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Keywords:	Oesophageal disease < GASTROENTEROLOGY, Gastrointestinal tumours < GASTROENTEROLOGY, Thoracic surgery < SURGERY, Surgical pathology < PATHOLOGY, Gastrointestinal tumours < ONCOLOGY

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Abstract

Introduction

Surgery for oesophageal and gastric cancers is associated with high morbidity, mortality and poor quality of life postoperatively. The Finnish National Esophago-Gastric Cancer Cohort (FINEGO) will be established with the aim of identifying factors that could contribute to improved outcomes in oesophago-gastric cancer.

Methods and analysis

All oesophageal and gastric cancer patients diagnosed in Finland between 1987 and 2015 will be identified from the Finnish national registries. The Finnish Cancer Registry and Finnish Patient Registry will be used to identify patients that fulfill the inclusion criteria for the study: 1) Diagnosis of oesophageal, gastroesophageal junction, or gastric cancer, 2) any major surgery for the diagnosed cancer and 3) age of 18 or over at the time of diagnosis. Clinical variables and complication information will be retrieved in extensive data collection from the medical records of the relevant Finnish hospitals, and complete follow-up for vital status from Statistics Finland. Primary endpoint is overall all-cause mortality, and secondary endpoints include complications, reoperations, medication use and sick leaves. Sub-studies will be implemented within the cohort to investigate specific populations undergoing oesophageal and gastric cancer surgery. The initial estimated sample size is 1800 patients with surgically treated oesophageal cancer and 7500 patients with surgically treated gastric cancer.

Ethics and dissemination

The study has been approved by the Ethical Committee in Northern Osthrobotnia, Finland and The National Institute for Health and Welfare, Finland. Study findings will be disseminated via presentations at conferences and publications in peer-reviewed journals.

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Strengths and limitations of this study:

- The main strength of the study is the population-based design with complete and accurate ascertainment and follow-up of all patients diagnosed with oesophageal or gastric cancer in Finland, counteracting selection bias.
- The inclusion of multiple potential confounding factors from the registries and patient records allows accurate analysis of a variety of exposures and end points.
- The sample size will large enough to enable robust survival and regression analyses in smaller sub-groups of patients.
- The main limitations of the study are the exclusion of patients not undergoing surgery and information lag of up to two years.

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Competing interests statement: The authors state no potential competing interests.

Author contributions:

The authors' contributions in the study were the following: JHK initiated the collaborative project, developed the study idea and data collection tools, obtained permissions and funding and drafted the study protocol. PO was involved in the statistical design, made substantial revisions to the protocol and was involved in the original concept, study design and implementation. All authors made substantial revisions to the protocol and were involved in the original concept, study design and implementation. JHK is the guarantor.

Data sharing statement:

We are willing to share anonymized data after the completion of the data collection upon request. Sharing the data will require ethical approval by the relevant committee, as well as approvals from the governmental agencies and local entities maintaining the relevant data.

Introduction

Gastric cancer is the third-, and oesophageal cancer the sixth leading cause of cancer death worldwide.[1] The incidence of oesophageal adenocarcinoma is increasing, while that of oesophageal squamous cell carcinoma and gastric cancer is decreasing in Finland,[2] similar to other Western countries.[3] The incidence of gastric cancer is slowly decreasing in majority of the countries across the globe.[4] However, both cancers are characterised by poor survival even after curatively intended surgery,[5, 6] and a "textbook outcome" may be achieved in less than half of the patients undergoing oesophago-gastric cancer surgery.[7] Studies on sick leaves,[8] or postoperative use of opioids as an outcome after oesophageal and gastric cancer surgery are lacking, while these are important outcomes for the patients. It has been shown that sick leaves affect for example job retention in cancer patients.[9]

Randomized trials in oesophageal and gastric cancer have provided quality evidence that neoadjuvant - and adjuvant therapies increase survival[10-13] and that minimally invasive surgical approaches reduce, or at least do not increase complications.[14, 15] Despite their good internal validity and lack of bias, randomized controlled studies in general have limited external validity and applicability to general population, and thus need to be complemented by quality observational studies to reliably assess the effects of implementation of trial results into practice.[16] Additionally, observational studies can provide evidence on questions that have not, or cannot, be evaluated in randomized trials.[16]

In Finland, high-quality registry data on these cancers is readily available.[17] Despite the good availability, the exposure and outcome data in the registries are not detailed enough for surgical research. Because of small population (5,5 million) sparsely populating Finland, the hospital-based cohorts containing detailed information are small, not necessarily generalizable and have potential selection bias. There are no previous coordinated nationwide population-

based research efforts with detailed clinical data on oesophago-gastric cancer. To overcome these challenges, an extensive retrospective nationwide data collection from the patient medical records is needed. The Finnish National Esophago-Gastric Cancer Cohort (FINEGO) was established to coordinate this effort.

Objectives

The overall objective of FINEGO is to reduce mortality and morbidity associated to oesophageal and gastric cancer, and to improve survivorship after oesophageal and gastric cancer diagnosis.

Among others, the specific aims of the FINEGO are:

- To establish important baseline data on national and regional trends in oesophageal and gastric cancer in Finland.

- To investigate associations between operational volume and mortality and morbidity outcomes, as well as survivorship in oesophago-gastric cancers.

- To assess the relevance of clinical characteristics and modifiable risk factors in relation to mortality and morbidity outcomes, as well as cancer survivorship.

Methods

A multicenter FINEGO-collaborative has been established to conduct large-scale epidemiological, clinical and clinicopathological studies in oesophago-gastric cancers. The collaborative includes one to two senior consultant upper gastrointestinal or thoracic surgeons as the local principal investigators (PIs) from all centres conducting oesophageal and gastric cancer surgery in Finland, as well as senior consultant oesophago-gastric pathologists and biostatisticians.

Study design

This study is a population-based, nationwide, retrospective cohort study in Finland. The initial study period is from January 1st, 1987 until December 31st, 2015, with follow up until December 31st, 2016. The study period will be expanded every 5 years to keep the cohort updated for the most recent data.

Inclusion and exclusion criteria

The patients fulfilling the following inclusion criteria are included in the study:

1) Primary cancer of epithelial origin in the oesophagus, the gastro-oesophageal junction or the stomach

2) Patient receives surgical treatment for the cancer (including curative, palliative, or rescue surgery i.e. surgery after curative chemoradiation)

3) Age at least or over 18 years during the time of diagnosis

Identification of the study participants

The immutable, 11-digit personal identification number assigned to each resident in the country allows reliable identification and combining the registry data with patient records.[18] The patients will be identified through the Finnish Cancer Registry, and the Finnish Patient Registry. The identification through both registries is done to ensure near 100% completeness on oesophago-gastric cancer diagnosis. The patients undergoing oesophageal or gastric cancer surgery will be identified using the operations codes in the Finnish Patient Registry. The Finnish Patient Registry will provide the hospital names and operation dates, based on which the relevant patient records will be retrieved from the archives of the relevant hospital districts.

Data collection

Registry data will be collected from *The Finnish Cancer Registry, The Finnish Patient Registry, The Population Register Centre, Statistics Finland* and *The Social Insurance Institution* (*KELA)-registry* (Table 1). The quality of data in these registries is known to be very high,[19-22] and reporting to the registries is mandatory by the Finnish Law. These registry data include the identifying information, the variables related to the socio-economy, and will be used to calculate the well-validated Charlson's comorbidity index[23] and annual hospital volumes. *The patient records* of the included patients identified from the registries will be scrutinized using standardized forms for clinical variables including patient characteristics and surgeon, outcome and complication information (Table 1). The scans of the original diagnostic tissue sample slides for the study patients will be retrieved from the respective regional biobanks for assessment and review of the histological parameters (Table 1).

The identifying information of the selected patients from each hospital district will be provided to the respective PIs and administrative personnel for obtaining the patient records data. The obtained registry data, medical and health records data, as well as the digitalized histological samples, will be entered into the study database and pseudonymised using study identifiers after the completion of the data collection. The hard copies of some of the study data will be kept in a safe deposit on the premises of University of Oulu. The identification variables from the registries will be kept in an encrypted and password-protected file with limited access granted to only the main biostatistician and the principal investigator of the project. The pseudonymised cohort without identifying information is available for the members of the collaborative for sub-studies within the framework specified below.

Data management and analysis plan

The data management and analyses in this study will be supervised and conducted by an expert biostatistician (P.O.). After finishing the data collection, a cohort profile will be published. For the cohort profile, number of new yearly cancer cases, and the yearly number of operated cancers will be calculated based on the registry data. The baseline characteristics, i.e. number of patients in each group of selected variables will be reported in tables. Overall all-cause mortality will be reported for each cancer type based on the life table method,[24] and depicted using Kaplan-Meier curves.

Each of the sub-studies will be planned in the collaborative with a detailed *a priori* study protocol describing the rationale, aims, hypothesis and statistical analysis plan including appropriate methods, potential confounding and biases for the particular research question, as well as the biostatistician involved in the analysis.

Sample size

One of the main strengths is the large sample size of the study. It is estimated that at least 6000 oesophageal and 25000 gastric cancer patients will be found in screening during the study period. Of these patients, estimated 30% have been operated for their cancer, yielding estimates of 1800 oesophageal and 7500 gastric cancer patients for the study.

With 1800 oesophageal cancer patients, the estimated power would be >80% to reliably detect weak associations (Hazard ratio [HR] = 1.15), given an equal distribution of patients in the exposure groups. With 7500 gastric cancer patients, the power would be >80 to detect an association at the level HR=1.07.

Permissions and registration

The study has been approved by ethical committee in Northern Osthrobotnia, Finland, as well as The National Institute for Health and Welfare, Finland. Relevant local permissions and registrations are applied by the collaborative.

Individual informed consent will not be sought from the patients whose data are used in this observational study. Obtaining the informed consent has been waived by the Finnish law. The study will be conducted in accordance with the Declaration of Helsinki.

Discussion

Oesophageal and gastric cancers have poor prognosis, even after curative surgery.[5, 6] The present population-based, nationwide retrospective cohort study will provide information on the recent time trends in the treatment of oesophageal and gastric cancer and identify new, and verify previously identified, modifiable factors related to morbidity, mortality and survivorship after oesophageal and gastric cancer surgery.

The strengths of the FINEGO-cohort include its population-based design with complete and accurate ascertainment and follow-up of all patients diagnosed with oesophageal or gastric cancer in Finland, counteracting selection bias. The combined use of registry and patient records data reduces information bias. The inclusion of multiple potential confounding factors from the registries and patient records allows accurate analysis of a variety of exposures and end points. The sample size will large enough to enable robust survival and regression analyses in smaller sub-groups of patients.

There are also limitations in the present study. All patients not undergoing surgery will be excluded, because examining the patient records for all the patients would increase the number of involved hospital districts and primary care centres significantly, reducing the feasibility of the data collection. As a result the few patients treated with endoscopic mucosal resection or endoscopic submucosal dissection will also be excluded. However, these approaches are not widely applied in the treatment of oesophageal or gastric cancer in Finland. Patients undergoing curatively intended or palliative chemo- and/or radiotherapy will also be excluded, reducing the possibilities to study patients with disseminated disease or not eligible for surgery. The cohort is planned to be updated every five years and there is a lag of up to two years, including quality checks and controls, before the registry data is made available for research, preventing the study group from getting the most recent data for

analysis even during the cohort updates. However, this lag will not reduce the relative sample size considerably, and the effect on follow-up in person-years is minimal due to high mortality rates of the cancers. Furthermore, there are some variables, including smoking history and alcohol use, that are not recorded in the registries and cannot be reliably retrieved from the patient records, as they are not routinely recorded by the health care personnel in a structured way. However, the data quality and missing data will be meticulously checked before running the sub-studies, and the missing data will be taken into account by using multiple imputation methods in the analyses to reduce bias from missing data.

Taken together, this population-based, nationwide retrospective cohort study will provide new evidence regarding various unanswered questions in oesophageal and gastric cancer surgery by combining epidemiological and clinical data, as well as complement randomized clinical trials by assessing their findings in an unselected population.

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Table 1. Data sources and dataset information

Data Source	Variables
The Finnish Cancer Registry	Personal identification number (age, sex) Diagnosis number Date of cancer diagnosis Tumour stage
The Finnish Patient Registry	Personal identification number (age, sex) Hospital admissions data -Admitting hospital -Dates of admission and discharge -Diagnosis codes -Operations codes
The Population Register Centre	Marital status
Statistics Finland	Education level Date of death Causes of death
KELA registry	Dispensed drugs -Type (ATC-code) -Date dispensed -Amount of dispensed drug Sick leave (start date, end date) Pension information (start date)
Patient records	Tumour stage information Anesthesia information -Type of anaesthesia -ASA classification* Surgery information -Type of surgery -Surgeon volume -Bleeding -Operation duration Complications -According to the ECCG -Clavien-Dindo classification Oncological treatment -Neoadjuvant and adjuvant treatment -Treatment modality -Complications Pathology -Tumour location and stage -Lymph node yield and resection radicality Hospital and ICU stay
Biobanks	Scans of original diagnostic slides

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Competing interests statement: The authors state no potential competing interests.

Author contributions:

JHK developed the study idea, concept and design, initiated the collaborative project, developed data collection tools, obtained permissions and funding, and drafted the study protocol. PO was involved in the statistical design, made substantial revisions to the protocol and was involved in the original concept, study design and implementation. TJK was involved in design and implementation of the study, and revised the protocol. AK was involved in design and implementation of the study, and revised the protocol. SL was involved in design and implementation of the study, and revised the protocol. TR was involved in design and implementation of the study, and revised the protocol. AR was involved in design and implementation of the study, and revised the protocol. JR was involved in design and implementation of the study, and revised the protocol. JS was involved in design and implementation of the study, and revised the protocol. ES was involved in design and implementation of the study, and revised the protocol. VT was involved in design and implementation of the study, and revised the protocol. TT was involved in design and implementation of the study, and revised the protocol. JHK is the guarantor.

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We are willing to share anonymized data after the completion of the data collection upon request. Sharing the data will require ethical approval by the relevant committee, as well as approvals from the governmental agencies and local entities maintaining the relevant data. Researchers interested in collaboration are welcome to contact Joonas Kauppila (joonas.kauppila@oulu.fi), the principal investigator (PI) of FINEGO, or one of the local PIs. The access to data is currently restricted, but the applications for other researchers can be submitted by the FINEGO investigators to the relevant agencies and entities for approval.

Introduction

Gastric cancer is the third-, and oesophageal cancer the sixth leading cause of cancer death worldwide.[1] The incidence of oesophageal adenocarcinoma is increasing, while that of oesophageal squamous cell carcinoma and gastric cancer is decreasing in Finland,[2] similar to other Western countries.[3] The incidence of gastric cancer is slowly decreasing in majority of the countries across the globe.[4] However, both cancers are characterised by poor survival even after curatively intended surgery,[5-8] and a "textbook outcome" may be achieved in less than half of the patients undergoing oesophago-gastric cancer surgery.[9] Studies on sick leaves,[10] or postoperative use of opioids as an outcome after oesophageal and gastric cancer surgery are lacking, while these are important outcomes for the patients. It has been shown that sick leaves affect for example job retention in cancer patients.[11]

Randomized trials in oesophageal and gastric cancer have provided quality evidence that neoadjuvant - and adjuvant therapies increase survival[12-15] and that minimally invasive surgical approaches reduce, or at least do not increase complications.[16 17] Despite their good internal validity and lack of bias, randomized controlled studies in general have limited external validity and applicability to general population, and thus need to be complemented by quality observational studies to reliably assess the effects of implementation of trial results into practice.[18] Additionally, observational studies can provide evidence on questions that have not, or cannot, be evaluated in randomized trials.[18]

In Finland, high-quality registry data on these cancers is readily available.[19] Despite the good availability, the exposure and outcome data in the registries are not detailed enough for surgical research. Because of small population (5,5 million) sparsely populating Finland, the hospitals are many, and the single-center cohorts containing detailed information are small, not necessarily generalizable and have potential selection bias. There are no previous

coordinated nationwide population-based research efforts with detailed clinical data on oesophago-gastric cancer in Finland. To overcome these challenges, an extensive retrospective nationwide data collection from the patient medical records is needed. The Finnish National Esophago-Gastric Cancer Cohort (FINEGO) was established as a researcher-led effort to coordinate this retrospective database.

Objectives

The specific objectives of the FINEGO are:

- To establish important baseline data on national and regional trends and changes over time in oesophageal and gastric cancer surgery, postoperative morbidity and long-term outcomes in Finland.

- To investigate associations between surgeon and hospital volume and postoperative morbidity and mortality in oesophago-gastric cancers.

- To assess the relevance of clinical characteristics, modifiable risk factors, such as preoperative feeding, surgical approach, type of neoadjuvant treatment, or method of analgesia in relation to mortality and morbidity outcomes, as well as cancer survivorship, such as postoperative medication use in esophago-gastric cancer.

- To investigate whether histological assessment could be used for prediction of prognosis in esophageal and gastric cancer.

Methods

A multicenter FINEGO-collaborative has been established to conduct large-scale epidemiological, clinical and clinicopathological studies in oesophago-gastric cancers. The collaborative includes one to two senior consultant upper gastrointestinal or thoracic surgeons as the local principal investigators (PIs) from all academic centres conducting oesophageal and gastric cancer surgery in Finland, as well as senior consultant oesophago-gastric pathologists and biostatisticians. The participating researchers will sign the needed professional confidentiality consents to be allowed access to patient data obtained from the registries.

Study design

This study is a population-based, nationwide, retrospective cohort study in Finland. The initial study period is from January 1st, 1987 until December 31st, 2015, with follow up until December 31st, 2016. The study period will be expanded every 5 years to keep the cohort updated for the most recent data.

Inclusion and exclusion criteria

The patients fulfilling the following inclusion criteria are included in the study:

1) Primary cancer of epithelial origin in the oesophagus, the gastro-oesophageal junction or the stomach

2) Patient receives surgical treatment for the cancer, including curative, palliative, rescue surgery i.e. surgery after curative chemoradiation, or endoscopical curative surgery, such as

endoscopic mucosal resection and endoscopic submucosal dissection

3) Age at least or over 18 years during the time of diagnosis

Identification of the study participants

The immutable, 11-digit personal identification number assigned to each resident in the country allows reliable identification and combining the registry data with patient records.[20] The patients will be identified through the Finnish Cancer Registry, and the Finnish Patient Registry by searching these registries for cancer diagnoses (Supplementary Table 1) and operation status and operations codes (Supplementary Table 2). The identification through both registries is done to ensure near 100% completeness on oesophago-gastric cancer diagnosis. The patients undergoing oesophageal or gastric cancer surgery will be identified using the operations codes in the Finnish Patient Registry. The Finnish Patient Registry will provide the hospital names and operation dates, based on which the relevant patient records will be retrieved from the archives of the hospitals in all 21 hospital districts in Finland.

Data collection

Registry data will be collected from *The Finnish Cancer Registry, The Finnish Patient Registry, The Population Register Centre, Statistics Finland* and *The Social Insurance Institution* (*KELA)-registry* (Table 1). The quality of data in these registries is known to be very high,[21-24] and reporting to the registries is mandatory by the Finnish Law. These registry data include the identifying information, the variables related to the socio-economy, and will be used to calculate the well-validated Charlson's comorbidity index (Supplementary table 3)[25] and annual hospital volumes. All registry data-derived variables are calculated by a

biostatistician. *The patient records* of the included patients identified from the registries will be scrutinized by the study nurses and the investigators using standardized forms for clinical variables, including patient characteristics and surgeon, outcome and complication information (Table 1 and Supplementary Text 1). The clinical variables have been decided on by the investigators in the FINEGO group. Key variables, such as those from the operations charts will be extracted by one of the investigators, while the nurse extracts information not considered prone to errors, such as administrative data and laboratory results. All records and the corresponding data collection forms will be scanned and saved for later use. *The histological samples* will be collected from the biobanks. These original, prospectively collected diagnostic slides from the pre-operative gastroscopy and the surgical specimen will be sought from the biobanks' archives for the study patients. The sample slides are retrieved according to the biobank policies, and scanned and digitized into a picture form for assessment and review of the histological parameters and neoadjuvant treatment response (Table 1).

The identifying information of the selected patients from each hospital district will be provided to the respective PIs and administrative personnel for obtaining the patient records data from the health care entities' archives. The obtained registry data, medical and health records data, as well as the digitized histological samples, will be entered into the study database and pseudonymised using study identifiers after the completion of the data collection. The hard copies of some of the study data will be kept in a safe deposit on the premises of University of Oulu. The identification variables from the registries will be kept in an encrypted and password-protected file with limited access granted to only the main biostatistician and the principal investigator of the project. The pseudonymised cohort without identifying information is available for the members of the collaborative for sub-studies within the framework specified below.

Data management and analysis plan

The data management and analyses in this study will be supervised and conducted by an expert biostatistician (P.O.). After finishing the data collection, a cohort profile will be published. For the cohort profile, number of new yearly cancer cases, and the yearly number of operated cancers will be calculated based on the registry data. The baseline characteristics, i.e. number of patients in each group of selected variables will be reported in tables. Overall all-cause mortality will be reported for each cancer type based on the life table method,[26] and depicted using Kaplan-Meier curves.

Each of the sub-studies will be planned in the collaborative with a detailed *a priori* study protocol describing the rationale, aims, hypothesis and statistical analysis plan including appropriate methods, potential confounding and biases for the particular research question, as well as the biostatistician involved in the analysis.

Data quality assessment

The data quality in the registries will be checked through comparing the collected clinical data against the data, namely type of surgery, and tumor stage obtained from the registries. Internal audit, where a random sample of the patient records of 50 esophageal cancer patients and 50 gastric cancer patients will be re-reviewed by an another investigator, and the differences between the two assessments will be checked against the original data collection. If there are signs of difficulties in the assessment of certain variables or systematic errors, these variables will be audited in more detail. As of now, no external audit is planned, but all study protocols,

data files, statistical syntax used to obtain the results, and the end-product will be kept for further potential audits.

Sample size

One of the main strengths is the large sample size of the study. It is estimated that at least 6000 oesophageal and 25000 gastric cancer patients will be found in screening during the study period. Of these patients, estimated 30% have been operated for their cancer, yielding estimates of 1800 oesophageal and 7500 gastric cancer patients for the study.

With 1800 oesophageal cancer patients, the estimated power would be >80% to reliably detect weak associations (Hazard ratio [HR] = 1.15), given an equal distribution of patients in the exposure groups. With 7500 gastric cancer patients, the power would be >80 to detect an association at the level HR=1.07.

Permissions and registration

The study has been approved by ethical committee in Northern Osthrobothnia, The National Institute for Health and Welfare, Statistics Finland and the Office of the Data Protection Ombudsman, Finland. Relevant local permissions and registrations are obtained by the collaborative from all the 21 hospital districts, namely the Lapland Hospital district, Länsi-Pohja hospital district, Kainuun Social and Health Care Joint Authority, The Hospital district of Northern Osthrobothnia, Soite, The Hospital District of South Ostrobothnia, Pirkanmaa Hospital District, Kanta-Häme Hospital District, Vaasa Hospital District, Satakunta Hospital District, Hospital District of Southwest Finland, Ålands hälso- och sjukvård, Joint Authority of the Helsinki and Uusimaa Hospital District, Päijät-Häme Hospital District, Kymenlaakso

Social and Health Services Carea, South Karelia Social and Health Care District (Eksote), North Karelia Central Hospital and Honkalampi Centre, East Savo Hospital District, South Savo Social and Health Services, Kuopio University Hospital District and The Central Finland Hospital District, as well as the relevant Biobanks, namely Auria Biobank, Helsinki Biobank, Biobank of Eastern Finland, Central Finland Biobank, Northern Finland Biobank Borealis and Finnish Clinical Biobank Tampere.

Individual informed consent will not be sought from the patients whose data are used in this observational study. Obtaining the informed consent has been waived by the Finnish law. The study will be conducted in accordance with the Declaration of Helsinki.

Patient and public involvement

Patients or public were not involved in the development of the research question and study design or conducting the present study.

Discussion

Oesophageal and gastric cancers have poor prognosis, even after curative surgery.[5 6] The present population-based, nationwide retrospective cohort study will provide information on the recent time trends in the treatment of oesophageal and gastric cancer and identify new, and verify previously identified, modifiable factors related to morbidity, mortality and survivorship after oesophageal and gastric cancer surgery.

The strengths of the FINEGO-cohort include its population-based design with complete and accurate ascertainment and follow-up of all patients diagnosed with oesophageal or gastric cancer in Finland, counteracting selection bias. The combined use of registry and patient records data reduces information bias. The inclusion of multiple potential confounding factors from the registries and patient records allows accurate analysis of a variety of exposures and end points. The sample size will large enough to enable robust survival and regression analyses in smaller sub-groups of patients. Compared to some global collaboratives, such as the Worldwide Esophageal Cancer Collaboration (WECC)[27] or Esophagectomy Complications Consensus Group (ECCG)[28], the FINEGO can contribute to the scientific community by producing results in a real-life setting including all patients operated for esophageal and gastric cancers in the country, while the collaboratives typically include a sample of patients operated in high-volume centres. Furthermore, the above mentioned collaboratives include only esophageal cancer, while the present study includes both esophageal and gastric cancer.

There are also limitations in the present study. The retrospective study design is potentially weaker in data quality, compared to a prospective study. However, the retrospective design enables obtaining a large number of patients more quickly than a prospective data collection, and the data quality in the registries the cohort is based on is known to be very high, and the

manually collected patient records data will be vigorously checked and validated for quality. Furthermore, a national quality registry for these patients is going to be established, and the prospective clinical data collected in that quality registry can be later used in the updates of the FINEGO-cohort to potentially improve the quality of the more recent data. All patients not undergoing surgery will be excluded, because examining the patient records for all the patients would increase the number of involved health care entities significantly to over 250, reducing the feasibility of the data collection. Patients undergoing curatively intended or palliative chemo- and/or radiotherapy will be excluded, reducing the possibilities to study patients with disseminated disease or not eligible for any type of surgery. The cohort is planned to be updated every five years and there is a lag of up to two years, including quality checks and controls, before the registry data is made available for research, preventing the study group from getting the most recent data for analysis even during the cohort updates. However, this lag will not reduce the relative sample size considerably, and the effect on follow-up in person-years is minimal due to high mortality rates of the cancers. Furthermore, there are some variables, including smoking history and alcohol use, that are not recorded in the registries and cannot be reliably retrieved from the patient records, as they are not routinely recorded by the health care personnel in a structured way. However, the data quality and missing data will be meticulously checked before running the sub-studies, and the missing data will be taken into account by using multiple imputation methods in the analyses to reduce bias from missing data.

Taken together, this population-based, nationwide retrospective cohort study will provide new evidence regarding various unanswered questions in oesophageal and gastric cancer surgery by combining epidemiological and clinical data, as well as complement randomized clinical trials by assessing their findings in an unselected population.

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Table 1. Data sources and dataset information

Data Source	Variables
The Finnish Cancer Registry	Personal identification number (age, sex) Diagnosis number Date of cancer diagnosis Tumour stage
The Finnish Patient Registry	Personal identification number (age, sex) Hospital admissions data -Admitting hospital -Dates of admission and discharge -Diagnosis codes -Operations codes
The Population Register Centre	Marital status
Statistics Finland	Education level Date of death Causes of death
KELA registry	Dispensed drugs -Type (ATC-code) -Date dispensed -Amount of dispensed drug Sick leave (start date, end date) Pension information (start date)
Patient records	Tumour stage information Anesthesia information -Type of anaesthesia -ASA classification* Surgery information -Type of surgery -Surgeon volume -Bleeding -Operation duration Complications -According to the ECCG -Clavien-Dindo classification Oncological treatment -Neoadjuvant and adjuvant treatment -Treatment modality -Complications Pathology -Tumour location and stage -Lymph node yield and resection radicality Hospital and ICU stay
Biobanks	Scans of original diagnostic slides

Supplementary Table 1. The diagnosis codes used to identify patients with esophageal and gastric cancer. The use of ICD-9 and ICD-10 overlapped, and therefore, both codes are used for searching for patients in 1995-1997.

	ICD-9 (before 1997)	ICD-10 (1995 and after)
Oesophageal cancer	150	C15
Gastric cardia cancer	151A	C16.0
Gastric cancer	151B - 151X	C16.1 - C16.9

Supplementary Table 2. The surgical codes used to identify patients undergoing surgical treatment for esophago-gastric cancer.

	THL Surgical Codes (1983-1996)	NOMESCO classification (1996 -)
Oesophageal resection	6201, 6202, 6203, 6204, 6205, 6209	JCC00, JCC10, JCC11, JCC12, JCC20, JCC30, JCC96, JCC97
Resection of the cardia	6301, 6320	Not applicable
Gastric resection:	6314, 6315, 6316, 6317, 6318, 6321, 6322, 6323, 6329	JDC00, JDC10, JDC11, JDC20, JDC30, JDC40, JDC96, JDC97, JDD00, JDD96
Endoscopic mucosal resection / Endoscopic submucosal dissection	Not applicable	JCA45, JCA52, JDA45, JDA52, JDH52

Supplementary Table 3. The definition of Charlson's comorbidity index.

The Charlson's comorbidity index will be calculated according to Armitage et al.[1] using hospital admissions up to 3 years before the index admission (surgery), and the index admission, and will exclude esophago-gastric malignancies.

Disease	**ICD-10 codes**
Myocardial infarction	I21*, I22*, I23*, I252
Congestive cardiac failure	I11, I13, I255, I42, I43, I50, I517
Peripheral vascular disease	I70–I73, I770, I771, K551, K558, K559, R02, Z958, Z959
Cerebrovascular disease	G45, G46, I60–I69
Dementia	A810, F00–F03, F051, G30, G31
Chronic pulmonary disease	I26, I27, J40–J45, J46*, J47, J60–J67, J684, J701, J703
Rheumatological disease	M05, M06, M09, M120, M315, M32–M36
Liver disease	B18, I85, I864, I982, K70, K71, K721, K729, K76, R162, Z944
Diabetes mellitus	E10–E14
Hemiplegia or paraplegia	G114, G81–G83
Renal disease	I12, I13, N01, N03, N05, N07, N08, N171*, N172*, N18, N19*, N25, Z49, Z940, Z992
Any malignancy	C00-C14, C17–C26, C30–C34, C37–C41, C43, C45–C58, C60–C76, C80–C85, C88, C90–C97
Metastatic solid tumour	C77–C79
AIDS/HIV infection	B20–B24

*Will be only taken into account for previous, not current, hospital admissions, because these are common complications after surgery and cause confounding to the comorbidity index.

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FINEGO clinical data collection form

Personal identification number:…….

1 Hospital: …….

2 Operation date:.....

3 Surgeon(s) 1:…….. (First name, Surname)
2: ……..
3: ……..

4 Anesthesiologist(s): 1:…….. (First name, Surname)
2:……..
3:……..

5 Operation codes:……..

6 Anesthesia codes:……..

7 Sex:
1. Man
2. Woman

8 Tumor localization
1. Upper 1/3 (upper border <25 cm from incisors)
2. Middle 1/3 (upper border 25-30 cm)
3. Lower 1/3 (upper border >30 cm)
4. Cardia, Siewert type 2 (center -1 - +2cm from Z line)
5. Cardia, Siewert type 3 (center 2-5cm below Z line)
6. Stomach body
7. Stomach distal
999 Not clear

9 Treatment determined in multidisciplinary meeting
0. No
1. Yes

10 Preop Treatment:
0. No
1. Yes
998. Not clear

11 Type of treatment:
1.Chemotherapy
2. Radiation
3. Radiation+Chemotherapy

12 Complications of neoadjuvant treatment
0. None, completed as planned

1. Yes, with delay/reduction, why _____

2. Yes, with termination, why _____

13 Preoperative lab

	Value	Date	Not available
Hb:	_____	_____	____
Alb:	_____	_____	____
Prealb:	_____	_____	____
CRP	_____	_____	____
BMI	_____	_____	____

14 ASA Class _____

15 Resection type: (circle)
1. Transthoracic resection: a. Ivor-Lewis, b. McKeown
2. Transhiatal resection
3. Total gastrectomy
4. Proximal gastrectomy
5. Distal gastrectomy
6. Other_____

16 Intent of surgical approach
1. Open surgery
2. Hybrid thoracoscopic
3. Hybrid laparoscopic
4. Totally minimally invasive (thoracoscopy + laparoscopy)
5. Totally laparoscopic (no thoracotomy/scopy)
5. Other_____

16.1 Only minimally invasive surgery: converted open?
0. No
1. Converted to hybrid
2. Yes

17 Lymphadenectomy

Esophagectomy
1. 2-field
2. Extended 2-field
3. 3-field

Gastrectomy
4. D0 lymphadenectomy
5. D1 lymphadenectomy
6. D2 lymphadenectomy
7. D3 lymphadenectomy
999. Unclear

18 Tumor length: …… mm

19 Substitute:
1. Stomach
2. Small intestine
3. Colon

20 Type of anastomosis:
1. Handsewn:
2. Staples

21 Location of anastomosis:
1. Neck
2. Thorax
3. Abdomen

22 Splenectomy:
1.Yes: why? ……
2. No

23 Use of energy devices
1. Bipolar (LigaSure)
2. Ultrascision (Harmonic),
3. Hybrid (Thunderbeat)
4. Other …….
5. No

24 Fundoplication:
1. Before surgery: type? ……
2. During surgery: type? ……
3. No

25 Frozen section (circle all that apply):
1. Distal resection margin
2. Proximal resection margin
3. Lymph node
4. None
998. Not clear

26 Jejuno-cath (feeding enterostomy):
1. Yes
2. No

27 Curative intended treatment:
1. Yes
2. No (palliative resection)
3. Rescue surgery (after curative chemoradiation)
998. Not clear

28 Duration of surgery: …… min (surgery start-stop)

29 Peroperative bleeding…… ml

For the following, count only midnights; morning Wednesday to evening Thursday = 1

30 Days at the ICU …..

31 Days in respirator: ……

32 Days in hospital: …….

33 Further treatment in:
1. Home
2. Health care center (terveyskeskus)
3. Another hospital
4. Rehabilitation center
5. Other _____

34 Complications in 90 days after operation:
1. No
2. Yes (fill in pages 6-10)

35 Reoperations in 90 days after operation:
1. No
2. Yes (fill in pages 6-10)

36 Adjuvant treatment
1.No
2. Chemotherapy
3. Radiotherapy

37 Adjuvant treatment status
1. Completed without complications
2. Complications: _____
3. Not completed, why?_____

38 Proximal resection margin: ….. mm

39 Distal resection margin: ….. mm

40 Circumferential resection margin: ….. mm

41 Histology:

1. Adenocarcinoma
2. Squamous cell carcinoma
3. High-grade dysplasia
4. Low-grade dysplasia
5. Other_____

999 Not clear

41.1 Laurén class:

1. Diffuse
2. Intestinal
3. Indeterminate

999. Unavailable

41.2 WHO histology classification (gastric cancer)

1. Papillary
2. Tubular
3. Mucinous
4. Signet ring / poorly cohesive
5. Other types, which_____

999. Unavailable

42 Preoperative stage (before any treatment)

T:

1 Tis
2 T1 – T3
3 T1
4 T2
5 T3
6 T4
7 Tx
8 T0

43 N:

1 N0
2 N1
3 N2
4 N3

999 not clear

44 M:

0 M0
1 MIa
2 MIb

999 Not Clear

45 Postoperative stage (According to PAD or patient records)

T:
1 Tis
2 T1 – T3
3 T1
4 T2
5 T3
6 T4
7 Tx
8 T0

46 N:
1 N0
2 N1
3 N2
4 N3
999 not clear

47 Lymph nodes with metastasis: …… pcs

48 Number of Lymph nodes examined:…… pcs

49 M:
0 M0
1 MIa
2 MIb
999 Not Clear

50 G/Differentiation:
1. G1, well differentiated
2. G2, moderately differentiated
3. G3, poorly differentiated
4. GX, cannot be assessed

51 Tumor stage:
0 0 (pat only op)
1 I
2 IIA
3 IIB
4 III
5 IV
6 IVA
7 IVB
8 No cancer/dysplasia
9 Complete response after neo
999 not clear

52 Micr radically:
0 No
1 Yes
999 Not clear

53 Macr radically:
0 No
1 Yes
999 Not Clear

54 R0/R1/R2
1 R0
2 R1
3 R2
999 not clear

55 Becker regression grade:
1. No tumor left (1a)
2. <10% tumor left (1b)
3. <10-50% tumor left (2)
4. >50% tumor left (3)
999. Not applicable

COMPLICATIONS

56 Complications during 30 days after surgery (circle) and 30-90 days after surgery (square)
-Mark the main categories and all sub-categories that apply!

1. Pulmonary complications
   a. Pneumonia
   b. Pleural effusion requiring additional drainage procedure
   c. Pneumothorax requiring treatment
   d. Atelectasis mucous plugging requiring bronchoscopy
   e. Respiratory failure requiring intubation
   f. Acute respiratory distress syndrome (ARDS)
   g. Acute aspiration
   h. Tracheobronchial injury
   i. Chest tube for air leak over 10 days postop

2. Cardiac complications
   a. Cardiac arrest requiring CPR
   b. Myocardial infarction (Troponin + ECG)
   c. Atrial dysrhythmia requiring treatment
   d. Ventricular dysrhythmia requiring treatment
   e. Congestive heart failure requiring treatment
   f. Pericarditis requiring treatment

3. Gastrointestinal complications

a. Esophagoenteric leak from anastomosis or conduit necrosis

i. Type 1: local defect requiring no change in therapy, treated medically or diet

ii. Type 2: requiring intervention, no surgery (radiology, stent, bedside opening)

iii. Type 3: Defect requiring surgery

b. Conduit necrosis/failure

i. Type 1: Focal conduit necrosis identified endoscopically, causes additional monitoring or non-surgical therapy

ii. Type 2: Focal conduit necrosis, treated by surgical therapy but not diversion

iii. Type 3: Conduit necrosis requiring conduit resection and diversion

c. Ileus preventing or delaying enteral feeding

d. Small bowel obstruction

e. Feeding J-tube complication

f. Pyloromyotomy/pyloroplasty complication

g. Clostridium infection

h. GI bleeding requiring intervention or transfusion

i. Delayed conduit emptying requiring intervention or delaying discharge, or requiring nasogastric tube >7 days

j. Pancreatitis

k. Pancreatic fistula

l. Liver dysfunction

m. Biliary leakage

4. Urologic

   a. Acute renal failure (doubling of baseline creatinine)

   b. Acute renal failure requiring dialysis

   c. Urinary tract infection

   d. Urinary retention requiring re-insertion of catheter, delaying discharge, or discharge with catheter

5. Thromboembolic

   a. DVT (ultrasound or angio verified)

   b. Pulmonary embolism

   c. Stroke (defined by CT or similar)

   d. Peripheral thrombophlebitis (clinically verified)

6. Neurologic / psychiatric

   a. Recurrent nerve paresis (mark: A unilateral, B bilateral)

      i. Type 1: Transient injury, requires no other therapy than dietary modification

      ii. Type 2: Injury requiring elective surgery (thyroplasty or medialization procedure)

      iii. Type 3: Injury requiring acute surgery due to aspiration or respiratory issues

   b. Other neurologic injury

   c. Acute delirium

   d. Delirium tremens (alcohol withdrawal symptom)

7. Infection

   a. Wound infection requiring opening wound or antibiotics

   b. Central line infection requiring removal or antibiotics

   c. Intra-abdominal abscess

   d. Intrathoracic abscess

   e. Sepsis

   f. Other infection requiring antibiotics, what ……

8. Wound/diaphragm

   a. Thoracic wound dehiscence

   b. Acute abdominal wall dehiscence / hernia

   c. Acute diaphragmatic hernia

9. Other

   a. Chyle leak (Mark: A. <1 liter per day, B >1 liter per day)

      i. Type 1: requires dietary modifications, but not totally parenteral nutrition

      ii. Type 2: requires totally parenteral nutrition

      iii. Type 3: requires surgery or other intervention (chest drains not included)

   b. Reoperation for reason other than bleeding, anastomotic leak or conduit necrosis, reason……

   c. Multiple organ failure

57 Clavien-Dindo classification for complications (only the most severe grade to be ticked)

0.	No complications
1.	Grade 1 (Any deviation form postoperative course, including antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy or opening the wound bedside)*
2.	Grade 2 (Blood transfusion, total parenteral nutrition or pharmacological treatment needed other than I)
3.	Grade 3 (Surgical, endoscopic or radiological intervention)
4.	Grade 4 (Life-threatening complications requiring IC/ICU-management, or stroke (not TIA) or any brain hemorrhage)
5.	Grade 5 (Death of a patient)

58 REOPERATIONS

Reoperation 1
Days from primary operation:_____
Reason for operation:_____
Result:_____

Reoperation 2
Days from primary operation:_____
Reason for operation:_____
Result:_____

Reoperation 3
Days from primary operation:_____
Reason for operation:_____
Result:_____