Author’s response to reviews

Title: Prognosis of Rectal Cancer Patients improves analog to Downstaging by intensified neoadjuvant Radiochemotherapy - a matched pair analysis

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Author’s response to reviews: see over
Dear Editor,

thank you very much for the excellent review of our manuscript (1442542886934130) entitled ‘Prognosis of Rectal Cancer Patients improves analog to Downstaging by intensified neoadjuvant Radiochemotherapy – a matched pair analysis’ by Schiffmann et al. We appreciate the reviewer’s effort to improve the manuscript and the chance to resubmit. The manuscript was modified according to the reviewers’ suggestions. For your convenience, all changes of the text’s body are marked.

Since it appears to be THE major concern about the manuscript, that we used the pathological stage rather than the clinical stage, I would like to address to this issue before going on the other helpful comments in detail: Undoubtfully, there is a significant overstaging in clinical staging of around 20%. This actually means, that neoadjuvantly treated patients have a survival advantage of 20% compared to not neoadjuvantly treated patients in the follow up just because they have been overstaged before. The only way to compare the groups for long term survival is by using the pathological stage – which is meant to be the gold standard. Of course, we do not show, how much each patient is downstaged, but we show the long term prognosis of downstaged resulting pathological stage. We really hope, that we could make this clear in the discussion but are open to suggestions for further explanations.

Responses to reviewers’ comments:

Reviewer Guoxiang Cai

1. It is unfair to draw a conclusion that neoadjuvant RCT can improve the prognosis of rectal cancer pts based on the post neoadjuvant RCT surgical pathological TNM stage. I would recommend to use the cTNM stage of pre-neoadjuvant therapy (stage 2/3) and the atching stage 2/3 without neoadjuvant therapy (pTNM stage).

   As pointed out above, there is a significant overstaging in clinical staging of around 20%. This actually means, that neoadjuvantly treated patients have a survival advantage of 20% compared to not neoadjuvantly treated patients in the follow up just because they have been overstaged before. The only way to compare the groups fairly is by using the pathological stage – which is meant to be the gold standard. Of course, we do not show, how much each patient is downstaged, but we show the long term prognosis of downstaged resulting pathological stage. We really hope, that we could make this clear in the discussion but are open to suggestions for further explanations.

2. Some important information was missed in this study:
First, there is no information about the postoperative chemo of the pts in the study group. And we do not know how many pts with pathological stage 2/3 underwent adjuvant radiochemotherapy in the control group.

   44.9% of the Control group received an adjuvant RCT. This number is shown in table 2. As the reviewer pointed out, we did not provide information about
the postoperative chemotherapy in the study group. We are happy to add this information in 'patients and methods'.

3. Second, the staging method was not mentioned.

We thank the reviewer for these very helpful comments and changed the text accordingly.

4. Third, the author did not mention the criteria of efficacy evaluation of neoadjuvant therapy.

Again, we thank the reviewer for this helpful remark – and changed the text accordingly.

Reviewer Jianmin Xu

1. Authors should state that are there different or same adjuvant therapy after rectal surgery between the 2 groups, because it is important element affecting prognosis

We thank the reviewer for this helpful remark – and changed the text accordingly.

2. In the 4th paragraph of Result, authors should state what are the exact 5- and 10-year survival data.

We have to admit, that this is a retrospective analysis. Therefore, not all patients have a follow up of five years. The follow up time is shown in table 3 and the measured (actuarial) outcome after this follow up time is shown in combination to the calculated (by Kaplan Meier) 5 year data. We cannot provide 10 year survival data.

3. The title “Prognosis of Rectal Cancer Patients improves analog to Downstaging by intensified neoadjuvant Radiochemotherapy – a matched pair analysis' is not clear, especially what “analog to” means

It means correspondent or equivalent. If the reviewer insists on changing the sentence, we will do that.

4. In results of abstract, “the actuarial cancer related and disease free survival was 67.9% and 70.4%” does mean “5-year”? 

No, as stated, these are the observed rates within the observation period. Please compare to answer 2.

5. In 2nd paragraph of Patients and methods, “irinotecan (initially 6 times, weekly, 40mg/m2; later 4 times, week 1,2,4 and 5 with 60mg/m2)” is not clear.

We changed it to once a week with 40mg/m2; later 4 times, once weekly in …
6. In Statistical analysis, “Statistical analysis was done using Pearson’s chi-square test of Fisher’s exact test” may not be right.

We thank the reviewer for clarification. We changed the expression.

7. In 4th paragraph of Results, “However, UICC-stage dependent survival benefits of the UICC 0-III (Figure 2) versus UICC IV (Figure 4) become apparent” should state the exact survival data

Thanks for the comment. In our opinion stating the exact data in addition to the curves would provide the information twice. All information can be taken from the figures. But – of course – if the manuscript could not be published without the changes, we would be happy to change it.

8. The figures showed disordered arrangement. For example, Figure 1,2 and 4 can be renamed as Figure 1a, 1b and 1c.

This seems to be a minor request, only. We would rather keep the numeration as in the manuscript. But – of course – if the manuscript could not be published without the changes, we would, again, be happy to change it.

9. The first 2 sentences in Conclusions can be redesigned as the last paragraph in Discussion.

We changed the manuscript according to the suggestions of the reviewer.

10. In Table 1, “Age” needs add “(mean or median)”.

Done as suggested.

We are very confident that the revised version now matches the requirements for publication in BMC Cancer. We would be very pleased if you and the reviewer would find this enhanced version suitable for publication.

In the name of all authors,

Sincerely yours,

Leif Schiffmann