Management of Patients with Biochemical Recurrence After Local Therapy for Prostate Cancer

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KEYWORDS

• Rising prostate-specific antigen • Prostate cancer • Hormonal therapy
• Androgen-deprivation therapy • Biochemical recurrence

KEY POINTS

- Nearly three-quarters of a million American men who have been treated with prostatectomy and/or radiation therapy experience an increasing prostate-specific antigen (PSA) level, a condition known as biochemical recurrence (BCR).
- Post localized therapy, some of these men develop distant metastases with time, but many years may pass before signs of clinical progression appear.
- Although androgen-deprivation therapy remains a reasonable option for some men with BCR, deferring androgen ablation or offering nonhormonal therapies may be appropriate in patients where the risk of clinical/metastatic progression and prostate cancer–specific death is low.
- Drug development in this space is a challenge because of the heterogeneous and prolonged natural history of biochemically recurrent prostate cancer, and the lack of short-term, validated surrogate end points for overall survival.

INTRODUCTION

Approximately 239,000 men will be diagnosed with prostate cancer in 2013, but 88% of these men will ultimately die from ischemic heart disease or other nonprostate cancer causes.[1,2] An estimated 60,000 to 70,000 men are diagnosed in the United States each year with biochemical recurrence (BCR), a state defined as rising prostate-specific antigen (PSA) after radical prostatectomy (RP) or radiation treatment,[3] and overall, three-quarters of a million men are estimated to be living with rising PSA after local therapy without evidence of overt metastatic disease.[4]

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The optimal management of patients with nonmetastatic, hormone-naive, biochemically relapsed prostate cancer remains largely unestablished at this time because of the lack of prospective randomized trials designed to address standards of care.[5] Treatment decisions remain largely intuitive at the present time. Recognizing the deficiency, this article describes a logical risk-based approach for therapeutic considerations and clinical research in this relatively common subset of patients. The approach is based on extensive data on the natural history of these patients at the Johns Hopkins Hospital (JHH). This article discusses this and other existing datasets and defines potential risk-benefit ratios of existing modalities of treatment.

DEFINITION OF BCR

The definition of BCR after local therapy varies based on the primary modality of treatment. After surgery, PSA levels greater than 0.2 ng/mL or greater than 0.4 ng/mL and rising are often considered evidence of BCR.[3] However, in 2007, the American Urological Association (AUA) reported on a review of more than 13,000 citations referencing BCR in patients with prostate cancer and found 54 different definitions of BCR after surgery and 99 different definitions of BCR after radiation therapy (RT).[6] The lack of consistently applied definitions of BCR limits the interpretation of data on natural history and some of the therapeutic considerations in these patients. Such inconsistencies are especially challenging for the interpretation and design of clinical trials.

BCR After RP

Among the 54 definitions of BCR after prostatectomy discovered by the AUA researchers, the most common was a PSA of greater than 0.2 ng/mL or a close variation. The authors, who were also members of the AUA Prostate Guideline Update Panel,[6] recommended that practitioners use a single definition of BCR after RP as follows:

> *It is recommended that biochemical (PSA) recurrence following radical prostatectomy be defined as a serum PSA of 0.2 ng/mL or greater, with a second confirmatory level of PSA of >0.2 ng/mL. The first postoperative PSA should be obtained between 6 weeks and 3 months following therapy. The date of failure should be defined as the date of the first detectable PSA level once this value has been confirmed.*

In establishing this recommended definition, however, the panel added two caveats. First, the higher levels of PSA (>0.4 ng/mL) would have much greater specificity for clinical and/or radiographic recurrence and progression, but the authors justified the use of 0.2 ng/mL by arguing it had "provided high sensitivity for recurrence as well as the greatest generalizability." Second, this definition is not an effective predictor of death from prostate cancer, suggesting that prognosis should be based on nomograms that consider Gleason score and PSA kinetics, although available nomograms have not been prospectively validated.

The panel acknowledged the appropriateness of reporting biochemical outcomes using additional PSA thresholds. Although some researchers who have designed clinical trials enrolling patients with BCR have adopted this AUA definition,[7] other researchers use 0.4 ng/mL and rising as the eligibility criterion, arguing that the higher value is more specific for future risk of clinical and radiologic progression.[8] For trial purposes, the authors consider PSA levels greater than 0.4 ng/mL and rising as evidence of BCR after surgery.