Author's response to reviews

Title: Can daily intake of aspirin and/or statins influence the behavior of non-muscle-invasive bladder cancer? A retrospective study on a cohort of patients undergoing transurethral bladder resection

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Author's response to reviews:

#1 Reviewer's report

Title: Can daily intake of aspirin and/or statins influence the behavior of non-muscle-invasive bladder cancer? A retrospective study on a cohort of patients undergoing transurethral bladder resection

Version: 2 Date: 10 November 2014

Reviewer: Lars Dyrskjot

Reviewer's report:

Pastore et al investigate the influence of aspirin and/or statins on NMIBC recurrence. A significant association between aspirin intake and decreased tumor recurrence frequency was observed. But overall the recurrence frequency was higher in the treated patients compared to untreated. Limited information is available about the effects of aspirin intake in NMIBC patients. Overall the presented findings are interesting, but it would be easier to interpret if data were presented differently.

Major Compulsory Revisions

1. The comparison between treated an untreated seems strange as different drugs are included in the treated patient group.

Answer: Thanks for this important consideration. We agree with your point of view, considering, as you referred “strange” the initial classification in treated and untreated patients. The comparison was done only to offer a general description of the results obtained between patients with or without daily assumption of drugs. In fact, as you surely observed, the most significant data were obtained by
the patients’ subsequent stratification for the different type of therapy assumed. In the final text-file, we removed the results comparison between treated and untreated patients, because, agreeing with your suggestion, it does not add any supplemental data, appearing just redundant.

2. The figures are difficult to read, and I think it would be much easier to transform this into a table with all comparisons and results available.

Answer: As correctly requested figure 1 was transformed into a table, giving all the results and the comparison available. Regarding the other figures we optioned to show data in this graphical presentation, because a complete results report was inserted in the “results” paragraph of the final manuscript. The graphical presentation seemed like the best and easiest way for the results comprehension.

3. Are aspirin intake also associated with decreased recurrence when stratifying for other risk factors? Multivariate analysis is mentioned in materials and methods, but it is not clear when this has been used.

Answer: Thanks for this important comment, as requested the multivariate analysis was performed using Kaplan Meier method, the figure was added and all the data regarding the for different groups are presented.

#2 Reviewer's report

Title: Can daily intake of aspirin and/or statins influence the behavior of non-muscle-invasive bladder cancer? A retrospective study on a cohort of patients undergoing transurethral bladder resection.

Version: 2 Date:17 June 2014

Reviewer: Teemu Murtola

Reviewer's report:

This manuscript describes a cohort study of 574 patients with non-muscle invasive bladder cancer (NMIBC) undergoing transurethral resection during 2008-2013. Disease recurrence after the primary operation was compared between patients who had used aspirin, statins, both or neither of studied the drug groups.

More recurrences and higher number of lesions at recurrence were observed in medication users overall compared to non-users. Among the medication users aspirin users had fewer recurrences compared to statin users, with the recurrence rate being comparable between aspirin users compared to medication non-users, but elevated in statin users compared to non-users.

I have the following comments:

Major compulsory revisions:

- The length of follow-up, as well as the end-points for study follow-up need to be described

Answer: The length of patients’ follow-up and the end-points were added in the methods paragraph.
- The conclusion that aspirin protects from NMIBC is an over-interpretation of the results. Figure 3 shows that there is very little difference in any of the end-points between aspirin users and medication non-users, with overlapping confidence intervals.

- What was the reference group for the p-values reported in this Figure? The medication non-users or statin users? I suspect the latter, whereas the former would be correct.

Answer: We do agree with your comment, and after the data review, we modified the manuscript conclusions giving a balanced interpretation.

The reference group for p values in figure 3 was the untreated group.

- You should re-do the analysis using Cox regression or Kaplan-Meier method with time-metric being the time since the primary TURB. This would be much more informative given that it would take into account also the time to recurrence.

Answer: As correctly observed and requested, a Kaplan Meier analysis was done. The results and figure are now added in the final manuscript.

Minor essential revisions:

Abstract
- Conclusions, Page 3:

Overstatement in conclusions. A single observational study cannot confirm or refute causal associations, especially given the limitations mentioned above.

Answer: As reported in the previous answer, we modified the manuscript abstract conclusions according to your observations, giving balanced interpretation of results.

Background
- Page 4, 2nd paragraph, the sentence beginning “Using our cohort of patients and the results of other studies on epithelial neoplasms....”

o This sentence remained unclear to me. What results from other studies did you use in your study?

Answer: Thanks for this comment, we changed the sentence in the final manuscript version.

Methods
- 1st paragraph: did you include only patients undergoing their primary TURB, or did you also include previously treated patients?

Answer: This is an important comment, because it allows to better explain the recruitment design, which included only previously untreated patients undergoing their primary TURB. This criteria has now been inserted in methods section.

- 2nd paragraph: Describe the 21 women that were excluded in order to obtain statistically homogeneous comparison groups. What there the exact reasons for
their exclusion?

Answer: The exact reason which induced us to exclude these 21 women was the lack of some follow-up data.

- Page 6, 1st paragraph: Did you only consider medication usage at baseline (the time of primary TURB) or did you also include medication usage during the follow-up?

Answer: We considered patients in treatment with aspirin (100 mg daily for at least 2 years), or with statins (# 20 mg daily for at least 2 years), or simultaneously with both drugs either at baseline, and during the 45 months of follow-up. Patients with uncertain data about continuity of these medication intake were excluded from this retrospective analysis.

Results
- It can be observed in Table 1 that medication users, especially statin users had more often high-grade and pT1 disease, which could explain the higher number of recurrences among them. The difference was not statistically significant, but this could be due to low numbers of study participants. You should include stratified analyses comparing recurrence by medication use separately in those with high-grade disease and in those with low-grade disease. Also stratification by smoking status and presence of carcinoma in situ would be informative.

Answer: Stratified analyses were included and the description of the outcomes was added in the manuscript (methods and results paragraphs). The stratification analyses were performed for every parameter (age, smoking status, category of drug assumption, stage and grade) except for cases reporting Cis, whose number was too little (only 16 cases, 3% of total enrolled population) to achieve statistical significance.

Table 1
- The proportions of men with carcinoma in situ should be added to the table.
- Report the numbers of patients who received intravesical instillation of chemotherapy at TURB. If you do not have this information, it should be mentioned as study weakness.

Answer: The number of patients with Cis and of the ones who received intravesical therapy was added in the table 1.

Figures
- What are the numbers reported inside the bars? Means or medians?
Answer: The reported number are means.

Discussion
- The p-values and proportions should not be repeated in this section, as they have already been reported in the Results-section.

Answer: p values and proportions were removed from this paragraph.
- Page 10, 4th paragraph: this paragraph discusses the potential significance of COX-2 in bladder carcinogenesis. However, the similar disease recurrence in aspirin users and medication non-users observed in this study does not support this.

Answer: We completely agree with your comment; in fact we reported that our study did not confirm the literature data supporting the role of COX-2 in bladder carcinogenesis.