Author's response to reviews

Title: Preoperativ serum C- reactive protein: a prognostic marker in patients with upper urinary tract urothelial carcinoma

Authors:

Barbara Stein (bjohann@gmx.de)
Andres J Schrader (ajschrader@gmx.de)
gerald Wegener (wegener.gerd@mh-hannover.de)
Christoph Seidel (seidel.christoph@mh-hannover.de)
Markus A Kuczyk (makuczyk@gmx.de)
Sandra Steffens (steffens.sandra@mh-hannover.de)

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Author's response to reviews: see over
Dear Christna Chap,

Thank you for your letter concerning our manuscript entitled: “Preoperativ serum C-reactive protein: a prognostic marker in patients with upper urinary tract urothelial carcinoma”. We have carefully studied all of the reviewers’ comments and revised the manuscript accordingly. Attached please find the revised manuscript as well as a list providing a detailed explanation of all revisions.

We hope that the manuscript is now suitable for publication in BMC Cancer and look forward to hearing from you soon.

Yours sincerely,

Sandra Steffens
Ms: 8145289788254924  (Stein et al.) – Revisions

Reviewer #1: Kazutaka Saito

This article demonstrated the prognostic impact of CRP in upper urinary tract urothelial carcinoma (UUT-UC) patients treated surgically. As a reference of Saito et al, the prognostic impact of CRP has been shown. Furthermore, the significance of CRP as a useful biomarker for UUT-UC has been described in a review (Nat Rev Urol. 2011;8:659). Therefore, I think this is a confirmatory study about the significance of CRP in UUT-UC patients. I have several comments.

Major Compulsory Revisions

1) In the patients section, authors shown that this study included 158 patients. However, 115 patients whose preoperative CRP values were available appeared to be evaluated in this study. How many patients were eligible in this study? Please specify.

   Answer: We have changed the number of Patients to 115 and explained in the material and methods why 43 Patients were excluded.

2) In the results section, author described that the current population constituted from 113 men and 45 women (total 158 patients). Again, I think that 115 patients whose preoperative CRP values were available were objective of this study. Patients’ demographics should be changed.

   Answer: Patients demographics were changed accordingly.

3) Why the population of ureter cancer was so small (total 7 patients)? The cancer specific survival rate of this cohort (the 5yr-rate of approximately 50%) would be worse compared to those of previous studies (around 70%). The follow up period were quite short (median of 16 months) for this type of analysis. Therefore this cohort appeared to be very biased one. The explanation is needed.

   Answer: The reviewer is right. The median survival is short and shorter in our analysis than in earlier trials. Exact data were added in the results section. We do not really have an explanation for this. As our institution is a tertiary referral center it is possible that disproportionately many patients with large tumors, poor differentiation and high comorbidity were included in our analysis.

4) The inclusion and exclusion criteria (e.g. the prior or concomitant bladder cancer, peri-operative chemotherapy) have not been sufficiently documented. That information could be added on the analysis.

   Answer: Inclusion and exlusion criteria were added.
5) The limitations of this study are the relative small number of patients, the short follow-up (median 16 months), the biased cohort, and retrospective nature of the study. The limitations section of this paper does not adequately discuss these points,

**Answer:** A detailed limitation section was added. The median/mean follow up was adjusted to the novel number of cases included (i.e. only those with available CRP values pre-surgically, n=115).

**Minor Essential Revisions**

6) In the patients section, Furman grading is a nuclear grading classification system for clear cell renal cell carcinoma.

**Answer:** This was a mistake, we used the pathological grading system according to the WHO standard. We changed that in the text and thank the reviewer to be so alert to find this mistake.

7) Authors added the statistical methods after each p value in tumor specific parameters paragraph. These statistical methods should be specified in the material and methods section.

**Answer:** Done.
Reviewer # 2: Charles Rosser

Reviewer's report:

In this interesting article by Stein et al. entitled Preoperative serum C-reactive protein: a prognostic marker in patients with upper tract urothelial carcinoma describes that using a cutoff of 5 mg/L, CRP can be a prognostic marker. In fact 78.9% vs. 36.4% of MIBC vs. NMIBC had elevated CRP. Similarly, 26.8% vs. 4.5% of patients with nodal disease had elevated CRP as did 16.9% vs. 2.3% of patients with distant metastasis. Multivariate analysis demonstrated that CRP, age and presence of mets corresponded to independent prognostic factors. Overall this is a straightforward simple to follow well-written manuscript. Below is a point-by-point critique of the manuscript.

TITLE: No issues

ABSTRACT: No issues

INTRODUCTION: Nice introduction. It lays the groundwork for the study.

METHODS: Who performed the CRP analysis? Your clinical lab or an investigational lab? Can the authors comment on if patients received pre-op or post-op chemotherapy since this could effect survival. Also was a lymph node dissection performed? If so then how extensive?

Answer: Our clinical lab performed the analysis (routine CRP diagnostics). We do know that none of the patients had received preoperative chemotherapy, however, we do not exactly know, how many patients received a post-OP / adjuvant chemotherapy. The regional lymph nodes were dissected only in patients who presented with enlarged/conspicuous lymph nodes in a pre-OP CT scan or in case of clinically enlarged nodes during surgery; an extended lymphadenectomy was not used routinely. All these information were included in the material and methods section.

RESULTS: No issues

DISCUSSION: Nice discussion. So the authors are just confirming what Saito et al previously reported, correct? Thus your finding is not novel. CRP can be effected by inflammatory of CVD---did any of your patients have these conditions? Could these conditions effect your results? Please list limitations of your study in a paragraph prior to your conclusion paragraph.

Answer: Unfortunately, in this retrospective analysis complete information on the prevalence of CVD was not available. A limitation section was added.

CONCLUSION: No issues

REFERENCES: No issues

TABLE 1: Change 1 at time of renal surgery to 1 at time of surgery.

Answer: Done
FIGURE1: What is your median follow-up? Can you accurately report the KM to 12.5 years? How many subjects are available for analysis at 2.5, 5, 7.5, 10 and 12.5 years?

Answer: The new (adjusted to n=115 pts. included) median/mean follow-up was calculated and included. Patients at risk for the different time points were added below figure 1.