Author's response to reviews

Title: In-depth investigation of the molecular pathogenesis of bladder cancer in a unique 26-year old patient with extensive multifocal disease: a case-report

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Version: 2 Date: 27 November 2009

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

We would like to thank you for reviewing our manuscript entitled: “In-depth investigation of the molecular pathogenesis of bladder cancer in a unique young patient with extensive multifocal disease: a case report” by Zuiverloon et al. for publication in BMC Urology. We have taken the reviewers comments and suggestions into consideration and processed this into our manuscript. A detailed overview of the changes is listed below. All changes are indicated in the revised manuscript with track changes. We believe that this has improved the quality of our manuscript and would like to thank all the reviewers for their suggestions. Hereby we would like to resubmit the revised paper.

We hope you share our vision that new insights into the molecular characteristics of young bladder cancer patients could lead to an improvement of the current surveillance protocol and find our work suitable for publication in BMC urology.

Yours sincerely,

Ellen C. Zwarthoff
Professor of Molecular Pathology
Corresponding author
Reply on reviewers comments

Date: 26-11-2009

MS: 2106539662305135

Title: In-depth investigation of the molecular pathogenesis of bladder cancer in a unique young patient with extensive multifocal disease: a case-report

Reviewer: Noboru Sakamoto

1. In the title, “an unique” may be correct?

When a "u" word is pronounced as though it begins with a "y" (yoo nique), it's treated more like the consonant sound of the y. So, a university, an umbrella, a usual day, an unusual day.

2. Young is unclear. I prefer “unique 26 years-old case with “ in the title.

The title of the manuscript has been changed to:
In-depth investigation of the molecular pathogenesis of bladder cancer in a unique 26-year old patient with extensive multifocal disease: a case-report

3. Which kind of second antibodies and how strong concentrations did you use in the histopathological analysis?

Visualization was done by Dako EnVision detection system, containing secondary antibodies to mouse and rabbit. This information was added to the “Materials and methods” section: FGFR3 and TP53 immunohistochemistry.
Reply on reviewers comments

Date: 26-11-2009

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Title: In-depth investigation of the molecular pathogenesis of bladder cancer in a unique young patient with extensive multifocal disease: a case-report

Reviewer: Kazunori Namiki

Reviewer has no comments on the manuscript
Reply on reviewers comments

Date: 26-11-2009

MS: 2106539662305135

Title: In-depth investigation of the molecular pathogenesis of bladder cancer in a unique young patient with extensive multifocal disease: a case-report

Reviewer: Alex Sgambato

1. In the methods, tissue samples paragraph he authors state that: “samples were first deparaffinized and DNA was extracted...”. It is not clear what type of samples were used for DNA extraction: tissue slices? How tick? How many?

Tumor tissue sections containing a minimum of 80% tumor cells were manually dissected from a 4 µ slide. Slides were deparaffinized and DNA was extracted. This information was added to the “Materials and Methods” section: Tissue samples.

2. It is not clear what overexpression of FGFR3 is referred to.

We analyzed FGFR3 and TP53 protein expression in normal urothelium by immunohistochemistry and this was used as a reference. This information was added to the manuscript in the “Materials and Methods section: FGFR3 and TP53 immunohistochemistry”.

3. The reviewer suggests that it would have been of interest to try to define the frequency of FGFR3 mutations in a subset of young patients.

We would like to thank the reviewer for this suggestion. Since bladder tumors in young patients are rare we could not analyze a larger subset of young patients in our medical center. We are aiming to investigate this in collaboration with multiple centers, but this will take some time to set up.

4. The authors seem to suggest that FGFR3 mutations in tumors might characterize young patients with high risk of recurrence. However: “FGFR3 mutations have been associated with BC tumors of low stage and grade and patients have a favorable prognosis”. How to conciliate these points?

We discern two types of young patients: (i) young patients with no molecular changes and (ii) young patients with molecular changes comparable to older BC patients. Patients with no molecular changes (i) have a low recurrence- and progression rate and patient type (ii) has a recurrence rate comparable to older patients as demonstrated in our case. Although older patients with FGFR3 mutations have been associated with tumors of low stage and grade and a favorable prognosis they have a high recurrence rate with 70% of all patients developing at least one recurrence within 5 years. Thus a young patient with an FGFR3 mutation requires frequent monitoring due to the possible high recurrence rate despite having a low chance of progression to muscle-invasive disease.
5. Manuscript should be checked carefully for English.

The manuscript was checked carefully for English and appropriate changes were made.

6. It might be useful to clarify what is intended for pack-years since not all readers might know it well.

We added information to the “Case presentation” section to explain the meaning of pack-years.