Rising PSA in Nonmetastatic Prostate Cancer

Rising prostate-specific antigen (PSA) in nonmetastatic prostate cancer occurs in two main clinical settings: (1) rising PSA to signal failed initial local therapy and (2) rising PSA in the setting of early hormone-refractory prostate cancer prior to documented clinical metastases. Most urologists and radiation oncologists are very familiar with the initial very common clinical scenario, commonly called "biochemical recurrence." In fact, up to 70,000 men each year will have a PSA-only recurrence after failed definitive therapy. The ideal salvage therapy for these men is not clear and includes salvage local therapies and systemic approaches, of which the mainstay is hormonal therapy. Treatment needs to be individualized based upon the patient's risk of progression and the likelihood of success and the risks involved with the therapy. It is unknown how many men per year progress with rising PSA while on hormonal therapy without documented metastases. This rising PSA disease state is sometimes called, "PSA-only hormone-refractory prostate cancer." As in the setting of initial biochemical recurrence, evidence-based treatment options are limited, and taking a risk-stratified approach is justified. In this article, we will explore these prostate cancer disease states with an emphasis on practical, clinically applicable approaches.

In 2007, nearly 219,000 men are expected to be diagnosed with prostate cancer,[1] approximately 90% will undergo definitive local therapy,[2] and around 30% to 35% will develop biochemical (ie, prostate-specific antigen [PSA]) recurrence within 10 years.[3] Thus, approximately 60,000 to 70,000 men each year develop initial PSA recurrence. Similarly, almost 30,000 men die of prostate cancer annually. Presumably almost all these men progress through hormonal therapy and succumb to the disease in the hormone-refractory disease state.

The natural history of the hormone-refractory nonmetastatic disease state is such that it may take 2 to 3 years between initial elevation in PSA on hormones to documented clinical metastatic disease. As such, there may be 60,000 to 90,000 men alive at any one time in this country with secondarily rising PSA nonmetastatic prostate cancer. In summary, this collective disease state is common, affecting many current era patients and the subject of many clinical encounters by urologists, radiation oncologists, and medical oncologists.

Definition of Primary PSA Recurrence

The goal of radical prostatectomy (RP) is to remove the entire prostate. Therefore, slight rises in PSA are used to indicate cancer recurrence, although the exact level that defines PSA recurrence is debatable. In general, PSA levels > 0.4 ng/mL[4] or > 0.2 ng/mL[5] are used in most studies. Recently, the American Urological Association published guidelines that establish the consensus definition of PSA recurrence after RP to be greater than 0.2 ng/mL and rising, as confirmed on a repeat test.[6] This definition is to establish recurrence for outcomes reporting; however, it may not be the appropriate cutpoint to initiate therapy.

Indeed, it is our practice in a patient with a consistent and clearly rising PSA, often based on ultrasensitive values, to occasionally begin salvage radiotherapy when the PSA is between 0.1 and 0.2 ng/mL. Because microscopic or focal benign prostate tissue can sometimes be left behind after RP and may produce some small amounts of PSA, it is clinically important to recognize that a PSA of 0.2 ng/mL may not always represent cancer recurrence. Therefore, in the majority of patients, we do wait until the PSA is > 0.2 ng/mL before beginning salvage treatments. Unfortunately, defining recurrence following radiation therapy (RT) is more difficult. Unlike after RP, PSA does not fall to undetectable levels after RT. Rather, radiation induces a slow and not always steady PSA decline. The median time to PSA nadir is around 18 months and possibly longer following brachytherapy. Also, slight transient PSA upswings ("PSA bounce") are not uncommon. Finally, the concomitant use of hormonal therapy and the variable time period of return to normal testosterone can complicate the interpretation of PSA recurrence.
In 1997, the American Society for Therapeutic Radiology and Oncology (ASTRO) convened a consensus panel to develop a recurrence definition. The definition developed by the panel required three consecutive PSA increases after reaching a nadir, or a single rise so great as to trigger the initiation of hormone therapy. The date of PSA failure is backdated to the midpoint between the PSA nadir and the first of the three rises. This backdating of the failure time introduces a bias that overestimates the success at shorter follow-up times (ie, PSA may be rising, but not enough follow-up has occurred to document three consecutive rises). In long-term studies, this definition introduces a bias in that no patient can recur “late” because all late recurrences are backdated to an earlier time, resulting in a leveling of the survival curve. Because of these concerns, ASTRO convened a new consensus panel that developed new recurrence definitions: a PSA value higher than absolute nadir plus 2 ng/mL, or a PSA value higher than absolute nadir plus 3 ng/mL. This new definition is called the “Phoenix” definition in some circles because the consensus panel meeting was held in Phoenix, Ariz. Importantly, both definitions date the failure as the time the PSA rose above the threshold for recurrence (ie, failure is no longer backdated).

**Natural History of Initial PSA Recurrence**

The natural history of PSA recurrence is usually long but varied. Pound and associates described 304 men with PSA recurrence following RP from Johns Hopkins Hospital who did not receive hormonal therapy until the time of metastasis. Moreover, very few received salvage radiation therapy. The median time from PSA recurrence to metastasis was 8 years, and from metastasis to death was 5 years. In a recent follow-up study by Freedland et al that included a slightly larger cohort, the median time from PSA recurrence to prostate cancer death was not reached after 16 years. In the latter study, however, although rare, prostate cancer deaths were seen as early as 1 year after PSA recurrence. Thus, although the natural history of recurrent prostate cancer is often one of a slowly progressing disease, in some men it can be very rapid. Moreover, patients today are younger than in the past, with a median age at diagnosis of 65 years. In younger men with few competing mortality risks, even a slowly progressive cancer can ultimately lead to cancer death.

**Risk Factors for Clinical Progression and Prostate Cancer Death After Initial Rising PSA**

Fifteen years ago, Carter and colleagues showed that changes in PSA over time could predict the likelihood of being diagnosed with prostate cancer. Shortly thereafter, PSA kinetics were shown to predict the risk of distant vs local failure among men with PSA recurrence after RT and RP. These initial observations have been confirmed in later studies. Recently, a rapid PSA doubling time (PSADT) has also been linked with prostate cancer death. The best cutpoint to define “rapid” PSADT is unclear. Various cutpoints have been described: 3 months, 6 months, 8 months, 10 months, and 12 months. Given multiple cutpoints, it is likely that the association between PSADT and risk of poor outcome is on a continuum. Indeed, D’Amico and colleagues found that among men with a PSADT > 3 months after either RT or RP, PSADT as a continuous variable was significantly associated with prostate cancer death. More recently, this continuum between PSADT and risk was demonstrated by Freedland and coworkers who identified three PSADT cutpoints separating men into four risk groups. Another issue regarding the use of PSADT is how to calculate PSADT: How many PSA measurements are needed and over what time period? Unfortunately, no clear standard methodology exists. Prior studies found that in the early time period after PSA recurrence, PSA rises exponentially with first-order kinetics. Thus, PSADT—which is based upon the natural log of PSA—is constant over time. Therefore, it is reasonable to calculate PSADT using two values as long as the two values are sufficiently spaced in time to avoid subtle variations in laboratory measurements from being interpreted as a rapid PSADT.

It is our practice to use the first two PSA measurements after recurrence (ie, ≥ 0.2 ng/mL) separated by at least 3 months before calculating a PSADT, with the exception of the patient with an extremely fast rise in PSA, in whom a shorter interval may suffice to determine PSADT. Whether a similar approach can be used for estimating PSADT using supersensitive PSA assays for values < 0.2 ng/mL is unknown. Another unresolved issue is whether other variables, such as Gleason sum or time to PSA recurrence, add useful information to the PSADT. To a certain degree, the debate is academic in that all three
variables are highly correlated: The patient with a rapid PSADT likely has recurred early with a high Gleason. Thus, if this patient has a poor outcome, should we ascribe it to the rapid PSADT, the early recurrence, or the high Gleason? While it is generally accepted that PSADT is the best prognostic factor currently available, some (but not all) [15,22] studies have found that the Gleason sum [9,10,23] and time to PSA recurrence [9,10,19,20] add information to the PSADT. Although PSADT is a valuable prognostic factor, what about the absolute PSA level? In studies that attempt to estimate the risk of a future event (ie, metastasis or prostate cancer death), zero is often defined as the time of recurrence, and thus all men have similar small-sized tumors. However, if one does not define time zero as the time of recurrence, but rather as whatever the current time is, then not all men have equal-sized tumors (ie, some men are evaluated at the time of recurrence and others years later). In that case, the size of the tumor, as approximated by the absolute PSA level, becomes a significant predictor of time to metastatic disease [24] or the likelihood that a bone scan or computed tomography (CT) scan done today will demonstrate metastatic disease [16].

Treatment Options for Initial PSA Recurrence

Salvage Radiotherapy

Rates of response to salvage RT have been modest, with results varying among studies [25-31]. In one of the largest studies to date, Stephenson et al examined 501 men treated with salvage RT from multiple institutions and found that the progression-free probability at 4 years was 45%. [28] A single-surgeon series of 223 men treated with salvage RT showed a similar 40% PSA response rate at 5 years. [31] However, both studies demonstrated that with continued follow-up, these modest 40% to 45% response rates may not be durable, with 10-year PSA response rates of only 25% to 30%. [28,31] The series by Stephenson was recently updated to now include 1,540 patients, all treated with salvage RT. [32] Overall long-term progression-free survival remains suboptimal, with a 6-year PSA progression-free survival of 32%, which approached only a 20% response rate at 10 years.

The variable most consistently linked with PSA recurrence–free survival is the absolute PSA value at the time of salvage RT. In general, the lower the PSA, the better the outcome. Similar to PSADT and risk of progression, however, there may not be an "optimal" cutpoint but rather a continuum. This is best exemplified by a more recent article from Stephenson and colleagues, in which increasing PSA values, treated on a continuum, were associated with poorer outcomes. [32] Specifically, the risk of recurrence rose dramatically as PSA rose above 0.2 ng/mL, until PSA reached 1.5 ng/mL (after which further PSA rises added only a modest amount of further risk). Thus, the message from that study of over 1,500 men was clear: earlier treatment resulted in better outcomes.

Other variables that have been correlated with success in some but not all studies include radiation dose, [29,30] Gleason sum, [28] positive surgical margins, [27,28] extracapsular extension, [27] lack of seminal vesicle invasion, [26,28,31] and the pre-RT PSADT. [25,28] One characteristic not correlated with salvage RT response is prostatic fossa biopsy. [25,26] Several studies found that men with positive vs negative biopsies had similar response rates, suggesting that fossa biopsies should not be included in the standard work-up of men with PSA recurrence after RP. Interestingly, from the extended Stephenson cohort, the authors found that predictors of death from prostate cancer in men who did not receive any salvage treatment (ie, rapid PSADT, high-grade disease, and early recurrence), may not be the best predictors of response to salvage RT. Rather, if high-risk disease is caught early, reasonable outcomes may be obtained with salvage RT. As such, a patient with a rapid PSADT should not necessarily be assumed to have metastatic disease and may still be a candidate for local salvage therapy. Moreover, this raises the exciting possibility that some men who harbor potentially life-threatening disease can be rendered long-term PSA recurrence–free with salvage RT. If true, it stands to reason that salvage RT could reduce prostate cancer deaths in this disease-state, although this remains speculative.

Importantly, many of these studies included small numbers, limiting the ability to detect important observations regarding predictors of success. It is likely that this limitation rather than true biologic differences between populations accounts for differences in results among studies. Although many patients—even those with adverse indicators—often achieve an initial PSA response, the impact of salvage RT on survival remains unknown.

Salvage Radical Prostatectomy for Recurrence After Radiation

Historically, salvage RP for men with recurrence after RT was rarely performed due to concerns.
about lack of efficacy and high morbidity. However, contemporary salvage RP series, in which men are selected based on a rising PSA rather than symptomatic recurrence, have more acceptable morbidity rates and improvements in both local and distant cancer control.[33,34] Two of the largest series to date demonstrate 10-year prostate cancer–specific survival rates of 65% to 73%.[33,34] Among highly selected patients, the complication rates approach those seen with primary RP, and quality-of-life outcomes are only modestly worse than those of primary RP patients.[35] Unfortunately, the time from PSA failure until salvage RP in these studies was long, with men in one study having a median of seven rising PSA values prior to surgery.[34] If men were offered salvage treatments at the time of PSA failure (ie, after the third rising PSA or after their PSA had reached nadir plus 2 ng/mL), outcomes might have been even better. However, given that even in contemporary series, up to 20% of patients require a cystoprostatectomy for adequate tumor excision[33] is enough to discourage most urologists. Furthermore, the risk of permanent stress or total urinary incontinence associated with salvage RP has limited its popularity. Up to 50% to 75% of men may have long-lasting or permanent incontinence. While an artificial urinary sphincter can alleviate this problem, many men are frightened by the prospect of more surgery and shy away from salvage RP.

Salvage Cryotherapy for Recurrence After Radiation

Another alternative for men with biochemical recurrence after RT is salvage cryotherapy. With the advent of third-generation cryotherapy machines using argon gas, smaller cryoprobes, and a "brachytherapy-like" approach, interest in salvage cryotherapy is rising. In terms of complications, Han and associates[36] recently reported initial results of a multicenter trial of third-generation cryotherapy. No major complications were noted, as opposed to previous cryotherapy generations, when rectal fistulas were a major problem. Similar to other reports of contemporary salvage cryotherapy,[37] impotence was nearly universal, although other side effects such as incontinence were low (< 10%).

In terms of efficacy, one difficulty arises in that unlike after primary treatment, there is no consensus on how to define failure following salvage therapy. Thus, some studies have used nadir PSA plus 2 ng/ mL and other studies have used a single cutpoint (ie, > 0.4 or > 0.5 ng/ mL).[38] Given these differing failure definitions, it is difficult to assess the efficacy of salvage cryotherapy when recurrence rates vary from 25% up to 60%. However, one of the largest studies to date—involving 131 men with a follow-up of 4.8 years—found a 5-year recurrence risk of 60%, defined as nadir PSA plus 2 ng/mL.

A prospective case series by Ismail et al[39] reported 5-year risks of recurrence (PSA > 0.5 ng/mL) to be 73%, 45%, and 11% for low-, intermediate-, and high-risk groups, based on pre-RT PSA, clinical stage, and Gleason sum. Specifically, the factors that predict a favorable response include precryotherapy PSA < 10 ng/mL, PSADT < 16 months, preradiation clinical stage T1/T2, biopsy Gleason ≤ 7, and having not received hormonal therapy during the initial radiation treatment. As opposed to salvage RP, salvage cryotherapy in the current era is associated with less risk of incontinence. For this reason, it is an appealing option for some men who may be reluctant to accept the higher incontinence morbidity of salvage RP.

Hormonal Therapy

The dramatic effect of hormonal deprivation therapy for prostate cancer was first described in 1941 by Huggins and Hodges,[40] a discovery for which Dr. Huggins shared the Nobel Prize in 1966. Today, hormonal therapy remains the standard treatment for advanced disease. However, unlike salvage local therapies aimed at cure, hormonal therapy is not curative: With long-term follow-up, hormone-refractory disease will develop in nearly all men, along with a second rising PSA, as discussed below.

The term "hormonal therapy" is used to refer to treatments aimed at either eliminating testosterone production (surgical or pharmacologic castration), preventing the binding of testosterone to cellular receptors (steroidal or nonsteroidal antiandrogens), or a combination of both (combined androgen blockade, or CAB).

While hormonal therapy results in dramatic tumor shrinkage and offers tremendous relief of symptoms for metastatic disease, its role for nonmetastatic PSA-only recurrence is controversial due to the fact that hormonal therapy is not benign. The negative impact on quality of life can be significant—hot flashes, bone loss, increased fracture risk, sexual dysfunction, loss of libido, memory loss, increased fat deposition, loss of muscle mass, and other metabolic changes (increases in cholesterol, insulin resistance) that may increase the risk of heart disease.[41] In addition, other
negatives include cost and possible drug reactions. Despite these negative effects, in well-selected patients, the possible benefits of delayed metastasis, reduced skeletal morbidity from metastasis, and prolonged survival may outweigh the risks and justify its use. Unfortunately, there are no prospective randomized trials of hormonal therapy for men with PSA-only recurrence. Therefore, we must extrapolate data from trials of either men with metastatic disease or those with locally advanced nonmetastatic disease, or rely on data from retrospective cohort studies. Whether such data apply to men with PSA-only recurrence is unknown.

**CAB vs Castration Alone**

One issue in this setting is whether CAB offers benefits over castration alone. CAB is more costly, with a slightly increased side-effect profile, including liver toxicity (more common with flutamide) and breast enlargement/tenderness (more common with bicalutamide [Casodex]).[42] Regarding efficacy, many studies have addressed this specific point with mixed results, providing ample studies to support either opinion. However, recent meta-analyses of CAB using nonsteroidal antiandrogens for men with metastatic disease suggest a relative reduction in prostate cancer death by 7% to 20%.[43,44] New guidelines from the American Society of Clinical Oncology (ASCO) generally support CAB over castration/luteinizing hormone-releasing hormone (LHRH) agonist alone, but this recommendation was intended for patients with metastatic disease, and the implications for PSA recurrence were not addressed.[45]

These modest results, combined with cost and quality-of-life side effects, have tempered enthusiasm for CAB among some physicians. However, these studies were largely performed before our understanding of the importance of PSADT in risk stratification. Thus, it is highly possible that through risk stratification, we can identify men who stand to benefit the most from CAB as well as those who stand to benefit little and may actually be harmed by CAB (or any hormonal therapy).

**Early vs Delayed Hormonal Therapy**

The timing of hormonal therapy was first studied in the 1960s. Although there is no clear consensus as to when to begin hormonal therapy, the scales are tipping toward early hormonal therapy—at least for some men.

In the 1960s and 1970s, the Veterans Administration Cooperative Urological Research Group compared early vs deferred hormonal therapy (either orchiectomy or estrogen) and found no differences in overall survival.[46] However, the patients in this study had far more advanced disease than typical patients today with PSA-only recurrence. Moreover, the use of estrogen and its cardiovascular morbidity may have biased the results against early hormonal therapy. The UK Medical Research Council compared immediate castration with deferred treatment among patients with locally advanced or asymptomatic metastatic disease.[47] Initial results demonstrated that early therapy delayed disease progression, delayed the onset of new metastatic pain, and significantly reduced prostate cancer and overall death. However, while longer follow-up confirmed the advantage of immediate hormonal therapy on improved disease-specific survival, there was no longer any difference in overall survival, reflecting increased mortality from other causes.[48] This study was criticized because some men in the delayed-treatment arm never received hormonal therapy, potentially biasing the results in favor of early therapy. However, the difference in findings between the initial and long-term results are intriguing: With limited follow-up, such that only those most likely to die from prostate cancer are at risk, early hormonal therapy was better. With longer follow-up, such that all men are at risk, no overall benefit was seen. This suggests that early hormonal therapy may be beneficial for some men (ie, those at highest risk) and have no benefit or possibly harm others (ie, those at lowest risk).

In a randomized study of immediate vs delayed hormonal therapy (ie, at the time of metastasis) among 98 men with microscopic nodal involvement at the time of RP, the Eastern Cooperative Oncology Group reported a significantly reduced all-cause and prostate-cancer-specific mortality favoring early treatment.[49] Men receiving delayed hormonal therapy had an 84% increased risk of all-cause death and a 309% increased risk of prostate cancer death at 11.9 years of follow-up. To date, only two retrospective studies examined the timing of hormonal therapy for men with PSA recurrence.[50,51] Among 1,352 men with PSA recurrence after RP, Moul et al[50] found that early hormonal therapy generally had no effect on time to metastasis. However, among high-risk men (pathologic Gleason ≥ 8 or PSADT < 12 months), early hormonal therapy (ie, starting when the PSA was < 5 or < 10 ng/mL) was associated with a 50% reduction in the risk of metastasis after a median follow-up of 3.7 years after recurrence. Follow-up was too short to analyze prostate cancer death. In the second study, among 247 men who failed RT and received salvage hormonal therapy, Shipley
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Published on Cancer Network (http://www.cancernetwork.com)

and colleagues[51] found that men who were given hormonal therapy prior to metastasis had a 3-year-longer overall survival from the time of RT than men who were started on hormonal therapy after metastasis developed. Those who received hormonal therapy prior to metastasis could be further stratified: Men who received hormonal therapy with a PSA < 20 ng/mL had a 1-year-longer overall survival from the time of initial RT than men with a PSA > 20 ng/mL when hormonal therapy was begun. While both studies suffer from the limitations of retrospective series, and thus, the delayed and early hormonal therapy arms may not have been balanced, both studies did suggest that early therapy is better—at least in high-risk men.

Nontraditional Hormonal Therapies

The significant quality-of-life consequences of hormonal therapy have generated interest in "nontraditional" hormonal therapies, of which the three most commonly used in the United States are high-dose antiandrogens alone, low-dose antiandrogen alone or an antiandrogen plus a 5-alpha-reductase inhibitor (so called peripheral androgen blockade, or PAD), and intermittent hormonal therapy. While interest in "triple therapy" (castration, antiandrogen, and 5-alpha reductase inhibition) is growing, the data are insufficient to comment on this approach. Analogous to the discussions above, there are no randomized prospective trial data for men with PSA-only recurrence. Therefore, we must again extrapolate from either the adjuvant setting or from men with metastatic disease. Whether these data apply to men with PSA-only recurrence is hotly debated.

High-Dose Antiandrogen Alone

Relative to castration, one study of high-dose antiandrogen alone (ie, bicalutamide at 150 mg/d) found that this strategy provided similar survival outcomes for locally advanced nonmetastatic disease, with similar or slightly better quality-of-life outcomes.[52] Three ongoing multinational prospective randomized trials of adjuvant high-dose bicalutamide vs placebo, known as the Early Prostate Cancer Program, were designed to allow pooling of data. Men with prostate cancer undergoing RP, RT, or watchful waiting (n = 8,113) were randomized to adjuvant high-dose bicalutamide or placebo for 3 years (North American study) or 5 years (Australia, Europe, Israel, South Africa, and Mexico; and Scandinavia studies). The primary end points are progression-free survival and overall survival. Tolerability is a secondary end point. Interim results with a median follow-up of 7.4 years demonstrate a 21% reduction in disease progression favoring bicalutamide, but no difference in overall survival.[53] However, the data are most interesting when broken down by disease stage and treatment. For men undergoing watchful waiting with localized disease (T1–2, N0/Nx), bicalutamide therapy had no effect on progression and was associated with a near significant worsening of overall survival by 20%. On the contrary, among men with locally advanced disease (T3-4, any N; or any T, N+) undergoing watchful waiting, bicalutamide was associated with a significant 40% reduction in progression and a near-significant 19% improvement in overall survival. Among men undergoing RP or RT for localized disease, bicalutamide had no significant effect—positive or negative—on progression or overall survival. However, for men with advanced disease, bicalutamide significantly decreased progression by 44% and 25% for RT and RP patients, respectively. Bicalutamide was also associated with a 35% significantly prolonged overall survival for RT patients, but no difference in survival among RP patients.

Importantly, high-dose bicalutamide results in breast enlargement and tenderness in up to 70% of patients.[53] A randomized trial found that prophylactic breast irradiation or tamoxifen (10 mg daily) prevents breast pain, with tamoxifen being more efficacious than breast irradiation.[54]

Peripheral Androgen Deprivation

PAD has recently come to define nontraditional "oral-only" hormonal approaches generally used to treat biochemical recurrence. As noted above, antiandrogens have been investigated as single-agent therapies for advanced prostate cancer. Studies have examined the efficacy of reduced drug dosages to limit possible drug-induced side effects while preventing disease progression.[55] In an effort to increase the efficacy of antiandrogens, investigators have also proposed the addition of a 5-alpha-reductase inhibitor that prevents the intracellular conversion of testosterone to dihydrotestosterone (DHT), thereby reducing the levels of DHT, which competes with antiandrogens for the androgen receptor. Indeed, finasteride, a 5-alpha-reductase inhibitor used in combination with the antiandrogen flutamide, has been previously shown to be effective in select prostate cancer
patients with advanced prostate cancer.[56,57] Preliminary reports (including one from our group) showed encouraging results of antiandrogen monotherapies[55] or combination regimens using antiandrogens and 5-alpha-reductase inhibitors.[58] Long-term follow-up of patients on combination low-dose flutamide plus finasteride showed a modest advantage over low-dose flutamide monotherapy in terms of treatment response and achieved PSA nadir.[59] In general, up to about one-third of patients have a durable PSA decline and stabilization for up to 5 years, with limited toxicities.

The advantage to the PAD approach is that side effects are lessened compared to traditional LHRH-based therapy. Specifically, since peripheral serum testosterone is not decreased in the circulation, there is no risk of osteoporosis. Furthermore, these oral therapy–only approaches may maintain libido and potency, a big selling point for younger men with preserved sexual function. As noted above with high-dose bicalutamide, the risk of gynecomastia and nipple tenderness is real and we generally recommend prophylactic breast irradiation before starting the medications. The main disadvantage is not knowing which agents and dose are most beneficial and not knowing if any ultimate survival advantage is associated with this approach. However, we believe that a "step-up" approach to traditional hormonal therapy is possible and effective if the PSA rises on PAD.

Furthermore, since the evidence basis even for traditional hormonal therapy is suspect, the use of PAD is just as reasonable in selected men with initial PSA recurrence as other recommendations.

**Intermittent Hormonal Therapy**

Three phase III trials are examining whether intermittent hormonal therapy results in survival rates similar to or better than continuous hormonal therapy while preserving better quality of life.[60] To date, however, no data show that intermittent therapy is better or worse than continuous therapy in terms of its effect on survival. As reviewed by Bhandari and colleagues,[60] a wealth of data demonstrate that quality of life can be improved by intermittent therapy. While this premise is true, it should be noted that following several months of hormonal therapy, it can often take several more months for testosterone levels to return to normal. Therefore, “time off therapy” is not equivalent to time with a normal testosterone level. That said, for some men in whom the side effects of hormonal therapy are particularly problematic, intermittent therapy may offer an advantage. Until more mature data are available, it is difficult to argue for or against intermittent therapy as a viable therapeutic option.

**Non-Hormonal-Based Therapies**

A number of substances have been and continue to be investigated as possible alternative nonhormonal treatment strategies for rising PSA following definitive management of prostate cancer. COX-2 inhibitors such as celecoxib (Celebrex), originally used as anti-inflammatory agents and later shown to exert antitumor activity, have been reported by Pruthi and colleagues[61] to slow the rate of rising PSA following RP or RT. Indeed, in another placebo-controlled trial of men with biochemical recurrence, mean PSA velocity was significantly decreased in men taking celecoxib compared to placebo.[62] Unfortunately, due to increased risk of cardiovascular morbidity, the US Food and Drug Administration halted clinical trials involving this class of drugs.

Pomegranate (Punica granatum) juice has also gained popularity, not only as a possible chemopreventive agent to decrease the risk for prostate cancer, but as a possible form of nonhormonal therapy for PSA recurrence following RP or RT. Indeed, phase II trials not only demonstrated excellent tolerability but also showed that mean PSADT was significantly prolonged after treatment with pomegranate juice.[63] Randomized placebo-controlled trials are forthcoming.

**Secondary Rising PSA in Nonmetastatic Prostate Cancer**

Rising PSA in nonmetastatic prostate cancer can also imply the later disease state of rising PSA while on hormonal therapy. This has come to be known as "PSA-only" or "nonmetastatic" hormone-refractory prostate cancer (HRPC). While less is known about this entity than the setting of initial rising PSA, it is, nevertheless, a perplexing prostate cancer disease state. This entity has arisen out of changing demographics of prostate cancer and changing treatment patterns. Specifically, most hormonal therapy given in the past decade was started for high-risk biochemical recurrence before the development of clinical metastases.

Twenty years ago, in the pre-PSA era, most hormonal therapy was started for traditional metastatic (M1-D2) prostate cancer; disease progression was assessed by traditional imaging (bone scans and CT scans), and hormone-refractory disease was determined by these clinical modalities. Now,
progression is detected by PSA levels and we, as clinicians, are faced with this new condition manifested by rising PSA on hormonal therapy, after antiandrogen withdrawal, and with negative imaging.

**Natural History of Secondary PSA Recurrence After Androgen Ablation**

The natural history of rising PSA in the setting of nonmetastatic HRPC is best reported by Smith et al.[64] These investigators considered the placebo arm of an aborted randomized controlled trial evaluating the effect of zoledronic acid (Reclast, Zometa) on time to bone metastasis in men with nonmetastatic prostate cancer and a rising PSA despite androgen deprivation therapy. Though premature closure of the study curtailed conclusive evidence about the efficacy of zoledronic acid in preventing bone metastasis, valuable insight was gained on the natural progression of castrate nonmetastatic HRPC.

In a cohort of 201 patients, 33% developed bone metastasis in 2 years, and the median bone metastasis–free survival was 30 months.[64] Baseline PSA, PSA velocity, and PSADT were all found to be independent predictors of shorter time to bone metastasis, metastasis-free survival, and overall survival. These results suggest that the rate of progression of PSA-only prostate cancer remains relatively low even after hormonal therapy. Moreover, the indolent course of secondary PSA-only progression dictates that future clinical trials in this specific setting will require large study populations to ensure adequate statistical power. Most importantly, it demonstrates that the factor most predictive of outcome in the PSA-only non-HRPC setting (ie, PSADT) is also one of the strongest predictors of outcome in the HRPC state.

**Treatment Options for Secondary PSA Recurrence**

No standard treatment is currently prescribed for men on failed initial androgen-deprivation therapy denoted by a rising serum PSA. Secondary hormonal manipulation, chemotherapy, and investigational drug preparations are the treatment strategies under investigation.**REFERENCE GUIDE**
For men on CAB, withdrawal of antiandrogens should elicit a biochemical response in 15% to 20% of men with HRPC.[65] Durability of response, which can last up to 2 years, is dependent on the type of antiandrogen being halted, but the average response duration is approximately 5 months. Secondary hormonal therapy with second-line oral antiandrogens (bicalutamide,[66] nilutamide [Nilandron][67]), estrogen-based therapies (diethylstilbesterol[68]), andrenolytics (ketoconazole[69]), and novel secondary hormonal therapies (gonadotropin-releasing hormone [GnRH] inhibitors[70]) have been studied. However, treatment response rates are highly variable and study cohorts usually include patients with metastatic HRPC.

Evidence of a survival benefit for metastatic HRPC patients receiving docetaxel has led to interest in investigating the early initiation of chemotherapy for nonmetastatic HRPC. Eastern Cooperative Oncology Group (ECOG) 1899 was designed specifically to compare secondary hormonal therapy with ketoconazole to chemotherapy with docetaxel.[71] Unfortunately, due to poor patient accrual, the study closed in 2005.

Other trials in this disease setting have likewise proved difficult. For example, a study of zoledronic acid vs placebo to delay bone metastasis was closed early due to a low event rate.[64] The problem of high discontinuation rates have also hampered the formation of robust conclusions in studies involving novel therapeutics for nonmetastatic HRPC, such as the phase III randomized placebo-controlled trial of atrasentan (Xinlay),[72] a selective endothelin-A receptor antagonist. Indeed, premature closure of well-designed clinical trials have been the major stumbling block in acquiring clinically useful information needed to form consensus guidelines for the treatment of PSA-only recurrent HRPC.

Putting It All Together

PSA-only relapse is the most common form of advanced prostate cancer seen today. The natural history is long but highly variable. Men with a rapid PSADT are at the greatest risk of progression. These men needed aggressive salvage therapy. While salvage therapies aimed at cure (RT, RP, and cryotherapy, depending on which primary therapy the patient had) are modestly effective, especially when administered early to men at low risk, they are less effective for men who need it the most. However, some men at high risk do achieve long-term PSA control. Moreover, the benefit of local control on quality of life is likely important. Longer-term studies are needed to assess the impact of these therapies on survival.
Once local salvage therapies fail, hormonal therapy is the most commonly used option. Increasing data suggests that early aggressive hormonal therapy for men with high-risk disease may delay metastasis and possibly improve survival, although this remains a contentious area. In addition, CAB appears to add some benefit relative to castration alone, at least for men with metastatic disease. Thus, it is imperative to identify early the patient with a high-risk recurrence for aggressive therapy. It is equal essential (if not more so) to identify the patient with a low-risk recurrence (ie, slow PSADT) because these patients have a prolonged, often indolent clinical course and are unlikely to derive any survival benefit from early hormonal therapy, in light of competing causes of mortality. For these men, early hormonal therapy offers only detriments to quality of life and may actually worsen survival. In our opinion, these men are best managed expectantly.

For men who experience secondary PSA-only recurrence after failed hormonal therapy and suffer nonmetastatic HRPC, what little data we have on the natural history of this disease-state shows that time to progression may be indolent as well. Clinical trials are sorely needed to provide evidence-based recommendations for management. In the meantime, risk stratification with reliable predictors such as PSADT may be used to determine who would benefit from chemotherapy and who may be appropriately managed by active surveillance.

The complexities of cancer care encompass numerous issues that are controversial, unresolved, or problematic—areas of confusion. From time to time, ONCOLOGY will highlight such issues, with expert considerations of the relevant literature and peer-review commentaries that offer different perspectives on the topic. Send your ideas for "areas of confusion" that we might explore in future issues (write to anash@cmp.com).

Financial Disclosure: Dr. Moul is a speaker for AstraZeneca and sanofi-aventis. Dr. Baez is a principal investigator in a sponsored grant for AstraZeneca. Dr. Freedland is a member of the advisory board and speakers bureau for AstraZeneca.

Supported by the Department of Surgery, Duke University School of Medicine, Department of Veterans Affairs, the Department of Defense, and the American Urological Association Foundation/Astellas Rising Star in Urology Award.

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