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Biochemical recurrence in prostate cancer: The EAU Prostate Cancer Guidelines Panel's recommendations.

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ABSTRACT

Biochemical recurrence (BCR) after primary treatment of localized prostate cancer (PCa) does not necessarily lead to clinically apparent progressive disease. To aid prognostication, the EAU Prostate Cancer Guideline Panel undertook a systematic review and successfully developed a novel BCR risk stratification system based on disease and PSA characteristics (i.e. EAU Low-risk BCR and High-risk BCR risk groups).

Patient Summary: Following treatment to cure prostate cancer, some patients can develop recurrence of disease identified on the PSA blood test (i.e. biochemical recurrence, or BCR). However, not everyone who develops BCR develops progressive disease (symptoms or evidence of disease progression on imaging). We have conducted a review of the literature and developed a classification system which enables us to predict which patients might progress in order to optimize treatment decisions.

INTRODUCTION

Following radical treatment for prostate cancer with either external beam radiotherapy (EBRT) or radical prostatectomy (RP), 27%-53% of patients develop 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 institute early salvage treatment, whilst treatment can be deferred in those with low risk of progression. The EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel performed a systematic review to better prognosticate patients with BCR in terms of clinical and metastatic progression, to optimize salvage treatment decisions. PSA persistence, defined as detectable or persistent PSA after RP, is a different stage of the disease associated with worse oncological outcomes and will not be discussed in this manuscript [2,3].

BIOCHEMICAL RECURRENCE DEFINED

There is heterogeneity of BCR definitions between and within the main curative interventions. After RP, the threshold that best predicts further metastases is a PSA > 0.4 ng/mL and rising [4,5]. Nonetheless, the goodness of fit of this definition remains modest with approximately 74% of patients developing metastatic progressive disease after 10 years follow-up. After primary RT, with or without short-term hormonal manipulation, the RTOG-ASTRO Phoenix Consensus Conference definition of BCR (with an accuracy of > 80% for clinical failure) is any PSA increase > 2 ng/mL higher than the PSA nadir value, regardless of the nadir value [6]. This definition appears to have the highest predictive accuracy in terms of developing metastatic disease following BCR. Although BCR is clearly associated with critical oncological endpoints (i.e. clinical failure, prostate cancer mortality and overall mortality), its effect size varies significantly across studies. Also, when 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 eight years and the median time from metastasis to death is a further five years [13]. **Therefore, the EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline 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 amongst patients who develop BCR, ranging from patients with a non-aggressive 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 an individualized risk for progression.** Additional stratification of patients with BCR is crucial to ensure timely commencement (generally before meeting the BCR threshold) or deferral of salvage treatment.

INDIVIDUALIZED RISK ASSESSMENT AND SALVAGE THERAPIES

Our systematic review identified several critically important prognostic factors [14]. In patients who underwent RP as primary treatment and who subsequently developed PSA recurrence, the main unfavorable prognostic factors were a PSA Doubling Time (PSA-DT) of ≤1 year and a final Gleason score of 8-10 (ISUP grade 4-5). For patients who developed PSA recurrence following primary RT, an interval from primary therapy to biochemical failure (IBF) of ≤18 months and a biopsy Gleason score (bGS) of 8-10 (ISUP grade 4-5) were the main unfavorable prognostic factors. Based on these findings, the **EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel recommends using a novel BCR classification system**, stratifying patients with BCR into **EAU Low-Risk BCR** (PSA-DT >1 year AND pGS <8 (ISUP grade <4) for RP, IBF > 18 months AND bGS <8 (ISUP grade <4) for RT) or **EAU High-Risk BCR** (PSA-DT ≤1 year OR pGS 8-10 (ISUP grade 4-5) for RP, IBF ≤18 months OR bGS 8-10 (ISUP grade 4-5) for RT). The risk grouping was externally validated recently. Tilki et al. assessed the discriminative ability of the EAU 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 years, the metastasis-free survival of the EAU Low-Risk BCR group (n=510) was 99.7% (95% CI 99.0-100%) compared to 86.7% (95% CI 83.4-90.1%) for the High-Risk BCR group (n=530). Furthermore, among a subset of 398 patients who did not receive salvage therapies before metastatic progression, results were similar. Trock et al investigated the impact of salvage radiotherapy (sRT) on PCSM in relation to PSA-DT for BCR after primary RP [16]. For patients with a PSA-DT <6 months, sRT resulted in a reduction of PCSM with a HR of 0.24 (95% CI 0.07-0.77) and 0.14 (95% CI 0.05-0.39) with or without

concomitant ADT. In patients with a PSA-DT > 6 months, however, they reported no significant effect of sRT with HRs of 0.66 (95% CI 0.28-1.58) and 0.85 (95% CI 0.45-1.59) with or without ADT. Furthermore, they concluded that in patients with a PSA-DT <6 months, sRT had a protective effect only when initiated within 2 years of BCR diagnosis. For patients with a PSA-DT ≥ 6 months, the delay in sRT initiation did not have any effect on reported outcomes [16]. This suggests that in patients with Low-Risk BCR after primary RP, delaying sRT is a safe treatment choice. In contrast, in patients with High-Risk BCR features, early sRT (before PSA levels rise to 0.5 ng/ml) is recommended [17,18]. A systematic review on salvage androgen deprivation therapy (ADT) for recurrent disease after primary treatment showed similar results and suggested that only patients with a PSA-DT < 6-12 months and a Gleason score >7 (ISUP grade >3) could potentially benefit from salvage ADT [19]. **Therefore, the EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline 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.** Ongoing randomized trials such as RADICALS will add important evidence in the next few years.

CONCLUSIONS

The EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel recommends stratifying each patient experiencing BCR after primary treatment for localized PCa into EAU Low-Risk BCR or EAU High-Risk BCR. The potential benefits and toxicities of initiating salvage treatment(s) should be discussed with each individual patient, while considering both its EAU BCR risk stratification and life expectancy. In the absence of risk factors, the non-aggressive 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 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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