Author’s response to reviews

Title: The natural history of secondary muscle-invasive bladder cancer

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Author’s response to reviews: see over
Dear Editor

Thank you for the reviewer's and editorial comments and for the opportunity to submit a revised version. The following changes were done in the manuscript according to the comments. All changes are highlighted in the manuscript in yellow.

**Referee 1**

**Comment 1:** Authors should define primary and secondary MIBC in the abstract.

**Response:** This was done.

**Comment 2:** That state that all pts had biopsies at 12 and 24 mo. Why is cystoscopy was normal?

**Response:** The reviewer is correct. This conclusion is not supported by the data. This was replaced by the more balanced sentence: Meticulous follow-up with liberal biopsy of any suspicious lesion may provide early diagnosis of invasive disease.

**Comment 3:** I would not use the term mutilation for a RC.

**Response:** The term "mutilation" was replaced by the term "disfigurement".

**Comment 4:** The prognosis for pts with MIBC is not unclear as stated. Given the grade, pT, nodes etc there is a stated range of CSS.

**Response:** It is difficult to understand the meaning of this comment; "not unclear" is "clear".

**Comment 5:** Did pts with HG Ta or T1 really have a second TUR BT in 1998?

**Response:** Yes, the policy of "second look" biopsies in the operating room was adopted in our institution very early by one of the authors (AS).
**Comment 6:** Most begin BCG after 2 weeks from surgery.

**Response:** Yes, as stated "initiated 10-20 days following the TURBT".

**Comment 7:** Why annual upper tract imaging? No data to support this.

**Response:** Upper tract surveillance was done annually only in patients with high-grade disease as is a common practice in many institutions. This was clarified in the text.

**Comment 8:** One would think CSS better with secondary MIBC as pts are under surveillance.

**Response:** There is conflicting data in the literature. Schrier et al for instance, showed a significantly worse prognosis in patients with secondary MIBC (reference 12 in the article).

**Referee 2**

**Comment 1:** The statement regarding the significant difference in T0 and T3 disease in the two groups should be deleted from the abstract (unless it turns out to be important, which is not now apparent) and clarified in the text by including the numbers and percents listed in Table 2. Is the difference in T0 statistically significant? Is the difference in T3? The statement as presented is unclear.

**Response:** The statement regarding the T0 and T3 is indeed unimportant and was removed from the abstract. The difference between the stage distribution of primary and secondary MIBC is statistically significant and was kept in the "results" section. The meaning of this "difference" however, is not clear.
Comment 2: The difference in survival at 2 and 5 years between the two groups calculated from initial diagnosis and onset of muscle invasion needs to be more clearly stated (for example, by repeating the primary survival figures and not requiring the reader to remember or re-read them).

Response: This part of the "discussion" was corrected accordingly.

Comment 3: Is it true that neoadjuvant chemotherapy was not used? If so, it should be stated. If it was used, the percent use in the two groups should be specified.

Response: Neoadjuvant chemotherapy was not used in any patient. This was added to the "methods" section.

Comment 4: Were all patients with T1 disease high grade? Grade should be clarified for T1.

Response: Yes, all T1 patients had high-grade disease. This was added to the "results" section.

Comment 5: A few typographic and/or English errors should be corrected: “from” rather than “form” under statistics on page 8, the statements “muscle invasion disease,” and “may allocate muscle invasion.

Response: All these were corrected.

Editorial Comments:
1. Abstract

Please can you revise the Background section of your Abstract. Please open with a sentence that puts your study into context, which then leads on to your study rationale and why you are conducting this research.

Response: This was done.
2. Ethical Approval and Methods

We would suggest rephrasing the opening section of the Methods (see below), so that the setting is included at the start - please do feel free to change this text where necessary. Please can you include the full name of the ethical committee that granted approval.

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Information was obtained from the Hadassah Hebrew University Hospital database for 760 patients treated for bladder cancer between 1998 and 2008. This retrospective study was approved by the Institutional Review Board Committee (PLEASE INCLUDE FULL NAME OF ETHICAL COMMITTEE) (IRB number 207-31.10.08).

Response: This was done

3. Acknowledgements

Following the Authors' Contributions section can you please include an Acknowledgements section. Please acknowledge anyone who contributed towards the article by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include the source(s) of funding for each author, and for the manuscript preparation. Authors must describe the role of the funding body, if any, in design, in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. Please also acknowledge anyone who contributed materials essential for the study. If a language editor has made significant revision of the manuscript, we recommend that you acknowledge the editor by name, where possible.

Response: No one was involved in preparations of the article beside the authors. The personal fund of the primary investigator was the only financial source of the project.
4. Tables

Please can you remove Tables 1 and 2 from the additional files and include these in the manuscript document. They should appear after the References.

Response: This was done.

5. Copyedit

We recommend that you ask a native English speaking colleague to help you copyedit the paper. If this is not possible, you may need to use a professional language editing service. For authors who wish to have the language in their manuscript edited by a native-English speaker with scientific expertise, BioMedCentral recommends Edanz (www.edanzediting.com/bmc1). BioMed Central has negotiated a 10% discount to the fee charged to BioMed Central authors by Edanz. Use of an editing service is neither a requirement nor a guarantee of acceptance for publication. For more information, see our FAQ on language editing services at http://www.biomedcentral.com/authors/authorfaq/editing.

Response: One of the authors (KCZ) revised the manuscript again and made changes.

6. Formatting

Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is important that your files are correctly formatted.

Response: This was done