The Evolving Definition of Advanced Prostate Cancer

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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.
[Rev Urol. *2004;6(suppl 8):S10-S17*]

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.[1,3] 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.[1] Age of diagnosis continues to decrease with a concomitant increase in the number of men diagnosed with early-stage or clinically localized disease.[1,4] 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.[1,4-6] 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.[1,7-9]

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.[9-11] 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.[11,12] 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.[10-12] 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.[12,13]

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.[14] 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

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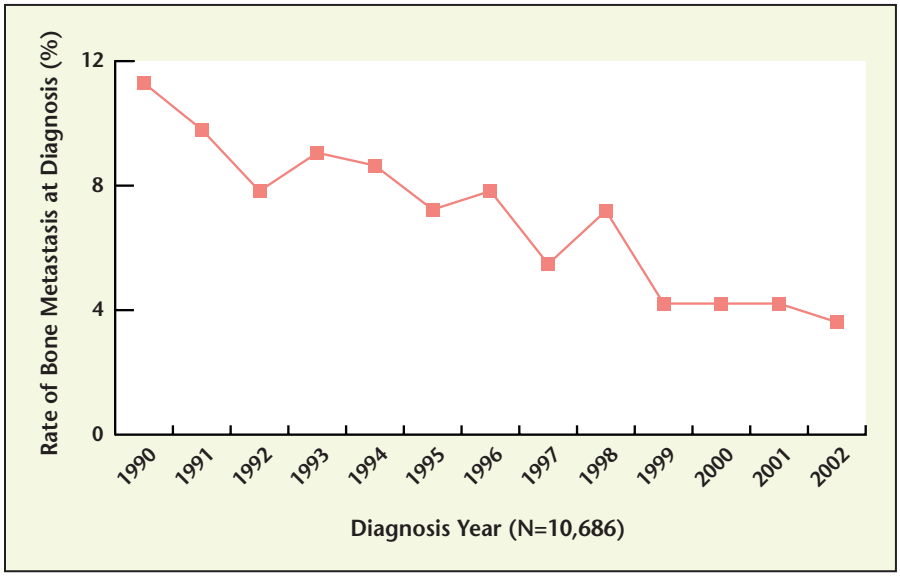

Figure 1. *Stage migration: Decreasing rate of patients presenting with clinical metastasis (stage D1/D2) at diagnosis. Data from Department of Defense Center for Prostate Disease Research.*

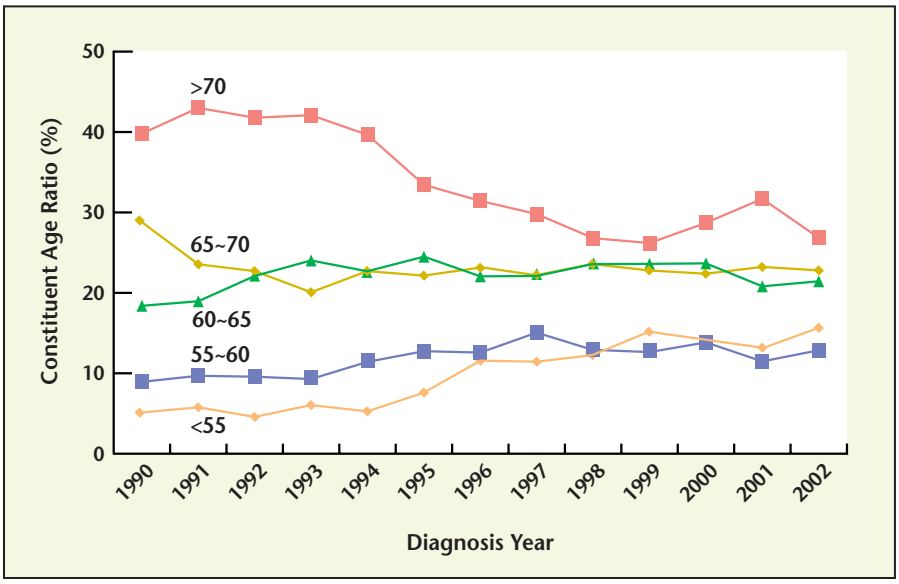

Figure 2 *Age migration: Decreasing age of patients diagnosed with prostate cancer. Data from Department of Defense Center for Prostate Disease Research.*

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.

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)

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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.[13,20] In a recently published article, D'Amico and colleagues[13] 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

Table 1
Risk Stratification in Clinically Localized Disease

Low Risk	PSA < 10 ng/mL and Gleason biopsy ≤ 6 and 1992 AJCC $T1_c$, 2_a
Intermediate Risk	PSA 10 – 20 ng/mL or Gleason biopsy 7 or 1992 AJCC $T2_b$
High Risk	PSA > 20 ng/mL or Gleason biopsy ≥ 8 or 1992 AJCC ≥ $T2_c$

PSA, prostate-specific antigen; AJCC, American Joint Committee on Cancer; T, tumor. Adapted from D'Amico AV et al.[13]

levels above 20 ng/mL or a Gleason score ≥ 8, or the 1992 American Joint Committee on Cancer tumor stage $T2_c$ 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 radiation therapy. 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.

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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

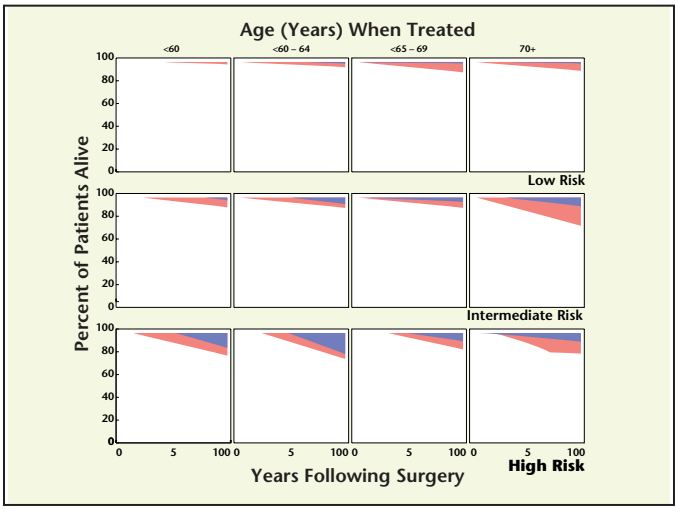

Figure 3. *Mortality (prostate cancer- and non-prostate cancer-specific) after radical prostatectomy stratified by age at time of initial therapy and pretreatment risk group. Blue, prostate cancer-specific mortality; red, non-prostate cancer-specific mortality. Reproduced with permission from D'Amico AV et al.[13]*

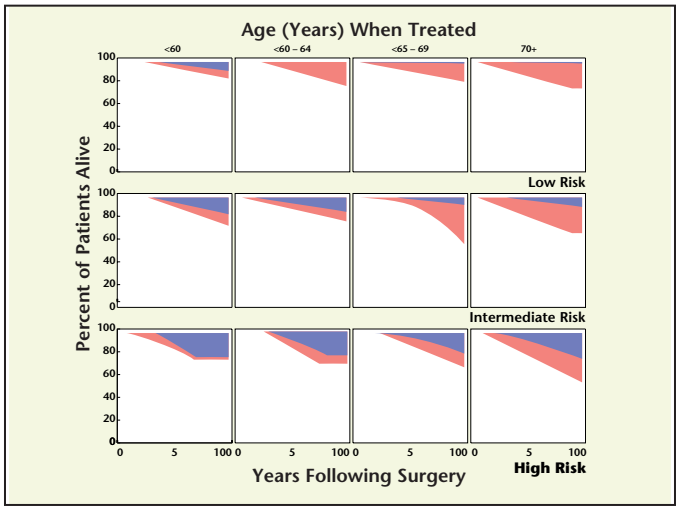

Figure 4. *Mortality (prostate cancer- and non-prostate cancer-specific) after radiation therapy stratified by age at time of initial therapy and the pretreatment risk group. Blue, prostate cancer-specific mortality; red, non-prostate cancer-specific mortality. Reproduced with permission from D'Amico AV et al.[13]*

prostate cancer in the current PSA era.[4,7,9] 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 side effects of hormone therapy, particularly for younger men
- Costs of hormone treatment, particularly if over a long period of time

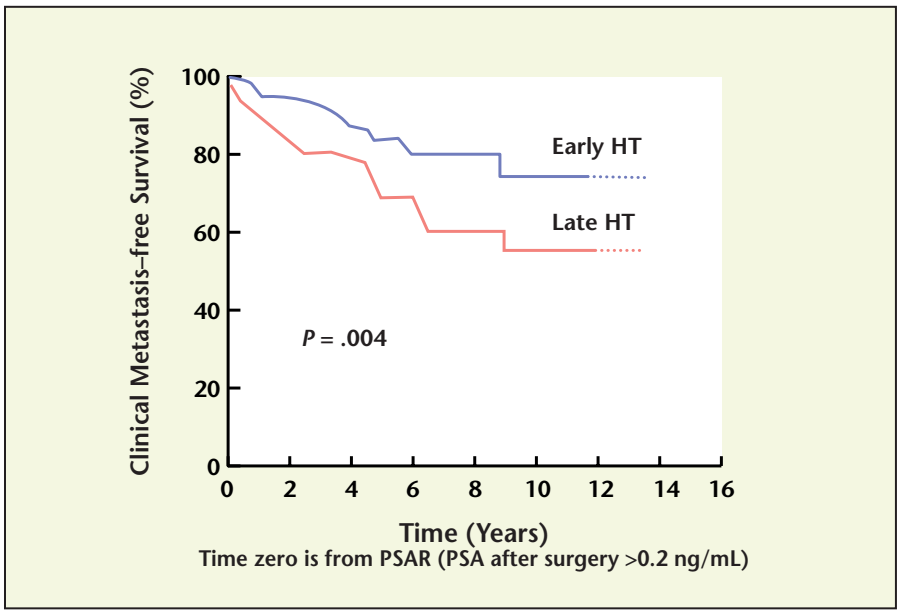

Figure 5. *Early hormonal therapy (HT) administered at PSA 5 ng/mL or less affects clinical metastasis survival in patients with pathological Gleason sum greater than 7 or PSA-DT 12 months or less. Time zero is from PSAR time. PSA, prostate-specific antigen; PSA-DT, PSA doubling time; PSAR, PSA relapse only. Reproduced with permission from Moul JW et al.*[9]

The classic study by Pound and associates[26] 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 and death for these surgically treated men: a relatively long period of time for the older patients, but not very reassuring or acceptable for the younger patients. Once again, the key is to take a risk-stratified approach to 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

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