Today, because of prostate-specific antigen (PSA) screening, prostate cancer in most patients is detected earlier and at younger ages than in the past. Despite this early detection and after definitive therapy, whether by radical prostatectomy (RP) or radiation therapy (RT), a biochemical recurrence will develop within 10 years of treatment in about 35% of men. With about 230,000 cases of prostate cancer diagnosed each year in the United States, it is estimated that a PSA-only recurrence develops in more than 50,000 men per year.

Although the natural history of PSA recurrence can be long, recent studies have helped us stratify men for varying risk of clinical progression and prostate cancer death with ever-increasing accuracy. In this review, we discuss PSA recurrence after primary therapy. We focus on the definition of recurrence, the natural history and risk factors for progression, the role of salvage therapies aimed at cure or palliation, and the timing of these therapies. We also offer advice on how to incorporate this information into clinical practice.

**PSA RECURRENCE DEFINED**

During RP, essentially all PSA-producing cells should have been removed. Therefore, slight elevations in PSA levels are used to indicate cancer recurrence. The exact level that defines PSA recurrence is debated, however. In general, a PSA level higher than 0.4 or 0.2 ng/mL has been used in most studies. PSA levels do not fall to undetectable levels after RT as they do after RP. Rather, radiation induces a slow and not always steady decline in PSA level. The median time to PSA nadir is about 18 months—and possibly longer following brachytherapy. In addition, slight transient upswings in PSA levels (PSA bounce) are not uncommon. Therefore, defining recurrence in this setting is more challenging.

In 1997, the American Society for Therapeutic Radiology and Oncology (ASTRO) convened a consensus panel whose members defined recurrence after RT as 3 consecutive elevated PSA values after reaching a nadir, or a single elevated value significant enough to trigger the initiation of hormone therapy. The failure date is backdated to the midpoint between PSA nadir and the first of the 3 elevated PSA values. This backdating introduces a bias that overestimates the success at shorter follow-up times (not enough follow-up has occurred to document failure). Moreover, in long-term follow-up studies, the failures are backdated to an earlier point in time, resulting in a leveling of the Kaplan-Meier curve, in contrast to outcomes after RP in which PSA-free survival continues to decline over time.

Because of the concerns mentioned above, ASTRO recently convened a new consensus panel that redefined recurrence: a PSA value higher than absolute nadir plus 2 ng/mL or a PSA value higher than absolute nadir plus 3 ng/mL. Both define the failure date as that when recurrence was met (ie, failure time is no longer backdated).

**NATURAL HISTORY OF PSA RECURRENCE**
The natural history of PSA recurrence can be quite long but varies. In a classic study at Johns Hopkins University, Pound and associates described 315 men with PSA failure following RP who did not receive hormonal therapy until the time of metastasis. The median time from PSA recurrence to metastasis was 8 years, and the median time from metastasis to death was 5 years.

In a recent follow-up study from Johns Hopkins that included a slightly larger cohort, the median time from PSA recurrence to prostate cancer death was not reached after 16 years of follow-up. However, prostate cancer deaths were seen as early as 1 year after PSA recurrence, although with very rare frequency. Thus, the natural history of recurrent prostate cancer is one of a slowly progressing disease, but in some men the progression can be quite rapid.

**RISK FACTORS FOR CLINICAL PROGRESSION AND PROSTATE CANCER DEATH**

Given this long but variable natural history, many investigators sought to identify risk factors to predict the likelihood of clinical progression and prostate cancer death. The variable that has most consistently been linked with adverse outcome is how fast the serum PSA level is rising, which is most commonly measured as PSA doubling time (PSADT).

Nearly 15 years ago, Carter and colleagues first demonstrated that changes in PSA levels over time could predict the likelihood of prostate cancer. Shortly thereafter, PSA kinetics were shown to predict the risk of distant versus local failure among men with PSA failure after RT and after RP. These initial observations were confirmed in later studies. A rapid PSADT has been linked not only to risk of metastasis but also to prostate cancer death. The association between PSADT and prostate cancer death is so strong that D'Amico and coworkers, in a study of men who received both RT and RP, suggested that a PSADT of less than 3 months could be used as a surrogate end point for prostate cancer death.

One issue has arisen when examining PSADT: What is the optimal cut point to separate high-risk from low-risk recurrence? Various cut points have been described at 3, 6, 12 months. Given these multiple cut points, it is likely that the association between PSADT and risk of recurrence is on a continuum. D'Amico and colleagues, in their analysis of RP and RT patients, found that among men with a PSADT of more than 3 months, PSADT as a continuous variable was significantly associated with risk of prostate cancer death. Most recently, this continuum between PSADT and risk was shown by Freedland and coworkers; multiple cut points were identified that stratified men into 4 risk groups (Table 1, Figure).
PSA Recurrence of Prostate Cancer:
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Other variables have been examined for their association with metastasis and prostate cancer death, although whether they add information to PSADT is debatable. For example, some but not all studies found that pathologic Gleason sum predicted time to metastasis or prostate cancer death. Similarly, controversy exists regarding the prognostic value of time to PSA recurrence: most but not all studies found it was an important predictor of outcome. Although the absolute PSA value is generally not predictive of time to metastasis or time to prostate cancer death after adjusting for PSADT, it is predictive of the likelihood of a bone scan being positive.

**SALVAGE RADIOTHERAPY**

The response rates to salvage RT have been modest, with results varying greatly across studies. In one of the largest studies to date, which pooled data from multiple institutions, the PSA-free progression rate at 4 years after salvage RT was 45%. Given this modest success, investigators have sought to identify risk factors for a favorable outcome after salvage RT. The variable that has consistently been linked with the success of salvage RT is the PSA value at the time of RT. In general, the lower the PSA value, the better the outcomes, although the best cutoff to define "lower" PSA values has varied among studies (ranging from less than 0.6 ng/mL to less than 2.1 ng/mL).

Other variables that have been correlated with successful salvage RT include the radiation dose...
given, the Gleason score, positive surgical margins, extracapsular extension, lack of seminal vesicle invasion, and the pre-RT PSADT. However, many of these studies included only a small number of men, limiting the ability to detect important observations about predictors of salvage RT success. It is likely that this limitation, rather than true biologic differences between study populations, accounts for differences in results among the various series.

Despite these recent publications, the ultimate impact of salvage RT on survival is still unknown. Most patients, including those with multiple adverse indicators, appear to achieve at least an initial response. Although the durability of this response is short-lived for most patients, it is still possible that the RT has shifted the biologic behavior of the cancer. Whether this is for better or worse requires more investigation.

SALVAGE RADICAL PROSTATECTOMY

Historically, salvage RP was not performed because of concerns about effectiveness and anxiety about operating on radiated tissue, which would make surgery more difficult and could result in unacceptable morbidity. However, contemporary studies of men who have undergone salvage RP, who were selected based on a rising serum PSA level rather than on a symptomatic recurrence, have more acceptable rates of morbidity and significant improvements in both local and distant cancer control rates. In 2 of the largest studies to date, the 10-year prostate cancer-specific survival rate after salvage RP was 65% to 73%.

Among carefully selected patients, the complication rates can approach those seen with primary RP, and quality-of-life outcomes are only modestly worse than those of primary RP patients. Even in contemporary studies, up to 20% of patients require a cystoprostatectomy for adequate tumor excision, which is enough to discourage most urologists from attempting salvage RP.

Salvage RP may offer some patients both local and distant disease control with a reasonable side effect profile, but it is still not commonly used in clinical practice.

SALVAGE CRYOTHERAPY

Another alternative for men with a recurrence after RT is salvage cryotherapy. With the advent of third-generation cryotherapy equipment using argon gas, smaller cryoprobes, and a "brachytherapy-like" approach, interest in salvage cryotherapy is on the rise.

Han and associates reported initial results of a multicenter trial of the use of third-generation cryotherapy. No major complications were noted with this therapy, as opposed to previous cryotherapy when rectal fistulas were a major problem. Similar to other reports of contemporary sal-vage cryotherapy, impotence was nearly universal and the incidence of other side effects, such as incontinence, was low (less than 10%). Follow-up was very limited; 77% of salvage patients had a PSA value lower than 0.4 ng/mL at 12 months. Long-term follow-up is needed to assess the impact of salvage cryotherapy on cancer control.

HORMONAL THERAPY

Hormonal deprivation therapy has been the most avidly used treatment for advanced prostate cancer since its description by Huggins and Hodges in 1941--a discovery for which Dr Huggins shared the Nobel Prize in medicine in 1966. However, unlike the salvage therapies mentioned above, hormonal therapy is not curative; with long-term follow-up, hormone resistance will develop in nearly all men.

The term "hormonal therapy" refers 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, known as complete androgen blockade (CAB). In addition, there has been a growing interest in intermittent hormonal therapy.

While hormonal therapy can result in dramatic tumor shrinkage and offers tremendous relief of
symptoms for men who have metastatic disease, its role in earlier-stage disease (ie, nonmetastatic PSA recurrence) is controversial. Few other topics in prostate cancer management generate as much heated debate.

The reason for the debate stems from the fact that hormonal therapy is not benign. The negative impact on quality of life can be significant: hot flashes, bone loss, increased risk of fractures, sexual dysfunction, loss of libido, memory loss, increased fat deposition, loss of muscle mass, and increased cholesterol level and other metabolic changes that may increase the risk of heart disease. Other negatives include cost and possible drug reactions. However, in the well-selected patient, the possible benefits of delayed metastasis, reduced skeletal morbidity from metastasis, and prolonged survival may outweigh the risks and justify use of hormonal therapy.

Unfortunately, there are limited data on the role of hormonal therapy for men with PSA-only recurrence and nonmetastatic disease. Therefore, we are left to extrapolate data from trials either of men with metastatic disease or of those with locally advanced nonmetastatic disease. However, whether such data can be applied to men with PSA-only recurrence is still a matter of debate. Below we discuss several studies on the role of hormonal therapy for prostate cancer in general, which may or may not be applicable to men with PSA-only recurrence.

One question that has received a lot of attention is whether CAB is more efficacious than medical/surgical castration alone. CAB is more costly and has an increased side effect profile compared with castration alone. Side effects include liver toxicity (more common with flutamide) and breast enlargement/tenderness (more common with bicalutamide). Is it more efficacious? Many studies have addressed this specific point with mixed results, thus providing ample studies to support either opinion. Although some investigators claim that CAB can cure 90% of patients, meta-analyses show the benefit of CAB to reduce the risk of prostate cancer death appears to be modest, ranging from a nonsignificant reduction of 7% to significant reductions of 13% to 20%.

These modest results, combined with cost and adverse effects on quality of life, have tempered enthusiasm for CAB among some physicians. Most of these studies, however, were performed before the importance of PSADT in risk stratification was understood. It is possible that through risk stratification, we can identify men who stand to benefit most from CAB and those who stand to benefit least and may actually be harmed by it (or by any hormonal therapy).

EARLY VERSUS DELAYED HORMONAL THERAPY

The timing of hormonal therapy is an extremely controversial topic that has been examined and reexamined for decades. There is still no consensus, although perhaps 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 with deferred hormonal therapy (either orchiectomy or estrogen) and found no differences in overall survival. However, the patients in that study had much more advanced disease than typical patients today with PSA-only recurrent disease. The use of estrogen, with its associated cardiovascular morbidity, suggests that these results may not apply to patients today.

The Medical Research Council in the United Kingdom compared immediate medical or surgical castration with deferred treatment among nearly 1000 patients who had locally advanced or asymptomatic metastatic disease. Initial results demonstrated that early therapy delayed disease progression, delayed the onset of new metastatic pain, and significantly reduced prostate cancer and overall death. 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.

This study was criticized because some men in the delayed arm never received hormonal therapy, potentially biasing the results in favor of early therapy. However, the differences in findings between the initial and long-term results are intriguing: with limited follow-up such that only those most likely to die of 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 strongly suggests that early hormonal therapy may be better for some men (ie, those at highest risk) but may have no benefit or may possibly harm others (ie, those at lowest risk).

In a randomized study of early versus delayed hormonal therapy among 98 men with microscopic nodal involvement at the time of RP, the Eastern Cooperative Oncology Group reported a significant reduced all-cause and prostate cancer-specific mortality favoring early treatment. In men who received immediate hormonal therapy, the mortality rate from prostate cancer at 7-year follow-up was 4.3%, compared with a mortality rate of 30.8% in men who were initially observed ($P < .01$). Furthermore, the recurrence rates were 18.8% versus 75% favoring immediate treatment. Whether this study can be extrapolated to justify a benefit for early hormonal therapy for men with PSA-only recurrence is unknown.

<table>
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<tr>
<th>Late* vs early† hormonal therapy</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>1.02</td>
<td>0.63-1.63</td>
<td>&gt;0.95</td>
</tr>
<tr>
<td>PSA recurrence within 1 year after surgery</td>
<td>1.38</td>
<td>0.64-2.99</td>
<td>0.41</td>
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To date, only one retrospective study examined the issue of the timing of hormonal therapy. Moul and colleagues reported a series of 1352 men with biochemical recurrence following RP. The investigators found that after a median follow-up of 3.7 years after recurrence, early hormonal therapy had no effect on time to metastasis among the overall cohort. The limited follow-up prevented meaningful analysis of prostate cancer death. Among men with high-risk disease (pathologic Gleason sum more than 7 or a PSADT of 12 months or less), early hormonal therapy (starting when the PSA values were less than 5 or less than 10 ng/mL) was associated with a 50% reduction in the risk of metastasis.

While no prospective randomized controlled trials have specifically addressed the timing of hormonal therapy in men with PSA-only recurrence, there is mounting evidence suggesting a benefit to early therapy in patients with high-risk disease. However, the side effects of traditional hormonal therapy must not be underestimated, particularly in men who are clinically well with only a rising serum PSA level. Furthermore, what exactly defines "early" therapy is still unclear, because all presented studies initiated treatment at different disease stages.

NONTRADITIONAL HORMONAL THERAPIES

While medical and surgical castration can have a dramatic effect on prostate cancer, as noted above, they carry significant quality-of-life concerns. Therefore, there is a clear need for effective but less toxic therapies. One such option is antiandrogen alone. The most extensively evaluated drug is bicalutamide. An overview analysis of 3 open, randomized, multicenter studies comparing bicalutamide with surgical or medical castration found that bicalutamide (50 mg/d) was less effective than castration with respect to time-to-treatment failure, time-to-objective progression, survival, and subjective response rate.

Standard-dose bicalutamide appears less efficacious than castration, but high-dose bicalutamide (150 mg/d) has been shown to provide a survival outcome similar to that of castration for men with locally advanced nonmetastatic disease. In addition, in this study, quality of life for patients who received high-dose bicalutamide appeared to be similar or slightly better than quality of life for those who had undergone castration.

The results from the Early Prostate Cancer Program that compared high-dose bicalutamide with placebo were reported. This study comprised 3 randomized, double-blind, placebo-controlled trials of similar design across 3 distinct geographic areas. Men (n = 8113) with prostate cancer undergoing RP, RT, or watchful waiting were randomized to receive adjuvant high-dose bicalutamide or placebo for 3 years (North America) or 5 years (Australia, Europe, Israel, South Africa, Mexico, and Scandinavia). The primary end point was progression-free survival and overall survival. Tolerability
was a secondary end point. Median follow-up after randomization was 5.4 years.

When data from the 3 studies were examined separately or combined, no significant difference in overall survival between the bicalutamide and placebo groups was observed. When the data were stratified by definitive treatment versus watchful waiting and stage of disease (local versus locally advanced), a very interesting observation was noted: among men who received RP or RT, bicalutamide was not significantly related to overall survival regardless of disease stage. When data from men who were managed with watchful waiting were examined, bicalutamide was associated with an improvement in overall survival, which did not reach statistical significance (hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.63 to 1.04; \( P = .10 \)) among men with advanced disease, but significantly worse overall (non-cancer-specific) survival among men with localized disease (HR, 1.23; 95% CI, 1.00 to 1.50; \( P = .05 \)). Thus, men with advanced disease who were managed with watchful waiting were 19% less likely to die while receiving bicalutamide, whereas men with localized disease who were managed with watchful waiting were 23% more likely to die while taking bicalutamide. These data echo results from previous studies: those at the highest risk likely gain a significant advantage with aggressive early hormonal therapy, while those at lowest risk are likely harmed by the same treatments.

An important clinical note related to high-dose bicalutamide is that breast enlargement and tenderness occur in up to 70% of patients. A randomized trial showed that prophylactic breast irradiation or tamoxifen (10 mg daily) could prevent the breast pain, with tamoxifen being slightly more effective than breast irradiation.

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