

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Prognosis of oesophageal adenocarcinoma and squamous cell carcinoma following surgery and no surgery in a nationwide Swedish cohort study
<b>AUTHORS</b>	Kauppila, Joonas; Mattsson, Fredrik; Brusselaers, Nele; Lagergren, Jesper

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Jane M Blazeby University of Bristol, UK
<b>REVIEW RETURNED</b>	18-Feb-2018

<b>GENERAL COMMENTS</b>	<p>This is a nicely written paper. It is useful to have a full picture of outcomes of patients with oesophageal cancer from a single country. Its useful to see how there have been changes over time. The authors recognise some of the areas that require more information - namely around the use of chemotherapy and/or radiotherapy in this patient population. There are several studies that show that neoadjuvant chemotherapy may influence survival and indeed neoadjuvant chemoradiotherapy is also important -</p> <p>My main concern is the use of the term in the title and elsewhere in the paper - non-operative. Somehow the implication is non-operative versus operative and it is very unclear whether this focusses on patients with localised disease or all comers (the latter I think) - therefore the non-operative - no surgery group includes all patients including those having palliative treatment for whom surgery would never be indicated - hence absolutely in appropriate to compare survival outcomes.</p> <p>It also does not recognise how selection bias will also favour surgery in patients sufficiently fit for operative treatment and randomised allocation needed to overcome those unmeasurable biases</p> <p>The paper implies that surgery is key to survival - however it is misleading it also says that it will help inform treatment recommendations - however, again that is misleading because of the lack of data on chemoradiation - and its application</p> <p>I wonder if it could also benefit from some speculation on why it may appear that women benefit more from surgery than men in terms of access to care (or is it because non-operated on women have less access to care than non-operative on men)</p>
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<b>REVIEWER</b>	J.W. Haveman
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	Department of Surgery University Medical Center Groningen, University of Groningen, the Netherlands
<b>REVIEW RETURNED</b>	19-Feb-2018

<b>GENERAL COMMENTS</b>	Well written manuscript of a group that has access to a unique Nationwide database. The results of this study add to the current literature, although are to a large extent not completely new. Strengths and limitations are adequately discussed.
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### VERSION 1 – AUTHOR RESPONSE

Editorial requests:

Q1. Please revise your title so that it includes your study's setting. This is the preferred format for the journal.

Revisions: The study title has been revised to include the setting: "Prognosis of oesophageal adenocarcinoma and squamous cell carcinoma following surgery and no surgery in a nationwide Swedish cohort study"

Q2. The introduction section is very brief. Can this be expanded to provide a more thorough overview of the background literature and rationale for carrying out the study?

Revisions: The introduction has been revised to include a more thorough overview of the literature and to clarify the study rationale (page 5, lines 3-12).

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Reviewer: 1 Reviewer Name: Jane M Blazeby Institution and Country: University of Bristol, UK  
Competing Interests: None declared

Q1: This is a nicely written paper. It is useful to have a full picture of outcomes of patients with oesophageal cancer from a single country. Its useful to see how there have been changes over time. The authors recognise some of the areas that require more information - namely around the use of chemotherapy and/or radiotherapy in this patient population. There are several studies that show that neoadjuvant chemotherapy may influence survival and indeed neoadjuvant chemoradiotherapy is also important –

My main concern is the use of the term in the title and elsewhere in the paper - non-operative. Somehow the implication is non-operative versus operative and it is very unclear whether this focusses on patients with localised disease or all comers (the latter I think) - there fore the non-operative - no surgery group includes all patients including those having palliative treatment for whom surgery would never be indicated - hence absolutely in appropriate to compare survival outcomes. It also does not recognise how selection bias will also favour surgery in patients sufficiently fit for operative treatment and randomised allocation needed to overcome those unmeasurable biases

Authors' response: We thank for the positive overall evaluation. We agree that the chosen terminology and some wordings might indeed be misleading. The "no surgery group" includes all patients that did not undergo oesophagectomy, i.e. all patients with metastatic disease or otherwise inoperable disease, patients with curatively intended chemoradiotherapy and those who were not fit enough for surgery. This is admittedly a very heterogeneous group, which we unfortunately cannot categorise better based on the limitations of the data available, but still of some potential interest to study in relation to time trends in survival.

The intent of the present study was to assess the changes over time in the prognosis of oesophageal adenocarcinoma and squamous cell carcinoma separately, and to examine whether these changes are different in patients undergoing surgery or not undergoing surgery separately.

It is interesting that patients undergoing surgery fare better now than 20 years ago, which could be due to better selection of patients for surgery, addition of neoadjuvant therapy, better surgery (centralisation), and other reasons. We agree that patients undergoing surgery are on average 10 years younger, healthier and do not have metastatic disease, which makes them already much better off from the beginning, and hence they cannot be compared to the patients not undergoing surgery. But that direct comparison was never the purpose of this study. The study aimed to examine changes in prognosis over time in all patients, as well as separately in those who underwent surgery and not.

Revisions: We have clarified the terms used by changing the wording operative – non operative to surgery – no surgery. We have also clarified the rationale and aims of the study in the introduction section to better reflect the questions the present study was intended to answer (page 5, lines 3-12 and line 20). The clinical heterogeneity of the no surgery patient group has been clearly expressed in the study limitations in the discussion section of the revised manuscript (page 14, lines 14-15).

Q2. The paper implies that surgery is key to survival - however it is misleading it also says that it will help inform treatment recommendations - however, again that is misleading because of the lack of data on chemoradiation - and its application

Authors' response: As there were no data available on neoadjuvant, adjuvant or definitive chemotherapy or chemoradiotherapy therapy in the national registries, the speculations on the reasons of prognostic trends largely relies on authors' knowledge on the changes in Swedish guidelines and regimens in oesophageal cancer treatment.

The topic whether survival after surgery is better compared to curatively intended chemoradiotherapy is not possible to study based on the data available for this study. There is some low-quality evidence suggesting equal outcomes after surgery versus curative (chemo)radiation. However, in this study we think it can be assumed that increase in use of definitive chemoradiotherapy is related to the more rapidly improving prognosis in squamous cell carcinoma patients not undergoing surgery, as it has become more often used regime in Sweden in the recent years, specifically for squamous cell carcinoma.

Revisions: The manuscript has been revised to more carefully avoid implying that surgery is the only factor contributing to improved prognosis. The recommendations in discussion section have been revised accordingly (page 16, lines 12-16).

Q3. I wonder if it could also benefit from some speculation on why it may appear that women benefit more from surgery than men in terms of access to care (or is it because non-operated on women have less access to care than non-operative on men)

Authors' response: The sex disparity in prognosis of esophageal squamous cell carcinoma, but not adenocarcinoma, is indeed an interesting topic. Women might be more readily and more often utilising health resources available to them. However, this does not explain why the sex disparity is greater in surgically patients compared to non-surgically treated squamous cell carcinoma patients.

Revisions: The discussion on sex disparities in prognosis of esophageal squamous cell carcinoma patients has been expanded (pages 15-16).

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Reviewer: 2 Reviewer Name: J.W. Haveman Institution and Country: Department of Surgery, University Medical Center Groningen, University of Groningen, the Netherlands Competing Interests: None declared

Q1. Well written manuscript of a group that has access to a unique Nationwide database. The results of this study add to the current literature, although are to a large extent not completely new. Strengths and limitations are adequately discussed.

Authors' response: We thank for the reviewer comments and the favourable evaluation.

#### **VERSION 2 – REVIEW**

<b>REVIEWER</b>	Jane M Blazeby University of Bristol UK
<b>REVIEW RETURNED</b>	19-Mar-2018
<b>GENERAL COMMENTS</b>	Thank you for the revisions I think that the manuscript is much better for these