A standardized definition of biochemical recurrence (BCR) after radical prostatectomy (RP) is necessary to compare outcomes from international studies, clinical trials, and for patient care. To date, both the American Urological Association and American Society of Radiation Oncology guidelines [1] and the European Association of Urology guidelines [2] recommend a definition of biochemical postprostatectomy recurrence as a detectable or rising prostate-specific antigen (PSA) value >0.2 ng/ml with a second confirmatory level >0.2 ng/ml. In this month’s issue of European Urology, Mir et al. analyzed data from a single center with patients followed in the era of ultrasensitive PSA assays [3]. They compared 14 definitions of BCR after RP and the risks of subsequent disease progression [3]. The aim of this comparison was to find the best measure to identify patients needing salvage treatment at the earliest stage of recurrence. Indeed, the pre–salvage treatment PSA level is one of the most influential factors on salvage therapy outcomes [4].

In the postsurgery setting, curable recurrences are treated mainly by salvage radiotherapy (SRT). In general, there is a progressive loss of tumor control that occurs with an increasing PSA value before SRT. For example, subgroup analyses from the Southwest Oncology Group’s SWOG 8794 trial demonstrate that SRT should be considered before a PSA value reaches >1.0 ng/ml [5]. Retrospective matched-control analyses have suggested that a 20% improvement in post-SRT disease-free survival was achieved when salvage treatment was started at a PSA level <0.2 ng/ml [6]. However, among patients with a pre-SRT PSA of <0.2 ng/ml were those without biological evidence of recurrence. As such, contamination may have overestimated outcomes of SRT. Most patients with very low but detectable PSA levels were included in adjuvant treatment arms in clinical trials when their disease became detectable. Two of three published randomized controlled trials assessing the benefit from adjuvant treatment included about 30% of patients with PSA >0.2 ng/ml in the “adjuvant” arm [7,8]. In the ARO trial, all patients had PSA <0.1 ng/ml [9]. Nevertheless, 59% of patients had detectable PSA ranging from 0.03 ng/ml to 0.1 ng/ml. More important, even if the link between pre-SRT PSA level and subsequent risk of SRT failure is established, the impact on metastasis-free and cancer-specific survival remains unknown. We do not really know how high that threshold could be before rendering SRT ineffective.

Findings presented in the study from Mir et al. suggested that biochemical definitions below currently accepted PSA thresholds would help early selection for salvage therapy in patients with adverse pathology [3]. Although the authors are to be congratulated for their efforts in addressing this important clinical problem, some issues could be improved in this work. The primary outcome measure was PSA progression, which is a clinically useful and commonplace metric; however, the authors did not assess more important end points such metastasis-free and cancer-specific survival. Furthermore, the secondary end point of treatment progression is a highly variable measure that depends on patient and physician preferences. The primary outcome was defined as a PSA level >0.1 ng/ml above the detectable

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PSA threshold studied. This definition does not necessarily match with the exponential biologic model of cancer progression. Moreover, this end point (BCR +0.1 ng/ml) varies with time and depends on the definition used for initial PSA failure. The time to progression (and its underlying prognostic value) from 0.03 ng/ml to 1.03 ng/ml (+3433%) is quite different than that to progression from 0.3 ng/ml to 0.4 ng/ml (+33%). The significance of achieving this end point would not be equivalent between subgroups stratified by BCR definition.

Are literature data so mature as to move forward a lower PSA threshold as an optimal definition of BCR (and potentially future clinical recurrence)? Physicians should not miss the big picture. Findings from the study of Mir et al. perfectly highlight that a PSA cut-off should not be considered the only variable defining disease recurrence and its ability to threaten quality of life or life itself [3]. In their study, Mir et al. reported that a single PSA value ≤0.1 ng/ml was associated with subsequent rising PSA levels in only 18–25% of patients with good pathologic features (with a 5-yr metastasis risk approaching 0%) compared with 73–88% of those with PT3b or pN1 or Gleason 8–10 cancer [3]. We should keep in mind that a measurable postoperative PSA level is related and proportional to the microscopic disease burden, except in highly undifferentiated tumors (where PSA level may not reflect disease volume or progression risk). In the study by Mir et al., the risk of 5-yr PSA progression was comparable in adverse pathology disease, whichever definition was used. The 5-yr risk of metastasis or death was also equivocal (>10%), regardless of the definition. Any detectable PSA level, even at the lowest levels, has poor prognosis in high-risk prostate cancer. In those cases, the debate should not stand concerning the time to salvage therapy but rather should concern adjuvant versus very early salvage therapy. It would have been interesting if the authors had assessed the impact of margin status on BCR definition. Positive margins have been clearly associated with improved outcomes after both adjuvant therapy and SRT [10,11].

Confirmatory analyses are needed to ascertain the diagnosis of recurrence [1,2]. About one-fourth of patients with persistently detectable PSA after RP (>0.1 ng/ml) will not experience definition-based BCR [12]. After 15-yr follow-up, the rates of systemic progression and specific mortality following BCR are about one-fourth and one-sixth, respectively, for long-term follow-up [13]. Results from Mir et al. confirmed these findings with a 5-yr PSA progression rate of only 75% in patients who responded to the standardized definition of PSA failure (>0.2 ng/ml and rising). Early salvage therapy may lead to overtreatment (and its risk of toxicity, including worsening of sexual and urinary control recovery) in a non-negligible number of cases. Moreover, PSA doubling time has been demonstrated to be an independent predictor of biologic aggressiveness, systemic disease, and oncologic outcomes after SRT, highlighting its predominant role in the treatment decision-making process [10,13].

The prognostic value of the time to BCR after treatment with intent to cure has been proven in patients who underwent radiotherapy [14]. Conflicting results are reported after RP [13,15]. Nevertheless, when looking at older series in which patients did not receive salvage therapy until the time of systemic progression, this time to BCR has been correlated with cancer-specific mortality [15]. The cancer-specific mortality was about twofold higher in patients experiencing biochemical failure during the first 3 yr after RP [13,15]. This factor has not been incorporated into the risk profile assessment reported by Mir et al. [3].

In oncology, we postulate that the faster we treat, the smaller the recurrence and the more effective the salvage treatment will be. In the postsurgery recurrence setting, this sentence sounds good concerning biochemical outcomes but must be balanced against the risks of overtreatment. Early salvage therapy should be for patients who will clinically progress and in whom this treatment will significantly prevent those complications. Although pre-salvage treatment PSA is independently associated with BCR risk after salvage treatment, the early salvage treatment decision-making process should be based on more individualized, more integrative, and less subjective recurrence measures. Given that no data currently support the impact of lowering the PSA threshold for defining recurrence using hard clinical end points, the full knowledge of all patient and disease characteristics should guide patient counseling and the decision to initiate salvage treatment.

Conflicts of interest: The authors have nothing to disclose.

References


Platinum Priority


Identifying the Candidates for Early Salvage Therapy After Radical Prostatectomy

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We appreciate the thoughtful commentary by Ploussard and Catto [1] regarding our paper [2]. In particular, the issue of overtreatment using secondary therapy for men with any adverse pathologic features is germane, given the recently published American Urological Association and American Society for Radiation Oncology guidelines regarding the use of postoperative radiotherapy [3]. The authors of these guidelines advocated that all patients with extraprostatic extension and/or positive surgical margins should be recommended to receive adjuvant radiotherapy, although the impact of this therapy on metastatic disease progression and mortality has not been definitively proven (one large mature trial showed a significant impact of adjuvant radiotherapy on these end points [4], and another larger trial in more contemporary patients did not [5]). Thus an approach using adjuvant radiotherapy for all patients with these features may subject low-risk individuals to the harms of radiation therapy (gastrointestinal and genitourinary toxicity and possible secondary malignancies) without benefit.

The theoretical disadvantage of salvage radiotherapy is that delays in its administration (relative to adjuvant therapy) may enable cancers to progress and be less curable.

To reduce this risk, we have identified biochemical recurrence (BCR) definitions below currently accepted prostate-specific antigen (PSA) thresholds that, in high-risk patients, are associated with a high probability of subsequent PSA rises. This may increase the likelihood that secondary therapy may be withheld until evidence of disease recurrence, thereby limiting treatment burden and toxicity to those who need it most. Further studies will be needed to determine whether “very early” salvage radiotherapy administered at these lower PSA thresholds will lead to improved cancer control and reduced prostate cancer-specific mortality. However, clinicians first needed evidence that BCR definitions based on lower PSA thresholds were reliable indicators of subsequent PSA progression. That is what our study endeavors to provide.

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