Author’s response to reviews

Title: Ultra-early versus early salvage hormonal therapy for post-prostatectomy biochemical recurrence in pT2-4N0M0 prostate cancer

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

Please find attached our revised manuscript entitled “Ultra-early versus early salvage hormonal therapy for post-prostatectomy biochemical recurrence in pT2-4N0M0 prostate cancer” by Taguchi 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 the 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affirm that authorization has been given to use any information conveyed by personal communication or by the release of unpublished experimental data.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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Dr. Charles Rosser’s Comments

1. How was it determined if a patient had ultra-early vs early salvage ADT? If doctor’s preference then what drove doctor to make the decision?

2. It is interesting that there is a definition for biochemical failure for Japanese. Is this definition widely accepted?

Responses

The doctors generally recommended early salvage ADT according to the General Rule for Clinical and Pathological Studies on Prostate Cancer of the Japanese Urological Association and others. However, some patients were anxious and wanted to have ultra-early salvage ADT, and the patient’s preference would have strongly influenced the doctor’s decision.

The definition of biochemical recurrence after radical prostatectomy (two consecutive PSA values \( \geq 0.2 \) ng/ml) is widely accepted in Japan. It is explicitly stated as the general rule according to the Japanese Urological Association.

We have changed the sentence on page 6, line 106 from [Patient allocation was not randomized, but depended on the clinician’s decision.] to [Patient allocation was not randomized. Doctors generally recommended early salvage ADT according to the General Rule for Clinical and Pathological Studies on Prostate Cancer of the Japanese Urological Association et al., but some patients were anxious and chose to have ultra-early salvage ADT (8).].

We have added reference 8 as: The Japanese Urological Association, the Japanese Society of Pathology and Japan Radiological Society: General Rule for Clinical and Pathological Studies on Prostate Cancer, the fourth edition: Kanehara and Co., Ltd; 2010.
3. What is the biology or natural history that would drive PSA kinetics to be different in Japanese? If true science behind it, then this is great. If not then to communicate amongst our colleagues we should adopt widely held standardized definition based on extremely large cohorts or prospective studies.

4. Another issue is the cohort is quite small for such a study.

**Responses**

We do not have specific evidence to suggest that PSA kinetics differ between Japanese and other populations. However, analyses of Japanese cohorts in the references cited below have shown unique findings regarding the efficacy of ADT. Indeed, radical prostatectomy and immediate adjuvant androgen deprivation therapy achieved excellent results, including a 10-year estimated overall survival rate of 85.7% in Japanese patients with pT3N0 prostate cancer (page10, line 176). We recognize the limitation of including only Japanese subjects in the cohort.

We also recognize that the small sample size was an additional study limitation.

We have changed the sentence on page 12, line 215 from [Other limitations were its retrospective design, selection bias, and lead time bias.] to [Other limitations were its retrospective design, selection bias, lead time bias, small sample size, and that the cohort included only Japanese subjects.].


5. I understand the concept of ultra early but would it be of benefit to use ultra sensitive PSA as authors remarked. So even if PSA is <0.2 if a rising PSA profile is seen then this is meaningful. An opportunity may have been missed here.

Response

We appreciate this insightful comment. We began using ultrasensitive PSA assays in September 2003 to evaluate PSA levels of 0.01 ng/mL.

We have added a sentence on page 7, line 115 [We began using ultrasensitive PSA assays in September 2003].

6. Also the researcher acknowledge how salvage XRT based on RTOG and EORTC is standard of care in the US and Europe. Once again why is this not standard of care in Japan? I am sure Asians, specifically Japanese, will be underrepresented. But is the biology different?

Response

We agree with the reviewer’s opinion, which is why we stopped this study in 2012 in light of the results of several other studies. However, our choice of salvage hormone therapy has some support. Salvage radiotherapy was not an established therapy prior to 2000, when we decided on our treatment policy for recurrent prostate cancer. The guidelines announced by EAU in 2001 stated that “Early endocrine therapy has been shown to be effective in achieving an undetectable PSA value in patients found to have advanced disease at the time of radical prostatectomy.” The validity of adjuvant radiotherapy subsequently gained support, as reflected in SWOG8794 (2009) and EORTC22911 (2007). 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.

We changed our policy after 2012 to take salvage radiation therapy into account and we look forward to further studies on ultra-early salvage ADT.


7. Are there large RCT from Japan with salvage ADT or salvage XRT?

Response
To the best of our knowledge, there are no published or ongoing large RCTs of salvage ADT or salvage XRT in Japan.

8. We know that ADT is associated with some real risks related to metabolic syndrome. Perhaps change the tone of the paper to say that this is hypothesis generating and then tell us what the forthcoming hypothesis is.

Response
We appreciate your suggestion. We hypothesized that ADT would be more efficacious than other treatments in recurrent tumors with small volumes.

We have added the following sentence to the Discussion on page 12, line 209 [Together with an excellent result of adjuvant ADT post-prostatectomy against pT3N0 prostate cancer,
ADT might be more efficacious than other treatments in small tumors. However, ADT is associated with some real risks related to metabolic syndrome.]

9. FIGURES: At 120 and 150 months there are barely any participates. Please end figure at 90 months.

Response

Thank you for this suggestion. We have revised Figure 1 accordingly.

Dr. Makito Miyake’s Comments

1. This study doesn’t mention about salvage radiotherapy for recurrent disease. How many patients received salvage radiotherapy in the cohort, 855 patients? What is the first choice for salvage treatment for recurrent disease, hormone therapy or radiotherapy? Hormone therapy is known to be harmful to men’s health. If possible, we should avoid hormone therapy and select radiotherapy instead of hormone therapy. The authors should explain this issue.

2. This study is retrospective. The reviewer had a feeling that the patients receiving ultra-early salvage hormone therapy had more progressive and advanced prostate cancer compared to those receiving early salvage hormone therapy. However, that’s not the case. What is the criteria for selecting ultra-early salvage hormone therapy (FPE positive, pT2<, RM positive, nodal metastasis positive etc)? We should not treat patients with hormone therapy if recurrence risk is low. The authors mention that it depended on the clinician’s definition. It seems ultra-early salvage hormone therapy is not widely-accepted therapy, but many patients received it. The authors should explain this issue.

Responses

We appreciate Dr. Miyake’s helpful comments. In this study, we excluded patients who underwent radiotherapy prior to or concomitant with hormonal therapy, in order to evaluate the efficacy of ADT alone. We have added the following sentence to the Methods (page 6,
patients who underwent radiotherapy prior to or concomitant with hormonal therapy and patients who received any neo-adjuvant therapy were excluded from the study.

For reference, among our 855 patients, 33 received salvage radiotherapy and 24 underwent adjuvant radiotherapy.

Regarding comment 2, we agree that this would be reasonable in an adjuvant setting, and overtreatment of patients at low risk of recurrence should be avoided. However, this study’s cohort consisted solely of patients with recurrent prostate cancer.

We agree with the reviewer’s opinion, which is why we stopped this study in 2012 in light of the results of several other studies. However, our choice of salvage hormone therapy has some support. Salvage radiotherapy was not an established therapy prior to 2000, when we decided on our treatment policy for recurrent prostate cancer. The guidelines announced by EAU in 2001 stated that “Early endocrine therapy has been shown to be effective in achieving an undetectable PSA value in patients found to have advanced disease at the time of radical prostatectomy.” The validity of adjuvant radiotherapy subsequently gained support, as reflected in SWOG8794 (2009) and EORTC22911 (2007). 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.

We changed our policy after 2012 to take salvage radiation therapy into account and we look forward to further studies on ultra-early salvage ADT.


3. What is the hormone therapy performed in the cohort? MAB, LHRH monotherapy or anti-androgen monotherapy?
Response

We started LHRH monotherapy as ADT and added anti-androgen therapy after the patient developed biochemical recurrence, at which point they were treated as censored in this study. We have indicated this in the Methods (page 7, line 112): [Patients who discontinued salvage ADT were treated as censored at the point of discontinuation.].

We have changed “hormonal therapy” to “androgen deprivation therapy (ADT)” throughout the text to clarify this.

4. What is the start point for prognosis analysis?

Response

We started the prognostic analysis from the day of radical prostatectomy (day 0), as indicated in Figure 1 and the revised Methods (page 7, line 113): [The median follow-up for all patients was 65.5 months (interquartile range [IQR]: 46–90.5 months) after radical prostatectomy.].

5. The author should assess QoL of these two groups.

Response

We thank Dr. Miyake for this helpful suggestion and agree that this would be a useful assessment in prostate cancer patients with ADT. However, the current study was unfortunately not designed to assess QoL and this measure was therefore not included in the Ethics Committee approval. Because measuring quality of life was not with the scope of this cohort, it would be an area deserving of further study.

Dr. Ian S Pagano’s Comments

1. As the authors wrote, "Randomized prospective studies with longer follow-up period are needed to confirm benefits of ultra-early salvage hormonal therapy." This research is
effective as either a pilot study or preliminary data, but not for substantive conclusions. I hope these preliminary findings lead to randomized controlled trials.

Response

We thank Dr. Pagano for this favorable comment. As noted, although the current study presented preliminary results to support our novel hypothesis, we agree that further randomized studies are needed to verify these results.