Biochemical Relapse After Primary Treatment for Prostate Cancer: Studies on Natural History and Therapeutic Considerations

Eli Rosenbaum, MD,1 Alan Partin, MD,2 and Mario A. Eisenberger, MD,1 Baltimore, Maryland

Key Words
Prostate cancer, biochemical relapse, prostate-specific antigen (PSA), PSA doubling time (PSADT), salvage therapy, systemic treatment

Abstract
After local treatment, a substantial proportion of patients with prostate cancer present with rising prostate specific antigen (PSA) serum levels as the only indication of disease activity. Evolving data derived from large databases that were predominantly retrospectively evaluated show that the natural history of these patients is quite variable. Various clinical and pathologic parameters have been shown to predict for the probability of development of distant metastasis, including the surgical Gleason score, time of PSA relapse after primary treatment, and PSA doubling time (PSADT). The PSADT appears to be the most important predictor of development of distant metastasis and prostate cancer-specific mortality. At present, no data support a standard management approach for these patients, and clinical trials pose a major challenge in view of the methodologic complexities involved. Patients and treating physicians should make major efforts to participate in clinical trials in this patient population. (JNCCN 2004;2:249-256)

Prostate cancer remains the leading cancer diagnosed in men in the United States. In 2003, experts estimated that 220,900 new cases would be diagnosed, which account for about 30% of all cancer cases diagnosed in men in that year.1 Approximately 85% of all cases diagnosed yearly are clinically localized and most are treated with radical prostatectomy (RP) or radiation therapy (RT) either by external beam or brachytherapy with a curative intent. After the introduction of the serum prostate-specific antigen (PSA) test, an increasing number of men presented with rising serum PSA levels after local treatment as the sole evidence of disease activity. Although the observation of rising serum PSA levels is indicative of recurrent disease, current data indicate that only a fraction of these patients will subsequently develop evidence of distant metastasis during their lifetime and die from the disease.

Based on information mostly from single institutions, the 10-year biochemical relapse-free survival rates of men with organ-confined disease treated using local therapeutic modalities in surgical and radiation series is approximately 50% to 65%.2–5 Although the precise statistics of treatment patterns are not available, we can estimate that approximately 100,000 cases are referred yearly for curative treatment in the United States. According to these figures and taking into account the biochemical relapse rates indicated above, it can be estimated that several hundred thousand men are currently seen in the clinics with rising serum PSA level as the only evidence of disease activity. The management of these patients poses a major challenge for all disciplines involved in the treatment of prostate cancer, primarily because of the widely variable outcome and undefined treatment standards. Clearly, adequate definition of the natural history of these patients would provide critical prognostic information for treatment planning.
Definition of PSA Recurrence

The definition of PSA relapse varies according to the primary modality of treatment used. After radical prostatectomy, preoperative PSA level should decline rapidly to an undetectable level, according to a 48- to 72-hour half-life. Based on the most-available PSA assays, a value of less than 0.1 ng/mL is considered undetectable. Controversy still exists regarding the most appropriate definition of PSA failure, however. At Johns Hopkins, biochemical relapse is defined as rising PSA levels of 0.2 ng/mL or higher. The ultrasensitive PSA assays detect changes at levels as low as 0.01; however, more studies are needed to better define the clinical significance of detectable PSA levels below 0.1 ng/mL.

After radiation therapy (external beam, brachytherapy, or a combination of both) the definition of biochemical relapse is more challenging. Time to the PSA nadir is usually longer (1–2 years), and persistent production of PSA may originate from remaining nonmalignant prostatic tissue. Transient rises in PSA after radiation therapy (“bouncing”), especially after brachytherapy, has also been reported.

The American Society for Therapeutic Radiology and Oncology (ASTRO) defined PSA recurrence after radiation therapy as three consecutive increases in PSA independent of the nadir value. The date of failure is the midpoint between the post-radiation nadir PSA and the first of the three consecutive rises. The use of three consecutive values reduces the risk of defining a false biochemical relapse because of the bouncing PSA phenomenon. Data from contemporary studies using primary treatment with radiation in patients with clinically localized prostate cancer will undoubtedly provide more precise information on the definition of biochemical relapse following this modality of treatment.

Clinical Course

The data on the natural history of patients with biochemical relapse after surgery or RT have been reported. A number of confounding factors determine the complexities involved in the adequate evaluation of these data. Among the most important issues are limited follow-up due to the relatively short-term availability of the PSA test, lack of strict follow-up guidelines, and the frequent implementation of androgen-deprivation treatment before the development of clinically evident distant metastases.

The first report, by Pound et al., described the Johns Hopkins Hospital experience on the natural history of progression of patients with biochemical relapse after a radical prostatectomy performed at that institution. No patient received any endocrine therapy before evidence of metastatic disease. The authors developed an algorithm based on the most significant predictive factors based on a multivariate analysis of the initial 1997 patients. The data were updated recently and are shown in Table 1. Of the 3,263 patients followed up after RP on the most recent published update, 329 experienced a biochemical relapse. After a mean follow-up time of 10.5 years, 144 of 321 (44%) patients developed metastatic disease. Median actuarial time from biochemical relapse to metastatic progression was approximately 7.0 years. Based on the Cox model, factors that predict the probability of distant metastasis over time include the timing of initial PSA elevation, (< or >2 years from the RP) Gleason score (5–7 vs. 8–10), and the PSA doubling time (PSADT; < or >10 months). Based on the update, the PSADT largely overrides the other factors in predicting the probability of development of distant metastasis and prostate cancer-specific mortality (Partin, personal communication, 2004).

Table 1 Probability of Metastasis-free Survival at 3, 5, and 7 Years After Biochemical Relapse

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Relapse</th>
<th>5–7</th>
<th>8–10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;2 y</td>
<td>&gt;10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>3 y</td>
<td>92%</td>
<td>66%</td>
<td>N/A</td>
</tr>
<tr>
<td>5 y</td>
<td>92%</td>
<td>34%</td>
<td>N/A</td>
</tr>
<tr>
<td>7 y</td>
<td>84%</td>
<td>27%</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Abbreviations: PSADT, prostate specific antigen doubling time; N/A, not available.
Source: Data are from Eisenberger et al.
D’Amico et al. evaluated various pretreatment and post-treatment prognostic factors of 381 patients with clinically localized prostate cancer who underwent primary treatment with RT. Post-treatment risk factors were also analyzed in 94 patients who experienced biochemical relapse. PSADT as a continuous variable was a significant predictor of overall and prostate cancer specific prognosis. In a separate study, D’Amico et al. demonstrated a hazard ratio of approximately 20 for prostate cancer-specific mortality (after a PSA recurrence) for men with a PSADT of less than 3 months. The type of initial treatment received (RP or RT) was not statistically significantly associated with time to prostate cancer-specific mortality, and the authors suggested that a PSADT of less than 3 months should be further evaluated as a possible surrogate end point for prostate cancer-specific mortality after surgery or radiation therapy.

The importance of the time to PSA relapse and the PSADT in predicting the outcome of these patients after either surgery or radiation therapy has been emphasized by multiple authors.

### Diagnostic Tests

The most commonly used imaging studies for staging these patients are a radionuclide bone scans, computed tomography (CT), and magnetic resonance imaging (MRI) of the abdomen and pelvis. However, all these tests have a fairly low yield in detecting metastatic sites in the early stages of biochemical relapse. The probability of a positive bone scan in an asymptomatic patient with serum PSA levels was reported to be less than 5%. In a study evaluating the role of CT scans in this population, about 14% of patients had positive scans within 3 years from the biochemical relapse; however, only 9.3% of the CT scans provided new clinical information (most confirmed palpable recurrences or bone metastasis already reported on bone scans). Serum PSA values and PSA velocity together were frequently able to predict abnormal findings of CT scans. The mean total PSA for the patients with positive CT scans was 27.4 ng/mL compared with 4.5 ng/mL for those with negative CT scans. The mean PSA velocity was 1.8 ng/mL/mo in patients with positive scans compared with 0.7 ng/mL in patients with negative CT scans. A more precise definition of the appropriate schedule for imaging these patients is needed; however, a baseline evaluation followed by yearly bone scans (and CT or MRI of the abdomen and pelvis) in patients with PSADT of less than 10 months seems reasonable at this time.

The ProstaScint scan (Indium-111 conjugated to a murine antibody to prostate-specific membrane antigen) is approved by the FDA for the initial diagnostic aid of patients with a biochemical relapse after RP; however, the usefulness of this test as a restaging tool in patients with biochemical relapse has not been well documented. This test has a significant problem: relatively high false-positive and false-negative results. A few small studies have compared the long-term results of salvage RT based on findings of the ProstaScint scan. Kahn et al. reported significantly better long-term PSA control after salvage RT in patients who had no evidence of extra prostatic uptake on their ProstaScint scans. Interestingly, the outcome reported that 22% of those with a positive distant uptake had long-term PSA control. Other studies also reported that evidence of extra prostatic uptake did not predict failure to achieve a long-term PSA response following local salvage therapy.

Other diagnostic tests frequently employed in the setting of the biochemical relapsed patient include a transrectal ultrasound with biopsy, endorectal MRI, and PET scans. Although no clear consensus exists on the diagnostic and therapeutic contributions of these tests and procedures, in our experience they infrequently provide decisive information for the management of these patients.

### Local Versus Distant Relapse

The overwhelming majority of patients with biochemical relapse are asymptomatic from the disease. Usually, no findings on physical examination or imaging modalities are available to use for distinguishing between local and systemic recurrence. In the absence of signs and symptoms, the strategy employed is to estimate the probability of local relapse using various clinical and pathologic factors related to the disease. The interval from the RP to biochemical relapse, surgical Gleason score, extent of pathologic involvement (capsule penetration, seminal vesicles, or lymph nodes) were reported by the Hopkins investigators several years ago to be important variables in predicting eventual local versus distant failure. Leventis et al. reported that the DRE of the prostatic fossa, pretreatment PSA, and recurrence PSADT predict which
patients will have biopsy-proven local recurrence. A response to salvage radiation was more likely in patients with low PSADT and actual pre-salvage treatment PSA level. Palpable lesions and those confirmed histologically did not predict the response to salvage radiation therapy. A PSADT (greater than or less than 6 months) was reported to be the most reliable factor for differentiating local from distant failure in patients treated with primary radiation therapy. Sartor et al. reported that the Gleason score (2–6 vs. 7–10) and PSA nadir (<1 vs. 1–4 ng/mL) predicted for local versus distant relapse after definitive radiation therapy.

Treatment Options

At this time, the only reasonable, well-documented, therapeutic approach with curative potential is salvage postoperative radiation therapy in patients who experience relapse after radical prostatectomy. After radical prostatectomy, the most commonly used treatment is external beam radiation therapy. The recommended dose in salvage external beam radiation according to the ASTRO consensus panel guidelines is at least 64 Gy. Single institution experiences indicate that a 25% to 50% durable undetectable PSA response with salvage RT. The variability in results is most probably because of patient selection criteria. Important factors influencing the probability of controlling the disease are the pathologic staging and surgical Gleason score in addition to the timing of PSA relapse after surgery. In most studies, the reported PSA thresholds associated with improved results from salvage RT are 0.6 to 2.7 ng/mL.

Stephenson et al. proposed a nomogram to predict the 2-year PSA progression-free probability (PPF) for salvage RT in patients with biochemical relapse after a RP. This study involved 375 patients followed for a median of 3 years after salvage RT. Patients with pre-RT PSA levels of less than 2 ng/mL, PSADT longer than 10 months, Gleason score of 2 to 7, and pT3a (positive margins at RP) had a 2-year PSA PPF of 65% to 95%. The pre-RT PSA, time from RP to the PSA relapse, and the RT dose were not reported as important predictors of outcome in the multivariate analysis.

A variable degree of success has been reported with salvage prostatectomy after external beam radiation primarily based on single institution reports. Three-year biochemical relapse free rates after salvage RP were reported in up to 50% of selected series of patients. A serum PSA of less than 10 ng/mL at time of surgery and pathologic evidence of organ confined disease are important indicators of outcome in these patients. Clearly, salvage prostatectomy requires experienced surgeons to ensure adequate removal of all evidence of disease at the cost of acceptable morbidity. The most common and severe sequelae from salvage prostatectomy are urinary incontinence (40% to 50%), bladder neck contractures (20% to 25%), rectal injury (5% to 15%), fistula (0% to 5%), thromboembolic events (5% to 8%), and definite impotence.

Other approaches requiring further study include salvage RP after brachytherapy, salvage brachytherapy after external beam radiotherapy (XRT) or RP, and salvage cryotherapy after XRT. Although preliminary, the available data suggest that these approaches are feasible and that potentially effective larger studies are needed to better define short- and long-term toxicities and therapeutic benefits.

Androgen Deprivation

The role of androgen deprivation in the treatment of patients with biochemical relapse remains undefined. Unfortunately, no studies employing an adequate “no treatment control arm” have been reported to date. Although existing data support the contention that immediate (early) hormonal therapy in these patients is likely to delay the onset of clinically evident distant metastasis, a survival benefit has not been documented. Long-term androgen deprivation is associated with multiple and frequently irreversible toxicity. This is especially important because the vast majority of these patients have no symptoms related to their disease.

The optimal timing of androgen deprivation in prostate cancer remains a major controversial issue of virtually all stages of this disease. Although the benefits by far override the side effects in patients with metastatic disease, its use in patients with biochemical evidence of disease only requires further study. Ongoing studies are testing an intermittent treatment approach compared with the standard continued androgen suppression in various stages of the disease, including the early disease setting. Preliminary data of ongoing phase III studies reported recently indicate that during the off-treatment intervals, 90% of patients had shown evidence significant of gonadal function with testosterone recovery within the normal ranges. Although that is preliminary, the authors of that study suggest that the
pattern of disease progression in patients with biochemically relapsed disease appears to be very similar in the groups receiving intermittent treatment and continued treatment. Because of its relatively good tolerance, the use of intermittent hormonal therapy is becoming more popular especially in patients in the high-risk group.

Another treatment explored in early stage prostate cancer is the use on antiandrogens as single agent. The most extensively developed drug in this setting is bicalutamide. Data in patients with metastatic disease suggest that bicalutamide (50 and 150 mg/d) as monotherapy is inferior to bilateral orchiectomy in prospective randomized trials. The evidence in patients without metastasis is too preliminary for definitive conclusions. One large international placebo-controlled study evaluated the adjuvant role of 150 mg/d of bicalutamide in high-risk patients treated with RP and RT or no treatment (watchful waiting). With a relatively short follow-up time, a statistically significant difference in progression was seen in favor of bicalutamide; treatment was unblinded and the study was terminated. Toxicity (gynecomastia, gastrointestinal) was significant and because of the early unblinding, survival data may not be reliable. Recently, researchers disclosed that with additional follow-up time, the number of deaths in the bicalutamide treatment arm was significantly higher than in the placebo arm. Clearly, further studies are needed.

Selection of Treatment Candidates

Table 1 summarizes the most recent experience reported by the Johns Hopkins investigators on the natural history of patients with biochemical relapse after radical prostatectomy. Recent evaluation of these data suggests that the PSADT significantly predicts for prostate cancer specific mortality in these patients. The 10-year survival rate in patients with PSADT of 10 months or less is 43% compared with 80% in patients with PSADT longer than 10 months (Partin, unpublished communication, 2004).

Observations across different series suggest that the median survival of patients with short PSADT (<12 months in radiation-treated patients) may be similar to patients diagnosed with early bone metastasis. D’Amico et al. reported the outcome of patients receiving primary radiation therapy (without hormonal therapy) based on their recurrent PSADT (Fig. 1). The median survival of patients with PSADT of 12 months or less in the series was about 5 years.

These figures are quite similar to the median survival of 52 months in patients with minimal (early) metastatic disease treated in a large prospective randomized study comparing bilateral orchiectomy with or without flutamide in patients with newly diagnosed M1 prostate cancer patients reported by Eisenberger et al. (Fig. 2). The similarities in distribution of
survival in the Kaplan-Meier curves of patients with PSADT of 12 months or less reported by D’Amico et al., and those with minimal metastatic disease reported by Eisenberger et al. suggest that patients with short doubling times represent a group of patients with subclinical metastatic disease in which aggressive treatment approaches should be vigorously evaluated in prospectively controlled studies (Figs. 1 and 2).

Many questions regarding the clinical course and management considerations in patients with biochemical relapse remain unanswered and physicians caring for these patients should attempt vigorously to support clinical trials. The PSADT will probably be the most important determinant of outcome and an important tool for selection of treatment in these patients. Some considerations for future research are proposed in Table 2.

In the absence of available studies, the current data, although preliminary, may allow for some reasonable therapeutic considerations. Physicians should inform patients that, at this point, no agreed upon standard approach and that significant toxicity is possible. In the group of patients with long PSADT, a reasonable alternative seems to be to offer these patients careful observation prior to initiating treatment. In view of the relatively favorable outcome, reasonable treatment options may include non-aggressive approaches such as intermittent hormonal therapy or a non-castrate anti-androgen monotherapy.

The most adequate time to initiate treatment in this group of patients is unclear. Their predicted survival is long and quality of life should be a major factor when approaching this decision. For patients with short PSADT, survival seems to be significantly less. These patients should be referred to centers involved in clinical trials for this patient population.

References


