Editorial Commentary

European association of urology biochemical recurrence risk stratification in the context of post-prostatectomy salvage therapy

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The management of biochemically recurrent prostate cancer following radical prostatectomy depends upon a number of clinical and pathological factors. Radiotherapy (RT) has long been a key component in the management of these patients, either in the form of salvage radiotherapy (SRT) for established biochemical relapse (1), or as adjuvant therapy to reduce the threat of relapse when risk factors suggest a significant risk. One key question which remains a point of contention is whether patients with clinicopathologic risk factors for relapse should receive adjuvant RT, early SRT, or even delayed or no SRT. Three modern randomized controlled trials (2-4) have compared early SRT *vs.* adjuvant radiation therapy and found no significant difference in biochemical progression rates, with worse toxicities in patients who received RT in the adjuvant setting, leading to the preference for early SRT for many patients in the post-prostatectomy setting. However, the general inclination towards early SRT is not without a number of remaining questions regarding the optimal timing and details of patient selection.

In this context, Preisser and colleagues are to be commended for their multi-center retrospective analysis (5) of the benefit of early SRT, defined therein as SRT while prostate-specific antigen (PSA) <0.5 ng/mL, compared with observation on the basis of the European Association of Urology (EAU) risk stratification for patients with biochemical recurrence (BCR) in the post-prostatectomy setting. Patients are defined as EAU BCR low-risk on the basis of a Gleason score <8 and PSA doubling time (PSADT) >12 months, while high-risk patients have a Gleason score ≥8 or PSADT ≤12 months. In this study, they examined the outcomes of 2,379 patients with BCR between 1989 and 2020 who underwent salvage radiation therapy or observation. Patients with lymph node-positive disease were excluded, as were those who received adjuvant radiation therapy.

Their results show that EAU BCR high-risk was independently associated with an increased hazard of death [hazard ratio (HR) =1.50, P<0.01] and cancer-specific death (HR =5.22, P<0.001) when compared with EAU BCR low-risk. Within the subgroup of patients with EAU BCR low-risk, there was no difference in 12-year overall survival (87% *vs.* 78%, P=0.2) or cancer-specific survival (100% *vs.* 96%, P=0.2) for patients who received early SRT compared with no SRT, suggesting that SRT may not even be indicated in the setting of biochemical relapse for these patients. Conversely, for EAU high-risk BCR patients, early SRT was associated with superior 12-year overall survival (81% *vs.* 66%, P<0.001) and cancer-specific survival (98% *vs.* 82%, P<0.001) in comparison with no SRT.

These findings underscore the need for an individualized treatment approach for patients with BCR following

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prostatectomy. The EAU BCR risk stratification is based upon the Gleason grade and PSADT, two well-studied clinicopathologic factors. However, there are a number of other clinical and treatment characteristics that may influence outcomes. The present study notes that pT3 or higher disease was independently associated with a greater hazard of death and cancer-specific death as compared to pT2 disease. Other factors that may provide additional information include the surgical margin status and the presence of regional nodal disease at the time of prostatectomy. The present study did not comment on surgical margin status and did not include patients with lymph node-positive disease, though other studies suggest that patients with these risk factors may be more likely to benefit from early initiation of therapy, including in the adjuvant setting (6,7).

Additionally, some key details of salvage therapy were not available in this study. As the study authors note, the rates and duration of androgen deprivation therapy (ADT) usage across the patient cohort are not known, yet these factors may have a significant impact on outcomes in the salvage setting (8-10). The optimal duration of ADT is still being elucidated, as both short-term and long-term ADT approaches have been incorporated in prospective trials (8,11) and is the subject of the RADICALS-HD randomized controlled trial, which compares 0, 6, and 24 months of ADT in patients receiving post-operative RT (12). Adding further complexity, intensification of ADT monotherapy has been explored in the randomized EMBARK trial in patients with BCR with high-risk features, defined with specific PSADT and absolute PSA thresholds, demonstrating that the addition of enzalutamide to ADT or enzalutamide alone resulted in superior metastasis-free survival outcomes as compared to patients who received ADT alone (13). With other prospective trials such as FORMULA-509 (14) suggesting a benefit to ADT intensification in conjunction with SRT in patients with elevated PSA at the time of salvage therapy, the appropriate role of intensified salvage ADT monotherapy in patients otherwise eligible for SRT remains to be adjudicated. Similarly, the variability and impact of elective nodal coverage in radiation therapy fields was not addressed. It is worthwhile to note the results of the RTOG 0534 'SPPORT' trial, which suggested that the combination of pelvic node irradiation and short-term ADT reduces the rate of distant metastases in patients who undergo SRT (8).

The incorporation of prostate-specific membrane antigen (PSMA) positron emission tomography (PET) imaging, in both the upfront and salvage settings adds further complexity to the equation. PSMA PET imaging provides superior detection of recurrence as compared to conventional imaging (15). The present study followed a cohort of patients largely treated in an era without PSMA PET. It is conceivable that the use of PSMA PET imaging at the time of BCR may serve to further risk-stratify patients, although admittedly the sensitivity of PSMA PET at low PSA values remains limited, with one prospective study estimating the detection rate at 38% for patients with a PSA <0.5 ng/mL (16). Interestingly, EAU BCR risk grouping may predict for a positive PSMA PET/CT independent of the PSA level following post-prostatectomy recurrence; in at least one study, the rate of PSMA PET positivity was 82% in patients with EAU BCR high-risk disease, compared with 49% in low-risk (17). A prospective observational study suggests that metastasis-directed therapy to PSMA avid oligometastases is well tolerated with good biochemical response rates, while long-term treatment outcomes are pending further study (18); these and other studies are needed to understand the optimal management of patients in the PSMA PET era.

The study used a PSA cutoff of <0.5 ng/mL for early SRT, a threshold below which initiation of SRT has been associated with improved outcomes including metastasis-free survival (19). However, even lower PSA thresholds have been identified in other work, suggesting that a lower PSA trigger for initiation of SRT may yield improvements in survival, particularly for patients with higher-risk disease (10).

Lastly, genomic classifiers may provide additional prognostic and predictive information in the salvage post-prostatectomy setting beyond traditional clinical and pathologic risk factors. A secondary analysis of the RTOG 9601 trial demonstrated that patients with Decipher low-risk disease may have a more modest 12-year absolute overall survival benefit of 2.4% with the addition of 24 months of bicalutamide in the salvage RT setting, as compared to an absolute 12-year overall survival benefit of 8.9% in patients with Decipher intermediate- or high-risk disease (9). At a PSA value <0.7 ng/mL, there appeared to be a negative impact on overall survival from the addition of long-term androgen blockade for patients with Decipher low-risk disease, whereas a survival benefit persisted in patients with intermediate or high-risk disease (9). It remains to be seen how Decipher should be more specifically incorporated alongside other clinical and pathologic factors such as PSADT and Gleason score to determine both the timing and intensity of salvage therapy.

In summary, Preisser *et al.* have shown that the EAU risk grouping is one factor for consideration in determining the need for early salvage radiation therapy in the management of patients with BCR following radical prostatectomy (5). However, the specific application of SRT as well as its timing and delivery remains highly complex and individualized, and future studies should aim to address and refine the incorporation of the numerous clinical, pathological, imaging, and genomic factors now available to ascertain optimal management within the multiple potential variations within this clinical situation.

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