Author's response to reviews

Title: Long-term results of radical prostatectomy with immediate adjuvant hormonal therapy for pT3 prostate cancer

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Author's response to reviews: see over
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Dear Dr. Henderson,

Please find attached our revised manuscript entitled “Long-term results of radical prostatectomy with immediate adjuvant androgen deprivation therapy for pT3N0 prostate cancer” by Sato et al., for further consideration for publication in BMC Urology.

We appreciate the reviewers’ thoughtful and constructive comments regarding the previous version of this paper. Please find our responses to these comments below. We hope that you will now find this revised manuscript suitable for publication in BMC Urology.

We confirm that neither the submitted paper nor any similar paper has been or will be submitted to or published in any other primary scientific journal, in whole or in part, other than as an abstract or preliminary communication. All the authors are aware of and agree with the content of the paper and with being listed as one of the authors. None of the authors have any financial or other interests that might be construed as a conflict of interest with regard to the submitted manuscript. We affirm that authorization has been given to use any information conveyed by personal communication or by the release of unpublished experimental data.

Please do not hesitate to contact me at the address below if you have any further questions about this manuscript

Thank you in advance for considering our manuscript.

Hiroshi Fukuhara,
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Editor's Comments

1. In the Methods section, please include the full name of ethical committee that approved your study
2. Please can you change the title of "Subjects and Methods section" to "Methods"
3. Please can you include an Acknowledgements section to appear after the Authors Contributions section

Responses

1. We have added the name of the ethics committee to the Methods section (page 7, line 96).
2. We have changed ‘Subjects and Methods’ to ’Methods’ (page 5, line 64).
3. We have added an ‘Acknowledgements’ section, as requested (page 16, line 252).

Dr. Zachary Smith’s Comments

1. Why was 5 years used as the duration of ADT for patients? Was ADT ever routinely stopped or was it continued indefinitely?

Response

Unfortunately, we do not have the randomized controlled trial data regarding the appropriate duration of ADT. However, Labrie et al. recorded two rises in PSA among 20 patients with T2-T3 cancer who stopped treatment after continuous combined androgen blockade (CAB) for more than 6.5 years, with a non-failure rate of 90%. In contrast, the non-failure rate was only 36% in 11 patients who received CAB for 3.5–6.5 years. They
suggested that long-term and continuous CAB offered the possibility of long-term control of localized or locally advanced prostate cancer. Their study differed from ours in that their patients did not undergo prostatectomy. However, we adopted a policy of long-term, continuous ADT that was continued indefinitely, though the duration was found to be at least 5 years by retrospective analysis. All patients continued ADT for at least 5 years and 30 (28.6%) patients stopped ADT during the follow-up period; 15 quit at 5 years after radical prostatectomy, and a further 15 at some point after 5 years.

We have added the sentence on page 2, line 23 [Immediate adjuvant androgen deprivation therapy was continued for at least 5 years].


2. On lines 161 and 162, you state "although advantage of adjuvant radiotherapy is confirmed, actual outcome rate is still inferior." I'm confused with what this means. In the preceding sentence you speak of salvage hormone therapy. Did you mean to state "...actual outcomes are still poor"? If you are implying that adjuvant therapy is inferior to salvage therapy, this is not true.

3. In the sentence beginning on line 182, "in accordance with their report, a subgroup cohort of pT3bNo patients achieved excellent outcomes...". Is this sentence referring to a subgroup cohort in the referenced study in the preceding sentence, or is did you perform a subgroup analysis in your current study?

Responses

Thank you for these helpful comments. We apologize for the confusion. We have deleted the sentences on page 11, lines 161–164 [Although advantage of adjuvant radiotherapy is confirmed, actual outcome rate is still inferior. Also, increased complication rate of rectal bleeding, urethral stricture and total urinary incontinence has noted in adjuvant radiotherapy arm.].

We did perform a subgroup analysis on pT3b in our current study and have therefore added ‘in our current study’ to the sentence on lines 187 to 190. [In accordance with their report,
a subgroup cohort of pT3bN0 patients achieved excellent outcomes, with 5- and 10-year cancer-specific survival rates were 95.2% and 89.9%] has been changed to [In accordance with this previous report, subgroup analyses of pT3bN0 patients in the current study demonstrated excellent outcomes, with 5- and 10-year cancer-specific survival rates were 95.1 and 90.8%, respectively.].

4. The general syntax of the paper could use some improvement. There are a few grammatical errors that sometimes make reading difficult. Reading through the sentence a couple times usually allows for understanding, but an editorial eye by someone proficient in medical English may be beneficial.

Response
The revised manuscript has been edited by a native English speaker.

5. You spelled Gleason incorrectly in both of the tables (it says "Gleasn score at biopsy")

Response
We apologize for this error. The spelling of Gleason has been corrected in Tables 1 and 2.

6. Your follow-up pathway after prostatectomy is quite robust (q1mo x 3mo, q3mo x 5 yrs). Is this standard practice in Japan or at your institution? Is this what you do for all prostate cancer patients or only for those pT3 or greater?

Response
Thank you for pointing this out. This is not the standard practice in Japan, but is the practice for patients with pT3 or greater at our institution.

Dr. Brian Chapin’s Comments
Subjects and methods 1. Immediate adjuvant hormone therapy implies undetectable PSAs at the time of initiation of systemic therapy. If this is correct please state. If a percentage of patients had failure to nadir to undetectable this information should be provided.

Response

We agree that the percentage of patients failing to reach nadir is important. However, we prioritized the immediate initiation of ADT, which was started 2–3 weeks after radical prostatectomy in most cases. We therefore did not check PSA levels. We have added the following sentence to page 5, line 74. [Undetectable PSA levels or PSA nadir were not required to be confirmed following radical prostatectomy.].

Subjects and methods 2. The authors state that a pelvic LND was completed on each patient but do not report on node findings. Clearly patients with pathologic node positive disease have a more significant risk of bcf and this information should be provided for the reader. Node positive patients should be looked at separately in the analysis.

Results 2. Lymph node status should be included in the univariate and multivariable analysis. If all were pNO this should be stated in the results along with median number of LNs removed. If some were pN+ this should be a variable in the analysis.

Responses

As the reviewer rightly points it out, the term ‘pT3’ cancer is confusing. This study did not include node-positive patients, and we only analyzed ‘pT3N0’ patients. We have therefore changed pT3 to pT3N0 throughout the text.

Twenty-one of 431 prostate cancer patients who underwent radical prostatectomy were node-positive. The median number of lymph nodes removed was 7.0. We have added the following sentence [The median number of lymph nodes removed was 7.0 (range 2-19)] on page 8, line 114.

Subjects and methods 3. I assume this was not a single pathologist review as it is not commented on by the authors.
**Results 4.** The table states 16% of patients with pT3 disease were Gleason 5-6. This seems rather high and inconsistent with the findings of others. Was the path re-reviewed or is this the reported path prior to the 2005 Gleason modifications. If these are indeed Gl 6 from pre 2005 they would likely be upgraded to Gl 7s post 2005. Recommend having a single GU pathologist review the path to confirm Gleason grade and stage.

**Responses**

All specimens were indeed reviewed by a single pathologist, Dr. T. Morikawa, who is one of the co-authors. Dr. Morikawa is a genitourinary (GU) pathologist, and is familiar with the 2005 Gleason modifications. All specimens were reviewed based on the post-2005 criteria. We have added the following sentence [All specimens were reviewed by a single pathologist.] on page 5, line 78.

**Results 1.** 14 patients received non-standard ADT regimens. This may have been selection bias based on pathology or patient preference. It makes it unclear if equivalent application of this therapy was provided to all patients. If anything this would potentially bias the results, underestimating the risk of recurrence in this population. For example if all 14 pts were NED throughout the study. I would consider excluding the patients receiving casodex, estramustine and other tx.

**Response**

We agree with and appreciate these comments. We excluded patients who were receiving casodex or estramustine. We have changed page 6, line 83 from [Immediate adjuvant therapy mainly included surgical orchietomy, administration of luteinizing hormone-releasing hormone (LHRH) analogs, bicalutamide, and maximum androgen blockade consisting of orchietomy or an LHRH analog together with bicalutamide.] to [Immediate adjuvant therapy included surgical orchietomy, administration of luteinizing hormone-releasing hormone (LHRH) analogs, and maximum androgen blockade consisting of orchietomy or an LHRH analog together with anti-androgens.]

We have changed page 8, line 119 from [Immediate adjuvant hormone therapy consisted of androgen suppression with orchietomy (n = 17), LHRH analog (n = 64), bicalutamide (n
maximum androgen blockade with orchiectomy or LHRH analog and bicalutamide (n = 17), estramustine (n = 3) or another regimen (n = 7).] to [Immediate adjuvant hormonal therapy consisted of androgen suppression with orchiectomy (n = 17), LHRH analog (n = 64), maximum androgen blockade with orchiectomy or LHRH analog and bicalutamide or other anti-androgens (n = 24).]

We have changed ‘hormone therapy’ to ‘androgen deprivation therapy’ throughout the text.

We have changed the number of patients analyzed; from 112 to 105. We have also added ‘the Gleason score at biopsy’ as an independent prognostic factor in multivariate analyses throughout the manuscript and amended Tables 1 & 2.

Results 3. It is unclear if any patients received adjuvant XRT or if XRT was only applied in the salvage setting. If they did not, why did they receive a non-standard/recommended therapy (ADT) without receipt of adj XRT, which has level I evidence to support its use.

Response

Radiotherapy was only applied in the salvage setting to clinically apparent (detected) foci, as described in the results. We agree with the reviewer’s opinion, and we therefore stopped this study in 2006 in light of the results of several studies. However, our choice of adjuvant hormone therapy has some support. Before 2000, when we decided on our treatment policy for pT3N0 patients, adjuvant radiotherapy was not an established therapy. The guidelines announced by EAU in 2001 stated that “radical prostatectomy for stage T3 prostate cancer often results in incomplete tumor excision and combination treatment with hormonal and radiation therapy is gaining popularity.” They continue: “The role of radical prostatectomy in margin-positive disease and in poorly differentiated extracapsular tumours remains doubtful. Furthermore, the use of combination treatments with hormonal manipulation and/or radiotherapy is still under investigation.” However, the validity of adjuvant radiotherapy subsequently gained support, as reflected in reference 5 (2009) and reference 6 (2006). Moreover, ADT was given more priority in Asia than in other areas because of less risk of side effects. The treatment options for post-radical prostatectomy recurrence in Asia for patients with no evidence of distant metastasis are 1) radiotherapy +/- ADT, 2) ADT, or
3) observation, according to the NCCN Clinical Practice Guidelines in Prostate Cancer Asia Consensus Statement in 2013.

After 2006 (when entry to this study ended), we changed our policy to take account of adjuvant radiation therapy.

We have changed page 13, line 207 from [These results indicate the limited success of hormone monotherapy even in a Japanese population.] to [The Asia Consensus Statement 2013 in the NCCN Clinical Practice Guidelines in Prostate Cancer states that androgen deprivation is a candidate treatment option for post-radical prostatectomy recurrence in Asian patients negative for distant metastasis.]

Discussion 1. The authors make comparison to other retrospective reported series of T3a or b disease. While it is important to draw attention to the available data making comparisons across retrospective studies is not helpful. This studies population is made up of mostly Gleason 7 or less patients, while other studies have majority of Gleason \( \geq 8 \). The authors comments "surgery alone might thus be of limited use in most patients with stage pT3N0M0 PCA" is not an appropriate conclusion based on the data provided. Please revise the statement to something along the lines of single modality therapy may not be sufficient in a large portion of patients with T3 PCa and a multimodality approach may be more beneficial, or something along those lines.

Response

Unfortunately, prospective studies of pT3 cases are rare. As you rightly point out, we were concerned that single-modality therapy involving radical prostatectomy might not be sufficient in a large proportion of patients with pT3 prostate cancer, and we therefore treated patients with radical prostatectomy and immediate adjuvant hormone therapy. According to your suggestion, we have changed the sentence on page 10, line 161 from [Surgery alone might thus be of limited use in most patients with stage pT3N0M0 prostate cancer.] to [Single-modality therapy involving surgery alone might be of limited use in patients with stage pT3N0M0 prostate cancer, and a multimodal approach may be more beneficial.].
Discussion 2. The studies presenting outcomes of T3 pts s/p RP only have fairly high rates of biochemical failure free survival and overall survival. Given those findings and the significant hazard ratio for pT3b disease my conclusions from this study would have been different. May consider revising to state that given the high success rate with RP alone in T3 patients, the greater risk of hormone-refractory biochemical progression free survival in pts with pT3b disease and the reported CSS and hormone refractory bcpfs in this series, future prospective studies are needed comparing additive effects of multimodal therapies in patients with pT3 disease to better select for a population of patients that may receive the most benefit. This is hypothesis generating as to what therapies may provide improved outcomes in a sub group of pT3 patients, but clearly a significant percentage of patients are being over treated with application of systemic therapy to all comers.

Response
We agree with and appreciate these comments.

Radical prostatectomy combined with immediate hormonal therapy achieved excellent outcomes in the current study. However, the results of other studies showed relatively high rates of cancer control, even with radical prostatectomy alone, indicating that radical prostatectomy may provide effective cancer control in some patient populations. Further prospective studies are needed to clarify which subsets of pT3 patients will benefit most from additional multimodal therapies after radical prostatectomy. As you noted, the current study identified a significant hazard ratio associated with the pT3b subset (or with higher Gleason score at biopsy). Patients with pT3b disease or with higher Gleason score at biopsy could thus be leading candidates for additive adjuvant therapies.

We have added the following sentences on page 14, line 226 [Further investigations, including prospective studies, are needed to compare the additive effects of multimodal therapies in patients with pT3N0, to allow the better selection of patient populations most likely to benefit from treatment. The current study indicated the significant hazard ratio for seminal vesicle invasion or with higher Gleason score at biopsy, suggesting that patients with pT3b or with higher Gleason score may be the leading candidates for such studies.].

Discussion 3. The final comment is that these findings are based on a pathologic result. The majority of these patients were consider of lower grade and stage at diagnosis and the T3
finding was only after RP. In my opinion this makes RP a very reasonable option for the initial treatment of PCa to help better select for patients who will require additional therapies.

Response

We agree with your opinion. In pathological T3 cases, radical prostatectomy and pathological findings may help cancer control by providing clear information on the risk of recurrence.

We have added the following sentences on page 15, line 232: [These findings were based on pathologic results. The majority of the patients included in the study were considered to have lower grade and stage at diagnosis, and T3N0 was only diagnosed after radical prostatectomy. These results suggest that radical prostatectomy is a reasonable option for the initial treatment of prostate cancer, and allow for the better selection of patients who will require additional therapies.].