Biochemical Recurrence in Prostate Cancer: The European Association of Urology Prostate Cancer Guidelines Panel Recommendations

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Abstract

Biochemical recurrence (BCR) after primary treatment of localized prostate cancer does not necessarily lead to clinically apparent progressive disease. To aid in prognostication, the European Association of Urology prostate cancer guidelines panel undertook a systematic review and successfully developed a novel BCR risk stratification system (groups with a low risk or high risk of BCR) based on disease and prostate-specific antigen characteristics.

Patient summary: Following treatment to cure prostate cancer, some patients can develop recurrence of disease identified via a prostate-specific antigen blood test (ie, biochemical recurrence, or BCR). However, not every man who experiences BCR develops progressive disease (symptoms or evidence of disease progression on imaging). We conducted a review of the literature and developed a classification system for predicting which patients might progress to optimize treatment decisions.

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1. Introduction

Following radical treatment for prostate cancer with either external beam radiotherapy (EBRT) or radical prostatectomy (RP), 27–53% of patients experience biochemical recurrence (BCR) [1]. However, not all patients with BCR go on to develop disease progression and metastatic disease, and the rate of such progression also varies. It is important to identify patients at high risk of progression to initiate early salvage treatment, while treatment can be deferred for those with a low risk of progression. The European Association of Urology (EAU)-European Association of Nuclear Medicine (EANM)-European Society for Radiotherapy and Oncology (ESTRO)-European Society of Urogenital Radiology (ESUR)-International Society of Geriatric Oncology (SIOG) prostate cancer guidelines panel performed a systematic review for better prognostication for patients with BCR in terms of clinical and metastatic progression to optimize salvage treatment decisions. Prostate-specific antigen (PSA) persistence, defined as detectable or persistent PSA after RP, is a different stage of the disease that is associated with worse oncological outcomes [2,3] and is not discussed in this manuscript.

2. BCR defined

There is heterogeneity of BCR definitions between and within the main curative interventions. After RP, the threshold that best predicts further metastases is PSA > 0.4 ng/ml that is rising [4,5]. Nonetheless, the goodness of fit of this definition remains modest, with approximately 74% of patients developing metastatic progressive disease after 10 yr of follow-up. After primary RT, with or without short-term hormonal manipulation, the Radiation Therapy Oncology Group-American Society for Therapeutic Radiology and Oncology Phoenix consensus conference definition of BCR (with accuracy of >80% for clinical failure) is any PSA increase >2 ng/ml higher than the PSA nadir, regardless of the nadir value [6]. This definition appears to have the highest predictive accuracy for metastatic disease following BCR. Although BCR is clearly associated with critical oncological endpoints (clinical failure, prostate cancer mortality, and overall mortality), its effect size varies significantly across studies. In addition, for men experiencing BCR after primary treatment, sufficiently long life expectancy is necessary for BCR to influence mortality [7–12]. In unselected relapsing patients, the median actuarial time to the development of metastasis is 8 yr and the median time from metastasis to death is a further 5 yr [13]. Therefore, the EAU-EANM-ESTRO-ESUR-SIOG prostate cancer guidelines panel recommends evaluating a patient’s life expectancy when considering further treatment. Nevertheless, current BCR thresholds for EBRT and RP do not have high predictive accuracy for the main oncological outcomes (in particular metastatic progression), with variable prognosis among patients who develop BCR, ranging from patients with a nonaggressive disease course to those with aggressive disease and high metastatic potential. The indication for further treatments should not be based on meeting a threshold PSA recurrence as defined above alone, but should depend on the individualized risk of progression. Additional stratification of patients with BCR is crucial to ensure timely commencement (generally before meeting the BCR threshold) or deferral of salvage treatment.

3. Individualized risk assessment and salvage therapies

Our systematic review identified several critically important prognostic factors [14]. For patients who underwent RP as primary treatment and subsequently developed PSA recurrence, the main unfavorable prognostic factors were a PSA doubling time (PSA-DT) of ≤1 yr and a pathological Gleason score (pGS) of 8–10 (International Society of Urological Pathology [ISUP] grade 4–5). For patients with PSA recurrence following primary RT, an interval from primary therapy to biochemical failure (IBF) of ≤18 mo and a biopsy Gleason score (bGS) of 8–10 (ISUP grade 4–5) were the main unfavorable prognostic factors. On the basis of these findings, the EAU-EANM-ESTRO-ESUR-SIOG prostate cancer guidelines panel recommends using a novel BCR classification system that stratifies patients with BCR into low-risk (PSA-DT >1 yr and pGS <8 [ISUP grade <4] after RP; IBF >18 mo and bGS <8 [ISUP grade <4] after RT) and high-risk BCR (PSA-DT ≤1 yr or pGS 8–10 [ISUP grade 4–5] after RP; IBF <18 mo or bGS 8–10 [ISUP grade 4–5] after RT), as summarized in Table 1. The risk grouping was recently externally validated. Tilki et al [15] assessed the discriminative ability of the BCR risk grouping in predicting metastatic recurrence and prostate cancer-specific mortality (PCSM) in a large population of patients (n = 1040) with BCR after primary RP [15]. After 5 yr, metastasis-free survival was 99.7% (95% confidence interval [CI] 99.0–100%) for the low-risk BCR group (n = 510) and 86.7% (95% CI 83.4–90.1%) for the high-risk BCR group (n = 530). Furthermore, for a subset of 398 patients who did not receive salvage therapies before metastatic progression, similar results were observed. Trock et al [16] investigated the impact of salvage RT (sRT) on PCSM in relation to PSA-DT for BCR after primary RP. For patients with PSA-DT <6 mo, sRT resulted in a reduction of PCSM, with hazard ratios of 0.24 (95% CI 0.07–0.77) and 0.14 (95% CI 0.05–0.39) for men with and without concomitant ADT.

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Characteristics</th>
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<tr>
<td><strong>BCR after radical prostatectomy</strong></td>
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<tr>
<td>Low-risk BCR</td>
<td>PSA-DT &gt;1 yr and pGS &lt;8 (ISUP grade &lt;4)</td>
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<tr>
<td>High-risk BCR</td>
<td>PSA-DT ≤1 yr or pGS 8–10 (ISUP grade 4–5)</td>
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<tr>
<td><strong>BCR after radiation therapy</strong></td>
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<tr>
<td>Low-risk BCR</td>
<td>IBF &gt;18 mo and bGS &lt;8 (ISUP grade &lt;4)</td>
</tr>
<tr>
<td>High-risk BCR</td>
<td>IBF ≤18 mo or bGS 8–10 (ISUP grade 4–5)</td>
</tr>
</tbody>
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*BCR = biochemical recurrence; PSA-DT = prostate-specific antigen doubling time; pGS = pathological Gleason score; ISUP = International Society of Urological Pathology; IBF = interval from primary therapy to biochemical failure; bGS = biopsy Gleason score.*

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respectively. However, for patients with PSA-DT > 6 mo, there was no significant effect of sRT, with hazard ratios of 0.66 (95% CI 0.28–1.58) and 0.85 (95% CI 0.45–1.59) for men with and without ADT, respectively. The authors concluded that for patients with PSA-DT < 6 mo, sRT had a protective effect only when initiated within 2 yr of BCR diagnosis. For patients with PSA-DT ≥ 6 mo, the delay in sRT initiation did not have any effect on reported outcomes [16]. This suggests that for patients with low-risk BCR after primary RP, delaying sRT is a safe treatment choice. By contrast, for patients with high-risk BCR, early sRT (before PSA levels rise to 0.5 ng/ml) is recommended [17,18]. A systematic review of salvage androgen deprivation therapy (ADT) for recurrent disease after primary treatment showed similar results and suggested that only patients with PSA-DT < 6–12 mo and pGS > 7 (ISUP grade > 3) could potentially benefit from salvage ADT [19]. Therefore, the EAU-EANM-ESTRO-ESUR-SIOG prostate cancer guidelines panel recommends offering close surveillance and possibly deferred salvage treatment to patients with low-risk BCR. Salvage ADT should not be offered to patients with low-risk BCR. For high-risk BCR, early restaging (including modern imaging) and early salvage therapy are recommended. It has repeatedly been shown that commercially available genomic tests such as Decipher can identify patients at risk of metastatic progression after primary treatment and influence treatment decision-making [20–22]. In future trials, the inclusion of genomic markers with the EAU BCR risk stratification might improve its discriminative power even more. Ongoing randomized trials such as RADICALS and the final analysis of the prospective PRO-IMPACT study will add important evidence in the next few years.

4. Conclusions

The EAU-EANM-ESTRO-ESUR-SIOG prostate cancer guidelines panel recommends stratifying patients experiencing BCR after primary treatment for localized PC into EAU low-risk and high-risk BCR groups. The potential benefits and toxicities of salvage treatment(s) should be discussed with each individual patient, while considering both the EAU BCR risk stratification and life expectancy. In the absence of risk factors, the nonaggressive course of the disease should be discussed to allow patients to make a well-informed decision. Further research should focus on refining this simple risk stratification to increase its discriminative power. For example, it could be expected that splitting up ISUP grade 2 and 3 disease within the classification or including genomic tests could improve its discriminative power even more. Researchers initiating trials on salvage therapies after primary RP or RT are encouraged to include this risk stratification into their patient inclusion protocol to optimize future patient care.

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Study concept and design: Mottet, Lam, Van den Broeck.

Acquisition of data: Mottet, Lam, Van den Broeck.

Analysis and interpretation of data: Mottet, Lam, Van den Broeck.

Drafting of the manuscript: Van den Broeck, Lam, Mottet.

Critical revision of the manuscript for important intellectual content: All authors.

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