Title: Endoscopy for gastroesophageal reflux disease and survival in esophageal adenocarcinoma

Short Title: Endoscopy for GERD and adenocarcinoma survival

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Abbreviations:

CI	Confidence interval
EAC	Esophageal adenocarcinoma
GERD	Gastroesophageal reflux disease
HR	Hazard ratio
ICD	International Classification of Diseases
NOMESCO	Nordic Medico-Statistical Committee Classification of Surgical Procedures
OR	Odds ratio

Novelty and Impact: Gastroesophageal reflux disease (GERD) is the main risk factor for esophageal adenocarcinoma and the most common indication for upper endoscopy, but whether current endoscopy practices prevent death in adenocarcinoma is unknown. In this nationwide cohort study of 6,600 patients with esophageal adenocarcinoma, the prognosis in adenocarcinoma was similar in patients with and without previous screening endoscopy for GERD. This indicates that endoscopy screening for GERD is unlikely to prevent mortality in esophageal adenocarcinoma.

ABSTRACT

Gastroesophageal reflux disease (GERD) is a risk factor of esophageal adenocarcinoma (EAC) and the most common indication for upper gastrointestinal endoscopy. Yet, whether GERD or endoscopy practice influence survival in EAC is largely unknown and was assessed in this study.

This nationwide cohort study included all Swedish residents diagnosed with EAC in 1997-2013 with follow-up to 2018. Exposures were history of GERD and endoscopies prior to EAC. The main outcome was EAC-specific 5-year mortality. Multivariable Cox regression provided hazard ratios (HRs) with 95% confidence intervals (CIs) adjusted for potential confounders.

Among 6,600 EAC patients (79.3% males, median age 70 years) followed for 9,138 person-years, 440 (6.7%) had GERD and 592 (9.0%) had ≥1 endoscopy before EAC diagnosis. GERD was associated with a decreased risk of mortality (adjusted HR 0.71, 95% CI 0.64-0.80), which was only slightly attenuated by adjustment for prior endoscopies (HR 0.79, 95% CI 0.70-0.90), and further adjustments also for tumor stage and surgical resection (HR 0.74, 95% CI 0.62-0.89). Compared to EAC patients without prior endoscopy, mortality was unchanged in GERD patients having undergone 1 or 2 endoscopies before EAC diagnosis (HR 1.02, 95% CI 0.80-1.31, for 1 endoscopy; HR 0.90, 95% CI 0.63-1.30, for 2 endoscopies), while the mortality was decreased in patients with ≥3 endoscopies (HR 0.55, 95% CI 0.36-0.85)**.**

This study indicates that GERD may be associated with a better prognosis in the event of EAC; however, the use of endoscopy screening has a limited impact on survival unless performed very frequently.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is one of the most common public health disorders with a prevalence of 10-25% in adults in Western populations.[1, 2] GERD is also the most common indication for upper gastrointestinal endoscopy.[3] Endoscopy may identify complications of GERD, including the premalignant metaplastic condition Barrett's esophagus and invasive esophageal adenocarcinoma (EAC), which is the most feared complication. GERD is the main risk factor for EAC with daily GERD symptoms increasing the relative risk of EAC 5- to 15-fold.[4] In the last few decades, the incidence of EAC has increased 6-fold in many Western populations, and the increase is predicted to continue.[5, 6] Most EAC patients present with regional or distant metastases, when the survival is poor. With localized EAC or early tumor stage, the 5-year survival is considerably better.[7]

If endoscopy for GERD identifies Barrett's esophagus, these patients are included into endoscopic surveillance programs, but there is limited evidence on how to manage the majority of individuals with GERD. A single screening endoscopy may be performed in a subset of patients with GERD, but it is unclear if this practice improves the survival in EAC.

The hypothesis of the present study was that GERD and use of endoscopy increase the likelihood of detecting EAC at an earlier and surgically resectable stage, thus improving the long-term survival in EAC. This hypothesis was tested in a large and unselected cohort of EAC patients in Sweden.

METHODS

Design

This nationwide, population-based cohort study included all patients in Sweden with a new diagnosis of EAC confirmed during January 1, 1997 to December 31, 2013. The exposures were history of GERD and upper gastrointestinal endoscopies before the EAC diagnosis. The main outcome was EAC-specific 5-year mortality in EAC. The secondary outcomes were all-cause 5-year mortality and completed surgical resection. Ethical permission was obtained from The Regional Ethical Review Board in Stockholm, Sweden (registration number 2017/2276-32).

Data collection

Data for each EAC patient were collected from three Swedish national health data registers: The Cancer Register, Patient Register, and Cause of Death Register. All healthcare providers in Sweden are required to report medical information of all patients to these registers according to Swedish law. Upon birth or immigration, Swedish residents are assigned a unique 10-digit personal identity number, which was used for identification of the study participants and for cross-linkage of data between registers. The data sources are presented below.

The Swedish Cancer Register was used to identify EAC patients and assess tumor stage. This register has recorded all types of newly diagnosed cancers in Sweden since 1958. The register holds tumor-specific data, i.e. site, histopathology, stage, and date of diagnosis. It

has 98% completeness for registration, 100% completeness for histological confirmation and 98% completeness for tumor stage of EAC.[8-10]

The Swedish Patient Register was used to assess history of GERD and endoscopy, as well as surgical resection. This register started in 1964 and became nationwide complete for in-patient healthcare in 1987 and specialized out-patient healthcare in 2001. The register contains clinical data, including dates of admissions and discharges, diagnoses, and surgical procedures. It has been validated for its high usefulness in large-scale and population-based studies.[11]

The Swedish Cause of Death Register provided data on mortality. This register has recorded date and causes of all deaths in Swedish residents, including those who die abroad, from 1952 onwards with a completeness of 100% and 99%, respectively.[12] Cause of death is registered on a yearly basis with a time lag, meaning that the follow-up for EAC-specific mortality was December 31, 2016. Date of death is continuously updated, allowing for a longer follow-up time for all-cause mortality (April 30, 2018).

Study cohort

The cohort consisted of all patients with a first-time EAC diagnosis recorded in the Swedish Cancer Register between January 1, 1997 and December 31, 2013. EAC was defined by the diagnosis code 150 for esophageal cancer and 151.1 for gastroesophageal junctional cancers according to the International Classification of Diseases, 7th revision (ICD-7), combined with the histological code 096 signifying adenocarcinoma according to the WHO/HS/CANC/24.1 classification.

Exposures

The exposure *history of GERD* was defined by the following diagnoses recorded in the Swedish Patient Register at least 3 months prior to EAC diagnosis: heartburn, hiatal hernia, gastroesophageal reflux disease with or without esophagitis, esophageal ulcer, or esophageal obstruction. Excluded were 49 patients with a diagnosis of Barrett's esophagus, representing a special subgroup of GERD patients undergoing endoscopic surveillance which is associated with improved survival in EAC.[13] The 3-month interval between GERD and EAC was used to exclude early EAC misclassified as GERD. ICD codes were used to identify all diagnoses (Appendix 1). To assess whether duration of GERD impacted on survival, the interval between the first GERD diagnosis and EAC was categorized into quartiles, where the first group was diagnosed with GERD between 3 months and 2 years before EAC, the second between 2 and 5 years, the third between 5 and 10 years, and the fourth >10 years before EAC. EAC patients without GERD constituted the reference group.

The exposure *endoscopy prior to EAC* was defined by the relevant procedural code in the Swedish Patient Register (Appendix 1), where all endoscopies conducted within 10 years of EAC diagnosis were counted. A 3-month cut-off was used to exclude endoscopies performed as part of the diagnostic work-up of an already existing EAC. Additional endoscopies conducted within 6 months of another endoscopy were not counted, because these often represent control endoscopies following the results of the last endoscopy. The number of endoscopies was categorized into four groups: 0, 1, 2, or ≥3. To identify whether time since last endoscopy was associated with survival, the interval between the last endoscopy and

EAC was dichotomized, where the first group had the last endoscopy more than 5 years before EAC, and the second group had the last endoscopy within 5 years before EAC.

Outcomes

The main outcome was *EAC-specific 5-year mortality*, defined as the time from EAC diagnosis until death specifically related to EAC until December 31, 2016 according to the Cause of Death Register.

The secondary outcome *all-cause 5-year mortality* was defined as the date from EAC diagnosis until date of death from any cause until April 30, 2018 according to the Cause of Death Register.

The secondary outcome *surgical resection of EAC* was defined as a surgical code corresponding to a completed endoscopic or surgical EAC resection until December 31, 2014 according to the Patient Register (Appendix 3).

Confounders and mediators

The potential confounders were age, sex, calendar year, and comorbidity. Data on age, sex, and calendar year at EAC diagnosis were retrieved from the Cancer Register. Comorbidities were identified at the period of EAC diagnosis in the Patient Register and were defined using the well-validated Charlson Comorbidity Index, which is based on specific ICD codes (Appendix 2).[14]

Potential mediators of any associations between GERD and outcomes were number of endoscopies, tumor stage, and surgical resection. Data on tumor stage were retrieved from the Cancer Register and information about endoscopies came from the Patient Register (Appendix 3).

Statistical analysis

Follow-up for mortality started at the date of EAC diagnosis and ended at the date of death, end of study period, or 5 years after cohort entry, whichever occurred first. In the figures, the product limit estimates of the EAC-specific 5-year survivor function were calculated for each category of GERD and endoscopies. Cox regression was used to determine crude and adjusted hazard ratios (HRs) with 95% confidence intervals (95%CI) for EAC-specific 5-year mortality and all-cause 5-year mortality. The main multivariable model provided HRs adjusted for sex (male or female), age (continuous variable), calendar year (discrete variable), and comorbidity (Charlson Comorbidity Index 0, 1, or ≥2). Because any inverse associations between GERD and mortality in EAC could be due to increased frequency of endoscopies, leading to earlier tumor stage and increased likelihood of surgical resection, adjustment for number of endoscopies (0, 1, 2 or ≥3), tumor stage (I, II, or III-IV), and surgical resection (yes or no) were added in explanatory models. If these variables would attenuate any associations between GERD and mortality in EAC, they would be regarded as mediators of these associations. In addition, a post hoc analysis modelling the association between last endoscopy before EAC (dichotomized into ≤5 years and >5 years) with EAC-specific 5-year mortality was conducted. The odds of undergoing surgical resection were assessed using logistic regression, which provided odds ratios (ORs) with 95%CI. Multivariable models

provided ORs adjusted for sex, age, calendar year, and Charlson Comorbidity Index with the same categorizations as presented above. To evaluate effect modification of GERD of potential associations between endoscopies and the three outcomes, an interaction term was included for the two variables. Thereafter the HRs and ORs were calculated for the association separately for the patients with and without GERD. Statistical analyses were performed in adherence to a pre-defined study protocol. All data management and analyses were performed by a senior biostatistician (FM), using the statistical package SAS version 9.4 (SAS Institute Inc., Cary, NC, USA.)

Data availability statement

The data that support the findings of this study are available from the Swedish National Board of Health & Welfare. Restrictions apply to the availability of these data, which were used under license for this study. Data are available with the permission of the National Board of Health & Welfare.

RESULTS

Study participants

The study cohort included 6,600 EAC patients. These participants were followed up for 9,138 person-years (mean 1.4 years) (Table 1). The majority of patients were men (79.3%) and the median age was 70.0 years (interquartile range 62.0 to 78.0 years). Of all participants, 440 (6.7%) had a history of GERD and 592 (9.0%) had undergone at least one endoscopy at median 2.2 years before EAC diagnosis. Compared to EAC patients without history of GERD, those with GERD had more comorbidity, earlier tumor stages, and higher surgical resection rates (Table 1). At the end of follow-up (maximum 5 years), 770 (11.7%) EAC patients were alive.

History of GERD and outcomes in esophageal adenocarcinoma

For patients with history of GERD, the cumulative proportion of death in EAC was decreased compared to EAC patients without GERD (Figure 1). The EAC-specific 5-year mortality was also decreased compared to EAC patients without GERD (adjusted HR 0.71, 95%CI 0.64 to 0.80) (Table 2). After additional adjustment for number of earlier endoscopies, the EAC-specific 5-year mortality was slightly attenuated, but remained decreased (HR 0.79, 95%CI 0.70 to 0.90). In an analysis restricted to EAC patients diagnosed after year 2005 (n=2,998), where the variables tumor stage and surgical resection were added to the model, the EAC-specific 5-year mortality remained decreased comparing patients with and without GERD (HR 0.74, 95%CI 0.62 to 0.89). The EAC-specific 5-year mortality in EAC patients with GERD remained decreased independently of the time-period between the first recorded GERD

diagnosis and the EAC diagnosis (Supplementary Table 1). The results for all-cause 5-year mortality were similar to those of EAC-specific 5-year mortality (Table 2). Associations between variables included in the models and EAC-specific 5-year mortality are presented in Supplementary Table 2.

The odds of surgical resection were increased among EAC patients with GERD, compared to those without GERD (adjusted OR 1.39, 95%CI 1.13 to 1.71) (Table 2). After additional adjustment for number of endoscopies, the association between GERD and resection rate was only slightly attenuated (OR 1.30, 95%CI 1.01 to 1.67) (Table 2).

Prior endoscopies and outcomes in esophageal adenocarcinoma

The cumulative mortality within 5 years of EAC diagnosis decreased with increasing number of previous endoscopies (Figure 2). Compared to EAC patients who had not undergone an endoscopy, the adjusted HRs for EAC-specific 5-year mortality were 1.02 (95%CI 0.80 to 1.31) for 1 endoscopy, 0.90 (95%CI 0.63 to 1.29) for 2 endoscopies, and 0.55 (95%CI 0.36 to 0.85) for ≥3 endoscopies (Table 3). Among EAC patients without GERD, earlier endoscopies did not influence the EAC-specific 5-year mortality (Table 4). Last endoscopy performed ≤5 years before EAC diagnosis was associated with improved EAC-specific 5-year mortality compared to endoscopy performed earlier (adjusted HR 0.80, 95%CI 0.65 to 0.99). The results for all-cause 5-year mortality were similar to those of EAC-specific 5-year mortality (Table 3 and 4).

The point estimates of surgical resection increased with number of endoscopies for GERD, but were not statistically significant (Table 3). Among EAC patients without GERD, there was no association between the number of endoscopies and resection rates (Table 4).

DISCUSSION

The results of this study show that EAC patients with history of GERD have a decreased risk of 5-year EAC-specific and all-cause mortality. The survival did not clearly improve in patients with 1-2 endoscopies within 10 years of EAC diagnosis but was substantially improved in patients with GERD with ≥3 prior endoscopies.

Among methodological strengths of this study is the population-based design with complete inclusion and follow-up of all EAC patients in Sweden during the study period. Other advantages include the high-quality data on exposures, outcomes, confounders, and mediators. The study was facilitated by the uniform Swedish healthcare system based on public health insurance and largely managed by public providers, making access and delivery of healthcare equal. Historical information on GERD and endoscopies was available, which enabled investigation of the prognostic role of multiple endoscopies. The large sample size and long follow-up allowed for precise risk estimates. There were virtually no losses to follow-up due to complete recording of participants. A limitation was that some potential confounding factors, e.g. obesity and tobacco smoking, were not adjusted for due to lack of data in the medical registers. Yet, the prognostic influence of these factors is limited and the adjustment for diseases associated with smoking and obesity in the Charlson Comorbidity Index should reduce any residual confounding. The occurrence of GERD may have been underestimated, and it is likely that mild GERD remained undiagnosed and severe GERD were registered. Thus, patients without a registered GERD diagnosis probably had less severe symptoms than patients with a registered diagnosis. The presence of patients with GERD in the unexposed group would however not explain associations, but only dilute them.

The literature has provided sparse and contradictory results whether endoscopy screening may improve outcomes in EAC. In a general practice setting, a high rate of endoscopy referrals has been associated with increased operability and decreased mortality in esophagogastric cancer, indicating that a low threshold for endoscopy may improve outcomes in upper gastrointestinal cancer.[15] Endoscopy for GERD recently before EAC diagnosis has been associated with earlier tumor stage and increased resectability, but the mortality was similar to that of patients without prior endoscopies.[16] A US cohort study of EAC patients found that endoscopy screening before EAC diagnosis improved the survival, whereas GERD was associated with earlier stage EAC without improving the survival.[17] In these smaller cohort studies, the search for past GERD and endoscopies was limited to just a few years which reduced the possibility to study influence of multiple endoscopies.[16, 17] These issues were overcome in the present study and the sample size was substantially larger.

In the present study, GERD was associated with a decreased risk of mortality in EAC even after adjustment for confounders and mediators, indicating an independent prognostic role. The adjustment for endoscopies, tumor stage, and resection rate only slightly attenuated the risk estimates, indicating that the influence of these factors is not the only explanation for this association. A similar observation was made in a recent study which found that EAC arising from specialized intestinal metaplasia had a better prognosis.[18] These findings suggest that GERD-related EAC may represent a less aggressive tumor than EAC unrelated to GERD, perhaps due to prognostic factors associated with GERD, such as health-conscious behavior or the use of proton-pump inhibitors. Independent of mechanism, the association between GERD diagnosis and improved surgical resection rates and survival in EAC highlights the importance of recognition and treatment of GERD by physicians.

The poor survival of EAC is mainly due to two factors: the lack of symptoms of early stage disease and an aggressive growth pattern. This is a challenge to most physicians, because it leaves a short time window for detection in a curable stage, thus requiring perfect timing of endoscopy screening. However, endoscopy screening occurs haphazardly rather than systematically, and most EAC are detected when symptoms of advanced disease become apparent. In this study, mortality was reduced among EAC patients with GERD who had repeated endoscopies (≥3 endoscopies/10 years), while one or two endoscopies per 10 years were not sufficient to have a significant impact on survival. This suggests that endoscopy has a limited role in preventing mortality in EAC unless performed often. A post hoc analysis indicated that endoscopy screening performed every 5 years may reduce mortality in adenocarcinoma, which indicates a potential time frame for repeating endoscopy. However, the notion that repeated endoscopies may reduce mortality in adenocarcinoma should be interpreted with caution, given that some of the protective effect may be explained by lead and length time bias (i.e. artificially improved survival). Mortality was not improved by frequent endoscopies in individuals without GERD, although the study was not powered to decisively reject this hypothesis. Endoscopy screening should have a similar effect on detecting EAC for patients with and without GERD. However, if GERD-related EAC is less aggressive, the time to detect curable EAC may be longer for these patients. Thus, longer endoscopy intervals may be permitted to detect GERD-related EAC.

GERD is a strong risk factor for EAC, but about 40% of EAC do not report a history of GERD.[19] Thus, screening based on GERD symptoms may miss these 40% with EAC. Already some 2 million (30% of all) endoscopies are performed annually for GERD in the United States

alone.[3] These endoscopies likely do not impact on survival in EAC and the vast majority who developed EAC had previously not received any endoscopy. Instead, most patients in this study were diagnosed at advanced tumor stage with resulting poor survival. Given the limited impact of endoscopy screening, alternative methods such as structured risk prediction modelling of identifiable risk factors may be an alternative to current practices, which is based on GERD symptoms.[20-22] The use of non-endoscopic screening methods may be applied in a primary care setting and may readily identify a population at high risk of EAC to monitor with frequent endoscopies.[23, 24]

In conclusion, this population-based cohort study presents two main findings. GERD-related EAC is associated with improved survival after adjustment of prognostic factors. However, endoscopy in these patients has a limited impact on survival in EAC unless performed very frequently. While GERD is the most common indication for endoscopy, most patients with EAC have not undergone a prior endoscopy, which suggests that current screening strategies for EAC are misdirected.

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TABLES

Table 1. Characteristics of esophageal adenocarcinoma patients with and without history of gastroesophageal reflux disease (GERD) in 1997-2013 in Sweden

	Number (%)	
	GERD	**No GERD**
	440 (6.7)	6,160 (93.3)
Age (years)		
≤55	38 (8.6)	765 (12.4)
56-65	112 (25.5)	1,448 (23.5)
66-75	136 (30.9)	1,879 (30.5)
≥76	154 (35.0)	2,068 (33.6)
Sex		
Men	357 (81.1)	4,879 (79.2)
Women	83 (18.9)	1,281 (20.8)
Calendar period of adenocarcinoma diagnosis (years)		
1997-2000	40 (9.1)	1,286 (20.9)
2001-2004	85 (19.3)	1,381 (22.4)
2005-2008	133 (30.2)	1,448 (23.5)
2009-2013	182 (41.4)	2,045 (33.2)
Charlson comorbidity index		
0	260 (59.1)	4,209 (68.3)
1	111 (25.2)	1,368 (22.2)
≥2	69 (15.7)	583 (9.5)
Endoscopies before adenocarcinoma		
0	170 (38.6)	5,838 (94.8)
1	168 (38.2)	285 (4.6)
2	56 (12.7)	31 (0.5)
≥3	46 (10.5)	6 (0.1)
Tumor stage[a]		
I	52 (22.5)	225 (6.4)
II	66 (21.0)	597 (17.1)
III-IV	126 (40.0)	1,932 (55.3)
Unstaged	71 (22.5)	739 (21.2)
Surgical resection of adenocarcinoma		
Yes	166 (37.7)	2,030 (33.0)
No	274 (62.3)	4,130 (67.0)

[a]Tumor stage data were available for patients diagnosed with EAC in 2005-2013 (n=3,857)

Table 2. Outcomes in esophageal adenocarcinoma patients with and without history of gastroesophageal reflux disease.

	Gastroesophageal reflux disease	
	No (n=6,160)	**Yes (n=440)**
EAC-specific 5-year mortality (HR, 95%CI)		
Crude	1 (reference)	0.71 (0.63-0.80)
Adjusted[a]	1 (reference)	0.71 (0.64-0.80)
Adjusted[b]	1 (reference)	0.79 (0.70-0.90)
All-cause 5-year mortality (HR, 95%CI)		
Crude	1 (reference)	0.74 (0.66-0.82)
Adjusted[a]	1 (reference)	0.74 (0.66-0.82)
Adjusted[b]	1 (reference)	0.81 (0.72-0.92)
Surgical resection (OR, 95%CI)		
Crude	1 (reference)	1.23 (1.01-1.51)
Adjusted[a]	1 (reference)	1.39 (1.13-1.71)
Adjusted[b]	1 (reference)	1.30 (1.01-1.67)

[a]Adjusted for age, sex, calendar year, and comorbidity.

[b]Adjusted for all above plus number of endoscopies.

Abbreviations: HR – hazard ratio; CI – confidence interval; OR – odds ratio

Table 3. Outcomes in esophageal adenocarcinoma among patients with gastroesophageal reflux disease stratified by endoscopy before adenocarcinoma diagnosis.

	0 endoscopy (n=170)	1 endoscopy (n=168)	2 endoscopies (n=56)	≥3 endoscopies (n=46)
EAC-specific 5-year mortality (HR, 95%CI)				
Crude	1 (reference)	1.03 (0.81-1.31)	0.90 (0.62-1.29)	0.53 (0.35-0.82)
Adjusted[a]	1 (reference)	1.02 (0.80-1.31)	0.90 (0.63-1.29)	0.55 (0.36-0.85)
All-cause 5-year mortality (HR, 95%CI)				
Crude	1 (reference)	0.97 (0.77-1.22)	0.83 (0.58-1.18)	0.56 (0.38-0.84)
Adjusted[a]	1 (reference)	0.96 (0.76-1.21)	0.83 (0.58-1.17)	0.58 (0.39-0.86)
Surgical resection (OR, 95%CI)				
Crude	1 (reference)	0.62 (0.40-0.97)	1.02 (0.55-1.89)	1.60 (0.83-3.07)
Adjusted[a]	1 (reference)	0.69 (0.44-1.10)	1.21 (0.63-2.30)	1.88 (0.95-3.71)

[a]Adjusted for age, sex, calendar year and comorbidity.

Abbreviations HR – hazard ratio; CI – confidence interval; OR – odds ratio

Table 4. Outcomes in esophageal adenocarcinoma among patients without gastroesophageal reflux disease stratified by endoscopy before adenocarcinoma diagnosis.

	0 endoscopy (n=5,838)	1 endoscopy (n=285)	2 endoscopies (n=31)	≥3 endoscopies (n=6)
EAC-specific 5-year mortality (HR, 95%CI)				
Crude	1 (reference)	0.98 (0.86-1.11)	0.99 (0.67-1.46)	0.95 (0.40-2.29)
Adjusted[a]	1 (reference)	0.91 (0.80-1.04)	0.93 (0.63-1.36)	0.96 (0.40-2.32)
All-cause 5-year mortality (HR, 95%CI)				
Crude	1 (reference)	1.03 (0.91-1.16)	0.97 (0.67-1.42)	0.90 (0.37-2.15)
Adjusted[a]	1 (reference)	0.94 (0.83-1.07)	0.90 (0.62-1.32)	0.89 (0.37-2.14)
Surgical resection (OR, 95%CI)				
Crude	1 (reference)	0.76 (0.58-0.99)	1.27 (0.62-2.62)	0.40 (0.05-3.45)
Adjusted[a]	1 (reference)	0.94 (0.71-1.24)	1.71 (0.80-3.64)	0.62 (0.07-5.52)

[a]Adjusted for age, sex, calendar year and comorbidity.
Abbreviations: HR – hazard ratio; CI – confidence interval; OR – odds ratio

Supplementary Table. Outcomes in esophageal adenocarcinoma among patients with gastroesophageal reflux (GERD) disease stratified by duration of GERD before adenocarcinoma.

	Duration of GERD before adenocarcinoma					
	No GERD (n=5,791)	**1 - ≤90 days (n=369)**	**90 days - ≤2 years (n=113)**	**2 - ≤5 years (n=102)**	**5 - ≤10 years (n=112)**	**>10 years (n=113)**
EAC-specific 5-year mortality (HR, 95%CI)						
Crude	1 (ref.)	1.02 (0.91-1.14)	0.78 (0.63-0.96)	0.64 (0.51-0.81)	0.73 (0.59-0.91)	0.69 (0.56-0.86)
Adjusted[a]	1 (ref.)	1.00 (0.89-1.12)	0.76 (0.62-0.94)	0.66 (0.52-0.83)	0.74 (0.60-0.93)	0.69 (0.55-0.86)
Adjusted[b]	1 (ref.)	1.00 (0.89-1.12)	0.86 (0.69-1.07)	0.76 (0.59-0.98)	0.86 (0.68-1.09)	0.72 (0.58-0.90)
All-cause 5-year mortality (HR, 95%CI)						
Crude	1 (ref.)	1.03 (0.92-1.15)	0.77 (0.63-0.95)	0.68 (0.55-0.85)	0.77 (0.63-0.95)	0.72 (0.59-0.89)
Adjusted[a]	1 (ref.)	1.00 (0.90-1.12)	0.76 (0.61-0.93)	0.70 (0.56-0.87)	0.78 (0.63-0.96)	0.71 (0.58-0.87)
Adjusted[b]	1 (ref.)	1.01 (0.90 - 1.13)	0.84 (0.68-1.04)	0.80 (0.63-1.02)	0.90 (0.72-1.12)	0.75 (0.60-0.92)
Surgical resection (OR, 95%CI)						
Crude	1 (ref.)	1.10 (0.88-1.37)	1.04 (0.70-1.54)	1.43 (0.96-2.13)	0.97 (0.65-1.45)	1.62 (1.12-2.36)
Adjusted[a]	1 (ref.)	1.20 (0.95-1.51)	1.12 (0.75-1.69)	1.49 (0.98-2.25)	1.16 (0.77-1.76)	1.97 (1.34-2.92)
Adjusted[b]	1 (ref.)	1.20 (0.95-1.51)	1.11 (0.72-1.73)	1.25 (0.79-1.98)	1.02 (0.65-1.60)	1.85 (1.24-2.75)

[a]Adjusted for age, sex, calendar year, and comorbidity.

[b]Adjusted for all above plus number of endoscopies.

Abbreviations: HR – hazard ratio; CI – confidence interval; OR – odds ratio

FIGURES

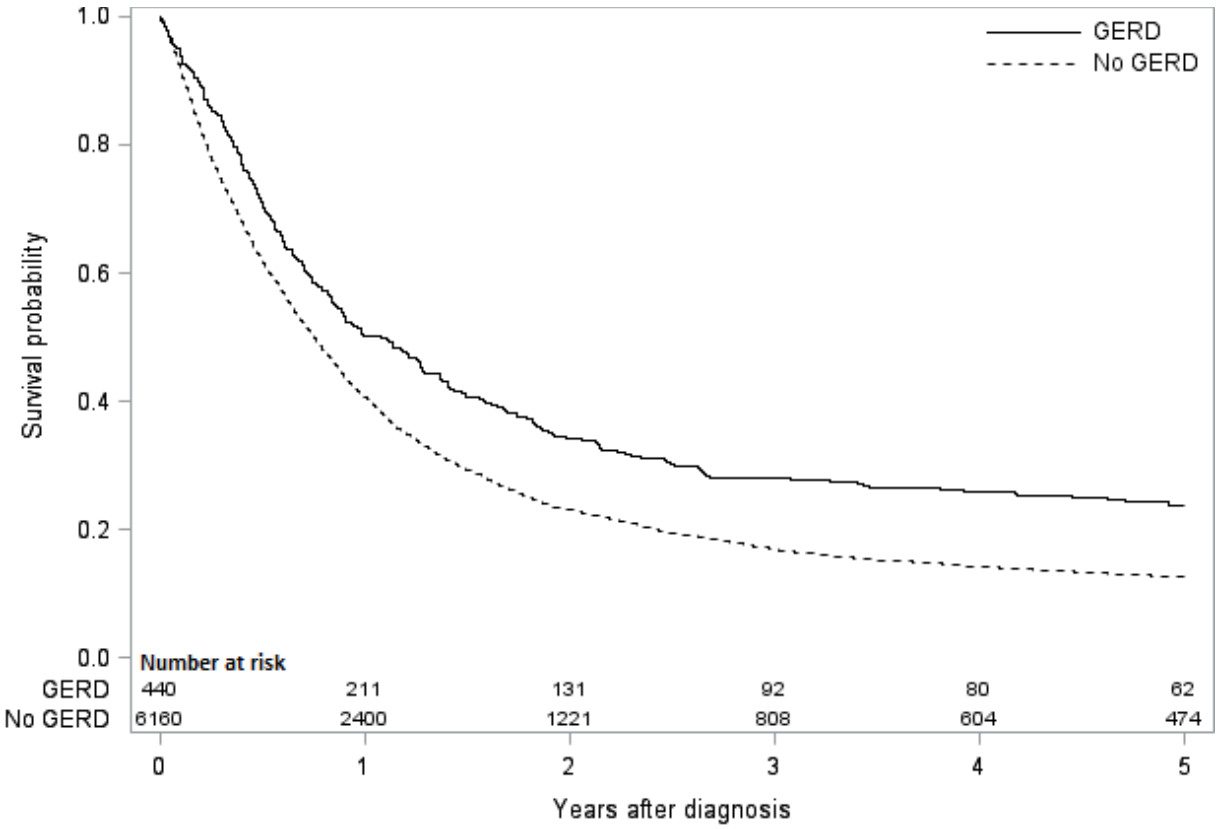

Figure 1. Cumulative EAC-specific mortality after diagnosis of esophageal adenocarcinoma among patients with and without history of gastroesophageal reflux disease
The proportion of patients alive is shown on the y-axis. The years after diagnosis and number of patients alive at the start of each subsequent year are shown on the x-axis.

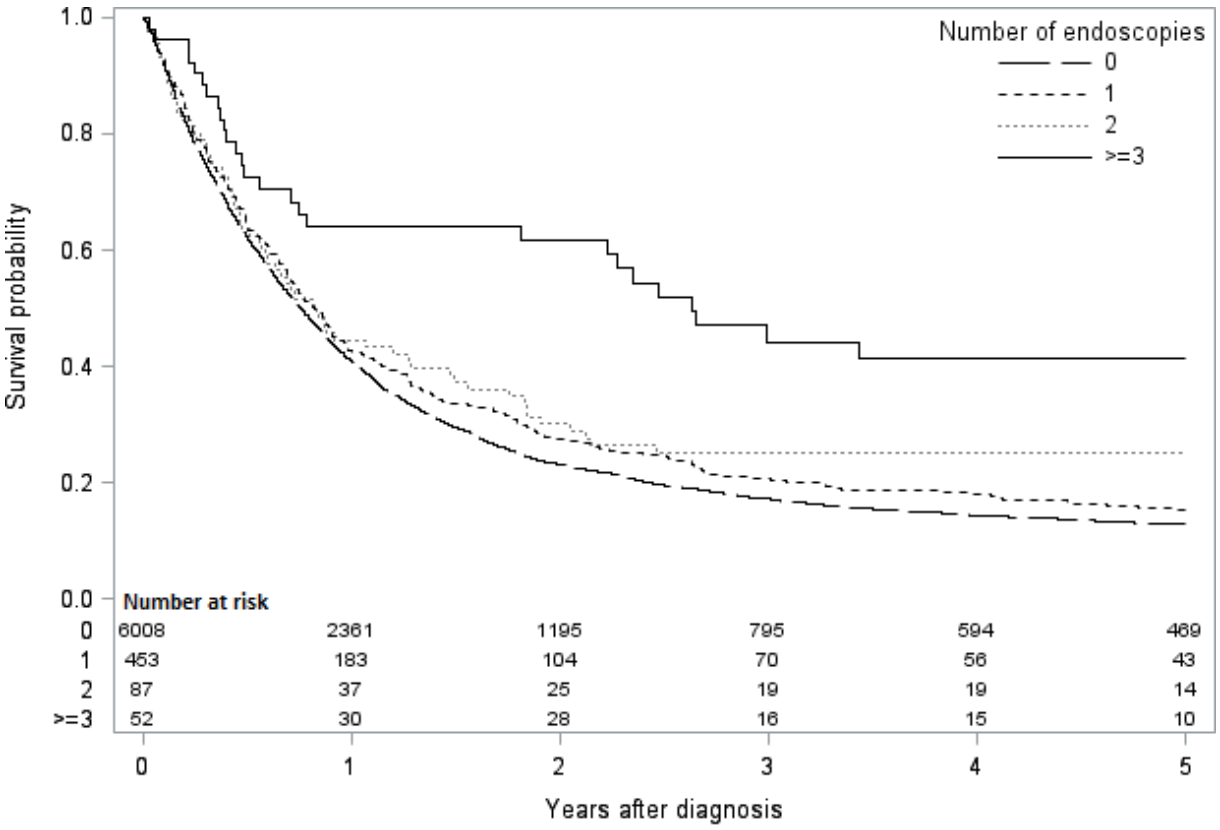

Figure 2. Cumulative EAC-specific mortality after diagnosis of esophageal adenocarcinoma stratified for number of endoscopies prior to esophageal adenocarcinoma

The proportion of patients alive at the start of each subsequent year is shown on the y-axis. The years after diagnosis and number of patients alive at the start of each subsequent year are shown on the x-axis.