PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cohort Profile: gastric cancer in the population-based, Finnish National Esophago-Gastric Cancer Cohort (FINEGO) study.
AUTHORS	Kauppila, Joonas H; Ohtonen, Pasi; Rantanen, Tuomo; Tyrväinen, Tuula; Toikkanen, Vesa; Pääaho, Minna; Valtola, Antti; Räsänen, Jari; Kallio, Raija; Sihvo, Eero; Saarnio, Juha; Karttunen, Tuomo J; Pohjanen, Vesa-Matti; Ristimäki, Ari; Laine, Simo; Kokkola, Arto

VERSION 1 - REVIEW

REVIEWER	Prof David Bowrey Department of Surgery University Hospitals of Leicester NHS Trust Leicester UK
REVIEW RETURNED	20-Jun-2020

GENERAL COMMENTS	This is a well written retrospective cohort study of patients with gastric cancer in Finland over four decades. The strengths of the paper lie in the meticulous data collection and the large sample. It is unclear to me what the aim of the paper was? The authors have not stated their research question or hypothesis. Although well written, the manuscript is very descriptive. It needs to address a research question and add to the existing body of evidence. I have a number of questions that the authors should consider 1) The manuscript reports patients over four decades. Although surgery has remained relatively unchanged in that time, there have been major changes in care pathways, such as open access endoscopy, endoscopic treatment of early gastric cancer, use of perioperative chemotherapy, perioperative care techniques. Is it appropriate to amalgamate patients drawn from such a long period of time? 2) In the abstract, the authors state that the database was setup to establish factors that could contribute to improved outcomes in oesophago-gastric cancer. When I read the abstract, I was expecting to read a multi-variate analysis of factors linked to outcome. The authors have not developed this theme and not produced any new evidence about potential factors. I consider that with such a large dataset, an exploratory multi-variate analysis should be undertaken 3) The report is written in a very descriptive manner. I would like the authors to present a hypothesis and test it. What is the research question being addressed? This should be stated, analysed and

	reported. A purely descriptive manuscript does not add significantly to the existing literature. This information can be captured from National cancer registries. 4) The authors state “However, there are many unclear topics and gaps of knowledge in the treatment of gastric cancer, such as whether high hospital or surgeon volumes, or oncologic treatment improve gastric cancer survival,[8] whether certain anastomotic techniques are associated with less postoperative complications,[9 10] and whether Siewert II gastric cardia cancer should be resected by oesophagectomy or gastrectomy,[11] to name a few. The population-based nationwide cohort would be the ideal study design to evaluate these questions,[12] as randomized controls would be either unfeasible, or would need to include a very large amount of patients” but have not then evaluated these factors. 5) It is slightly confusing having the terminology switch between gastric cancer and esophago-gastric cancer. Looking at the figures, this was essentially an audit of gastric cancer, that included either a small number of patients with oesophageal cancer, or more likely, patients with junctional cancer who underwent oesophagectomy. Restricting the terminology to gastric cancer would be simpler. 6) The inclusion criteria were “Primary cancer of epithelial origin in the oesophagus, cardia, or stomach” yet only 243 of the 10,457 underwent oesophagectomy or oesophago-gastrectomy, while 10,140 underwent gastrectomy. This does not match up with other National datasets from Finland, that show an incidence of 1 per 100,000/annum for oesophageal cancer and 4 per 100,000/annum for stomach cancer. A greater number of oesophageal cancers would be expected. The reviewer assumes that the focus was gastric cancer and perhaps the small number of oesophageal cancers should be removed from the database? 7) Cancer staging in the Results should be given according to the TNM/UICC classification 8) No data has been provided on postoperative outcomes, pathology quality indicators, extent of resection 9) In this cohort, there was a very low uptake of perioperative chemotherapy (12%). This is very different practice to that in the UK, where 80-85% of patients receive perioperative chemotherapy. 10) To make comparisons, the authors should present the number of operations per 100,000 population so that the trend can be visualised.

REVIEWER	MARIA PAULA CURADO ACCAMARGO CANCER CENTER - SAO PAULO BRAZIL
REVIEW RETURNED	22-Jun-2020

GENERAL COMMENTS	the aim of this paper is to describe the profile of FINEGO a retrospective cohort on data of esophagus and gastric adenocarcinoma the period is from 1987 to 2016 this is a descriptive study aiming to describe the study profile in Finland population regarding hospital and surgeon volume and surgical thecniques . title i suggest Finnish National Esophago gastric cancer cohort (FINEGO) - A description of a preliminary results ... strengths and limitations one of the strenghts is that first the data is complete while in the paper it shows lack of data and accuracy (for example regarding

	morphological classification) .It seems that the database is not complete yet...please clarify introduction add in figure 1 the reference link of the finish cancer registry and date there is no mention of the histological classification such as Lauren (1965) or WHO types please describe the diferences between the finish cancer registry and patient registry the authors say it is national cohort but there are six hospital involved in this collaboration how about the others ? inclusion criteria :basis of diagnosis it is histology ? or there are others basis of diagnosis included in the FINEGO such as cytology ?. Please add data quality for all variables available at FINEGO at the present report please mention data completeness for each variable add a supplementary material with all variables available in FINEGO clarify how other researchers can have access to the data for research Data completeness : 31,1 % has infornatiom on education why? what o mean by the follow up is virtually complete ? it 100% ? this a surgical cohort of patients with gastric cancer some variables are of questionable quality why? you said that the registry is of surgery but all treatment modalities were included so i understand all treatments are in the database why for hospital volume you count benign and malignant surgery ? findings to date- it will be better to stratify the cases distribution by period of 5 or 10 years to identify cases distribution and treatment changes please clarify why both registries has to have same patients registered .. table 2 demographics - i think it could be by period .. treatment 97% went to gastrectomy all total gastrectomy ? the term for mortalities could be replaced by deaths about 6,474 deaths due to the surgery ? or to the cancer recurence ? future plans i understood that the database was ready but you mention that half of the gastric cancer patients records were destroyed .. why ? this a ongoing project please describe the variables complete and incomplete and by year you have a lot of good plans but first make sure the quality of your data describing morphology classification strengths and limitations you mention it is in the initial phase what is missing to finalize the whole cohort ? for survival the best prognosis factor is stage according with international rules such AJCC are you planing to evaluate survival by TNM Stage to improve comparability ? do you have access to clinical information of these patients ?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Q1: This is a well written retrospective cohort study of patients with gastric cancer in Finland over four decades. The strengths of the paper lie in the meticulous data collection and the large sample. It is

unclear to me what the aim of the paper was? The authors have not stated their research question or hypothesis. Although well written, the manuscript is very descriptive. It needs to address a research question and add to the existing body of evidence. I have a number of questions that the authors should consider.
Authors' response: Thank you for your kind comments.
As stated in the BMJ Open instructions for authors: "The cohort profile is an article type set up in BMJ Open to fill the space between a study protocol and a results paper. Cohort profiles should describe the rationale for a cohort's creation, its methods, baseline data and its future plans. Cohorts described should be long-term, prospective projects and not time-limited cohorts established to answer a small number of specific research questions.
If a cohort has yet to complete recruitment or baseline data collection, it should be submitted as a study protocol. Papers addressing a specific research question using cohort data should be submitted as a Research paper."
Thus, the aim of the study was to describe the baseline information on gastric cancer patients included in the FINEGO cohort. A separate study on esophageal cancers in FINEGO has been submitted to BMJ open (revised version submitted after reviewer comments).
We have clarified this in the abstract and introduction.

Q2: The manuscript reports patients over four decades. Although surgery has remained relatively unchanged in that time, there have been major changes in care pathways, such as open access endoscopy, endoscopic treatment of early gastric cancer, use of perioperative chemotherapy, perioperative care techniques. Is it appropriate to amalgamate patients drawn from such a long period of time?
Authors' response: We agree that this might lead to some challenges when evaluating certain treatments that are heavily related to time. However, we feel that the long inclusion window will allow effective evaluation of time trends of cancer demographics and treatment, as well as some of the factors associated to survival. Furthermore, we have data on the year of operation which can be used as an indirect adjustment to alleviate this problem in the future analyses.
We have added to the discussion around this issue in the Strengths and weaknesses section
---

Q3: In the abstract, the authors state that the database was setup to establish factors that could contribute to improved outcomes in oesophago-gastric cancer. When I read the abstract, I was expecting to read a multi-variate analysis of factors linked to outcome. The authors have not developed this theme and not produced any new evidence about potential factors. I consider that with such a large dataset, an exploratory multi-variate analysis should be undertaken
Authors' response: We are planning multiple studies on the unanswered questions presented in the introduction in the future, upon finalizing the data collection. Furthermore, the data needed for the underlined problems is not yet available (see also answer to Q23 to reviewer #2). However, the study was submitted as a "cohort profile", which by definition is a description of the cohort.
In this light, we feel that adding multivariable analysis would change the purpose of the paper from descriptive "cohort profile" to a "research paper". Therefore, we have not added a multivariable analysis.

Q4: The report is written in a very descriptive manner. I would like the authors to present a hypothesis and test it. What is the research question being addressed? This should be stated, analysed and reported. A purely descriptive manuscript does not add significantly to the existing literature. This information can be captured from National cancer registries.

Authors' response: We agree that hypothesis-based testing is crucial when evaluating research questions. However, in this study, we only aimed to describe and discuss the baseline data of the gastric cancer patients included in the FINEGO cohort (as suggested in the BMJ open author instructions).
Furthermore, we disagree with the reviewer that the study does not add significantly to the literature. For example, cancer registry does not contain all the patients nor the data presented in this study, but the data is compiled from separate registries. It will also promote the study for collaboration purposes.

Q5: The authors state "However, there are many unclear topics and gaps of knowledge in the treatment of gastric cancer, such as whether high hospital or surgeon volumes, or oncologic treatment improve gastric cancer survival,[8] whether certain anastomotic techniques are associated with less postoperative complications,[9 10] and whether Siewert II gastric cardia cancer should be resected by oesophagectomy or gastrectomy,[11] to name a few. The population-based nationwide cohort would be the ideal study design to evaluate these questions,[12] as randomized controls would be either unfeasible, or would need to include a very large amount of patients" but have not then evaluated these factors
Authors' response: Indeed, the mentioned things are some of the reasons to compile such a cohort as FINEGO. However, these questions cannot yet be answered with the data currently available. The clinical data collection from patient records and pathology review of the original tissue slides is still in progress.
We have revised the future plans section to include discussion of this matter.

Q6: It is slightly confusing having the terminology switch between gastric cancer and esophago-gastric cancer. Looking at the figures, this was essentially an audit of gastric cancer, that included either a small number of patients with oesophageal cancer, or more likely, patients with junctional cancer who underwent oesophagectomy. Restricting the terminology to gastric cancer would be simpler.

Authors' response: Thank you for this important notion. The FINEGO includes all esophageal and gastric cancers. However, only gastric cancer is described in this manuscript, and esophageal cancers have been submitted as a separate paper to BMJ Open.
We tried to clarify this issue by amending the cohort description section.

Q7: The inclusion criteria were "Primary cancer of epithelial origin in the oesophagus, cardia, or stomach" yet only 243 of the 10,457 underwent oesophagectomy or oesophago-gastrectomy, while 10,140 underwent gastrectomy. This does not match up with other National datasets from Finland, that show an incidence of 1 per 100,000/annum for oesophageal cancer and 4 per 100,000/annum for stomach cancer. A greater number of oesophageal cancers would be expected. The reviewer assumes that the focus was gastric cancer and perhaps the small number of oesophageal cancers should be removed from the database?

Authors' response: As described above, esophageal cancers have been described in a separate paper, and the present one includes gastric cancer. Misclassification between distal esophageal/cardia/proximal stomach cancer is a known problem, which we are unable to assess with only registry data from the national registries. We aim to evaluate the exact location of the cancers from patient records as well as from pathology slides review.

Q8: Cancer staging in the Results should be given according to the TNM/UICC classification

Authors' response: We agree that TNM/UICC classification is the most used and reported classification. Unfortunately, this information is not reliably available from the cancer registry and not available to us. However, cTNM and p/ypTNM will be evaluated from patient records and pathology slides review.

Q9: No data has been provided on postoperative outcomes, pathology quality indicators, extent of resection

Authors' response: In this study, we reported only register data. Unfortunately, no postoperative outcomes, quality indicator or resection extent data was available from the registries. Therefore, these data are to be assessed from patient records and pathology slides review, which is on-going with estimated completion in 2022.

Q10: In this cohort, there was a very low uptake of perioperative chemotherapy (12%). This is very different practice to that in the UK, where 80-85% of patients receive perioperative chemotherapy.

Authors' response: Thank you for this notion. I agree that the uptake of perioperative chemo was low. This has also been discussed in the manuscript. However, as the incidence of gastric cancer dropped quite drastically during the long study period, the proportion of chemotherapy seems even lower than it actually was during the perioperative chemotherapy era. Furthermore, we suspect that cancer registry might not have captured all patients undergoing perioperative chemotherapy, which is a question to be evaluate in the future upon completion of patient records data collection.

We have expanded the discussion on this issue in the manuscript in the Strengths and limitations section.

Q11: To make comparisons, the authors should present the number of operations per 100,000 population so that the trend can be visualised.

Authors' response: The population of Finland increased from 4,9 million to 5,5 million during the study period. This means that the decreasing trend was even steeper than depicted in the original figure

The number of operations is now presented per 100,000 population (total population of Finland the corresponding year) as suggested.

Reviewer: 2

Q1: the aim of this paper is to describe the profile of FINEGO a retrospective cohort on data of esophagus and gastric adenocarcinoma the period is from 1987 to 2016
this is a descriptive study aiming to describe the study profile in Finland population regarding hospital and surgeon volume and surgical thecniques .

Authors' response: Actually, the aim of the study was only to present the baseline data and demographics for gastric cancer patients included in the FINEGO esophago-gastric cancer cohort.

Q2: i suggest Finnish National Esophago gastric cancer cohort (FINEGO) - A description of a preliminary results ...

Authors' response: Thank you for your suggestion. However, the author instructions of the "Cohort profile" publications in BMJ open limit the form of the title and require all cohort profiles to be titled

"Cohort Profile: ... " We have considered some alternative titles, but did not come up with good alternatives that would as accurately present the study as the current one. As no actual results are presented in the profile, we think that “preliminary results” would be an overstatement.

Q3: one of the strenghts is that first the data is complete while in the paper it shows lack of data and accuracy (for example regarding morphological classification) .It seems that the database is not complete yet...please clarify

Authors’ response: We apologize for this inconsistency. We mean that the inclusion of the patients is complete, and many of the variables are complete. However, some registry-based variables might not be. As the data collection goes on, complete clinical and pathology data are collected from each patient.
The cohort was formed using the national registries (Patient, cancer, education and death registries). The aim of the present Cohort profile was to present national registry data related to the gastric cancer in the FINEGO cohort. In the meantime, the baseline data presented in this profile gives an idea of the final cohort and can be used for some research questions.

Q4: add in figure 1 the reference link of the finish cancer registry and date

Authors’ response: Thank you for this notion. The reference and date are already in their place in the figure legend of Figure 1. Missing reference link in the figure is due to the separate submission of figures in the online submission system, not allowing references.

Q5: there is no mention of the histological classification such as Lauren (1965) or WHO types

Authors’ response: We agree that histology is very important. However, information on Laurén subtypes was so scarce (the absolute majority were only reported as adenocarcinoma NOS) that we decided to leave it out as we are currently in progress of evaluating Laurén and WHO histology classifications from the original sample slides that are being collected from the biobanks and hospital archives. This will however take some more years to complete and will be reported in future studies.

Q6: please describe the diferences between the finish cancer registry and patient registry

Authors’ response: In general, patient registry collects information on all hospital discharges including diagnosis and surgery codes for all inhabitants in the country, while the cancer registry provides more specific information on cancers. We have clarified the sections describing the registries in the “Cohort description” section.

Q7: the authors say it is national cohort but there are six hospital involved in this collaboration how about the others ?

Authors' response: There are authors from six major upper GI hospitals involved. However, all patients from all hospitals in the country are included in the study. The smaller hospitals were more actively involved in gastric cancer treatment in the earlier years of the cohort, but the majority of these surgeons are not practicing anymore. Therefore, no collaborators from these hospitals are not present even when patients from these institutions are used.

Q8: inclusion criteria :basis of diagnosis it is histology ? or there are others basis of diagnosis included in the FINEGO such as cytology ?.

Authors' response: Any diagnosis of gastric cancer (including cytology, though rarely used) together with surgical or endoscopic treatment for cancer is sufficient for including the patients in the study. However, all diagnoses will be verified using patient records.

Q9: Please add data quality for all variables available at FINEGO at the present report please mention data completeness for each variable

Authors' response: The data are complete unless otherwise stated. Any missing data have been indicated under the "missing" group in the tables if there were any.

Q10: add a supplementary material with all variables available in FINEGO

Authors' response: This supplementary data was already published in the supplement for the study protocol in 2019: https://bmjopen.bmj.com/content/bmjopen/9/1/e024094.draft-revisions.pdf
We have added these information as a supplement.

Q11: clarify how other researchers can have access to the data for research

Authors' response: Currently, the best way to access data is through the P.I. of the study due to the amendments of the study approvals required from various organizations and government bodies in Finland upon initiation of collaboration. It is also relevant whether the potential collaborators are originated in- or outside EU.
We have expanded the "Collaboration" section.

Q12 Data completeness : 31,1 % has infornatiom on education why?

Authors' response: The education registry was introduced in 1970 including information on education obtained starting from 1970. However, as the median age diagnosis is 70 years, most of the patients have done their primary and secondary education during years 1940-1970, resulting in the majority having missing education information.
The information on education registry was expanded in the Cohort description and Strengths and weaknesses sections.

Q13: what o mean by the follow up is virtually complete ? it 100% ?

Authors' response: Follow up is 100% complete for vital status and date of death, and >99% for cause of death. We have clarified this in the text.

Q14: this a surgical cohort of patients with gastric cancer some variables are of questionable quality why?

Authors' response: These variables are originated and derived from the national administrative registry data. The issues with certain variables have been discussed in the Strengths and limitations section. However, upon completion of the patient records data collection we are able to validate these registry data and to show whether or not they are reliable for research purposes.
We expanded the discussion of variable completeness in the Strengths and limitations section.

Q15: you said that the registry is of surgery but all treatment modalities were included so i understand all treatments are in the database

Authors' response: We included patients with cancer that underwent curative palliative or endoscopic surgery only. All patients without surgical resections were excluded.
We have clarified this matter in the Cohort description section
---

Q16: why for hospital volume you count benign and malignant surgery ?

Authors' response: Dysplasia and unclear tumors can be counted as benign. We see that the prior phrasing might be misleading in the context of this manuscript. We mean that we included all gastrectomies in the patients included in FINEGO in the calculation of annual volumes of gastrectomy. This is now more accurately phrased in the manuscript.

Q17: findings to date- it will be better to stratify the cases distribution by period of 5 or 10 years to identify cases distribution and treatment changes

Authors' response: Thank you for this suggestion. We are preparing a separate time trends research article on gastric cancer to evaluate the trends of gastric cancer treatment and mortality in more detail. Therefore, we prefer not to present the time trends here, but to focus on the main aim; describing the baseline demographics of the gastric cancer patients in the FINEGO cohort. As stated in the manuscript, the evaluation of time trends will be presented separately in the future.

Q18: please clarify why both registries has to have same patients registered ..

Authors' response: We included patients with gastric cancer in either cancer registry or patient registry to ensure complete accrual. Both registries having patients registered is more a measure of quality. Those patients that were discharged with cancer diagnosis but not reported to the cancer

registry might be less likely to actually have gastric cancer compare to those with registry records in both registries. However, as we are evaluating the diagnoses and treatments in the patient records, we decided to include all patients with possible surgically treated gastric cancer in the registry search.

Q19: table 2 demographics - i think it could be by period ..

Authors' response: We agree that showing demographics by period would give an insight on the time trends, which we aim to assess in the future. However, we feel that comparing time trends would make the article a research paper, not cohort profile. See also answer to Q17.

Q20: treatment 97% went to gastrectomy all total gastrectomy ?

Authors' response: Gastrectomy included all types of gastrectomy, including both total and partial gastrectomy. We added this information in the Findings to date section.

Q21: the term for mortalities could be replaced by deaths

Authors' response: We agree that it could be replaced at some instances, and have done this. However, we prefer the term mortality for most instances.

Q22: about 6,474 deaths due to the surgery ? or to the cancer recurence ?

Authors' response: The 6,474 cancer deaths were due to cancer based on the death registry causes of death. Most of these deaths were due to cancer recurrence, but include also early postoperative, surgery-related deaths.

Q23: future plans
i understood that the database was ready but you mention that half of the gastric cancer patients records were destroyed .. why ?

Authors' response: We wrote "At the time of writing, approximately half of the gastric cancer patient records have been collected or identified as destroyed." By this we mean, that we know what happened to approximately half of the patient records. However, we have received most of the records and only minority have been destroyed. The exact number of records is still unclear as these are in manual form and currently being evaluated by the study nurses for completeness and that all requested information have been received from the hospitals.
By the Finnish Law, hospitals are mandated to keep patient records at least until 12 years have passed since the patient has died, as well as for patients that had been born on certain days on the month. However, all hospitals have not destroyed the records after 12 years. As the data collection from the patient records is finalized, we will be able to state the accurate proportion of destroyed patient records.

We clarified this matter in the Future plans section

Q24: this a ongoing project please describe the variables complete and incomplete and by year

Authors' response: The completeness of registry data is indicated in Tables 2 and 3 and are complete unless there are cases mentioned under the heading "missing". For the time trends evaluation, please see replies to Q17 and Q19. All clinical patient records variables and pathology variables are still incomplete as we are in the progress of collecting these data.

Q25: you have a lot of good plans but first make sure the quality of your data describing morphology classification

Authors' response: Thank you for the compliment. We had no reliable data on morphology (Laurén classification). In addition to the clinical data collection from the patient records, we have several pathologists working on the assessment of morphology, Lauren classification and WHO classification from the original sample slides of the patients to retrieve this information.

Q26: you mention it is in the initial phase what is missing to finalize the whole cohort ?

Authors' response: By initial phase, we mean the data collection of 1987-2016 patients. The next phase will be the patients operated during 2017-2021.
Finalizing the initial phase of the cohort the patient records of the 10,000+ patients will need to be assessed by surgeons, and the original sample slides by pathologists, which will take a considerable amount of time still.

Q27: for survival the best prognosis factor is stage according with international rules such AJCC are you planing to evaluate survival by TNM Stage to improve comparability ?

Authors' response: We are planning to evaluate survival by TNM stage once we have collected these information from the patient records. Cancer registry does not have complete information on TNM stage but only their own local, locally advanced, advanced classification, as described in the Cohort description section. We also aim to evaluate the corresponding TNM stages for the cancer registry classification.

Q28: do you have access to clinical information of these patients ?

Authors' response: We are currently collecting and evaluating the patient records from these patients. However, this will take two to three more years to complete, so these data will not be available for this manuscript. The current profile is only based on the data available from the national registries used to identify the patients.

VERSION 2 – REVIEW

REVIEWER	Maria Paula Curado Accamargo cancer center ,Sao Paulo ,Brazil
REVIEW RETURNED	30-Aug-2020

GENERAL COMMENTS	"defined as mortality for esophago-gastric cancers to reduce misclassification" - but your study it is about gastric mortality - line 20 page 51 in table 3 there are 145 esophagectomies described ..for gastric cancer ? i think it was for esophagus cancer ..

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
No comments indicated.

Reviewer: 2

Q1: "defined as mortality for esophago-gastric cancers to reduce misclassification" - but your study it is about gastric mortality - line 20 page 51

Authors' response: The reviewer brings up a very important issue in the diagnosis of esophagogastric junction tumors. The cohort profile is indeed focused on gastric cancer.
However, as Lindblad et al showed in their fine work (published in Ann Surg 2006, 243: 479-485), gastric cardia tumors are very often misclassified (and reported to cancer registries) as esophageal or gastric cancers. As the clinical determination of the location is difficult, and often reported with several ICD-10 codes during the diagnostic pathway due to clinicians believing the tumor to localize to a certain location, the registries include several cancer diagnoses and the coding is also misclassified. In our study on registry completeness of esophageal cancer, we also showed that in Finland, this misclassification is often present, and many of the patients diagnosed with esophageal cancer had died of gastric cancer (Kauppila JH, Acta Oncol 2020, In press). We also believe that this is true vice versa.
On the contrary, being diagnosed with both esophageal and gastric cancer is very rare, especially in Finland due to the different risk factor profiles of gastric cancer and esophageal adenocarcinoma (which is the more common type nowadays). Both cancers are of poor prognosis, and undergoing a surgical removal of the tumor is therefore even more rare in those patients with both cancer types. Therefore, we wanted to take into account the aforementioned misclassification and coding errors and defined cancer deaths as deaths due to either esophageal and gastric cancers.
We added an explanation with a reference to the work by lindblad et al. to page 10, line 8.

Q2: in table 3 there are 145 esophagectomies described ..for gastric cancer ? i think it was for esophagus cancer ..

Authors' response: Thank you for noting this. I also refer to my previous comment on misclassification and coding of these tumors. Gastric cardia adenocarcinomas are currently being classified as gastric

cancers according to the ICD-10. However, according to the WHO, siewert II cancers (or more specifically gastric cardia cancers extending to the esophagus) should be classified and treated as esophageal adenocarcinoma. Siewert III cancers are classified and treated as gastric cancer. Currently, we are restricted to ICD-10 codes when it comes down to the register data.
For example, in our study (Kauppila JH et al. Gastric Cancer 2018, 21: 533-541) using Swedish population-based data from 2001-2005 including only Siewert II-III cancer, we saw that 67% of the siewert II cancers and 23% of the siewert III cancers underwent esophagectomy.
As our cohort includes gastric cancer, including cardia cancers, we think that it is natural to some of the patients to undergo esophagectomy. However, during the patient records data collection, we plan to evaluate the “true” location of all these tumors and then aim to validate the registry data in relation to these location data collected from the patient records.
This issue has been already commented on page 16, line 11.