Rising PSA After Local Therapy Failure: Immediate vs Deferred Treatment

By Judd W. Moul, MD

Patients whose only sign of recurrence after local therapy for prostate cancer is a rising prostate-specific antigen level (PSA-only recurrence) have become more common. We have developed two models to predict PSA-only

Introduction

The prostate-specific antigen (PSA) era (1988 to present) has dramatically altered the epidemiology of prostate cancer in the United States and in many other industrialized countries.[1] Although the prevalence of prostate cancer has fallen somewhat since its peak in the early 1990s, the American Cancer Society still estimates that approximately 179,000 new cases will be diagnosed in 1999.[2]

An unprecedented stage migration has accompanied this large shift in incidence. The Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute noted a 52% decline in the rate of distant metastatic (stage D) prostate cancer between 1990 and 1994.[3] At the same time, the rate of diagnosis of localized disease skyrocketed. Our Department of Defense Center for Prostate Disease Research database at Walter Reed Army Medical Center (WRAMC) found that the incidence of localized prostate cancer (stages A and B) increased from approximately 50% of cases in 1988 to more than 75% of cases by 1996.[1]

Along with this change in stage distribution has come a change in treatment patterns. The SEER program found that rates of radical prostatectomy rose from 17.4 cases per 100,000 in 1988 to 54.6 cases per 100,000 in 1992.[3] By 1992, 36.6% of patients with locoregional disease underwent radical prostatectomy, and 32.3% received radiation therapy.

Furthermore, there has been a shift in the age-adjusted rates of these treatments. Most notably, there was a three- to fourfold rise in the rate of radical prostatectomy in men 45 to 59 years old, and a two- to threefold rise in men 60 to 69 years of age.[3] Rates of radiation therapy also increased one- to twofold in 45- to 79-year-old men.

In the late 1990s, clinicians are now seeing the effects of the boom in the diagnosis and localized treatment of prostate cancer of the early 1990s. A large number of generally younger men who were treated for clinically localized prostate cancer have experienced a recurrence of their disease. Figure 1 illustrates the problem clinicians are facing.

With more than 50,000 men per year developing a PSA-only recurrence (indicated only by an elevated PSA level, as will be discussed in the next section), it is obvious that this is a key issue for urologists, radiation oncologists, medical oncologists, and, perhaps most importantly, the patient and his family.

Assessment of PSA-Only Recurrence After Prostatectomy

The PSA level at which to define treatment failure after radical prostatectomy varies in the literature. Some series have used any detectable level; others, a single value > 0.4 or 0.5 ng/mL; and still others, two consecutive values ≥ 0.2 ng/mL. At our hospital, employing the Abbott IMx assay, we use the criterion of two values ≥ 0.2 ng/mL, or any single value ≥ 0.5 ng/mL.

In clinical practice, it generally is quite obvious when radical prostatectomy patients develop a PSA-only recurrence because their PSA becomes detectable and continues to rise. The use of an ultrasensitive PSA assay may result in the identification of relapsing patients 1 to 2 years earlier than can be achieved with a conventional assay.

The timing of the rise in PSA level after surgery also is important. Patients whose PSA never falls to an undetectable level in the postoperative period generally are considered to have systemic disease. However, some of these men who do not attain an undetectable PSA after surgery do respond to
salvage radiation to the prostatic bed. This suggests that systemic disease is not universal in this setting. Likewise, a PSA level that rises rapidly during the postoperative period may be indicative of metastatic disease. Patients whose PSA level remains undetectable for long periods (1 to 4 years) and then gradually rises are considered to have local disease recurrence.

After Radiation Therapy

Until recently, the definition of PSA-only recurrence after radiation therapy was widely debated. In 1997, the American Society for Therapeutic Radiology and Oncology (ASTRO) convened a consensus panel to determine guidelines for PSA-only recurrence (biochemical failure) after radiation therapy.[4] The panel agreed on the following four guidelines:

1. Biochemical failure is not a justification per se to initiate additional treatment. It is not equivalent to clinical failure. Biochemical failure is, however, an appropriate early end point for clinical trials.

2. Three consecutive increases in PSA level provide a reasonable definition of biochemical failure after radiation therapy. For clinical trials, the date of failure should be the midpoint between the postirradiation nadir PSA level and the first of three consecutive rises. (The use of three, rather than two, consecutive values reduces the likelihood of falsely characterizing a "bouncing" PSA level as a biochemical failure. This phenomenon results when sequential determinations of PSA level show one or two rises, followed by a fall and a subsequent failure to rise again.)

3. As yet, no definition of PSA-only recurrence has been shown to be a surrogate for clinical progression or survival.

4. Nadir PSA level is a strong prognostic factor, but no absolute level is a valid cut-off point for identifying successful and unsuccessful treatments. Nadir PSA level is similar in prognostic value to pretreatment prognostic variables.

Prediction of PSA-Only Recurrence

Because early adjuvant therapy may be beneficial to patients with localized disease in whom treatment is destined to fail, many studies have evaluated a variety of prognostic variables in an attempt to identify individuals who are at high risk of disease recurrence after surgery. The following variables have shown a significant correlation with PSA-only recurrence[5-15]: pretreatment PSA level; prostatic acid phosphatase level; prostatectomy specimen Gleason sum; pathologic stage; tumor volume; endorectal coil magnetic resonance imaging results; DNA ploidy; race; and, more recently, molecular biomarkers, such as p53, bcl-2, and Ki-67. Recently, some investigators have combined prognostic variables into models or equations that can be used to predict the likelihood of recurrence.

Johns Hopkins Model

Partin et al[10] at The Johns Hopkins Hospital were the first group to develop a simple biostatistical model equation that categorized post–radical prostatectomy patients into three risk groups (low, intermediate, and high risk) based on their likelihood of serologic failure. Many preoperative and pathologic variables were analyzed. However, after multivariate regression analysis, only three variables were included in the final model to select adequately for risk stratification after surgery. Sigmoidal transformation of PSA level (defined in equation in middle column), prostatectomy Gleason sum, and specimen confinement (margin status) were incorporated into an equation that calculated the relative risk of recurrence ($R_w$) as: $R_w = (0.061 \times PSA_{ST}) + (0.54 \times postoperative \text{Gleason sum}) + (1.87 \times \text{specimen confinement})$

Specimen confined = organ confined or extracapsular extension with negative margins.
Specimen confined = organ confined or extracapsular extension with negative margins.

Patients were then stratified into three risk groups depending on their calculated value of $R_w$. This model employed traditional variables that are assessed at most institutions, making this form of risk assessment a practical clinical tool that can be used in decisions concerning adjuvant therapy. The model allows those patients at high risk for recurrence to be identified shortly after surgery, while
their tumor burden is theoretically at a minimum.

**Department of Defense Center for Prostate Disease Research Models**

Our research group at the Department of Defense Center for Prostate Disease Research at WRAMC and the Uniformed Services University also has been working to develop prognostic models that will predict PSA-only recurrence after radical prostatectomy. Although the Johns Hopkins model[10] has provided a great start, it was developed for patients with clinical stage B2 (T2b or T2c) and may not be applicable to the majority of patients who are being treated in the late 1990s.

Using data from 378 patients of all clinical stages at WRAMC and data from 91 patients in a separate hospital validation cohort, we performed similar modeling using traditional prognostic factors.[15] The prognostic variables that significantly correlated with disease recurrence were incorporated into a model equation that calculates the relative risk of recurrence ($R_r$) as: $R_r = \exp [(0.51 \times \text{race}) + (0.12 \times \text{PSA}_{\text{st}}) + (0.25 \times \text{postop Gleason sum}) + (0.89 \times \text{organ confinement})]$

Race was defined as [1] if the patient was African-American or [0] if he was Caucasian or another race. Sigmoidal transformation of PSA ($\text{PSA}_{\text{st}}$) was calculated using the equation:

$$\text{PSA}_{\text{st}} = \frac{10}{1 + e^{6.8704-(0.9815 \times \text{PSA level})}}$$

The postoperative Gleason sum was defined as a continuous integer value (range, 2 to 10). Organ confinement was defined as [1] if the tumor was organ-confined (no extraprostatic extension) or [0] if the tumor was non-organ-confined (extraprostatic extension and/or positive margins).

Table 1 shows the 3- and 5-year Kaplan-Meier disease-free survival rates for the three risk groups for both the WRAMC model cohort of 378 patients (top panel) and the validation cohort of 91 independent patients (bottom panel). We have placed this traditional model equation into our urologic clinic local area computer network. Each clinician can enter patients’ race, PSA level, Gleason sum, and pathologic stage into the Microsoft Excel program postoperatively, and the program will automatically calculate the $R_r$ and show the recurrence information that appears in Table 1. We can print this information and use it as an aid for counseling patients with regard to adjuvant therapies. This model is now available for use on our World Wide Web home page (www.cpdr.org).

In addition to this recurrence model using traditional prognostic factors, we developed a model to predict recurrence after radical prostatectomy using traditional clinical and pathologic variables combined with the results of molecular biomarker assays (p53 and bcl-2 immunohistochemistry of radical prostatectomy specimens).[16]

Our models are initial attempts to combine prognostic factors and take advantage of advances in hospital-based desktop computers so as to improve patient care. However, large, multicenter, prospective studies are needed to fine-tune existing prognostic models and to develop similar models for patients who receive external-beam radiotherapy or brachytherapy.

**Treatment of PSA-Only Recurrence**

Treatment of PSA-only, or serologic-only, recurrence after radical prostatectomy or radiotherapy is controversial. Options for patients who have undergone surgery include observation; external-beam radiotherapy to the prostatic bed; traditional full hormonal therapy, including orchietomy, luteinizing hormone releasing hormone agents, or combined hormonal therapy; and nontraditional hormonal therapy, including intermittent hormonal therapy, antiandrogen monotherapy, or medical combinations, such as an antiandrogen and a 5-alpha-reductase inhibitor. For patients who have received radiation therapy, the choices are similar, with the exception that salvage prostatectomy and cryotherapy are options for carefully selected patients.

**Radiation for PSA-Only Recurrence After Radical Prostatectomy**

The value of adjuvant external-beam radiotherapy for pathologic stage C prostate cancer after radical prostatectomy has been debated for years.[17] To date, no randomized study has been reported to prove or disprove the benefit of adjuvant radiotherapy in this setting. Nonrandomized case series have been conflicting, with most reports showing only that radiation reduces the local recurrence rate.

With regard to the use of radiation therapy for a postoperative elevation in PSA level, the data are even more controversial and preliminary. In patients with either stage C disease or PSA-only recurrence, the dilemma is that the clinician does not know whether these patients have disease that is localized within the potential field of radiation, or whether they have systemic occult metastases. Furthermore, even if the disease is localized, it is unclear whether the acceptable radiation dose will eradicate the residual/recurrent cancer.

A complete review of this topic is beyond the scope of this article. However, Forman and Velasco[18]
recently wrote an excellent review of the subject. In this review, they express great optimism about the use of radiation therapy in this setting and generally recommend early intervention when the PSA level is ≤ 2.0 ng/mL using radiation doses of 66 to 70 Gy.[18] They state that patients with a PSA level ≤ 2 ng/mL have an 80% chance of being disease-free 4 years after postoperative radiotherapy.[18]

Conversely, a recent study from The Johns Hopkins Hospital portrays a more pessimistic view of radiation therapy for patients with a rising PSA level after surgery.[19] Of 1,699 men who underwent a radical prostatectomy between 1982 and 1995, 82 patients with an elevated PSA level only (N = 57) or a local recurrence (N = 25) after surgery received radiation alone and were followed for a minimum of 2 years. Mean preradiation PSA levels were 2.2 ng/mL in the PSA-only recurrence patients and 4.1 ng/mL in the local recurrence patients.

Of the 82 men, 17 (21%) had an undetectable PSA level (< 0.2 ng/mL) for ≥ 2 years following radiation therapy. The 5-year actuarial PSA recurrence-free rate after radiation therapy was 10%. The PSA level did not remain undetectable for ≥ 2 years in any patient with a Gleason sum > 8, positive seminal vesicles, or positive lymph nodes. Furthermore, only 1 (6%) of 16 men who developed a PSA-only recurrence in the first year after surgery was rendered disease-free by radiation therapy. In contrast, patients who had a delayed PSA-only recurrence had a higher likelihood of responding to radiation therapy. Specifically, among men who had a PSA-only recurrence 5 or more years after surgery, the 2-year disease-free survival rate after radiotherapy was 44%.

Although the pretreatment PSA level was not a statistically significant predictor of the outcome of radiation therapy, patients with a low starting PSA level tended to have a better outcome. For the 17 patients who had an undetectable PSA at 2 years after radiation, the mean starting PSA level was 1.7 ng/mL, as compared with 3.1 ng/mL for patients who did not remain disease-free. With larger series and careful selection, as advocated by Forman and Velasco,[18] future studies may find that radiation therapy is beneficial in the subset of surgical patients with a low Gleason sum, no seminal vesicle involvement, negative lymph nodes, and a low PSA level at recurrence (< 2.0 ng/mL) that does not rise during the first postoperative year.

**Salvage Radical Prostatectomy for Radiation Therapy Failure**

Salvage radical prostatectomy has been shown to produce long-term disease-free survival.[20-23] Despite the fact that salvage surgery is the only proven curative option for prostate cancer that recurs after radiation therapy, it has not gained widespread acceptance because of its associated morbidity and high recurrence rate, as compared with surgery for previously untreated prostate cancer.[20-23] Morbidity is substantial, with a 40% to 50% incidence of postprostatectomy incontinence, universal impotence, and a higher risk of operative complications, such as rectal injury and reoperation.[22]

Salvage radical prostatectomy should be considered only for carefully selected men who have clinically organ-confined disease before original radiation therapy and who still have clinically organ-confined disease at the time of PSA-only recurrence. In general, this would include men who had a low to intermediate Gleason sum (≤ 6), a low pretreatment PSA level (< 10 ng/mL), and a low initial tumor stage (T1c or T2a). At the time of PSA-only recurrence and consideration for salvage treatment, the patient still should have a favorable Gleason sum (≤ 6), tumor stage (≤ T2b), and PSA level (ideally, < 2.0 ng/mL). Patients also should be well informed of the potential morbidity of this surgery, particularly incontinence, and carefully documented informed consent should be obtained.

**Salvage Cryotherapy for Radiation Therapy Failure**

Cryotherapy using transperineal cryoprobes that are placed under transrectal ultrasound guidance has been performed in patients with prostate cancer since 1990.[24] Investigators at the M. D. Anderson Cancer Center have had the most experience using percutaneous cryoprostatectomy to treat clinically localized prostate cancer recurrences after radiation therapy.[25] In 143 patients, the rate of postcryotherapy incontinence was 28% with a commercial urethral warming device, 89% with an alternate homemade urethral warmer, and 88% when two separate salvage cryotherapy procedures were performed. The overall rate of postcryotherapy incontinence was 43%, and 72% of incontinent men required two or more absorbent pads per day.

The authors did not believe that postcryotherapy incontinence improved as surgeons gained more experience with the procedure, but they also believed that it was not worsened by a potentially more effective double-freeze technique. They concluded that cryoprostatectomy should be considered investigational.

However, this statement, which was published in 1997, must be put into current context because the commercial urethral warmer has since been approved by the FDA. Furthermore, the American
Nontraditional Hormonal Therapy

Nontraditional hormonal therapy includes intermittent hormonal therapy,[28] 5-alpha-reductase inhibitors,[29] antiandrogens alone, or oral combinations, such as finasteride (Proscar) and flutamide (Eulexin).[30] Intermittent hormonal therapy will not be discussed further; however, low-dose oral hormonal therapy will be reviewed briefly. The advantages and disadvantages of the low-dose oral approach are outlined in Table 2, and selected published series are summarized in Table 3. In general, these approaches preserve potency in men who were potent at the start of treatment, and they are designed to limit the long-term side effects of full hormonal therapy while delaying or preventing disease progression. Currently, only short-term follow-up data on nontraditional low-dose hormonal therapies are available, and no multicenter, randomized trials have been conducted. Therefore, the long-term efficacy of these therapies is unknown. I believe, however, that these approaches will continue to increase in popularity as younger, healthier men are faced with PSA-only recurrence and want to avoid the immediate and long-term side effects of full hormonal therapy. Many men and their physicians will elect to "buy time" before embarking on traditional hormonal treatment.
Summary

Prostate-specific antigen-only recurrence after prior radical prostatectomy or radiation therapy is a common scenario that clinicians face in the late 1990s. Treatment options include observation, radiation for patients who have undergone surgery, salvage surgery or cryotherapy for patients who have had radiation therapy, and traditional or nontraditional hormonal therapy. A recent review article by Waxman et al.[31] provides a more complete overview of this topic.

In general, radiation therapy for PSA-only recurrence after radical prostatectomy is likely to benefit only those men who have no adverse pathology (ie, men with a Gleason sum < 8, negative seminal vesicles, or negative lymph nodes), who have a low PSA level (≤ 2 ng/mL) at recurrence, and who do not develop a PSA-only recurrence during the first year after surgery. Salvage radical prostatectomy or cryotherapy for recurrence after radiation therapy should be reserved for carefully selected men whose disease still has a high likelihood of being organ-confined. Furthermore, because these salvage procedures are associated with a relatively high risk of incontinence and other morbidity, patients must be fully informed and carefully counseled about these risks.

Hormonal therapy is probably the single most beneficial treatment for PSA-only recurrence. The Medical Research Council study confirms a survival benefit for early hormonal therapy that is most pronounced in patients with M0 disease. Whether these results can be extrapolated to patients with a PSA-only recurrence is debatable, but they suggest that hormonal therapy is a reasonable choice for such patients. Both nontraditional low-dose oral hormonal therapy alone and intermittent hormonal therapy are gaining popularity. The potential potency-sparing benefit of these therapies is appealing, as is their lower incidence of severe side effects compared with full hormonal therapy. However, the long-term efficacy of these approaches is unknown.

More clinical trials are needed to determine the best treatments, alone and in combination, for PSA-only recurrence.

References:


27. The Medical Research Council Prostate Cancer Working Party Investigators Group: Immediate vs


Source URL:
http://www.diagnosticimaging.com/review-article/rising-psa-after-local-therapy-failure-immediate-vs-deferred-treatment-1

Links:
[1] http://www.diagnosticimaging.com/review-article