Author's response to reviews

**Title:** Risk factors for biochemical recurrence after Robotic Assisted Radical Prostatectomy: a single surgeon experience

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**Author's response to reviews:** see over
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Dr. Jose Karam
Section Editor
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Dear Dr. Karam

We would like to thank the reviewers for their constructive criticisms, which greatly helped us in improving the revised manuscript. We have carefully addressed all concerns and modified the revised manuscript accordingly. Please find below a detailed point-by-point response to each suggestion:

Reviewer: Kenneth Iczkowski

1. **On page 7, please give a time frame for PSA level >0.2. Is it on one occasion or on two separate occasions? Some studies require two measurements of >0.2.**

   The definition of PSA failure on this study was based on two separate occasions. We have now indicated this the sentence in the revised manuscript. We added the number at risk and number of events on the revised Figure 1.

2. **The median follow-up is stated to be 22 months (1 month to 5 years) on page 8. Presumably with the very short follow-ups such as 1 month, biochemical recurrence intervened. The ranges of follow-up should be given for the failure group and the non-failure group. Then, in Figure 1, BCR-free survival should be given only out to the number of months as the patient with the shortest follow-up. The Kaplan-Meier curve goes out to 90 months, which misrepresents the scale since the longest follow-up is**
60 months (5 years). But, even that is problematic because a non-failure patient with 12 months of follow-up should not be included on a curve that extends to 60 months. The Kaplan-Meier curve will under-represent the number of failures unless the maximum follow-up on the horizontal axis equals the shortest follow-up. K-M curves as constructed may not be feasible, or the K-M curves should be restricted to patients with at least 36 months' follow-up to qualify for inclusion in, for example, a curve extending to 36 months.

The longest follow up was 88 months so that the x-axis was set up to 90 months. We agree with the reviewer that our follow up (median 16 months) was so short that K-M curves might be misleading. So we added the number at risk on all K-M curves and their x-axis has been set to 60 months which we hope will now enables the readers to interpret.

3. On page 8, line 125 it is stated that 98 (85%) of positive margins were unifocal. Table 2 should break down the analysis at least according to unifocal and multifocal margins and compare them to each other. Other studies have done more than this, such as looking at margin length or locations.

We agree with the reviewer that foci of PSM should be critical to this analysis. We performed univariate analysis evaluating unifocal and multifocal margins in which the unifocal and multifocal PSM demonstrated the significantly increased risk of BCR as compared to negative surgical margins and have included this in the revised Table 2, but these variants are overlapped with positive surgical margins so the multivariate analysis was omitted. Also we broke down the location of PSM in the supplemental table 1.

4. Page 9 line 132. This is a badly worded and uninterpretable sentence: "...first operative period were (Fig. 1F.... What is first operative period--what is the duration? Again, on page 10, line 147 it says "early operative period." What is the time frame of early operative period?
We divided the operative period into 2005-2007, 2008-2010 and 2011-2013. We have clarified at various points in the manuscript what this means. For instead we have indicated mentioned the period 2005-2007 as early operative period which included first consecutive 102 cases.

5. *Page 24, in the Table 1, PSA should be clarified as “preoperative PSA.”*

   The text has been corrected.

6. *There are grammatical, word usage, and spelling issues to a moderate degree, and these should be fixed by the authors. Page 6 Jefferson should be capitalized.*

   The text has been corrected.

7. *Page 12 had significantly higher rate of BCR compared to late period---> had a significantly higher rate of BCR compared to the later period.*

   The sentence has been corrected.

8. *P. 13 line 207. a single surgeon. Line 208 stage and early postoperative... Throughout the paper, place a space between a number and a unit such as ml.*

   The text has been corrected.

**Reviewer: Jose Karam**

**Major Compulsory Revisions:**
-Please use medians and interquartile range for all continuous variables (not mean)

These data are added in the revised table 1.

-Please insert the number at risk/number of events under the Kaplan Meier curves

We agree with the reviewer that this is an important issue, which was raised by another reviewer. Our follow up (median 16 months) was so short that K-M curves might be misleading. So we added the number at risk on all K-M curves and their x-axis has been set to 60 months which now enables the readers to better interpret this data. Also the number of events is added in Figure 1-A, which gives a time frame for PSA level > 0.2.

-Was it salvage XRT or adjuvant XRT?

We excluded the patients (n = 9) with adjuvant XRT from this study to elucidate the natural history of localized PCa treated with surgery as the single modality.

-Did any patient receive hormones?

None received hormones in this study, which also help to elucidate the natural history of localized PCa treated with surgery as the single modality.

-What investigations were done when patients had BCR?

BCR was evaluated on an individual basis. Patient age and comorbidities, initial risk stratification, pathologic features, and absolute PSA and PSA velocity were taken into account when considering additional treatment. If indicated, patients were restaged with abdominal and pelvis computed tomography and bone scan prior to recommending salvage therapy. Patients were enrolled in clinical trials when appropriate.
What was the breakdown of PSM per pT stage? please specify in pT3a and pT3b.

The data are added in the supplemental table 2.

Did the PSM improve in pT2 versus pT3a and pT3b over time?

The data are added in the supplemental table 2, which shows that PSM did not significantly improve over time.

How come 73 patients never had a postoperative PSA? Were these patients that had surgery but were never seen again in clinic or received a communication from their referring physician (if applicable) about the PSA status?

Our hospital is a tertiary referral center and many of the patients were from outside our geographic area and are followed locally.

Why were 9 patients that received adjuvant treatment excluded? Why did these patients receive adjuvant treatment? For pT3a/b status? or for positive margins status? or both?

In order to elucidate the natural history of localized PCa treated with surgery as the single modality, we excluded the patients (n=9) with adjuvant radiation or hormonal treatment who had positive lymph node (n=2), pT3b (n=2), pT3a with positive surgical margin (n=3), pT3a with tertiary GS 5 (n=1) and high GS (4+5) with positive surgical margin (n=1).

How was Cox regression done?

Based on the results of univariate analysis, we chose age and the variants that were significantly associated with BCR for multivariate Cox regression analysis. As mentioned above, PSM foci are omitted because they completely overlapped with positive surgical margin
What statistical software was used?

We used JMP version 9. This is added in the revised manuscript.

What was the median (not mean) follow up for the entire cohort and for those who did not have BCR?

The median follow up for the entire cohort and for those who did not have BCR were 16 and 15 months, respectively. These data are added in the revised table 1.

The authors rightfully acknowledged the limitations of the study including short follow-up time, lack of information about size and multifocality of the PSM.

Following the suggestion of another reviewer, we have analyzed the foci of PSM on BCR and broke down the location of PSM in the supplemental table 1.

Sincerely,

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