Author's response to reviews

Title: The use of early postoperative prostate-specific antigen to stratify risk in patients with positive surgical margins after radical prostatectomy

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Author's response to reviews: see over
Dear editor,

thank you for letting us revise the manuscript. The comments raised several important issues and the revision has improved the quality of the manuscript. We hereby resubmit the revised manuscript after having considered all advised corrections.

SPECIFIC COMMENTS:
1) Line 69 – “specimens,” not “specimen”
Correction: line 69 “specimens”

2) MAJOR COMPULSORY REVISIONS: Lines 80 and 81 – the authors state that not all patients with PSM develop BCR; however, not all patients with BCR develop true cancer progression. Therefore, the authors’ stated desire to correctly identify those patients most likely to benefit from adjuvant management needs to take the next step of ferreting out those patients whose BCR leads to local/ systemic progression and cancer-specific death.
Answer: We fully agree with this major comment and we are aware that our results related to biochemical recurrence provide only limited information about the cancer outcome.
Correction: line 274 “Nevertheless, presented results should be analyzed with caution, as patients with BCR do not necessarily share the same long-term cancer outcomes. Our results will need re-evaluation as our follow-up matures to yield meaningful data on cancer specific survival, as the most relevant endpoint.”

3) Line 97 – “remaining” and not “remained”
Correction: line 97 “remaining”

4) Line 110 – “Of these 183 patients, 63,” not “Out of them, 63”
Correction: line 110 “Of these 183 patients, 63”

5) Line 113 – “patients treated with neo-adjuvant hormonal and/ or radiation therapy,” rather than “patients with the evidence of hormonal therapy and/or radiotherapy”
Correction: line 113 “patients treated with neo-adjuvant hormonal and/ or radiation therapy”

6) Line 140 – “statistically significant” not “statistical significant”
Correction: line 142 “statistically significant”

7) MAJOR COMPULSORY REVISIONS: Line 108 – the authors indicate that they derived their cohort from patients who pre-operatively contained clinically localized prostate cancer. Please expand on this – e.g., how many were T1c, T2a, T2b, and T2c? This could make a difference in terms of the surgical approach by the urologist – specifically, extrafascial, fascial, or intrafascial extirpation of the prostate gland; and this, in turn, can impact on whether the surgical margin will be positive, above and beyond its pathologic stage at surgery.
Answer: Thank you for your good comment. We agree that it is important to specify the clinical stage distribution and the frequency of biochemical recurrence.
Correction: line 148 “Considering the clinical stage the distribution of the patients was as follows: T1c (n=64), T2a (n=28), T2b (14) and T2c (n=10). The frequency of BCR did not differ significantly (p=0.08) between clinical T categories: T1c (38%), T2a (54%), T2b (71%) and T2c (60%).”
8) MAJOR COMPULSORY REVISIONS: Lines 142 – 143 – the authors indicate that follow ranged from 6 to 69 months with median follow-up of 31.4 months. That is 0.5 years to 5.75 years. While that is long enough for assessment of BCR, it is a bit short for more significant outcomes including systemic progression and death due to prostate cancer. Admittedly, the intent of the study was to assess the role of ultrasensitive PSA testing in the context of BCR and adjuvant radiation therapy. However, the missing piece of the study is whether the immediate addition of radiation makes a difference in final outcome.

*Answer: This is a valid point and we made changes in the “Discussion” section which are related to your comment number 2.*

*Correction: line 274 “Nevertheless, presented results should be analyzed with caution, as patients with BCR do not necessarily share the same long-term cancer outcomes. Our results will need re-evaluation as our follow-up matures to yield meaningful data on cancer specific survival, as the most relevant endpoint.”*

9) Line 147 – “Except at day 14,” not “Except at the day 14”

*Correction: line 153 “Except at day 14”*

10) MAJOR COMPULSORY REVISIONS: Line 149 and Table 1 – in reference to Table 1, the table is clean and easy to read. However, I would like expansion of the term “Pathologic extracapsular extension.” Do the authors mean pT3a or pT3a and b?

*Answer: We agree that proper explanation of pT3 subdivision is needed.*

*Corrections:*

- line 123 “Extraprostatic extension was defined as the extension of the tumor beyond the confines of the gland into the periprostatic soft tissue.”
- line 152: “extraprostatic extension in 51 (43.9%) patients and seminal vesicle invasion in 11 (9.48%) patients.”

Table 1

<table>
<thead>
<tr>
<th>Pathologic extraprostatic extension</th>
<th>25 (45.5%)</th>
<th>26 (42.6 %)</th>
<th>0.393</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seminal vesicle invasion</td>
<td>8 (14.5%)</td>
<td>3 (5%)</td>
<td>0.077</td>
</tr>
</tbody>
</table>

11) Line 156 – “Apart from non-significant,” not “Apart of non-significant”

*Correction: line 165 “Apart from non-significant,”*

12) MAJOR COMPULSORY REVISIONS: Lines 173 – 178 – the authors make a few assumptions in this paragraph, which, in essence, is at the heart of their study: Namely, what difference does the application of radiation therapy play in ultimate outcome in these patients – or, at the very least, what did the addition of radiation do to the patients’ serum PSA values? Admittedly, the authors set up the argument well in their Introduction, but, in the final analysis, there is a little bit of circular arguing if the goal is to reduce the serum PSA level below 0.2 ng/ml when we know upfront that the majority of these patients do not ultimately die from prostate cancer.

*Answer: We know that the endpoint of the study at this moment is the low level of PSA and we hope to focus in the future on more relevant endpoints. This will be emphasised in previously described comment.*

*Correction: line 274 “Nevertheless, presented results should be analyzed with caution, as patients with BCR do not necessarily share the same long-term cancer outcomes. Our results will need re-evaluation as our follow-up matures to yield meaningful data on cancer specific survival, as the most relevant endpoint.”*
13) MAJOR COMPULSORY REVISIONS: The other point that is begged in this paragraph and, in essence, throughout the study is the nuances of a positive surgical margin (PSM). As the authors astutely suggest, it’s not just PSM, yes or no, it’s where the margin is positive, how many margins are positive, and what the extent of margin positivity is, as well as other details such as Gleason pattern of cancer at the margin, cautery effect, etc. These are factors which could also play a significant role in predicting who will progress to not only BCR but also systemic progression and prostate cancer specific death.

Answer: Thank you for this comment. Together with our reading pathologist we have analyzed the pathologic reports of all the patients and following findings were added to the text.

Correction: line 155 „Of all PSM locations, 15 (13%) were apical, 20 (17%) at the bladder neck and 81 (70%) at the posterolateral site. A total of 46 patients (40%) had PSM ≤ 1mm. Neither the location (p=0.216) nor the extent of PSM (p=0.405) had any significant impact on the frequency of BCR.”

14) Line 190 – “cancer in the last decade,” not “cancer in last decade”
Correction: line 193 „cancer in the last decade”

15) Lines 185 – 186 – “Comparable results were found in the present study,” not “Compatible results were found in present study”
Correction: line 195 „Comparable results were found in the present study”

16) Line 208 – “Several explanations may explain,” rather than “Several explanations were suggested in order to explain”
Correction: line 211 „Several explanations may explain”

17) Line 212 – “impression of a PSM,” rather than “impression of positive surgical margin”
Correction: line 215 „impression of a PSM”

18) Line 215 – “in the surgical bed who would be the best candidates for immediate adjuvant treatment” rather than “in surgical bed, those patients who would be the best candidates for immediate adjuvant treatment”
Correction: line 218 „in the surgical bed who would be the best candidates for immediate adjuvant treatment”

19) MAJOR COMPULSORY REVISIONS: Line 218 – while it is true that there is no general consensus on how to report PSM, this does not obviate the need to collect more detailed information so as to begin the process of building an argue for or against the role of said information in the reporting and subsequent management of a PSM. In other words, it strikes me as “logical” that a PSM that is focally involving a cauterized posterior inked margin is likely to be predicted by their model not progress and, as such, require radiation therapy. This, in turn, might eliminate the need for more testing with an ultrasensitive PSA marker. Ultimately, we have no way of testing this hypothesis based upon the authors’ study parameters.

Answer: This is very good comment. One of the goals of the study was to point at the unreliability of different pathological features of PSM. As the response to your comment number 13 we added more detailed analysis of associative factors of PSM (extent and location), which did not bring improvement in the prediction of BCR. In the discussion section we offer several potential reasons leading to false impression of PSM. On other hand the results imply that PSA testing early after the surgery may present a reliable and readily available parameter associated with the treatment outcome.
20) Lines 220 – 221 – not sure I completely agree with this statement as some institutions can clear surgical margins via frozen section analysis and, as such, eliminate PSM from multivariable models in predicting who will develop BCR and death due to prostate cancer.

**Answer:** We are aware that there are different views on the value of frozen section analysis and since this is not the main topic of this paper, we dare to leave this comment unchanged together with the reference to the literature.

21) Line 234 – eliminate “already” before “…at day 14”

**Correction:** Line 242 “already” omitted

22) Lines 236 – 237 – please change to read “However, as time from surgery increased, the predictive power of ultrasensitive PSA measurements increased. For example, the calculated AUROC curves for day 30 and day 60 were 74% and 84%, respectively.”

**Correction:** Line 244 “However, as time from surgery increased, the predictive power of ultrasensitive PSA measurements increased. For example, the calculated AUR for day 30 and day 60 were 74% and 84%, respectively.”

23) Line 254 – change to read “1 of 16 patients”

**Correction:** Line 263 “1 of 16 patients”

24) Line 258 – remove comma after argued

**Correction:** Line 267 comma omitted

25) Conclusions – needs to be reworked something as follows: The present study provides insights into the role ultrasensitive serum PSA measurements plays in determining who will develop BCR and, as such, be candidates for early radiation and/or hormonal therapy. The kinetics of post-RP serum PSA decline may allow better stratification of patients who would benefit from immediate radiation therapy.

**Correction:** Line 280 “The present study provides insights into the role ultrasensitive serum PSA measurements plays in determining who will develop BCR after radical prostatectomy and, such as, be candidates for secondary treatment. The kinetics of postoperative PSA decline may allow better stratification of patients who would benefit from immediate radiation therapy.”

**Editorial Request:**

1. Editorial Comments:
This is a good study and deserves publication after certain aspects of the study are expanded and revisions made to the manuscript. The first reviewer has made some very thorough criticisms of the manuscript and if the authors can follow through on those, it will represent an improvement.

line 86 - The reference is a superscript; needs to be in brackets like other references

**Correction:** line 86 “[2]”. 
The term extracapsular extension is not the most valid because the prostate has only an incomplete pseudocapsule. The commonly accepted term is extraprostatic extension, meaning tumor cells in fat. This term should be substituted throughout.

Line 221, Table 1 – extracapsular substituted by “extraprostatic”

I am in agreement with the reviewer that additional follow-up of the patients is needed to document how many had systemic recurrence and how many had death; do not stop the study at just biochemical recurrence.

“Nevertheless, presented results should be analyzed with caution, as patients with BCR do not necessarily share the same long-term cancer outcomes. Our results will need re-evaluation as our follow-up matures to yield meaningful data on cancer specific survival, as the most relevant endpoint.”

Many articles on prostate margin status have taken into account the location of positive margins (base worse than apex) or the linear extent of positive margins (focal versus extensive). If the authors have access to any of this information from the pathology reports and could analyze it, that would increase the value of the study.

“Of all PSM locations, 15 (13%) were apical, 20 (17%) at the bladder neck and 81 (70%) at the posterolateral site. A total of 46 patients (40%) had PSM ≤ 1mm. Neither the location (p=0.216) nor the extent of PSM (p=0.405) had any significant impact on the frequency of BCR.”