnosed prostate cancer, and we have performed hundreds of these procedures over the past 9 years. Patients with diabetes and those who are using anticoagulants appear to be at particular risk of rectal injury. The other risk factor appears to be the interval between the patient's initial radiation treatment and the second; all three events occurred in men who had their second radiation treatment less than 5 years after their first.

### *Patients with PSA doubling times between 3 and 12 months*

Roughly 70% of patients with advanced prostate cancer who have a rising PSA level after surgery or radiation therapy fall into this category. Management of this group is controversial and is the focus of several large randomized clinical trials currently under way. For the present, I offer these men external-beam radiation therapy, using a three-dimensional conformal technique, combined with a short course (6 months) of hormonal therapy for radiosensitization, based on a randomized study in the de novo setting that showed a survival benefit from just such a course.<sup>7</sup> I do not treat the pelvis. I treat only the prostatic bed and anastomosis, using a total of 66.6 Gy if the results of a digital rectal examination and imaging studies are negative or 70.2 Gy if prostatic disease is palpable or can be visualized.

### *Managing the complications of postoperative irradiation*

Less than 5% of patients will experience rectal bleeding 6 months to

3 years following pelvic irradiation (median, 1.5 years). Argon plasma coagulation offers a safe and effective noncontact method of providing hemostasis and should be the standard approach to controlling rectal bleeding from chronic radiation proctopathy.<sup>8</sup>

Radiation cystitis affects only 1%–2% of patients, but when it happens, it is annoying and can be difficult to treat. Median time for development of cystitis is 3 years post irradiation, but it can occur as late as 7 years after radiation treatment. Management of radiation cystitis consists of continuous bladder irrigation and/or hyperbaric oxygen.

Impotence is fairly common following definitive treatment for prostate cancer. If patients don't become impotent initially from surgery, they are likely to lose erectile function after receiving radiation treatment, particularly if they have also received hormonal therapy. Oral agents for treating erectile dysfunction (sildenafil [Viagra], vardenafil [Levitra], or tadalafil [Cialis]) should be tried first, followed by alprostadil urethral suppositories (MUSE), injectables, vacuum pumps, or penile prostheses, depending upon the patient's motivation.

## Summary

Patients with a rising PSA level following initial surgery or radiation therapy for prostate cancer are a heterogeneous group. If the level is rising quickly, doubling less than every 3 months, immediate hormonal therapy is justifiable, as is recommending the patient join a clinical trial of chemotherapy. If the PSA level is rising slowly, doubling slower than every 12 months, the options include postoperative radiation therapy or observation—with observation reserved for the elderly and men with significant comorbid illness. For those in between, salvage local irradiation is recommended, possibly combined with a short course of hormonal therapy. As in managing a rising PSA level in de novo prostate cancer, knowl-

edge of PSA kinetics can help us make better clinical decisions in the face of a biochemical recurrence.

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#### ABOUT THE AUTHOR

*Affiliation:* Dr. D'Amico is Professor of Radiation Oncology and Chief, Genitourinary Radiation Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA.  
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## PSA velocity: the view from 30,000 feet

Steven J. Tucker, MD | The Angeles Clinic & Research Institute, Los Angeles, CA

PROSTATE SPECIFIC ANTIGEN (PSA) doubling time is currently one of the most important surrogates in predicting the disease course in prostate cancer (PC). PSA velocity is not only valuable when assessing PSA-recurrent androgen-dependent PC but also localized disease, metastatic PC, and PSA-recurrent androgen-independent PC. Despite its clear clinical utility (and the enthusiasm for it), there are some limitations to the routine use of PSA doubling time and caveats one should heed. The intervals used need to be defined and additional PC markers considered; the frequency and form of PSA testing must be taken into account, including predicting velocity from "micro" values to "macro" values.

Many of the studies cited by Dr. D'Amico relied on PSA testing performed at annual or semi-annual evaluations. In contrast to Dr. D'Amico's observation, I suspect PSA testing (and re-testing) is often performed more frequently, and that can lead to greater variation in PSA values. Further, men with recurrent

PC and 'PSA anxiety' consult numerous physicians. That leads to variation in laboratory settings, assay technique, and intraindividual variation.<sup>1</sup> Consistency in PSA testing (including locations and technique) as well as frequency can help minimize these technical concerns. Rather than testing and evaluating PSA results over shorter intervals, broad or long-term patterns of doubling time may provide a more realistic evaluation.

Less well understood is the way in which inflammatory conditions, active infections, and use of antimicrobial therapy can alter PSA production and thus result in variations of predicted PSA doubling time. The use of concurrent medications, as well as complementary and alternative therapies, affects results, and a number of medicines have an active role in expression or secretion of PSA.<sup>2</sup> Additional markers of PC progression are available but are less well validated, including markers of neuroendocrine differentiation (chromogranin-A, neuron specific enolase), prostate metastasis (prostatic acid phosphatase), and bone formation and resorption (bone-specific alkaline

phosphate, urinary N-telopeptide, or amino terminal pro-collagen peptides). Future studies may also evaluate circulating PC tumor cells or PC specific DNA.

Lastly, in some patients, PSA values increase steadily, only to reach a new steady state for an undefined period of time. This malignant equilibrium can last for years and then unpredictably progress to exponential growth. I often advise PC patients that we should not make a significant clinical decision based on a single PSA value. PSA values and velocity should be assessed with as broad a view as possible.

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*Dr. Tucker is Director, Prostate and GU Oncology Program at The Angeles Clinic & Research Institute, Los Angeles, CA. He can be reached at [stucker@theangelesclinic.org](mailto:stucker@theangelesclinic.org).*