Editorial Commentary

Helpful tool or blunt instrument?—the European Association of Urology Biochemical Recurrence Risk Classification as a decision-making tool for salvage radiotherapy

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We read with interest the recent publication by Preisser and colleagues on the use of the European Association of Urology (EAU) Biochemical Recurrence (BCR) Risk Classification as a decision tool for salvage radiotherapy (SRT) (1). The authors have completed a multi-centre study involving 2,379 patients with BCR after radical prostatectomy. When stratified by the EAU Risk Classification elaborated by Van den Broeck *et al*. (2), this tool's prognostic value was validated. The authors also suggest that the EAU Risk Classification can predict radiotherapy (RT) benefit based on a significant overall survival (OS) and cancer-specific survival (CSS) improvement with early SRT. This was seen in the EAU high-risk but not the low-risk BCR groups. In our view, however, there are important limitations to the referenced study, relating to both its design and the utility of its findings, which led us to question its usefulness as a SRT decision tool.

A key weakness of this study is the potential confounding effect of androgen deprivation therapy (ADT), which is not accounted for. Although this is appropriately acknowledged by the authors, that does not mitigate its impact on the utility of their findings, specifically in the high-risk group. The addition of androgen suppression to salvage RT is known to positively impact progression-free survival and OS as demonstrated by the GETUG-AFU 16 (3) and RTOG 9601 (4) randomized trials, respectively. Therefore, a potential imbalance of ADT use in the 'no SRT' versus 'early SRT' groups could certainly have impacted oncological outcomes—the extent of which remains unknown without accounting for this important variable.

Another potential limitation is that other relevant outcomes were not evaluated in this study: for example, metastasis-free survival (MFS) and alternate endpoints such as ADT-free survival. MFS is known to have a positive association with CSS and OS in localized prostate cancers (5) and typically considered an endpoint of relevance and importance to patients. Chronic use of ADT is also likely meaningful to patients as ADT use is linked with morbidity and reduction of quality-of-life scores (6,7), although one could argue that there are potential trade-offs between the morbidity associated with SRT versus chronic use of ADT. Nevertheless, a more comprehensive analysis capturing and reporting rates of MFS and ADT-free survival between groups would add clarity to the study.

The other set of limitations relate to the EAU BCR Risk Classification definition itself, as this categorizes patients into high- or low-risk categories solely based on two clinical characteristics: Gleason score and prostate-specific antigen (PSA) doubling time (PSADT). While Gleason score post radical prostatectomy specimens is a fairly reproducible category, estimation of PSADT for patients with very low PSA levels is less so. There is evidence that (very) early recurrent PSA levels—of which the kinetics & doubling

time would be evaluated to inform early SRT decision-making—do not necessarily represent later PSADT (8) (i.e., the recurrent PSA ranges upon which the EAU BCR risk grouping was developed). Also, low PSA levels may also be subject to greater error margins (9) or not reproducible for assays where the lower limit of sensitivity falls in the 0.1–0.2 range. This can result in discrepant or non-reproducible PSADT results in the ranges of PSA that precede the threshold for SRT, thus potentially causing misclassification of patients.

Compared to other available nomograms used clinically to estimate benefit from SRT (by quantifying risk of biochemical and metastatic events with and without treatment), the EAU BCR definition seems insufficient for this purpose. For instance, the Tendulkar update (10) of the Stephenson nomogram—and additional refinements that have incorporated PSA kinetics into predictive nomograms (11)—represent more sophisticated clinical decision aids or sharper tools. Meaningful characteristics that are statistically associated with biochemical relapse including margin positivity, extracapsular extension, seminal vesicle involvement, PSA kinetics, and PSA level at the time of salvage are taken into consideration. Likewise, specific questions about the proposed intervention, including RT dose and ADT use, are factored into the nomogram resulting in a more refined prediction model of treatment benefit.

Finally, we argue that adopting the BCR Risk Classification alone as a decision aid for SRT will leave clinicians ill-equipped for the future. The use of prostate-specific membrane antigen positron emission tomography (PSMA-PET) is increasing in the BCR setting, with detection rates approaching 50% at PSA values of 0.2–0.5 ng/mL (12) and with data supporting the predictive value of molecular imaging for SRT (13). Roberts and colleagues have suggested that the utility of BCR risk groups is significantly augmented by PSMA-PET data when incorporated into prediction of event-free survival (14). Furthermore, Zamboglou *et al.* have developed and validated a nomogram integrating PSMA-PET that estimates individual patient outcome post-SRT based on the finding that nodal uptake reduces the likelihood of achieving biochemical control (15). Genetic tumor biomarkers represent another set of interesting prognostic and likely predictive models that are currently in clinical use. In one study evaluating the role of Decipher, researchers reported on higher metastatic events for patients with high Decipher scores with greater benefit of ADT plus RT in this risk category (16). These examples highlight our discipline's efforts to integrate emerging data—both imaging and genetic—to sharpen our clinical decision-making tools, honing them for contemporary and future use.

In conclusion, using a simple decision-making tool may be quick and easy, but it could be insufficient to meet clinical needs of the present and future. By dichotomizing the SRT decision into BCR low- versus high-risk groups (with the idea being to omit versus offer SRT, respectively), there is a risk of oversimplifying a complex and nuanced clinical situation. It seems more plausible that a risk spectrum exists where patients at either end may not benefit from SRT. However, an intermediate population could certainly see benefit from a local-regional treatment strategy like SRT, both in terms of oncological as well other patient-relevant outcomes. Moreover, on the heels of the recently-published EMBARK trial demonstrating MFS benefit of enzalutamide in high-risk BCR (17), we should strive for greater rather than lesser sophistication for patient selection so as to better integrate SRT with evolving systemic therapies. In other words, when sharper tools are available (and being further refined), why should we and our patients settle for what is arguably a blunt instrument?

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Footnote

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