Peer Review File

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Reviewer A

The editorial comment is well-written and organized. Some minor grammatical corrections are required.

RESPONSE: Thank you for this comment. We have combed through the text carefully and made some small grammatical corrections as requested.

Reviewer B

Interesting editorial regarding the Preisser et al. paper. Sound rationale for comments made but are missing some key elements and perhaps some tempering of the conclusion would be helpful.

RESPONSE: Thank you for your assessment. We have adjusted the conclusion paragraph as requested.

Much of the criticism of the EAU Risk groups does not refer to the source document that the risk groups were made from large meta-analysis from Van den Broeck et al. Eur Urol 2019, it actually isn't discussed or cited.

RESPONSE: Thank you for highlighting this important point- we have now referenced the original study reporting the EAU Risk Classification system in our manuscript.

The Tendulkar nomogram is complex and actually doesn't account for PSADT, which was shown in the systematic review to be more predictive. Suggest the authors consider these differences.

RESPONSE: This is an excellent point. We have discussed and cited a reference incorporating PSADT/kinetics into predictive nomograms of salvage radiotherapy in the context of the Tendulkar nomogram.

There are some inconsistencies, particularly in regard to PSA doubling time calculation at low PSAs. General convention is that rising PSA > 0.1-0.2 ng/ml is biochemical recurrence, so criticisms of calculators for PSA <0.1 are not really relevant.

RESPONSE: Thank you for this comment. We have replaced this point with one clarifying our argument regarding some of the challenges inherent to PSADT calculation using ultra low PSA values.

The criticism of absent ADT data should be tempered, given the fact that RTOG9601 subsequently showed no benefit of ADT in low-risk patients (10.1001/jamaoncol.2020.0109), which for the Preisser study where median PSA was 0.3, ADT is unlikely to help with improving OS.

RESPONSE: This is a fair point and indeed our argument was meant to focus on the absence of ADT use data in the 'high risk' group. We have clarified our position within the text so as to address the Reviewer's point.

There is an absence of relevant literature, such as comparison of EAU Risk groups with PSMA PET and biochemical outcome (eg. Roberts et al BJU Int https://doi.org/10.1111/bju.15762). This paper supports the authors point that PSMA PET is probably more predictive than EAU risk groups, but their combination is even more powerful.

RESPONSE: Thank you for this excellent suggestion. We agree it strengthens our position on this specific point and is complementary to the Zamboglou study that is cited. Therefore, we have incorporated this interesting reference, as per the Reviewer's suggestion.

Reviewer C

This is an extremely well written editorial regarding the recently published manuscript "European Association of Urology Biochemical Recurrence Risk Classification as a Decision Tool for Salvage Radiotherapy—A Multicenter Study". There are several interesting points all of which are relevant to the initial manuscript. The references appear appropriate and this manuscript does not require copy editing prior to publication.

The editorial as currently written is more than sufficient for publication; however, a few items the editorialists may wish to consider are listed below.

- In the age of early salvage PSA, PSA doubling times may not be a valid surrogate for the parameter upon which the EAU's risk score was developed (as I understand it was developed at a time of late salvage). As mentioned, there is variability in the PSA measurement, which is a limitation to applying PSA DT on the patient level. In review of the cited manuscript, the coefficient of variability does appear to be reasonable for the referenced assay in the post-operative setting and the usual range (tenths of a ng/mL), and this fact, in general, brings to light a general problem in utilizing PSA In clinical decision making (also true of the Telndulkar / Stephenson nomogram). Another data point in proof of the author's general argument, I believe, is that early PSA DT is not indicative of late PSA DT as demonstrated by a team of investigators in PMID: 19549124. This may be relevant because the data currently available to physicians who are emptying early salvage RT may not be indicative of that which the EAU risk grouping was developed.

RESPONSE: This is an excellent reference. The Reviewer is correct that it strengthens our

argument and we have worked on incorporating this important point into the revised manuscript.

- PSA doubling times may also not be able to be obtained in circumstances where (very) early salvage is favored at a threshold of PSA of 0.1-0.2 (based on the RADICALS, RAVES, GETUG) cut offs, especially in centers where the lower limit of sensitivity of the assay is at 0.1-0.2. Of note, while RTOG 0534 initially did collet this parameter for the first 471 patients the study was amended in 2009 to eliminate the collection of PSA DT, the accrual rate increased suggesting that this parameter may not be well captured in many clinical practices (PMID: 35569466 ;paragraph 1 of Results)

RESPONSE: Thank you for this fascinating insight which nicely articulates the challenges and nuances of evaluating PSA & calculating PSADT pre-SRT. We have included a sentence regarding the challenges associated with decision-making based on very low PSA levels, which is reflective of the reviewer's point here.

- The Stephenson nomogram to my knowledge has further been update most recently in the manuscript indexed under PMID: 34016556. This may be of interest to the editorialists if they are not aware of this publication because the topic of this update was to study the individuals in whom PSA kinetic information was available. Again, this publication utilizes patients from the 1980s and likely the PSA DT is not indicative of those values derived in the clinic today due to changes in practice patterns from late to early salvage RT.

RESPONSE: It is an excellent suggestion to cite this more recent nomogram update we and agree that doing so further strengthens our argument re: the value of existing decision tools for SRT. This has been incorporated into the revised manuscript.