Author's response to reviews

Title: Impact of surgical technique (open vs. laparoscopic) on pathological and long term functional outcomes following radical prostatectomy

Authors:

  Jonas Busch (jonas.busch@charite.de)
  Ahmed Magheli (ahmed.magheli@charite.de)
  Mark Schrader (mark.schrader@uniklinik-ulm.de)
  Serdar Deger (S.Deger@kk-es.de)
  Kurt Miller (kurt.miller@charite.de)
  Michael Lein (MLein@klinikum-offenbach.de)

Version: 4
Date: 10 January 2014

Author's response to reviews: see over
Dear editors and reviewers,

Thank you for the further very helpful comments. We would like to again address each point to improve our manuscript in order to meet the high publication criteria of BMC Urology.

Please note that all new changes are now marked in green, changes from the initial review are still in yellow. Please also find the initial review with our responses further below.

Yours sincerely
J. Busch
A. Magheli

Reviewer's report
Title: Impact of surgical technique (open vs. laparoscopic) on pathological and long term functional outcomes following radical prostatectomy
Version: 3 Date: 7 October 2013
Reviewer: Akira Miyajima

Reviewer's report:
Several systematic reviews have shown LRP is superior than RRP or that they are at least comparable in terms of functional and oncological outcomes (Eur Urol 55: 1037, 2009, 62: 405, 2012).
The authors mentioned, “Surgeon experience is more relevant than surgical technique applied.” I guess this means it depends on a learning curve. However, they responded, “This study was not designed to address the learning curves or complications within our patient population.” PSM also seems different according to surgeon experience. Unfortunately they haven’t shown that. PSM is a quite strong predictor for biochemical failure. They need to show analysis of recurrence.

Thank you for these remarks. We would like to clarify that the aim of the current study expressed in the title of the manuscript is to evaluate the pathological and long-term functional outcome in our cohort. It is well known and controversially discussed that positive surgical margins do have an impact on biochemical recurrence (BCR). However BCR is not the subject of our analysis and would distract the reader from our main aim. Additionally the study was not designed for the purpose of evaluating BCR.

They responded, “Fewer LRP patients received a nerve sparing treatment, which might be associated with preoperative patient selection and the technically difficult nature of nerve sparing in LRP.” This is definitely a bias. What kind of case chooses NVB spare? RRP 80% cases underwent NVB sparing while lower
than 50% of LRP cases did. This looks strange. I believe this bias affects functional and oncological outcomes including recurrence rate and PSM.

Selection for nerve sparing at the two different campi of our institution (CCM and CBF) was also based on different surgical schools and mind sets. To clarify this further we have updated the following section the material and methods section: “Between 2003 and 2007 more than 3,000 men underwent radical prostatectomy (RP) for clinically localized adenocarcinoma of the prostate at the Charité Department of Urology at two different campi, Campus Charité Mitte (CCM) and Campus Charité Benjamin Franklin (CBF). LRP was exclusively performed at CCM, while RRP was performed at CBF”

Reviewer's report
Title: Impact of surgical technique (open vs. laparoscopic) on pathological and long term functional outcomes following radical prostatectomy
Version: 3 Date: 3 October 2013
Reviewer: Phillip M Pierorazio
Reviewer's report:
The authors, for the most part, addressed the issues brought up in the first review. There is one MINOR ESSENTIAL REVISION which should be addressed. The authors should be applauded for reporting very real positive surgical margin rates both overall and for pT2 disease. One of the revisions stated that nerve-sparing was performed at the discretion of the surgeon for oncologic control and patient preference. For LRP, the nerve sparing rate was much lower and the positive surgical margin rate much higher for pT2 disease. I am a supporter of minimally invasive RP (including laparoscopy), however this data certainly makes it seem like LRP is an inferior operation in terms of both cancer control and functional outcomes OR there is a major discrepancy between nerve-sparing reporting and margins. You would expect a very low margin rate if most LRP operations were wide resections of the NVB. Please address this issue in the discussion to facilitate publication of this manuscript.

Thank you for these valuable remarks. One major issue is indeed the evaluation of the pathological specimens by two departments of pathology at the above mentioned two different campi with different protocols. As shown in other publications this could have had a significant impact on positive surgical margin status. As mentioned above we added this aspect of two different campi to the material and methods section
Initial Review and reply

Reviewer: Akira Miyajima
Reviewer's report:
The authors investigated functional and pathological outcomes of LRP and RRP, and they concluded that both are comparable in terms of function and oncological outcome.
1. Surgical margin rates were different between RRP and LRP in this setting. What is the reason? tumor volume? surgical technique? LPR seems more positive. Which part margin was more positive?

- The overall positive surgical margin rates were different (22 vs. 26%) but not statistically significant. A detailed analysis of locations of positive margins was not done for this study. Therefore discussion of possible locations known from the literature or our experience remains speculative. In our opinion LRP seems to have higher positive margin rates, which may not transfer into higher recurrence rates. However analysis of recurrence rates was not part of this investigation therefore conclusions cannot be drawn in to this effect.

2. In RRP cases, 83.3 % patients underwent bilateral nerve sparing. Is there any protocol for nerve sparing? This rate was obviously higher than LRP nerve sparing.

- In our RRP cases nerve sparing techniques were performed in a combined fashion (antegrade and retrograde) within an intrafascial approach. Fewer LRP patients received a nerve sparing treatment, which might be associated with preoperative patient selection and the technically difficult nature of nerve sparing in LRP. In general nerve-sparing techniques were performed based on patients’ preference and wish for oncological safety. Please note, this last sentence was added to the material and methods section.

3. The authors compared functional outcomes by experience of the surgeon. How many cases do we need to do prostatectomy to reach the satisfied level? How about complication rate?

- Although we believe that answering this question is tantamount to comparing and assessing the success of different radical prostatectomy techniques, we unfortunately do not have the answer. This study was not designed to address the learning curves or complications within our patient population.

Reviewer: Phillip M Pierorazio
Reviewer's report:
Summary: The authors randomly review >300 patients who underwent RRP and LRP, comparing surgical and functional outcomes after each surgery. Major findings include similar rates of positive surgical margins, similar functional outcomes are achieved in each modality and outcomes that only appear to vary based on surgical technique.
Review: There are a number of serious methodological flaws that make this
paper unpublishable in its current form. These flaws seriously contend the conclusions. However, if remedied, this paper may be suitable for publication.

Specific Comments/Critiques: MAJOR COMPULSORY REVISIONS

1) The study lacks a power calculation. Is there a reason 330 patients were randomly selected? Why not all patients and then a matched analysis? The choice of analysis needs to be further discussed.

   - The acquisition of detailed follow-up data was only feasible for a limited number of patients at the time the study was performed.

2) Table 1 demonstrates a number of important variables that are similar among these randomly selected groups. However, a number of important data points are missing:
   a. How many patients were selected from each surgeon’s experience?
   b. What was the experience level of each surgeon while performing the operation? (ie. What was the average case number of selected RRP and LRP patients?)

   - Radical prostatectomies for these 340 randomly selected patients were performed between August 2003 and July 2007. For LRP 500 and RRP 500 surgeons, 85 and 82 patients were selected respectively. Similarly for LRP 200 and RRP 200 surgeons, 87 and 86 patients were selected respectively. The two most experienced surgeons had already performed about 500 cases prior to the selected study cohort. Correspondingly the two less experienced surgeons had only performed about 200 consecutive cases prior to their study cohort.
   - This information was added to the material and methods section.

3) In general there are more than a handful of typos that make the manuscript difficult to read. For instance, there is a typo on page 4, table 2 is also misreferenced and the formatting of the tables makes them hard to interpret.

   - Thank you for these remarks. We corrected all mistakes. Additionally the manuscript was again revised by a native speaker (NL).

4) I would not consider 0-1 pads as No Incontinence. Patients who wear even 1 pad per day because of occasional leakage are not continent. This should be clarified.

   - We understand and value your point. Based on our clinical experience most continent patients who would not need a single pad are indeed using a “safety pad” even though it stays dry. It was for this reason that we characterized patients who used 0-1 pad as continent. We have published this approach previously in concordance with many other authors.

5) Overall positive surgical margin rate is high, but within limits of the reported literature. What is the PSM rate in pT2 disease? This is an easily obtainable outcome measure than may speak to quality of surgery and nerve sparing?
- The rate of pT2 R1 was significantly lower in RRP compared to LRP (10.5 vs 17.5%, p=0.006). This information was added to table 1, the results section and to the discussion.

6) While the chi-squared test for IIEF is not significant there certainly seems to be a clinical difference between IIEF categories among RRP and LRP. Nearly double the proportion of patients undergoing RRP had mild-moderate ED while 50% of patients undergoing LRP had severe ED. If the p-value is accurate this study may certainly be underpowered to detect a difference in ED among groups. If so, the authors should consider adding more data points or at least addressing this issue in the discussion.

- We do see the point that our study might show weak statistical power. However the chi-square test is the most suitable statistical means to compare the study groups with respect to IIEF.

7) One of the major differences in the groups that is not well addressed in the results is the much higher proportion of non-nerve sparing using in LRP despite similar pathological outcomes. It is unclear from the manuscript why more patients undergoing minimally invasive surgery have less nerve-sparing if they present with the same preoperative characteristics and have similar pathological outcomes. It certainly introduces a bias that the LRP surgeon(s) have toward these patients.

- This remark is similar to the first reviewer’s comment.
- In our RRP cases nerve sparing procedures were performed in a combined fashion (antergrade and retrograde) within an intrafascial approach. Fewer LRP patients received a nerve sparing treatment, which might be associated with preoperative patient selection and the technically difficult nature of nerve sparing in LRP. In general nerve-sparing techniques were performed based on patients’ preference and wish for oncological safety. Please note, this last sentence was added to the material and methods section.

8) The conclusions regarding surgeon experience cannot be drawn given the data that is presented. While it is certainly provocative that the surgeon with less RRP experience had worse outcomes, this data is not granular and care needs to be taken when drawing conclusions from it. It is not enough to say surgeon 1 has X experience and surgeon 2 had Y experience (with X>Y). It should be easy to chronologically number the cases and determine at exactly what level was each surgeon when RRP and LRP were performed. Otherwise there is potentially huge bias that needs to be addressed because surgeon 200 may have performed all of the RRP early in his career and all the LRP later (as with many surgeons) and therefore the conclusions are not valid.

- This is another important aspect of our study. LRP surgeons only performed the laparoscopic technique and were not trained for open prostatectomy. RRP surgeons exclusively performed open prostatectomies.

Reviewer: Dogu Teber
Reviewer’s report:
The authors could demonstrate a nice single center experience with two techniques of radical prostatectomy. However several papers has commented on this topic the interesting point is that surgical experience is more important than the used technique. It would be of interest how many cases they define as experienced surgeon : After 500 cases ? And what is the consequences in terms of training ? The course of the individual learning curve would be nice supplement in this analysis.

- Unfortunately the study design does not allow an analysis of learning curves for each of the four surgeons since cases were randomly selected and do not represent a consecutive series of cases.

And in the year 2013 one should comment on the role of robotic surgery as a possibility to reach a high quality in shorter time? - is there evidence in the literature for this ? This should be discussed....

- We have added a notation for this in the discussion section. RARP cases were not part of this investigation although we agree that this technique offers solutions for problems that exist with LRP.