Author's response to reviews

Title: Changes in Quality of Life the first year after oesophagectomy for cancer - an indicator for timing of support

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Author's response to reviews: see over
Revision notes

Thank you very much for the review of the submitted paper, MS: 1538497230101554 - *Quality of Life measurements as an indicator for timing of support after oesophagectomy for cancer - A prospective study*. We have now made changes in the manuscript according to the constructive criticism made by the reviewer. All changes are highlighted in the text. We have also answered all questions and hope that you will reconsider the paper for publication.

Kind regards
Marlene Malmström and co authors

Reviewer 1: Marco Scarpa

Introduction

1. the sentence "Today there is a lack of knowledge about how the patients QOL fluctuate during the first postoperative year." does not take in account of a recent paper (J Gastrointest Surg. 2013 Mar;17(3):421-33.)
   Comment: We have now reformulated the sentence to ease the understanding (Page 3, line 80-84). The suggested paper is interesting but focuses as far we can see it on specific aspects of QOL and the potential association between QOL and patient’s and disease characteristics. The paper is however now added to the manuscript.

2. the sentence "There is no consensus regarding what impact factors that affect the patients QOL after surgery." is rather obscure. Please, reformulate it.
   Comment: Sentence removed since it is explained in the following sentence

Methods

1. the sentence “This prospective study was a separate part of a randomized controlled trial carried out at Skåne University hospital" suggest a bias of the study because the population included in the study was selected and randomized in two arms. Please, address this issue in the discussion
   Comment: All patients selected for the study followed the list of inclusion criterias irrespective of which arm they were randomized into. Thus, no selection bias present at this level. We adjusted our final findings regarding randomization to PPI treatment or not (ie the study design) and found that patients who received PPIs had a better outcome as compared to those without. This is according to our opinion not regarded as bias. Clarification on this issue is now added in the paper (page 9, line 287-297).

2. table 3 showed that less than half of patients answered at 12 months and this is expected in a esophageal cancer patients group. However, this data arise some doubt on power of the tests. please, address this issue.
   Comment: The drop out at 12 months is as the reviewer pointed out expected due to the severity of the diagnosis. Therefor imputation of missing forms/answers has been conducted to ensure power. Information about imputation has been added in the method section (page 6, line 202-204).
3. The sentence "When evaluating the original data we failed to prove a perfect normal distribution" suggest that Friedman ANOVA should have been used. Please, address this point.

Comment: Friedman’s test is a non-parametric test for repeated measurements of variance. However, there are several limitations with Friedman’s test. One limitation is that it can not adjust for potential impact factors that we have chosen to adjust for. Another limitation is that Friedman’s test can only answer whether or not the results of the whole groups have changed over time, but not when the change appeared or disappeared over time. Thus, Friedman’s test can not answer our questions when the change appeared, and can not answer the question regarding impact factors for the change. An alternative to using the parametric repeated measurements ANOVA using non-parametric statistics would force us to do repeated statistical testing with the risk of increasing the no of type II errors, with results that even more would violate the statistical rules that applies to these tests. Furthermore, we did not do any ‘statistical fishing expeditions’ with the results to find out the maximum no of significances between the studied parameters but kept to our original hypotheses. The results were calculated with both uni- and multivariate methods (information added page XX Line XX). Finally, the actual results of the p values indicate a very high level of significance, a fact that indicate solid findings.

Results

1. Figure 1 and figure 3. I am not so sure that you can create a cumulative score of QLQ C30 and OES18. Please, verify and justify.

Comment: Figure 1, 3 and 5 are now removed as recommended by the reviewers.

Reviewer 2: Krzysztof Tomaszewski

1. Major language corrections, both grammatical and lexical, are needed throughout the whole manuscript. Please refer the manuscript to a native speaker for necessary corrections.

Comment: The manuscript has now been referred to a native speaker for language revision.

2. Regarding Table 2 - as many factors can influence an individuals’ quality-of-life, the authors should also present (in the demographic characteristics) the marital status of the participants, as well as information whether the patients lived alone/with spouse/children etc.

Comment: We agree that there are factors other than those used in this study that may influence the patients QOL. However information about marital status and however they lived alone are not available. This is now addressed as a potential limitation in the methodological considerations section (page 9, line 282-284).

3. The following statement from the Conclusions "Treatment with proton pump inhibitors improves the results." needs to be changed to reflect that PPI use only produced a significant change in the QLQ-OES18 scores, which was not reflected in the QLQ-C30.
Comment: The fact that PPI had a positive effect on the symptom scales (both QLQ-OES18 and QLQ-C30) but not the function scales are now clarified on page 11, line 352-353.

4. The "Methodological considerations" part of the Discussion should be shortened as parts of it are not crucial to the manuscript.
Comment: The methodological consideration section has been shortened.

5. The Discussion section needs to be considerably improved, focusing more on the results of the study and their implications:
Comment: Changes have been made throughout the discussion section.

- first, the Authors need to clearly state, in a separate subparagraph, the limitations of the current study;
Comment: Limitations are now highlighted in the methodological considerations section page 9, line 279-284).

- secondly, the Authors should supply a possible explanation for the QoL nadir seen at 2 months post-surgery;
Comment: Now added (page 9, line 306-310).

-thirdly, having both the QLQ-C30 and the QLQ-OES18 scores, the Authors should supply a proposition/suggestion of a support program that could be implemented in the mentioned patients at the 2 month post-surgery time point.
Comment: Now added (page 10-11, line 340-348).

6. Figures 1, 3 and 5 do not present enough data to justify the use of figures. Please present all the data from Figures 1, 3 and 5 in a form of a single table (or incorporate them into Figures 2, 4, 6).
Comment: Since all reviewers suggest that the figures 1, 3 and five add little to the results we have now removed the figures.

7. The overlapping parts of "Statistics" and "Instruments and measurements" should be deleted.
Comment: Now deleted

Minor essential revisions
1. Minor spelling mistakes have to be corrected e.g. 8:th -> should be 8th / "After surgery also functions have also been shown negatively affected [1-3]." -> double use of the word "also" or "bout" -> instead of "about" etc..
Comment: Now changed
Reviewer 3: David J Bowrey

1. This manuscript is of interest but it needs major restructuring. It is not entirely clear what the message is. The title, aim and text do not closely align. The real aim is to describe in detail the components of validated QOL instruments at many time points during the 1st year after oesophagectomy. The reviewer is not convinced that the aim is to allow channelling of resources to specific timepoints. The authors should decide on the focus, either a descriptive study or allowing channelling of resources, and go with that. If the latter, the authors should elaborate in much more detail, what resources will be allocated to this patient group.

Comment: This study is a descriptive study focusing on how QOL changes over time the first postoperative year after oesophageal cancer surgery. The results are to be used as an indicator of when during the first year the patients QOL is most severely affected so that the healthcare system could provide support that is timed according to the patients needs.

The title has been changed to clarify the focus of the study (page 1 line 1-3).

Information about that this is an descriptive study has been added (page 4, line 134).

2. The patients are a subgroup of those included in an RCT which is described. This should be made even more explicitly clear in the introduction and aims. Further, the results should present the findings comparing the two groups (PPI vs no PPI). That was the purpose of the original study. The current findings should at least in part be presented that way.

Comment: This study is a separate study focusing on patients QOL. The issue is addressed in the discussion section (page 9, line 287-297).

3. It is possible for the authors to comment on power and sample size. The original RCT was powered to differing stricture rates in the groups?

Comment: This study is a descriptive study focusing on how QOL changes over time. Since the aim is not to compare groups or evaluate effect, no power calculation is conducted for this study.

4. A PRISM figure showing patient disposal would be helpful?

Comment: Unfortunately we are not familiar with PRISM figures but have interpreted it as being related to drop outs over time (?). In such case answer frequency and drop outs over time is presented in table 3. If this is not answer to your question please specify and we will be glad to answer it.

5. The results appear contradictory - they need more explanation. The QLQ30 is reported as not influencing QOL in the first paragraph, yet is reported as significant in the subsequent sentences. The reviewer suspects this is just a matter of syntax and needs clearer text.

Comment: Now changed

6. The Discussion should be simplified. It is very wordy and does not read easily. Leave the reader with a simple take home message.

Comment: Changes has been conducted throughout the discussion section.
7. It should be clarified when the patients were randomized for inclusion. The reviewer suspects that they must have been randomized pre-operatively.
   Comment: Information added (page 5, line 155).

Minor
8. Figures 1, 3 and 5 add little and could probably be omitted
   Comment: Since all reviewers suggest that the figures 1, 3 and five add little to the results we have now omitted them.

9. The authors should consider amending the title to reflect the emphasis of the paper.
   Comment: Now changed (page 1, line 1-3).

10. "choked" has been mis-spelt
    Comment: Now changed

11. In the Introduction, paragraph 2 can be removed. Paragraph 4 should be promoted to paragraph 2.
    Comment: Since patients suffering from oesophageal cancer often go through advanced surgery and strenuous rehabilitation as well as have a short expected survival compared to other gastrointestinal cancers we believe it is important to provide the reader with a short introduction to the patient group. Therefore we would prefer to keep the paragraphs in the original order.