The Evolving Definition of Advanced Prostate Cancer

Judd W. Moul, MD, FACS
Division of Urologic Surgery and Duke Prostate Center (DPC), Duke University School of Medicine, Durham, NC

Each year more patients present with prostate cancer at increasingly younger ages and with earlier stage disease, resulting in the potential for longer survival time, longer-term hormonal therapy, and a heightened risk of developing biochemical recurrence after treatment. It seems clear that clinicians need to broaden the definition of “advanced” prostate cancer to include recent knowledge that will influence the form and timing of treatment as well as the monitoring of disease progression. A more contemporary definition should include patients with lower-grade disease and with an increased risk of progression and/or death from prostate cancer along with those with widely disseminated metastatic disease. Treatment alternatives for these patients should be evaluated based on a risk stratification equation toward a goal of the greatest efficacy and the least patient harm over time given that increasing numbers of these patients are entering treatment long before they develop widespread osteoblastic metastases.


© 2004 MedReviews, LLC

Key words: Advanced prostate cancer • Risk stratification • Prostate-specific antigen • Early hormonal therapy • Metastasis • Recurrence • Biochemical recurrence • Hormones

Prostate cancer, second only to skin cancer incidence among men in the United States, will affect an estimated 230,100 men during 2004.1 It is further estimated that 1 in 6 US men will develop prostate cancer during his lifetime and that over 70% of these cases will be among men older than age 65.1,2 Incidence rates reached a peak in the mid 1990s, following widespread use of prostate-specific antigen (PSA) screening programs; these rates subsequently declined and currently are increasing, albeit at a less rapid pace.1,2 Prostate cancer
remains the second leading cause of cancer deaths among US men, accounting for close to 30,000 deaths annually, a total that is exceeded only by the number of deaths from lung cancer. Age of diagnosis continues to decrease with a concomitant increase in the number of men diagnosed with early-stage or clinically localized disease. In addition, over the past 10 years the age-adjusted death rate has decreased approximately 15%, partly due to earlier detection and in part to improved treatment of both early stage and advanced disease. As increasing numbers of men are living longer with prostate cancer, larger proportions will eventually present to our collective practices with rising PSA levels. Such PSA relapses, conservatively estimated to affect around 50,000 men each year, have become the most common form of advanced prostate cancer in the current PSA era.

Contemporary Prostate Cancer
Traditionally, “advanced” prostate cancer was defined as disease that had widely metastasized beyond the prostate, the surrounding tissue, and the pelvic lymph nodes, and was considered incurable by most clinicians and patients. The average patient had symptomatic stage D-2 disease and the most common symptom was bone pain that caused physicians to seek therapy for this form of the disease. However, given the changing face of the disease (ie, younger, healthier, better informed men with lower-grade disease), and the fact that the pathogenicity of the cancer and the risk of its metastasis were not considered, it seems clear that we need to rethink the definition of advanced prostate cancer. The current evidence suggests that patients with significant risk of progressive disease and/or death from prostate cancer should be included in the definition and that any patient with cancer outside the prostate capsule with disease stages as low as T3/N0/M0 clearly has “advanced” disease and should be treated accordingly.

Evolving Definition of Advanced Prostate Cancer
Currently, younger and healthier men are being diagnosed with prostate cancer and treated with a variety of modalities (eg, hormonal therapy, brachytherapy, and external beam radiotherapy) for locally advanced disease, as well as older men with rising PSA levels years after being treated with a radical prostatectomy. Both scenarios define current advanced disease and underscore the necessity of modifying the disease definition and treatment plans to reflect this broader spectrum of patients and disease states.

The definition now must be broadened to reflect younger, healthier men with a significant risk of disease progression, the potential for longer survival, and possibly prolonged treatment with hormone therapy. With the acceptance and proliferation of PSA screening, there has clearly been a stage migration in disease; many otherwise healthy patients now present with local lymph node metastasis or stage T3 disease that progresses to distant metastasis. Most of these patients do not have any significant comorbidities and very few have bone metastasis at diagnosis (Figure 1). Analysis of the Department of Defense Center for Prostate Disease Research (CPDR) database demonstrates this migration with decreasing proportions of patients presenting with bone metastasis at the time of diagnosis.

A contemporary definition of advanced prostate cancer should consider including stages C and D1.
of diagnosis (Figure 1). In 1990, almost 12% of these men were diagnosed with advanced disease (D1/D2); 12 years later, less than 5% of the newly diagnosed patients had metastatic prostate cancer. Thus, a contemporary definition of advanced prostate cancer should consider including stages C and D1.4,12 In addition to the stage migration, CPDR data also documented a clear age migration of the disease (Figure 2).15 In the early 1990s, prostate cancer was mainly a diagnosis of men over age 70. Over the years, as we have moved through the PSA era (1991-present), the proportion of men diagnosed under age 55 more than doubled to almost 15% of all cases.4 Thus, we are seeing younger and younger patients being diagnosed with localized prostate cancer, all with the potential of long-term survival as well as long-term hormonal therapy.

We are seeing younger and younger patients being diagnosed with localized advanced prostate cancer, all with the potential of long-term survival as well as long-term hormonal therapy.

of diagnosis (Figure 1). In 1990, almost 12% of these men were diagnosed with advanced disease (D1/D2); 12 years later, less than 5% of the newly diagnosed patients had metastatic prostate cancer. Thus, a contemporary definition of advanced prostate cancer should consider including stages C and D1.4,12 In addition to the stage migration, CPDR data also documented a clear age migration of the disease (Figure 2).15 In the early 1990s, prostate cancer was mainly a diagnosis of men over age 70. Over the years, as we have moved through the PSA era (1991-present), the proportion of men diagnosed under age 55 more than doubled to almost 15% of all cases.4 Thus, we are seeing younger and younger patients being diagnosed with localized prostate cancer, all with the potential of long-term survival as well as long-term hormonal therapy.

We are seeing younger and younger patients being diagnosed with localized advanced prostate cancer, all with the potential of long-term survival as well as long-term hormonal therapy.

Evolving Treatment for Advanced Prostate Cancer
Concomitant with the changing definition of advanced prostate cancer is the continuing evolution of treatment regimens for the disease. Now, more than ever, it is important to balance the risk of treatment with the benefits derived because of the likelihood of longer survival and the probability of disease progression with increasing symptoms, resulting in a decreased quality of life over an extended period of time. In addition, there is growing acknowledgment that prognostic markers such as age, PSA levels, Gleason scores, and tumor stage can help identify those patients most likely to experience disease progression and death from prostate cancer.13,15-19 The use of such a risk stratification system, particularly for younger patients, permits modification of the timing and form of the treatment prescribed. Currently, treatment for advanced prostate cancer is being modified to include:

- Neoadjuvant/adjuvant hormonal therapy
- Earlier use of hormonal therapy
- Risk-stratified early Rx in PSA-recurrent disease
- Traditional versus nontraditional hormonal therapy
- Luteinizing hormone-releasing hormone agonists (the mainstay of treatment for some 50 years)
- Antiandrogen monotherapy
- Intermittent hormonal therapy (appealing because it minimizes potentially deleterious effects of long-term hormonal treatment)

Clearly many contemporary men are better informed about health in general and their disease in particular and thus, there is much less blanket acceptance of traditional hormonal therapy with its accompanying side effects that could last for many years. Many of these men are concerned about such therapy and are looking to us for alternatives, particularly given the possibility of long-term treatment.

Risk Stratification
As indicated previously, stratifying the risk of disease progression is important in determining the timing and treatment regimens for patients with locally advanced prostate cancer.15,20 In a recently published article, D’Amico and colleagues17 presented PSA-era validation of a risk stratification nomogram for clinically localized prostate cancer. Patients categorized as having “high risk” localized disease (Table 1) have PSA...
levels above 20 ng/mL or a Gleason score $\geq 8$, or the 1992 American Joint Committee on Cancer tumor stage T2c or T3. These patients, particularly the younger men, could now be defined as advanced prostate cancer patients because of their increased risk for death from the disease, even though it is detected at a localized stage. The study included data from 2 multi-institutional databases of more than 6000 patients treated with either radical prostatectomy or radiotherapy. The data were combined and stratified according to pretreatment risk (low, intermediate, and high) and age at initial therapy. As shown in Figure 3, surgery is effective during the first 10 years, but prostate cancer-specific mortality remains significant, particularly for the men at high risk. Similarly for the men who were treated with external beam radiation, mortality from prostate cancer was quite high among those in the high-risk category (Figure 4). These data demonstrate that there is obvious room for improvement in multimodality therapy, underscoring the premise that high risk patients, receiving either surgery or radiotherapy, could be considered to have contemporarily advanced disease.

### Biochemical Recurrence

Rising PSA levels after initial/radical therapy is frustrating and disappointing for both urologists and patients, particularly the younger patients who are generally relatively healthy otherwise. Since approximately 40% of men who originally receive localized treatment will eventually experience PSA-only recurrence, PSA relapse has become the most common form of advanced disease.

**Surgery is effective during the first 10 years, but prostate cancer-specific mortality remains significant for high risk younger men.**

---

### Table 1

**Risk Stratification in Clinically Localized Disease**

<table>
<thead>
<tr>
<th>Risk Stratification</th>
<th>PSA and Gleason Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Risk</strong></td>
<td>PSA &lt; 10 ng/mL and Gleason biopsy $\leq 6$ and 1992 AJCC T1c, $2_{a}$</td>
</tr>
<tr>
<td><strong>Intermediate Risk</strong></td>
<td>PSA 10 – 20 ng/mL or Gleason biopsy 7 or 1992 AJCC T2b</td>
</tr>
<tr>
<td><strong>High Risk</strong></td>
<td>PSA $&gt; 20$ ng/mL or Gleason biopsy $\geq 8$ or 1992 AJCC $\geq T2c$</td>
</tr>
</tbody>
</table>

PSA, prostate-specific antigen; AJCC, American Joint Committee on Cancer; T, tumor.

Adapted from D'Amico AV et al.13
prostate cancer in the current PSA era.4-7 Rising PSA levels usually represent the earliest sign of advanced disease and/or an indication of residual tumor with an implicit negative impact on the patient’s natural life span and his quality of life.21,22 Both the urologist and the patient face challenging treatment decisions.7

**Early Hormone Therapy**

One of the dilemmas faced by clinicians treating a young patient with PSA relapse is whether to initiate hormone therapy early in the course of the secondary treatment. Arguments favoring early hormonal therapy include the fact that the clinical situation is fairly easy to define and monitor, and the increasing evidence demonstrates clear survival advantages associated with early hormone therapy for high risk malignancies.23,24 In addition, as Dr. Brawer points out in this supplement,25 in both the adjuvant and neoadjuvant setting, early hormonal therapy may increase the cure rates of conventional therapies. Another powerful argument for initiating hormone treatment early in biochemical recurrence is that “watchful waiting” is no longer an acceptable option for most men. Many contemporary men and their families are increasingly better informed than their counterparts a decade or so ago. Thus, many men faced with rising PSA levels consider metastatic disease to be an inevitable consequence of treatment delay and understandably are concerned.

Arguments for early hormonal therapy are countered, however, by a number of factors, including:

- The long natural history for most men of rising PSA levels before clinical metastases and death
- No randomized controlled clinical trials to confirm the survival advantage or to document the long-term effects of such therapy

The classic study by Pound and associates26 reported an average of 8 years between PSA relapse after a radical prostatectomy and clinical manifestation of metastatic disease. Once hormone therapy was initiated, the patients lived, on average, for another 5 years. In total, there was an average of 13 years separating biochemical recurrence when determining the appropriate therapy to be recommended and pursued.

**Early Versus Delayed Therapy**

In our recently published article in the *Journal of Urology*,9 we reported results of early versus delayed hormonal treatment for PSA-only recurring prostate cancer after a radical prostatectomy among 1352 patients in the CPDR database. Differences in outcome and time to the development of clinical metastasis were measured, stratified by risk status (high risk PSA recurrence versus lower risk PSA relapse) and time of hormone therapy initiation (ie, early [after PSA only relapse but before clinical metastasis] or late [therapy at time of clinical metastasis or none received by follow-up]). The median

---

*Figure 5. Early hormonal therapy (HT) administered at PSA 5 ng/mL or less affects clinical metastasis survival in patients with pathological Gleason sum greater than 7 or PSA-DT 12 months or less. Time zero is from PSAR (PSA after surgery >0.2 ng/mL). Reproduced with permission from Moul JW et al.9*
follow-up period was 5.5 years after PSA relapse. We found a benefit for early hormonal therapy when it was administered at PSA ≤ 5 ng/mL versus those who started therapy with a PSA > 5 ng/mL (Figure 5). However, this benefit was limited to patients who had high risk PSA relapse. The high risk PSA-only recurrence was defined as those patients who developed a rising PSA doubling time that was ≤ 1 year or had a Gleason score of 8, 9, or 10 in their radical prostatectomy specimen. Results indicated that the high risk individuals with biochemical recurrence who received early hormonal therapy experienced a delayed time to the development of bony metastasis. Thus, the natural history of bone metastasis in this group of men was changed. And similarly, high risk men who received early hormone therapy with PSA levels ≤ 10 ng/mL also experienced delayed clinical metastasis (Figure 6). However, when data for the entire cohort were analyzed, there was no such delay in the development of clinical metastasis with early hormonal therapy (Figure 7). The reason for this apparent discrepancy is that risk of progression was not taken into account in this analysis. The total sample included all men with a biochemical recurrence (PSA > 0.2 ng/mL), regardless of risk stratification. Nonetheless, this study was the first to demonstrate a clinical disease-free survival benefit for early hormonal therapy and PSA-only relapse. It also emphasizes the critical importance of risk stratification as we demonstrated a benefit for high risk individuals, patients with rapid PSA doubling time, and patients with high-grade disease. For such patients, it seems reasonable to use early hormonal therapy.

It must be cautioned, however, that these data are from a database, not a randomized clinical trial, and thus the outcomes may change with additional years of follow-up and as more patients are treated with hormone therapy for PSA relapsing disease. In addition, an overall survival benefit could not be determined given the relatively short follow-up...
period (5.5 years), although we were able to demonstrate delayed bone metastasis among high risk patients.

Doubling time. With regard to PSA recurrence, PSA doubling time is critically important.\textsuperscript{27,28} As previously indicated, a doubling time of less than 1 year clearly identified high risk individuals—individuals who had delayed bone metastasis when hormone therapy was started early. With D’Amico and colleagues\textsuperscript{28} we studied PSA doubling time < 3 months and found a direct correlation between this short doubling time and death from prostate cancer. Thus it seems clear that PSA doubling time is a very important prognostic factor in biochemical recurrence and that early hormone therapy should be considered in efforts to delay metastatic disease when the doubling time is less than 3 to 12 months.

Conclusion
Since the introduction and widespread use of PSA testing in the late 1980s, the face of advanced prostate cancer has been changing, and this change is profound. Years ago, advanced prostate cancer patients typically were men with bone metastasis. Nowadays, we are increasingly seeing younger patients, patients with biochemical recurrence, and patients with locally advanced prostate cancer. These men all have potentially advanced prostate cancer with its attendant poor prognosis.

Currently, high risk localized disease and PSA recurrence are the most common presentations of advanced prostate cancer. Although PSA relapse is becoming so much more common, there are still no randomized controlled clinical trials to help us make informed clinical decisions based on more contemporary data. Observational data, however, seem to indicate that high-risk individuals (ie, those with high-grade disease and with PSA doubling time less than 12 months) benefit from early hormone therapy. The long-term consequences of such therapy, however, are unknown and may be potentially deleterious.\textsuperscript{28,30}

The final question concerning the efficacy of early versus late hormone therapy for PSA relapse remains unanswered because of the need for longer follow-up in order to assess overall and improved survival for men with advanced prostate cancer. We await with great anticipation results from additional research and directed clinical trials.

References
3. Stephenson RA. Population-based prostate cancer trends in the PSA era: data from the

Main Points
- There is a profound change in the face of advanced prostate cancer. High-risk localized and prostate-specific antigen (PSA) recurrence are the most common forms of “advanced” prostate cancer. More men diagnosed with advanced prostate cancer enter treatment long before they develop distant metastases.
- Because many patients with T3 disease or local lymph node metastases progress to distant metastases, the concept of advanced prostate cancer should also include stages C and D1 (T3, T4, and any T N1).
- Many men treated for clinically localized disease will progress rapidly and, depending on their age, general health, and selected prognostic markers, should be included in the advanced-disease category.
- There are no randomized controlled clinical trials to guide clinicians in treatment decisions for men with PSA recurrent disease. Current observational studies, however, indicate the utility of taking a risk-stratified approach to PSA relapse patients and the form and content of their treatment.
- Men with high grade disease (Gleason score above 7) and those with short PSA doubling time (under 12 months) have delayed clinical metastasis if they receive early hormonal therapy. It is unknown if early hormonal therapy for PSA recurrent disease will improve prostate cancer-specific or overall survival.
Advanced Prostate Cancer: Evolving Definition