PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Reoperation after oesophageal cancer surgery in relation to long-term survival: a population-based cohort study
AUTHORS	van der Schaaf, Maartje; Derogar, Maryam; Johar, Asif; Rutegård, Martin; Gossage, James; Mason, Robert; Lagergren, Pernilla; Lagargren, Jesper

VERSION 1 - REVIEW

REVIEWER	Alain Demers University of Manitoba, Canada
REVIEW RETURNED	28-Dec-2013

GENERAL COMMENTS	The authors have put together an interesting and well written paper. They do a fair utilization of administrative databases and chat review, and they properly assess their limitations. I have minor comments that you will find below. 1. The text in the abstract is in many instances a copy from the core of the paper. Original sentences would be appreciated. 2. Introduction, second paragraph: “The potential role of reoperation is uncertain”. This clause in unclear. It would be clearer is it was “the potential role of reoperation in lowering survival from esophageal cancer is unclear and could be mediated through…” 3. Why the authors did decide to include reoperations that happened within 30 days of the initial resection? Why not choosing 45 days, 60 days or 20 days? Did the authors do a sensitivity analysis? 4. In the Methods the authors say “Detailed information on tumour characteristics and surgical details were acquired through manual review of medical records from the operation charts and histopathology reports retrieved from all relevant hospitals throughout Sweden”. I am sure that was an amazing amount of work to bring all this information together. I would like to see more information on how that was done, or at least a reference. 5. In the Methods the authors enumerate 9 adjustment variables. There is very little information on the provenance of this information, which should be added to the text. For some variables like age it is not necessary but for comorbidity, for instance, that would be useful.

	6. The authors do not provide potential solutions or guidance in relation to their main conclusion “the need to consider any actions that might prevent complications and reoperation”. I would strongly to suggest to present ideas especially that the authors have a wide experience in surgery. 7. In a few places in the text the authors say that “… which means that the all-cause mortality within 5 years closely mirrors disease specific mortality”. The authors have (or don’t present) any data to support that statement. The authors have to change that statement and to stick to the information they have. As they say in the discussion, their statement is supported by reference [9] but if they don’t have the data that remains an assumption. 8. Footnote of Table 2: “§χ2 of the difference between groups”. Is this a chi-square? Please spell out the word. 9. For the sake of curiosity, when you look at Figure 1 you see that there is an increase in mortality around one year and just after 3 years. Any explanations for that? 10. I question the presentation of mortality ratios for more than five years after diagnosis in Table 3. This is not part of the initial analytical plan and the reversal of the trends complicate the interpretation of the results. I would remove this part of the analysis. The authors say that there are conflicting results on the role of severe surgical complications on long-term survival. A more elaborate discussion of these results would be interesting since they relate directly to the topic of the study. Any explanation why some results are conflicting? Study designs, populations?

REVIEWER	Professor George Hanna St Mary's Hospital, Imperial College, London, UK
REVIEW RETURNED	03-Feb-2014

GENERAL COMMENTS	I thank you for the opportunity to review this manuscript entitled, ‘Reoperation after Oesophageal cancer surgery in relation to long-term survival: a population-based cohort study.’ This is well conducted and well written observational study that has generated some findings from a large series of patients undergoing oesophageal cancer surgery. The study period of 23 years is extensive and with a large series of 1822 patients this represents a robust analysis of this subject that has previously not been reported in the setting of oesophagectomy. Through this analysis the main finding of this paper is that reoperation within 30-days of oesophagectomy is associated with an increase in long-term mortality between 90days and five years. I only have a few comments that I feel should be clarified and may improve the manuscript. 1. Abstract: Please mention that you are looking at reoperation within 30days of primary surgery, this is otherwise confusing to the reader. 2. Demographics compared in this study included the usage of

	neoadjuvant therapy. However if available it is important to distinguish concurrent chemoradiotherapy from chemotherapy alone in this analysis. 3. Likewise other important prognostic factors must be included in the model if they are available; minimally invasive oesophagectomy and lymph node harvest. 4. Table 1 provides detailed information regarding the aetiology of reoperation. It would be of interest to perform a subset analysis of these patients who underwent reoperation to determine if a specific aetiology of reoperation was associated with a greater risk of long-term mortality. 5. The volume threshold used in your study to distinguish centers was 9 per year. Do you think that is an adequate volume threshold? I note from the study period the average number of resections was 100 per annum. 6. The discussion is well considered and well written. Blood transfusion has been previously linked with long-term mortality and cancer recurrence. Was this a factor that you evaluated in this study? Patients returning to theatre will be more likely to receive blood transfusion at this time, which may be an important confounding variable to consider.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name Alain Demers
Institution and Country University of Manitoba, Canada
Please state any competing interests or state 'None declared': No competing interest

The authors have put together an interesting and well-written paper. They do a fair utilization of administrative databases and chart review, and they properly assess their limitations. I have minor comments that you will find below.

1. Comment to the author: The text in the abstract is in many instances a copy from the core of the paper. Original sentences would be appreciated.
Response: Thank you for this comment, which we have adopted in the revised abstract.
Revision: We have rewritten parts of the abstract to accommodate this comment.

2. Comment to the author: Introduction, second paragraph: "The potential role of reoperation is uncertain". This clause in unclear. It would be clearer is it was "the potential role of reoperation in lowering survival from esophageal cancer is unclear and could be mediated through…"
Response: Thank you for pointing this out. We have rewritten this sentence in the Introduction section.
Revision: We changed the above-mentioned sentence to: "The potential effect of reoperation in lowering long-term survival after oesophagectomy is uncertain, and could be mediated by several biological mechanisms. For example, the additional surgical trauma that further triggers an inflammatory response could lower the efficacy of bodily defence mechanisms, including destruction and removal of circulating tumour cells, and thus pave the way for early recurrence from micro metastases".

3. Comment to the author: Why the authors did decide to include reoperations that happened within 30 days of the initial resection? Why not choosing 45 days, 60 days or 20 days? Did the authors do a sensitivity analysis?
Response: We decided before the study was initiated to use a cut-off for re-operations that was likely to be directly associated with the oesophagectomy, but yet not too short. Since there is no agreed

upon cut-off for capturing early re-operations associated with surgery, we instead use a commonly used cut-off for short-term mortality, which is traditionally 30 days.
Revision: The following text was added to the Discussion section: “The use of a cut-off of 30 days of surgery for assessing re-operation might results in missing of later re-operations. However, we decided before the study was initiated to use a cut-off that was likely to be directly associated with the oesophagectomy, but yet not too short. Since there is no agreed upon cut-off for capturing early re-operations associated with surgery, we instead use a commonly used cut-off for short-term mortality, which is traditionally 30 days.”

4. Comment to the author: In the Methods the authors say “Detailed information on tumour characteristics and surgical details were acquired through manual review of medical records from the operation charts and histopathology reports retrieved from all relevant hospitals throughout Sweden”. I am sure that was an amazing amount of work to bring all this information together. I would like to see more information on how that was done, or at least a reference.
Response: Thank you for this comment. Several researchers have been working on the collection of this data. The methods are described in detail in two other publications, which we have added in the revised Methods section. Nevertheless, we have added some information on where and how all information was obtained.
Revision: We added the following references to the Methods section 1) Derogar M, Sadr-Azodi O, Johar A, Lagergren P, Lagergren J. Hospital and surgeon volume in relation to survival after esophageal cancer surgery in a population-based study. J Clin Oncol 2013;31(5):551-7 and 2) Rouvelas I, Zeng W, Lindblad M, Viklund P, Ye W, Lagergren J. Survival after surgery for oesophageal cancer: a population-based study. Lancet Oncol 2005;6(11):864-70.
The following text was adjusted and added to the Methods section: “Detailed information on tumour characteristics and surgical details were acquired through manual scrutiny of medical records from the operation charts and histopathology reports, with accompanying referral notes, retrieved from all relevant hospitals throughout Sweden. One reviewer, who was kept blinded for the study outcome to ensure objectivity, reviewed all histopathological reports according to a predefined protocol to ensure uniformity. The accuracy of the histopathological review was assessed by two researchers who independently reviewed 100 patient records, showing high accuracy (>90% concordance).”

5. Comment to the author: In the Methods the authors enumerate 9 adjustment variables. There is very little information on the provenance of this information, which should be added to the text. For some variables like age it is not necessary but for comorbidity, for instance, that would be useful.
Response: Thank you for this comment. We have added information on the source of the variables.
Revision: We added the sources of the covariate variables to the Methods section. We added the following sentence to the Methods section: “Information on comorbidities was obtained from the Swedish Patient Register, information on tumour stage and histological type of tumour, surgical radicality and neo-adjuvant treatment was extracted from histopathological records and accompanying referral notes”.

6. Comment to the author: The authors do not provide potential solutions or guidance in relation to their main conclusion “the need to consider any actions that might prevent complications and reoperation”. I would strongly to suggest to present ideas especially that the authors have a wide experience in surgery.
Response: Thank you for this valuable comment. We have added a paragraph on ideas in the Discussion section.
Revision: We added the following paragraph with ideas and suggestions to prevent reoperation in the Discussion section: “It stresses the need for preventive measures to reduce the need for reoperation. In this population the 3 most common performed types of reoperation were explorative laparotomy (19%), re-operation for anastomotic leak (17%) and wound revision (20%). Several studies have showed that a higher surgeon or hospital volume might reduce post-operative mortality and morbidity

(Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. N Engl J Med 2002;346(15):1128-37, Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. N Engl J Med 2003;349(22):2117-27; Derogar M, Sadr-Azodi O, Johar A, Lagergren P, Lagergren J. Hospital and surgeon volume in relation to survival after esophageal cancer surgery in a population-based study. J Clin Oncol 2013;31(5):551-7; Brusselaers N, Mattsson F, Lagergren J. Hospital and surgeon volume in relation to long-term survival after oesophagectomy: systematic review and meta-analysis. Gut 2013; and Rouvelas I, Lagergren J. The impact of volume on outcomes after oesophageal cancer surgery. ANZ J Surg 2010;80(9):634-41). High volume surgery is facilitated by centralisation of the care for oesophageal cancer patients. Centralisation might be an effective measure for prevention of severe post-operative complications. A recent study showed that patients with comorbidity that compromises the cardiovascular status leading to a compromised perfusion of organs (e.g. hypertension, diabetes, congestive heart failure and renal failure), have a higher risk of anastomotic leak. This finding indicates that pre-operative optimisation of the cardiovascular status might also decrease the risk of severe complications requiring reoperation".

7. Comment to the author: In a few places in the text the authors say that "… which means that the all-cause mortality within 5 years closely mirrors disease specific mortality". The authors have (or don't present) any data to support that statement. The authors have to change that statement and to stick to the information they have. As they say in the discussion, their statement is supported by reference [9] but if they don't have the data that remains an assumption.
Response: This is a valid comment, and we do have access to the disease-specific mortality. We have therefore analysed the disease-specific 5-year survival to support the statement.
Revision: Results of the analyses of disease specific 5-year survival were added to the Results section and the results are presented in Table 3. In the Methods section we added a sentence about these analyses: "The study outcomes were was all-cause early-, late- and disease-specific mortality." "Disease specific mortality" was defined as death of tumour recurrence occurring between 90-days and 5 years of surgery. If a cause of death included oesophageal cancer (diagnosis codes 150 according to ICD7) in the Swedish Causes of Death Registry we assumed that patients died of tumour recurrence." We added the following paragraph to the Results section: "During the follow-up period, 954 (74%) patients died of reported tumour recurrence. The disease-specific mortality within 90 days and 5 years of surgery was 28% increased among patients who were reoperated (adjusted HR 1.28, 95% CI 1.04-1.59) (Table 3)."

8. Comment to the author: Footnote of Table 2: "§χ2 of the difference between groups". Is this a chi-square? Please spell out the word.
Response: Thank you for pointing this out. We will spell out the word.
Revision: We spelled out Chi-squared in footnote of Table 2.

9. Comment to the author: For the sake of curiosity, when you look at Figure 1 you see that there is an increase in mortality around one year and just after 3 years. Any explanations for that?
Response: The survival curve in Figure 1 curve looks a bit bumpy. The most likely explanation is probably chance. Speculatively, the increase in mortality after one year might be explained by the fact that most patients that die of disease recurrence or progression die within the first year, while the increase in mortality after 3 years might be due to comorbidities. However, we believe that these crude survival curves need to be interpreted with caution, and prefer not to add any specific discussion about this, since it would be too speculative.
Revision: -

10. Comment to the author: I question the presentation of mortality ratios for more than five years after diagnosis in Table 3. This is not part of the initial analytical plan and the reversal of the trends complicate the interpretation of the results. I would remove this part of the analysis.

Response: This is yet another valid comment, and we have removed these results.
Revision: The results of the “more than five years” analyses were removed from Table 3 and from the Results section.

11. Comment to the author: The authors say that there are conflicting results on the role of severe surgical complications on long-term survival. A more elaborate discussion of these results would be interesting since they relate directly to the topic of the study. Any explanation why some results are conflicting? Study designs, populations?
Response: Thank you for this comment. Differences in classification of complications, and especially the classification of severity differed or that information on interventions was not available in the existing studies. We have added a discussion on this.
Revision: We added the following text to the Discussion section: “These differences might be due to differences in classification of the severity of the complications and the lack of information on interventions.”

Reviewer: 2
Reviewer Name Professor George Hanna
Institution and Country St Mary's Hospital, Imperial College, London, UK
Please state any competing interests or state ‘None declared’: None declared

I thank you for the opportunity to review this manuscript entitled, ‘Reoperation after Oesophageal cancer surgery in relation to long-term survival: a population-based cohort study.’ This is well conducted and well written observational study that has generated some findings from a large series of patients undergoing oesophageal cancer surgery. The study period of 23 years is extensive and with a large series of 1822 patients this represents a robust analysis of this subject that has previously not been reported in the setting of oesophagectomy. Through this analysis the main finding of this paper is that reoperation within 30-days of oesophagectomy is associated with an increase in long-term mortality between 90days and five years. I only have a few comments that I feel should be clarified and may improve the manuscript.
1. Comment to the author: Abstract: Please mention that you are looking at reoperation within 30days of primary surgery, this is otherwise confusing to the reader.
Response: Thank you for pointing this out.
Revision: The fact that we studied reoperations within 30 days of surgery was added in the abstract.

2. Comment to the author: Demographics compared in this study included the usage of neoadjuvant therapy. However if available it is important to distinguish concurrent chemoradiotherapy from chemotherapy alone in this analysis.
Response: This is a valid comment. We do, however, not have information on type of neo-adjuvant therapy, i.e. whether it was chemoradiotherapy or chemotherapy, but In Sweden, the use of chemoradiotherapy has dominated whenever neo-adjuvant therapy has been used. This information was added in the Methods section.
Revision: The following text was added in the Methods section: “Data on the type of neo-adjuvant therapy used, i.e. chemoradiotherapy or chemotherapy, was not available, but in Sweden, the use of chemoradiotherapy has dominated whenever neo-adjuvant therapy has been used.”

3. Comment to the author: Likewise other important prognostic factors must be included in the model if they are available; minimally invasive oesophagectomy and lymph node harvest.
Response: Thank you for this comment. Minimally invasive oesophagectomy was however virtually never performed in Sweden during the study period, so this variable would not be possible to add to the model.
Lymph node harvest was added as a covariate to the revised analyses. However, due to missing data on lymph node harvest in many patients, these were lost in that analysis. Furthermore, when adding

lymph node harvest in the multivariable model, it did not significantly influence the results (Chi-square p-value 0.687). Therefore, we decided not to include lymph node harvest in our final analyses, but added this above information in the revised manuscript.
Revision: The following text was added in the Methods section: “We also considered lymph node harvest as a potential confounder, but this variable did not significantly influence the results (Chi-square p-value 0.687), and since there was a substantial rate of missing data on lymph node harvest, we decided not to include this variable in the final multivariable model.”

4. Comment to the author: Table 1 provides detailed information regarding the aetiology of reoperation. It would be of interest to perform a subset analysis of these patients who underwent reoperation to determine if a specific aetiology of reoperation was associated with a greater risk of long-term mortality.
Response: This is an interesting comment. The reason why we did not do such analyses in the original manuscript was that we expected severe power problems. However, at the reviewer’s request we did subgroup analyses for the three most commonly occurring reoperations in our study: exploratory laparotomy, reoperation for anastomotic insufficiency and wound revision. We found increased point HRs for each of these reoperation types, and reoperation for anastomotic insufficiency rendered a statistically significantly increased HR of mortality. These new results were added in the Results section and in a new Table 4.
Revision: We added the following sentence to the Methods section: “We also analysed the impact of each of the most common types of reoperations on mortality between 90 days and 5-years of surgery in subgroup analyses.” And we added the following sentence to the Results section: “In a subgroup analysis of the 3 most common types of reoperations, i.e. exploratory laparotomy, reoperation for anastomotic insufficiency and wound revision, the point HRs were increased for each type of reoperation (Table 4), and patients reoperated for anastomotic insufficiency had a statistically significantly increased hazard of mortality (adjusted HR 1.82, 95% CI 1.19-2.76).”

5. Comment to the author: The volume threshold used in your study to distinguish centers was 9 per year. Do you think that is an adequate volume threshold? I note from the study period the average number of resections was 100 per annum.
Response: Thank you for this remark. Choice of cut-offs is often a matter of debate, and to avoid trying to define a suitable cut-off, we simply chose to use the median surgeon annual volume as the cut-off in the model.
Revision: The rationale for the cut-off for surgeon volume was clarified in the Methods section: “To avoid selecting a suitable cut-off for surgeon annual volume, we simply chose to use the median as the cut-off.”

6. Comment to the author: The discussion is well considered and well written. Blood transfusion has been previously linked with long-term mortality and cancer recurrence. Was this a factor that you evaluated in this study? Patients returning to theatre will be more likely to receive blood transfusion at this time, which may be an important confounding variable to consider.
Response: This is another interesting question. However, we do not have information on blood transfusion, so we cannot analyse this variable. We did however add a discussion point about this question.
Revision: The following text was added in the Discussion section: “Finally, blood transfusion has been linked with a worse long-term mortality and increased cancer recurrence in different types of cancer, (Liu L, Wang Z, Jiang S, et al. Perioperative allogenenic blood transfusion is associated with worse clinical outcomes for hepatocellular carcinoma: a meta-analysis. PLoS One 2013;8(5); Uccella S, Ghezzi F, Cromi A, et al. Perioperative allogenic blood transfusions and the risk of endometrial cancer recurrence. Arch Gynecol Obstet 2013;287(5); Acheson AG, Brookes MJ, Spahn DR. Effects of allogeneic red blood cell transfusions on clinical outcomes in patients undergoing colorectal cancer

surgery: a systematic review and meta-analysis. Ann Surg 2012;256(2)), including oesophageal cancer (Tachibana M, Tabara H, Kotoh T, et al. Prognostic significance of perioperative blood transfusions in resectable thoracic esophageal cancer. Am J Gastroenterol 1999;94(3):757-65). Unfortunately, we did not have information on blood transfusion in the study, but it can be assumed that patients returning to theatre are more likely to receive blood transfusion, and speculatively, blood transfusion may be a mechanism that contributes to the main finding of this study."