Author’s response to reviews

Title: Neoadjuvant hormonal therapy is a feasible option in laparoscopic radical prostatectomy

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Author’s response to reviews: see over
Dear Prof. Henderson:

Thank you for your E-mail of September 28, 2012 and for the reviewers’ comments concerning our manuscript entitled “Neoadjuvant hormonal therapy is a feasible option in laparoscopic radical prostatectomy”. We have carefully studied the comments and have made corrections and revisions. We wish at this time to resubmit this revised version of the paper for your consideration in BMC Urology as an original article.

The reviewers’ comments were helpful and gave us a better perspective on our work. Our responses are listed below. Revised portions in the manuscript will be found in red.

【Responses to the Editor’s comments】

1. Is a pelvic lymphadenectomy performed? In case of affirmative answer, it would be interesting a comparison of possible nodal involvement between LRP alone and LRP with NHT group.

   Pelvic lymphadenectomy was performed in all cases. There was no case of possible nodal involvement. Therefore, no mention was made of it.

2. It’s not specified what kind of NHT (LHRH + anti-androgen or anti-androgen alone ? ) is performed in Group A (3 months or less) and in Group B (more than 3 months): considering the significative result obtained in the 2-year BCR rate between the two groups, I think it could be an important aspect.
There was no statistical difference between the two groups in the kind of neoadjuvant hormonal therapy. This information was added in Table 1.

3. Is it possible to describe if the patients have a previous abdominal surgery history?

Yes. The following sentences were added in Results. “There was also no difference in the complication rate between the two groups on the history of abdominal surgery. Several patients had experienced an appendectomy or total gastrectomy, but had no effect on the complication rate in such patients (data not shown).”

**[Responses to the Reviewer 1]**

1. Minor essential Revision. LRP is no more an “emerging” treatment for PCA.

“Emerging” was changed to “standard”.

2. Discretionary Revisions. There are few reports or RP after NH; however introduction should provide some insights also on the at least minor incidence of NHT on overall survival and disease free survival for high risk prostate cancer.

   According to reviewer’s comment, we have added papers in References and added to the Introduction as follows:

   “However, one study[8] reported a decrease in seminal vesicle invasion rate with NHT. Therefore, the aim of this retrospective study was to compare the results of LRP in patients who did and did not receive NHT prior to LRP especially in high risk PCA patients.”

3. Major Compulsory Revisions. This is the central point of the paper, as long as NHT has always been used for high risk PCA patients. A further description of baseline PCA in both groups is mandatory. Use of D’Amico classification for preoperative risk stratification is warranted.

   According to the reviewer’s comment, we classified the patients according to the D’Amico classification in Table 1, 2. In addition, the Discussion was revised as follows:
“In the present study about 25% were low risk patients according to the D’Amico classification (PSA<10 ng/mL, biopsy Gleason score < 7, cT1) with an associated low risk of BCR after RP alone.” And “In our study, there was no difference in preoperative risk between the two groups (LRP alone vs. LRP with NHT) in Table 1. However, the number of pathological stage T3 patients was significantly lower in the NHT group. Table 2 shows the high risk PCA patients tended to be higher in the long-term NHT group, but the BCR rate was significantly lower. Although this was a retrospective study, a longer NHT period might decrease the active capsular penetration and seminal vesicle invasion, and as a result prevent the biochemical recurrence.”

4. Major Compulsory Revisions. Data seems to be correct and exposed clearly; the only remark is that it would be further explanatory to provide stratification of gleason score stating instead of simple mean and standard deviation; i.e.: gleason 3+3 group A, gleason 3+3 group B and so on…

According to the reviewer’s comment, we have added the stratification of gleason score in Table 1, 2. There was no significant difference between the two groups.

5. Discretionary Revisions. Again use of standard classification of complications as Clavien-Dindo would be more explicative and standardize.

According to reviewer’s comment, we have added the sentence “Surgical complications were monitored according to the Clavien-Dindo Classification.” in Methods, and “All complications were less than grade 1 in the Clavien–Dindo Classification, and were treated as routine procedures.” in Results.


According to the reviewer’s comment, we revised the pathological stages in Table 2. In the longer NHT group (Group B), only one patient showing BCR was the one in stage pT3b.

7. Major Compulsory Revisions. Refer to preoperative oncological risk and comorbidities among the two groups is warranted as previously highlighted.

According to the reviewer’s comment, we added the sentence as follow in Discussion:
“A Japanese preoperative nomogram was reported which indicated the probability of extracapsular penetration after surgery is 15-27% in low risk patients. [20] Patients were informed of the probability and the risk of comorbidity before surgery. When the patient chose the NHT, it was performed according to the waiting time for the operation. There was no comorbidity in long-term NHT group. To truly assess the appropriateness of NHT requires a careful consideration of the growing evidence of risk of the cardiac and metabolic diseases associated with such long-term exposure to androgen deprivation.”

8. Major Compulsory Revisions. The discussion is very interesting and takes into account relevant papers on this topic (NHT and PCA); however, a brief insight also in outcomes of open and robot assisted prostatectomy series and NHT could be useful.

According to the reviewer’s comment, we added the following to the Discussion:

“Nowadays, robot-assisted laparoscopic radical prostatectomy (RALP) is gaining in popularity for the treatment of clinically localized PCA. The benefits of RALP are minimally invasive surgery with wide and 3-dimensional vision and delicate control of instruments. These are considered more reasonable and safe, and constitute an effective treatment modality superior to not only RP but also LRP. Therefore, RALP after NHT might be a feasible option in localized PCA patients.”

9. Minor Essential Revisions. Again reference to different risk categories would be needed in the conclusion; as the authors state a few lines before NHT might be beneficial only for high risk patients. Prostatectomy for Low and intermediate risk PCA might be delayed (even for months) without altering pathological stage and oncological outcomes.

We need to re-emphasize that only a limited number of large institute exist in Japan where LRP can be performed. This obviously imposes a long waiting period before the procedure can be scheduled for many cases of PCA. Consequently, many cases are treated with NHT to suppress the progression of malignancy. We are encouraged that LRP was shown to be safe and effective in treating PCA in patients who had received NHT. Moreover, we believe the longer period of NHT can reduced the PSM, and also improve the BCR free survival for LRP.
【Response to the Reviewer 2】

1. Please comment on why the impact of NHT on clinical outcomes (overall survival and BCR) in patients undergoing LRP would ultimately be any different compared to open prostatectomy?

   We thought this might be partly due to the recent advances of surgical instruments, for example, clear view system, or superior blood coagulation devices. Actually, the positive margin rate in the apex of prostatectomy specimens was decreased in our institute, because we could clearly resect in adequate layer even when LRP was performed on obese patients compared to RP.

2. Please go into more detail about why nerve sparing patients were omitted. Most patients with low-risk disease (a large subset of patients in this study) would prefer a nerve sparing procedure.

   Generally, we recommended the nerve sparing operation for low risk PCA patients. But there were few patients who expressed the hope for nerve sparing. In our institute, almost all patients did not hope to maintain erectile function because they had not been sexually active.

3. A study by Freedland et al (J Urol 2006; 175: 1298-302) found no significant difference in BCR for patients with low risk disease whose surgery was delayed up to six months. Therefore, is NHT really needed in patients who can undergo a LRP within six months? Additionally, shouldn’t patients who can’t be scheduled for more than six months undergo an open procedure?

   According to the reviewer’s comment, we added the sentence as follow in Discussion:

   “A Japanese preoperative nomogram was reported which indicated the probability of extracapsular penetration after surgery is 15-27% in low risk patients. [20] Patients were informed of the probability and the risk of comorbidity before surgery. When the patient chose the NHT, it was performed according to the waiting time for the operation. There was no comorbidity in long-term NHT group. To truly assess the appropriateness of NHT requires a careful consideration of the growing evidence of risk of the cardiac and metabolic diseases associated with such long-term exposure to androgen deprivation.”
And we thought that the patients who could not be scheduled for more than six months should undergo an open procedure. But a few patients chose the combined androgen blockade (CAB) at first, and after more than one year of CAB, they hoped LRP. We could safely perform LRP in such patients.

We wish to thank the reviewers for their helpful comments which have helped in the revision and in producing a more balanced and better account of our work. manuscript has been carefully reviewed by an experienced medical editor whose first language is English and who is specialized in the editing of papers written by physicians and scientists whose native language is not English. Your consideration of our paper for publication in *BMC Urology* will be greatly appreciated.

Sincerely,

Noriyasu Kawai, M. D., Ph. D.