

December 4, 2019

Revision of Manuscript NO: 51925

Title: Trends in treatment and overall survival among patients with proximal esophageal cancer

Authors: Judith de Vos-Geelen, Sandra ME Geurts, Margreet van Putten, Liselot BJ Valkenburg-van Iersel, Heike I Grabsch, Nadia Haj Mohammad, Frank JP Hoebers, Chantal V Hoge, Paul M Jeene, Evelien JM de Jong, Hanneke WM van Laarhoven, Tom Rozema, Marije Slingerland, Vivianne CG Tjan-Heijnen, Gerard AP Nieuwenhuijzen, Valery EPP Lemmens

Dear prof. Jin-Zhou Tang,

Thank you for considering our revised manuscript, '**Trends in treatment and overall survival among patients with proximal esophageal cancer**' for publication in World Journal of Gastroenterology.

We would like to thank you for the additional comments after review. Please find attached the rebuttal to your comments.

We look forward to receiving your response in due course.

On behalf of the authors,

Yours sincerely,

A handwritten signature in black ink, appearing to be 'JDVG', enclosed within a circular scribble.

Judith de Vos-Geelen

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Additional comments from the editors:

1. Please revise and perfect your manuscript according to peer-reviewers' comments. **Please provide the response to the reviewers' comments.**

Response: We addressed the reviewers' comments in the reply letter submitted on November 15, 2019. I have attached the reply letter at the end of this document.

2. **Please provide language certificate letter by professional English language editing companies (Classification of manuscript language quality evaluation is B).**

Response: L. Valkenburg-van Iersel is a native speaker and coauthor of this manuscript. A Bilingual Certificate has been submitted to F6Publishing system on November 15, 2019. The English grammar, which was classified as Grade B in the primary submitted manuscript, was refined in the revised version of our manuscript submitted on November 15, 2019.

3. **Is the PPT file correct? Please find the file enclosed in the e-mail.**

Response: The PPT file provides the correct content of the figures. I have added slides 6, 9, and 11, demonstrating the intended design of the figures.

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Dear prof. Lian-Sheng Ma,

We sincerely thank you for considering our paper for publication and providing us the opportunity to revise our manuscript. We thank the reviewers for the effort and thoughtful comments regarding our manuscript. Please find enclosed our responses to the reviewers comments.

Reviewer 1:

I would like to thank authors for conducting this population-based retrospective study to evaluate the change in the treatment trend and survival of the cervical and upper thoracic esophageal cancer. The article is well written. Although the idea of the study is not completely novel and we have seen other similar studies, the body of literature still needs more information focused on patients with proximal esophageal cancers and in line with that this study is helping to fill the current knowledge gap.

We thank the reviewer for the compliments on our work and the provided recommendations.

Recommendations:

1. Overall survival has been defined as the time from diagnosis to death from ANY cause. The risk of this definition is that it does not differentiate between cancer-related or cancer-unrelated causes of death. This becomes more challenging when we

are drawing our conclusion across the "time" axis. As a matter of fact, we know that, for instance, ischemic heart disease is the leading cause of death globally (Lancet. 2018;392:1736-1788) and there has been a significant improvement in the treatment of such disorders, hence survival benefit, since 1989; same story for diabetes, infections, etc. Therefore, the possibility of survival benefit secondary to treatment of disorders not-directly related to cancer should be discussed as well. To address this issue, either a subgroup analysis based on the cause of death should be added to the paper, or if data is not available, this needs to be mentioned as a significant limitation with the possibility of confounding the survival benefit as one of the major outcomes of the study.

Response: We thank the reviewer for this recommendation. Unfortunately, disease specific cause of death is not collected in the Netherlands Cancer Registry. Due to the high background mortality in proximal esophageal cancer based on the major proportion of patients with high risk factors, we did not perform relative survival analyses. Hence, we chose to present overall survival outcome. We agree with the reviewer that the risk of non-cancer related death over time is expected to be reduced. Therefore, we have adapted the Discussion accordingly: 'The current study showed that period effect in the multivariable model disappeared after including treatment modality. These findings suggest that improvements in the (non-surgical) treatment had a substantial effect on the observed improvement in OS. However progress in OS may also have partly occurred due to advancements in the management of non-cancer related high mortality disorders, e.g. cardiovascular disease.^[1] Figures from Statistics Netherlands show that the remaining life expectancy for, for example, an average 65 year old person was 17 years in 1989 and 20 years in 2014.^[2] Whether this increase in life expectancy is also seen in the high-risk population presented in our study is unknown.'

In addition, the limitation section has been adapted: 'Furthermore, data regarding risk factors, e.g. smoking behaviour and alcohol consumption, comorbidity, performance status, and disease specific cause of death were not available, resulting in a risk of residual confounding.'

2. If data is available, it will be helpful to know about major risk factors of esophageal cancer such as smoking status and alcohol use, and that if such factors had any affect on such a patient population's survival. Thank you.

Response: We thank the reviewer for this comment. This population-based study in the field of the rare disease proximal esophageal cancer is unique presenting relatively high numbers of patients. We certainly agree with the reviewer that information on additional variables, e.g. smoking status, alcohol use, and comorbidities, could provide relevant additional information. Unfortunately, these variables are not included in the Netherlands Cancer Registry. To clarify the missing data on smoking and alcohol, the limitation section has been changed accordingly: 'Furthermore, data regarding risk factors, e.g. smoking behaviour and alcohol consumption, comorbidity, performance status, and disease specific cause of death were not available, resulting in a risk of residual confounding.'

Reviewer 2:

Recommendations:

1. I am not sure if it is solid to claim "Survival has significantly improved in non-metastatic proximal esophageal cancer, which was associated with an increased use of chemoradiation. Overall survival and treatment patterns for metastatic disease did not change significantly over time.". It is hard to say that the baseline is even during different periods. Statisticians must be consulted.

Response: We thank the reviewer for this suggestion. We agree with the reviewer that statistical consultation is crucial. Dr. Sandra ME Geurts and prof. Valery EPP Lemmens are senior epidemiologists, trained in datamanagement and statistical analysis, and designed the study and dr. Sandra ME Geurts performed the analysis. A sentence has been added to the section 'Statistical analysis': 'The statistical review of the study was performed by two senior epidemiologists.'

The multivariable model presenting hazard ratios for overall survival of patients diagnosed with non-metastatic proximal esophageal cancer, demonstrated that there was an improvement in overall survival in the more recent years. After including the different

treatment modalities in the multivariable model, the period effect disappeared, suggesting an important role for improved treatment strategies in the management of proximal esophageal cancer. The current study showed that there has been a striking change with a robust implementation of definitive chemoradiation, in accordance with the international evolution, as demonstrated in our previously published review.^[3]

We edited 'likely to be' in the following sentence: 'Overall survival significantly improved in non-metastatic proximal esophageal cancer, likely to be associated with an increased use of chemoradiation.'

Furthermore, in line with the comments of reviewer 1, reviewer 2 questions whether the baseline is even over time. Please see our proposed revisions on this topic in our response to reviewer 1.

2. Also this manuscript only recorded the treatment such as chemotherapy and radiotherapy. Detailed information such as the specific regime or dose for chemotherapy and radiotherapy is not recorded. These information may also effect the final conclusion.

Response: Indeed, we did not supply detailed information on regimen and dose of chemotherapy and radiotherapy, as this information was not collected by the data clerks of the Netherlands Cancer Registry. However, we do not think that this has influenced the final conclusion, since we noticed over the years an increasing use of chemoradiotherapy and, in parallel, an improvement in overall survival. To clarify, we added the following paragraph in the MATERIAL AND METHODS section: 'Type of surgical treatment and details on chemotherapy or radiotherapy were not collected by the data clerks of the Netherlands Cancer Registry.'

Reviewer 3:

This is an interesting manuscript focusing on trends in treatment and overall survival among patients with proximal esophageal cancer. The text is strictly logical.

We thank the reviewer for the positive comments on our manuscript.

Recommendations:

1. The detailed schemes of surgery, CRT and endoscopic resection should be described.

Response: We acknowledge the reviewer's suggestion that it would be of interest to retrieve additional information on treatment schedules and techniques. These variables are lacking in the current large population-based study, and as such this omission was included in the limitation section: 'The NCR does not include information on treatment techniques, schedules, and its related toxicities, causing interpretation adversity.'

Additional revisions initiated by authors

We have incorporated some additional changes to improve the readability of our manuscript.

Revisions Editor questions

We refined English grammar and added the journal specific requirements.

Yours sincerely,

Judith de Vos-Geelen

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Oncology and Developmental Biology
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REFERENCES

- 1 Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; **392**(10159): 1736-1788 [PMID: 30496103 PMCID: PMC6227606 DOI: 10.1016/s0140-6736(18)32203-7]
- 2 **Statistics Netherlands.** Available from: <https://opendata.cbs.nl/statline/#/CBS/nl/dataset/37360ned/table?ts=1573737810723> (accessed November 14, 2019).
- 3 **Hoeben A,** Polak J, Van De Voorde L, Hoebers F, Grabsch HL, de Vos-Geelen J. Cervical esophageal cancer: a gap in cancer knowledge. *Annals of Oncology* 2016; **27**(9): 1664-1674 [DOI: 10.1093/annonc/mdw183]