Author's response to reviews

Title: Long term follow-up in patients with initially diagnosed low grade Ta non-muscle invasive bladder tumors: tumor recurrence and worsening progression.

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Author's response to reviews: see over
December 22, 2013

Dr. Hayley Henderson, MD,
Executive Editor, BMC Urology

Dear Dr. Henderson,

We wish to thank you and the members of the Editorial Board for the helpful comments on our manuscript entitled “Should we perform longer follow-up in patients with initially diagnosed low-grade, Ta non-muscle invasive bladder tumors?” (Manuscript number: 1121263703103829).

We have carefully reviewed the comments of the reviewers and have addressed each concern in the attached response letter. We additionally have made changes to our manuscript to adequately address the comments of the reviewers.

We hope we have satisfactorily completed the manuscript such that it will now be acceptable for publication in BMC Urology.

Sincerely yours,

Hiroaki Kobayashi, Eiji Kikuchi, Shuji Mikami, Takahiro Maeda, Nobuyuki Tanaka, Akira Miyajima, Ken Nakagawa and Mototsugu Oya

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RESPONSE TO REVIEWER’S COMMENTS
Manuscript number: 1121263703103829
Manuscript title: Should we perform longer follow-up in patients with initially diagnosed low-grade, Ta non-muscle invasive bladder tumors?

Responses to comments of Reviewer #1:
Thank you for your suggestions and positive comments regarding our manuscript. We have corrected our manuscript according to your comments. The changes are highlighted in red font in the revised manuscript.

1. First sentence in abstract: should remove the word “and”. We retrospectively reviewed 190 patients with primary low grade Ta bladder cancer. Would also make this change in the first sentence of the discussion.

Response) As suggested, we removed the “and” and changed the descriptions.

2. Histology: is the histology Ta transitional cell carcinoma?

Response) We added the following sentence, “All of the tumors were histologically confirmed as urothelial carcinoma.” as the last sentence of the first paragraph in the Methods section of our revised manuscript.

3. Results: first paragraph last sentence: was significantly higher than that for multiple tumors (45.9%, p=0.001) (Figure 1A) and also higher for patients not receiving intravesical instillation (71.3% vs 50.3% with IVI, p=0.007) (Figure 1B).

Response) As pointed out, we corrected the sentence in our revised manuscript (page 7).

4. Second sentence, second paragraph results section: “WP to high grade pTa, pTis, any grade and pT1, or concomitant CIS of bladder was seen in 4, 8, 5 patients”. This sentence does not make sense. Be careful with “and” and “or”. This sentence describes 4 groups but reports on only 3 numbers.
Response) We changed the explanation of the definition of WP to “(1) high grade Ta, all T1 or Tis/concomitant CIS of bladder recurrence, (2) upper urinary tract recurrence (UTR), or (3) progression to equal to or more than T2” in the Methods section. And as pointed out by Reviewer #1, we corrected our description to “WP to high grade Ta, all T1, or Tis/concomitant CIS of bladder recurrence was seen in 4, 8, and 5 patients, respectively” in the revised manuscript (page 7).

5. Specifically when looking at late recurrences, data on smoking history (continued) would be very important in determining whether these recurrences were actually secondary to the risk imposed by the initial diagnosis or of continuing environmental insult.

Response) Smoking status is a well-known risk factor for poor outcome in bladder cancer and the strong association between smoking and primary NMIBC recurrence was observed in previous studies [1] [2] [3]. As indicated by the reviewer, we re-evaluated whether smoking status was associated with recurrence or WP in our low-grade Ta NMIBC patients. Smoking status was classified as 1) nonsmokers; those who had never smoked during their lifetime, 2) ex-smokers; those who had quit smoking before the diagnosis, and 3) current smokers; those who still smoked regularly at the initial TUR-BT.

As shown in the revised Table 1 (below), overall, 100 of 190 (52.6%) were nonsmokers, 56 (29.5%) were current smokers, and 27 (14.2%) were ex-smokers. Univariate and multivariate analyses demonstrated that smoking status was not a predictor for tumor recurrence (revised Table 2 shown below). The results were also re-analyzed in order to compare nonsmokers + ex-smokers with current smokers, but the results were the same.

Kaplan-Meier curves demonstrated that the 5-year recurrence free survival rate for nonsmokers (63.7%) was not significantly higher than that for ex-smokers (51.1%) (£0.397) or current smokers (61.4%) (£0.968). The 5-year WP free survival rate for nonsmokers (93.5%) was not significantly higher than that for ex-smokers (95.0%) (£0.762) or current smokers (89.2%) (£0.378).
Furthermore, there was no association between late recurrence and smoking status, as shown in the revised Table 3 (below).

Table 1. Clinical characteristics of all 190 patients.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Recurrence (+)</th>
<th>Recurrence (-)</th>
<th>p value</th>
<th>WP (+)</th>
<th>WP (-)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>190</td>
<td>82</td>
<td>108</td>
<td></td>
<td>21</td>
<td>169</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>62.9</td>
<td>63.0</td>
<td>62.9</td>
<td></td>
<td>64.9</td>
<td>62.7</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>22-89</td>
<td>26-83</td>
<td>22-89</td>
<td></td>
<td>47-83</td>
<td>22-89</td>
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<tr>
<td>≤70</td>
<td>128</td>
<td>56</td>
<td>72</td>
<td>NS</td>
<td>14</td>
<td>114</td>
<td>NS</td>
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<tr>
<td>&gt;70</td>
<td>62</td>
<td>26</td>
<td>36</td>
<td></td>
<td>7</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>156</td>
<td>72</td>
<td>84</td>
<td>NS</td>
<td>19</td>
<td>137</td>
<td>NS</td>
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<tr>
<td>Female</td>
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<td>10</td>
<td>24</td>
<td></td>
<td>2</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Multiplicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Solitary</td>
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<td>41</td>
<td>73</td>
<td>0.017</td>
<td>7</td>
<td>107</td>
<td>0.016</td>
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<tr>
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<td>76</td>
<td>41</td>
<td>35</td>
<td></td>
<td>14</td>
<td>62</td>
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</tr>
<tr>
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<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
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<td>107</td>
<td>53</td>
<td>54</td>
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<td>10</td>
<td>67</td>
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<td>Smoking</td>
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<td></td>
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<td>60</td>
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<td>Current</td>
<td>56</td>
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<td>27</td>
<td></td>
<td>9</td>
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<tr>
<td>Ex-smoker</td>
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<td>10</td>
<td>17</td>
<td></td>
<td>2</td>
<td>25</td>
<td></td>
</tr>
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<td>7</td>
<td>3</td>
<td>4</td>
<td>0</td>
<td>7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*IVI: intravesical instillation, WP: worsening progression.

Table 2. Univariate and multivariate analyses for tumor recurrence and WP in overall patient population.

<table>
<thead>
<tr>
<th></th>
<th>Recurrence</th>
<th>WP</th>
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<tr>
<td></td>
<td>Univariate</td>
<td>Multivariate</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>p value</td>
</tr>
<tr>
<td>Age (≤70 vs. &gt;70)</td>
<td>0.465</td>
<td>0.444</td>
</tr>
<tr>
<td>Gender (male vs. female)</td>
<td>0.152</td>
<td>0.412</td>
</tr>
<tr>
<td>Multiplicity (solitary vs. multiple)</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treatment (observation vs. IVI)</td>
<td>0.007</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking (nonsmoker vs. smoker)</td>
<td>0.501</td>
<td>0.606</td>
</tr>
</tbody>
</table>


Table 3. Clinical characteristics of 76 patients with a tumor-free period of more than 5 years from initial diagnosis.


6. Discussion should be more general. Currently, the discussion is a synopsis of brief sentences describing prior retrospective literature. This could be significantly improved.

Response) We have changed the Discussion section to be more general in nature as suggested and added a discussion of smoking status.

7. Need to discuss smoking status.

Response) We discussed the association between smoking status and bladder recurrence in the Discussion section of the revised manuscript.
Smoking status is a well-known risk factor for poor outcome in bladder cancer and the strong association between smoking and primary NMIBC recurrence was observed in previous studies [1] [2] [3]. However, our results revealed that smoking status is not associated with bladder recurrence rate, WP rate, or late recurrence rate. One of the reasons for our negative result is that the relatively lower percentage of smokers and lower amount of smoking in Japanese NMIBC populations. Further studies with a larger population are warranted in order to evaluate the association between smoking status and tumor outcome in low grade Ta NMIBC.

8. The conclusion should more closely match the results. It appears that the overwhelming majority of patients (>85%) will not recur after a 5 year disease free interval. Unfortunately, no specific risk factors were identified in this study to help guide longer follow up in the small proportion destined to recur. Again, smoking status prior to and after initial diagnosis would be important in determining the “true non-modifiable risk” of recurrence. The data showing less than 15% of patients having a recurrence (mostly low risk) does not necessarily support the conclusion “suggesting a need for longer term follow up”.

Response) In our patients with low grade Ta tumors, 14.5% were late recurrence, which means a tumor-free period of more than 5 years was observed. All patients whose cancer recurred in years 5 and 10 in our study were diagnosed at a follow-up cystoscopy. Meanwhile, recurrence in 2 patients who were tumor-free beyond 10 years was found by gross hematuria. These results suggest that follow-up cystoscopy can be discontinued at around 10 years from the initial diagnosis in patients with low grade Ta bladder cancer.

Therefore, we changed the conclusion to “Our results suggest that routine follow-up of patients with low grade Ta bladder cancer is needed up to 10 years from the initial diagnosis.”
Response to Reviewer #2:
Thank you for your suggestions and positive comments regarding our manuscript. We have corrected our manuscript according to your comments. The changes are highlighted in red font in the revised manuscript.

A. Major Compulsory Revisions
1. Were the recurrences and therefore progressions detected due to symptom (hematuria etc.) or during the routine surveillance cystoscopies?

Response) Among 82 patients who had tumor recurrences in our study, the recurrence was detected due to symptoms (gross hematuria) in only 3 patients (3.7%). One patient experienced hematuria when he had WP 4 years after the initial diagnosis, and 2 patients after more than 10 years from the initial diagnosis. Therefore, most of the patients who had recurrence (96.3%) could be diagnosed by the routine follow-up cystoscopic examination. We added these sentences in the Results section (page 7 and page 9) of our revised manuscript.

2. Patients who continue to smoke are prone to recurrences. These data is missing but of importance for analysis. If the recurrences/progression over 5 years occurred mostly/only smokers one may suggest that long term follow-up should be conducted only/mainly in smokers.

Response) The same comments were made by Reviewer #1 (comments No 5 and No 7). Please see our responses above.

3. Did the authors record initial tumor size/volume? This is a well-known predictor for recurrence.

Response) In our database, tumor size/volume was not included routinely because of the inaccuracy of measurements of tumor size by cystoscopic findings. To evaluate the tumor size by radiological imaging such as ultrasound, CT scanning or MRI could be carried out but not all patients
underwent those imagings. This is a limitation of our study and we addressed it in the Discussion section in our revised manuscript (page 12).

4. The title of the paper is a bit misleading. Only 76/190 patients were followed more than 5 years. Most progressions and recurrences occurred within 5 years.

Response) As pointed out by Reviewer #2, we changed the title based on the revised conclusion of our study to “Long-term follow-up in patients with initially diagnosed low grade Ta non-muscle invasive bladder tumors: tumor recurrence and worsening progression”.

5. The authors state in their conclusions that late recurrence and WP occurred at a constant rate. It is unclear to me what they mean by constant rate?

Response) As pointed out by the reviewer, the “constant rate” was an inappropriate phrase so we removed it from the revised manuscript.

In fact, 14.5% were late recurrence, which means a tumor-free period longer than 5 years was observed in our patients with low grade Ta tumors. All patients who experienced recurrence in years 5 and 10 in our study were diagnosed at a follow-up cystoscopy. Meanwhile, recurrence in 2 patients who were tumor-free beyond 10 years was found by gross hematuria. These results suggest that follow-up cystoscopy can be discontinued around 10 years from the initial diagnosis in patients with low grade Ta bladder cancer.

Therefore, we changed the conclusion to “Our results suggest that routine follow-up of patients with low grade Ta bladder cancer is needed up to 10 years from the initial diagnosis.”