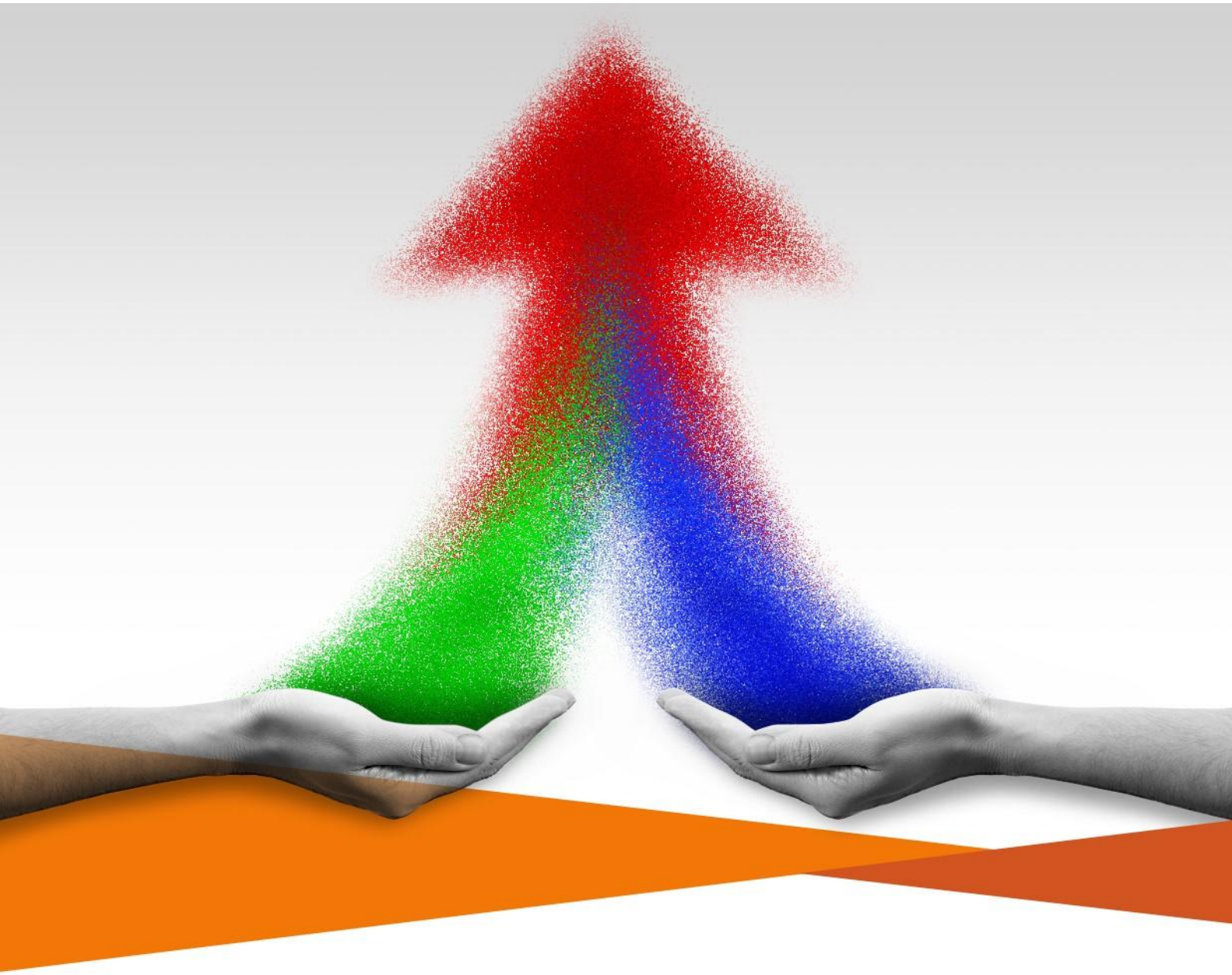

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Title: Sex differences in the prognosis after surgery for esophageal squamous cell carcinoma and adenocarcinoma

Short title: Sex and prognosis in esophageal cancer

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Key words: Esophagus; neoplasm; mortality; prognosis; sex; gender; surgery

Abbreviations: CI, confidence interval; HR, hazard ratio

Article category: Cancer epidemiology

Novelty and Impact: It is uncertain whether sex associates to prognosis in esophageal squamous cell carcinoma and adenocarcinoma. In this population-based nationwide cohort study in Sweden between 1987-2010 (n=1816) the women who underwent esophagectomy for esophageal squamous cell carcinoma had better prognosis than men, especially those with early tumor stages. No sex differences in prognosis were found for oesophageal adenocarcinoma.

Abstract

Some investigations suggest a better prognosis in women compared to men with esophageal cancer but these differences are uncertain. The aim of this study was to clarify whether sex influences the prognosis after esophagectomy for esophageal squamous cell carcinoma and esophageal adenocarcinoma. A population-based and nationwide cohort study included almost all patients who underwent esophagectomy for esophageal cancer in Sweden in 1987-2010, with follow-up until 2016. Patients' sex was analyzed in relation to risk of mortality. Multivariable Cox regression provided hazard ratios (HR) with 95% confidence intervals (CI), adjusted for calendar period, age, education, comorbidity, tumor stage, neoadjuvant therapy, and surgeon volume. Among 1816 participants, 1024 (56%) had esophageal squamous cell carcinoma (355 [35%] women), and 792 (44%) had esophageal adenocarcinoma (103 [13%] women). Compared to men, women had a decreased overall all-cause mortality in esophageal squamous cell carcinoma (HR=0.73, 95% CI 0.63–0.85). Stratified analyses showed decreased mortality limited to women aged >55 years (HR=0.71, 95% CI 0.61–0.83), but in all tumor stages, particularly stages 0-I (HR=0.54, 95% CI 0.37–0.79). Women also had decreased 90-day all-cause mortality, 5-year all-cause mortality, and 5-year disease-specific mortality in esophageal squamous cell carcinoma compared to men. For esophageal adenocarcinoma, no sex differences were found for any of the mortality outcomes. Thus, women who undergo esophagectomy for esophageal squamous cell carcinoma seem to have better prognosis than men, especially those with early tumor stages, whereas no sex differences in prognosis were found for esophageal adenocarcinoma.

Novelty & Impact Statement: IJC-18-1617.R1

While sex differences are suspected of influencing esophageal squamous cell carcinoma, whether sex is associated with the disease remains unclear. In this population-based cohort study in Sweden, among patients who underwent esophagectomy for esophageal squamous cell carcinoma between 1987 and 2010, women were found to have better prognosis than men. In particular, women exhibited decreased 5-year all-cause and 5-year disease-specific

mortality, with notably lower mortality for women with early-stage tumors. By comparison, for esophageal adenocarcinoma, no sex differences were found in prognosis. The findings draw attention to potentially important prognostic differences between the sexes specifically for esophageal squamous cell carcinoma.

Introduction

Esophageal cancer is the 6th most common cancer-related death globally, and the overall 5-year survival is less than 20%.[1-3] The strongest prognostic factor is tumor stage, but fitness (mainly determined by comorbidity and age) is also important for evaluating whether patients are eligible for curatively intended surgery or not.[4]

A characteristic of esophageal cancer is the strong male predominance in incidence in both main histological subtypes, i.e. squamous cell carcinoma and adenocarcinoma,[5] which may be due to differences in risk factor exposures and sex hormonal factors.[6, 7] A few register-based studies have suggested a sex disparity in the prognosis of esophageal cancer, but these have not analyzed the histological subtypes separately.[8-11] In studies that have analyzed the histologic types separately, women diagnosed with esophageal squamous cell carcinoma had a possibly better prognosis than men, while no sex differences were found for esophageal adenocarcinoma.[12-14] However, these studies were limited by low coverage of the study population, small sample size, or inability to adjust for relevant confounding variables.[12-14] Potential sex differences may be explained by differences in the distribution of the main prognostic factors between the sexes, i.e. tumor stage, socioeconomic factors (educational level), and comorbidity,[15-17] but these factors have not been adjusted for in the existing literature. Thus, it remains uncertain if there are any sex differences in prognosis in esophageal cancer.

The present study aimed to clarify whether sex influences the survival in esophageal squamous cell carcinoma and esophageal adenocarcinoma separately by conducting a

population-based cohort study with long and complete follow-up and adjustment for prognostic factors.

Methods

Design

This was a population-based and nationwide cohort study including at least 98% of all patients diagnosed with squamous cell carcinoma or adenocarcinoma of the esophagus who underwent esophagectomy in Sweden between 1987 and 2010, with follow-up until May 31, 2016. The study exposure was female versus male sex. The primary outcome was overall all-cause mortality, and secondary outcomes were 90-day all-cause mortality, 5-year all-cause mortality, and 5-year disease-specific mortality. The data used for this study were retrieved from nationwide Swedish registries and medical records (presented below). All Swedish residents have a personal identity number, a unique 10-digit identifier, which is assigned upon birth or immigration.[18] Linkage of register and patient records information into one study database was then done using the personal identity number. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden. By the Swedish Law, informed consent is not needed for register-based research in Sweden.

Data collection

Register data: Earlier versions of this cohort have been described in previous studies examining esophageal cancer surgery.[19-22] In brief, patients with esophageal cancer were identified from the Swedish Cancer Registry, which has 98% nationwide completeness in the recording of this cancer,[23] and likely even higher completeness for those who undergo resectional surgery. The nationwide Swedish Patient Registry was used to identify patients who had undergone surgical resection, and also to provide information about patients' age, sex, and comorbidity. This registry has 99.6% positive predictive value for esophagectomy.[24] Comorbidity was defined and categorized using the well-validated and most updated version of the Charlson Comorbidity Index.[25] The nationwide Swedish Longitudinal Integration

Database for Health Insurance and Labour Market Studies (LISA) provided information on patients' education levels. Mortality data were obtained from the nationwide Swedish Cause of Death Registry, which has 100% complete information for date of death, and at least 96% completeness for cause of death.[26]

Medical records data: To collect more detailed clinical data, surgery charts and pathology records were retrieved from all hospitals conducting esophagectomies in Sweden during the study period. The data from these medical records were assessed and categorized according to a detailed protocol to ensure uniformity.[20] The medical records provided valid information about tumor location, stage and histology, type of surgery, neoadjuvant therapy, and the number of esophagectomies conducted by each surgeon (surgeon volume). Tumor stage was classified based on the 7th edition of tumor-node-metastasis (TNM) system of the Union Internationale Contre le Cancer.[27] The cumulative surgeon volume was defined according to an algorithm described in detail elsewhere.[19] Briefly, surgeon names were extracted from the operation charts, and the surgeon with the highest number of esophagectomies at the index operation was considered responsible for the surgery. Cumulative surgeon volume was calculated as the total number of esophagectomies the surgeon had been responsible for at the time of the index surgery during the study period. Open transthoracic resection with intrathoracic anastomosis was the most common (>95%) surgical procedure and the preferred reconstruction was a gastric tube which was pulled up and anastomosed to the proximal esophagus in the chest or neck.

Statistical analysis

Multivariable Cox regression was used to calculate hazard ratios (HR) with 95% confidence intervals (CI). The crude model was without any adjustments, whereas the main model was adjusted for the following potential confounders (with categorizations): 1) calendar period of

surgery (1987-1994, 1995-2002, or 2003-2010), 2) age at surgery (continuous), 3) education level (<10 years, 10-12 years, or >12 years of formal education, based on the Swedish school system), 4) comorbidity (Charlson Comorbidity Index score 0, 1, or ≥2), 5) tumor stage (0-I, II, or III-IV), 6) neoadjuvant therapy (yes or no), and 7) cumulative surgeon volume (<7, 7-16, 17-46, or >46). In order to test the hypothesis that different levels of female hormones before and after menopause influence mortality, the analysis was stratified by the age groups ≤55 years and >55 years.[12] The analyses were also stratified by tumor stage 0-I, II, and III-IV. The Kaplan-Meier method was used to verify the proportional hazards assumptions and to estimate the survival functions and the log-rank test was used to calculate p-values. All p values were two-sided, and p values below 0.05 were considered statistically significant. Missing data were limited and thus handled by carrying out a complete case analysis, i.e. patients with missing data on any variable were excluded. All statistical analyses were carried out by an experienced biostatistician (KW), who followed an *a priori* specified study protocol, defining and categorizing the exposures, outcomes and covariates, as well as the statistical methods. The statistical software IBM SPSS v24.0 (IBM Corp., Armonk, NY) was used for all statistical analyses.

Results

Patients

Among 1821 patients with esophageal cancer who underwent esophagectomy for esophageal cancer in Sweden during the study period, 1024 (56%) had squamous cell carcinoma (669 [65%] men and 355 [35%] women) and 792 (44%) had adenocarcinoma (689 [87%] men and 103 [13%] women). Five patients with unknown or mixed histology were excluded from the study, resulting in 1816 patients. The distribution of patient characteristics was similar in men and women independent of the histologic type of esophageal cancer (Table 1). In total, 1544 (85%) patients died during follow-up, including 208 (11%) who died within 90 days of surgery and 1361 (75%) within 5 years of surgery. The cause of death was esophageal cancer for 1198 (88%) of the patients who died within 5 years of surgery.

Sex and prognosis in esophageal squamous cell carcinoma

In patients who underwent esophagectomy for esophageal squamous cell carcinoma, the relative risk of overall all-cause mortality was 27% lower in women than in men (adjusted HR 0.73, 95% CI 0.63–0.85) (Table 2, Figure 1). Women also had statistically significantly lower 90-day all-cause mortality, 5-year all-cause mortality, and 5-year disease-specific mortality compared to men (Table 2). In patients aged ≤55 years, there was no sex difference in the risk of overall all-cause mortality, or for any of the secondary mortality outcomes. In patients aged >55 years, the risk of overall all-cause mortality (adjusted HR 0.71, 95% CI 0.61–0.83) and all secondary mortality outcomes was lower in women than in men (Table 3). The prognosis was better in women than men for each tumor stage group (Table 4). In women with tumor stage 0-I, the risk of overall all-cause mortality was almost half that of men (adjusted HR 0.54, 95% CI 0.37–0.79), and the corresponding HRs were 0.74 (95% CI 0.59–0.93) for stage II tumors and 0.79 (95% CI 0.63–1.00) for stage III-IV tumors. Women also had lower HRs

for all secondary mortality outcomes for each tumor stage compared to men, although some of these estimates were not statistically significant (Table 4).

Sex and prognosis in esophageal adenocarcinoma

In patients who underwent esophagectomy for esophageal adenocarcinoma, the risk of overall all-cause mortality was not statistically significantly lower in women than in men (adjusted HR 0.83, 95% CI 0.65–1.08). Women and men had a similar risk of 90-day all-cause mortality, 5-year all-cause mortality, and 5-year disease-specific mortality (Table 2). There were no differences in mortality in the analyses stratified by age groups or tumor stages in any of the mortality outcomes (Table 3 and Table 4).

Discussion

This study suggests that women who undergo esophagectomy for esophageal squamous cell carcinoma have consistently better prognosis than men, and this sex difference is more pronounced in patients with early tumor stage. No sex differences in prognosis were found for esophageal adenocarcinoma.

The validity of the study was improved by the population-based design with virtually complete inclusion and follow-up of patients. The information regarding sex (exposure) and mortality (outcome) was highly correct, and information about all established prognostic factors (confounders) was enabled by using a combination of data from high-quality registries and medical records. The use of a predefined data retrieval form and a specific study protocol reduced the risk of chance findings and systematic errors. Confounding is a threat to most observational studies, but this was counteracted by adjusting for several well-established prognostic factors. Yet, confounding by other factors that might potentially influence the prognosis, e.g. smoking and alcohol abuse, cannot be ruled out, which limits the analysis.[16, 17] However, confounding by these exposures should have been reduced by the adjustment for education, because the highest obtained education is strongly associated with smoking and alcohol use, as well as mortality from these causes in Sweden.[28, 29] Chance might influence the results, particularly in the age-stratified analyses where the statistical power was low. However, the large sample size provided robust estimates of the main analyses and the results were consistent in the sub-group analyses.

A few earlier studies have indicated a better prognosis in women with esophageal cancer compared to men.[12-14] A Swedish register-based study from our group indicated a lower overall all-cause mortality in women with esophageal squamous cell carcinoma (HR 0.83,

95% CI 0.78–0.89, n=4631), but not in women with esophageal adenocarcinoma.[30] However, that study lacked detailed clinical information and thus could not adjust for relevant prognostic factors.[30] This interesting finding in combination with the limited ability to adjust for confounders prompted us to conduct the present study. Another register-based study based on the Surveillance, Epidemiology, and End Results (SEER) database in the United States suggested that compared to men, women have better survival in loco-regional esophageal squamous cell carcinoma if aged >55 years (HR 0.91, 95% CI 0.86–0.95, n=11,960), and no sex differences in mortality were found for esophageal adenocarcinoma.[12] That study was population-based with 34.6% coverage of the population, but lacked accurate information regarding tumor stage, comorbidity, and socioeconomic factors. A population-based study of 703 patients with esophageal cancer from the Netherlands also showed better survival (HR 0.56, 95% CI 0.32–0.99) in women, but the histological types of esophageal cancer were not separated.[14] A population-based study of 426 patients with esophageal squamous cell carcinoma from Iran found no clearly decreased 5-year survival in women with esophageal cancer compared to men (HR 0.91, 95% CI 0.72–1.15), but that study was small and a decreased mortality could not be dismissed.[31] Taken together, some previous studies have also suggested better survival in women with esophageal cancer, especially squamous cell carcinoma. The present study supports that sex is a prognostic factor in esophageal squamous cell carcinoma, but not adenocarcinoma, and that this influence seems to remain after adjustment for prognostic factors, i.e., tumor stage, comorbidities, educational level, neoadjuvant treatment, and surgeon volume.

The mechanisms explaining the observed sex difference in esophageal squamous cell carcinoma are unclear.[32] Studies have indicated a role of estrogens in the etiology of esophageal squamous cell carcinoma,[7, 33-35] but no studies have examined whether estrogens influence the prognosis. The age-stratified analysis of the present study showed no sex

differences in esophageal squamous cell carcinoma survival in patients ≤55 years, when the inhibitory effects of estrogen is expected to be greater compared to after the age of 55. This suggests that estrogens might not be the most important factor mediating the sex disparity in prognosis. However, this subgroup analysis was underpowered, and the lack of information on medications containing estrogen, estrogen and progesterone expression, and history of oophorectomy further limits this analysis. Interestingly, androgen exposure can increase the risk of esophageal squamous cell carcinoma in rats,[36] and facilitate the growth of human esophageal squamous cell carcinoma cells.[37] In addition, activation of androgen receptors might increase inflammatory signaling and progression of esophageal squamous cell carcinoma by up-regulating interleukin 6 (IL-6) in tobacco-using individuals.[38] The sex differences in prognosis might also be related to socioeconomic and lifestyle factors,[28, 29] although adjustment for educational level did not change the results of the present study. The adjustment for education level might not take sex disparities in alcohol use into account. Some research suggests that alcohol and tobacco use is much greater in men with esophageal cancer compared to women,[39] and studies have shown that alcohol drinking[40, 41] and smoking[41] are associated with poorer survival in esophageal squamous cell carcinoma patients, with a seemingly multiplicative effect. Regarding adenocarcinoma, the association with smoking is weaker and alcohol is not a risk factor, which might explain the observed disparity in survival between the main histological types of esophageal cancer.[42] Another possible explanation is that women may seek healthcare at earlier tumor stage. However, the analyses showed a consistently better prognosis when the tumor stage groups were analyzed separately. Taken together, differences in sex hormone levels and lifestyle factors are possible explanations for the observed sex disparity in esophageal squamous cell carcinoma survival, but this remains to be answered in future research.

If the results of this study are confirmed in subsequent investigations, some future clinical and research implications may be considered. Speculatively, intensified treatment and follow-up might be warranted in men with esophageal squamous cell carcinoma, and if sex hormones are involved it might be relevant to examine if adjuvant anti-androgenic treatment may improve the prognosis in patients who have undergone surgery for esophageal squamous cell carcinoma.

In conclusion, this population-based cohort study indicates that among patients with esophageal squamous cell carcinoma aged >55 years, women have a better prognosis than men after esophagectomy. This was found for each tumor stage. No sex differences in prognosis were found for esophageal adenocarcinoma. Efforts should be made to identify the reasons for the sex disparity in survival of the esophageal squamous cell carcinoma patients.

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share data upon request after ethical approval has been approved by the relevant committee and the governmental agencies that maintain the data.

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Tables

Table 1. Characteristics of 1,816 patients who underwent surgery in 1987-2010 in Sweden for esophageal squamous cell carcinoma or adenocarcinoma

	Esophageal squamous cell carcinoma		Esophageal adenocarcinoma	
	Men	**Women**	**Men**	**Women**
	Number (%)	Number (%)	Number (%)	Number (%)
Total	669 (65)	355 (35)	689 (87)	103 (13)
Time period				
1987-1995	333 (67)	164 (33)	158 (86)	26 (14)
1995-2002	178 (62)	109 (38)	238 (87)	37 (14)
2003-2010	158 (66)	82 (34)	293 (88)	40 (12)
Mean age, in years	64.5	65.5	65.3	66.5
Education				
<10 years	338 (66)	174 (34)	338 (89)	44 (12)
10-12 years	228 (67)	115 (34)	239 (84)	45 (16)
>12 years	73 (61)	46 (39)	96 (90)	11 (10)
Missing	30 (60)	20 (40)	26 (90)	3 (10)
Charlson's Comorbidity Index				
0	437 (66)	230 (35)	368 (85)	64 (15)
1	152 (66)	77 (34)	192 (89)	23 (11)
≥2	80 (63)	48 (38)	129 (89)	16 (11)
Tumor stage				
0-I	138 (66)	72 (34)	180 (85)	32 (15)
II	261 (63)	154 (37)	219 (89)	28 (11)
III-IV	267 (68)	126 (32)	287 (87)	42 (13)
Missing	3 (50)	3 (50)	3 (75)	1 (25)
Neoadjuvant therapy				
No	395 (62)	239 (38)	517 (87)	77 (13)
Yes	274 (70)	115 (30)	171 (87)	26 (13)
Missing	0 (0)	1 (100)	1 (100)	0 (0)
Cumulative surgeon volume				
Lowest quartile (<7)	196 (69)	89 (31)	172 (84)	32 (16)
Second quartile (7-16)	150 (68)	71 (32)	154 (89)	19 (11)
Third quartile (16-46)	157 (61)	100 (39)	164 (89)	21 (11)
Fourth quartile (>46)	136 (61)	86 (39)	184 (88)	26 (12)
Missing	30 (77)	9 (23)	15 (75)	5 (25)

Table 2. Risk of mortality after surgery for esophageal squamous cell carcinoma and adenocarcinoma comparing men and women, expressed as hazard ratios (HR) with 95% confidence intervals (CI)

Model	Squamous cell carcinoma			Adenocarcinoma		
	Number	Men HR (95% CI) Reference	Women HR (95% CI)	Number	Men HR (95% CI) Reference	Women HR (95% CI)
Overall all-cause mortality (main outcome)						
Crude	1024	1.00	0.73 (0.64–0.84)	792	1.00	0.87 (0.69–1.11)
Adjusted*	935	1.00	0.73 (0.63–0.85)	753	1.00	0.83 (0.65–1.08)
90-day all-cause mortality						
Crude	1024	1.00	0.56 (0.37–0.83)	792	1.00	1.31 (0.70–2.42)
Adjusted*	935	1.00	0.56 (0.37–0.85)	753	1.00	1.20 (0.60–2.37)
5-year all-cause mortality						
Crude	1024	1.00	0.73 (0.63–0.85)	792	1.00	0.92 (0.71–1.19)
Adjusted*	935	1.00	0.75 (0.64–0.87)	753	1.00	0.88 (0.67–1.16)
5-year disease-specific mortality						
Crude	1024	1.00	0.76 (0.65–0.89)	791	1.00	0.87 (0.65–1.16)
Adjusted*	935	1.00	0.77 (0.65–0.91)	752	1.00	0.79 (0.58–1.09)

*Adjusted for calendar period, age, education level, comorbidity, tumor stage, neoadjuvant therapy, and surgeon volume.

Table 3. Risk of mortality after surgery for esophageal squamous cell carcinoma and adenocarcinoma comparing men and women, stratified by age at surgery, expressed as hazard ratios (HR) with 95% confidence intervals (CI)

Model	Squamous cell carcinoma			Adenocarcinoma		
	Number	Men HR (95% CI) Reference	Women HR (95% CI)	Number	Men HR (95% CI) Reference	Women HR (95% CI)
Overall all-cause mortality (main outcome)						
≤55 years						
Crude	137	1.00	0.86 (0.58–1.28	121	1.00	0.80 (0.40–1.62)
Adjusted*	128	1.00	0.91 (0.58–1.43)	119	1.00	0.81 (0.36–1.82)
>55 years						
Crude	887	1.00	0.71 (0.62–0.83)	671	1.00	0.87 (0.67–1.13)
Adjusted*	807	1.00	0.71 (0.61–0.83)	634	1.00	0.83 (0.63–1.09)
90-day all-cause mortality						
≤55 years						
Crude	137	1.00	1.77 (0.54–5.80)	121	1.00	0.78 (0.10–6.21)
Adjusted*	128	1.00	1.42 (0.35–5.75)	119	1.00	1.85 (0.12–27.91)
>55 years						
Crude	887	1.00	0.48 (0.31–0.75)	671	1.00	1.40 (0.73–2.67)
Adjusted*	807	1.00	0.50 (0.32–0.78)	634	1.00	1.25 (0.61–2.58)
5-year all-cause mortality						
≤55 years						
Crude	137	1.00	0.87 (0.57–1.34)	121	1.00	0.76 (0.36–1.56)
Adjusted*	128	1.00	0.90 (0.56–1.45)	119	1.00	0.74 (0.32–1.74)
>55 years						
Crude	887	1.00	0.71 (0.61–0.83)	671	1.00	0.96 (0.73–1.26)
Adjusted*	807	1.00	0.73 (0.61–0.86)	634	1.00	0.95 (0.71–1.27)
5-year disease-specific mortality						
≤55 years						
Crude	137	1.00	0.98 (0.63–1.52)	121	1.00	0.77 (0.35–1.70)
Adjusted*	128	1.00	1.04 (0.64–1.71)	119	1.00	0.70 (0.28–1.77)
>55 years						
Crude	887	1.00	0.73 (0.62–0.86)	670	1.00	0.89 (0.66–1.22)
Adjusted*	807	1.00	0.75 (0.63–0.89)	633	1.00	0.84 (0.60–1.18)

*Adjusted for calendar period, age, education level, comorbidity, tumor stage, neoadjuvant therapy, and surgeon volume.

Table 4. Risk of mortality after surgery for esophageal squamous cell carcinoma and adenocarcinoma comparing men and women, stratified by tumor stage (0-I, II, or III-IV), expressed as hazard ratios (HR) with 95% confidence intervals (CI)

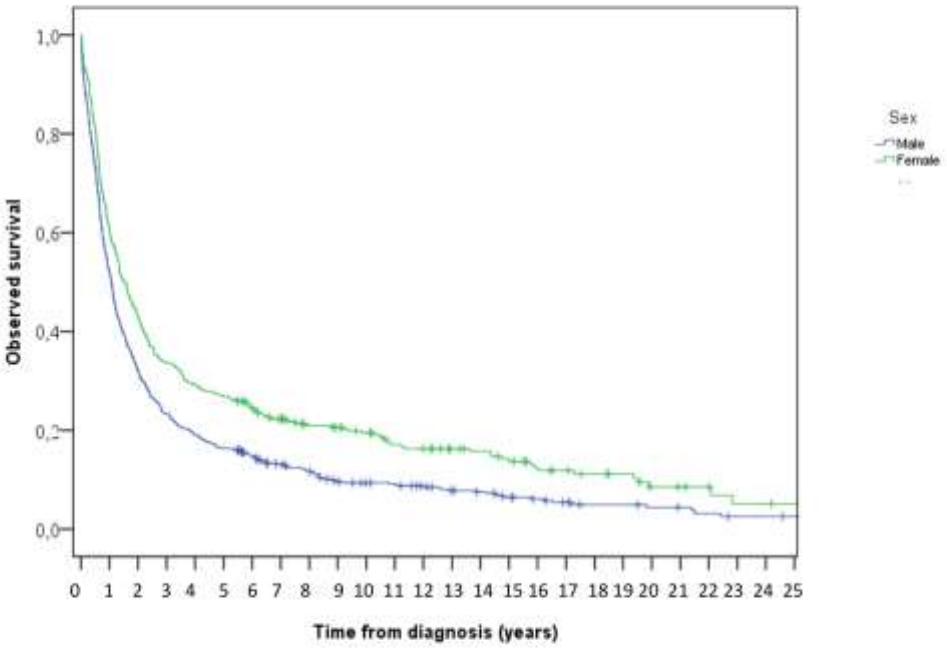
Model	Squamous cell carcinoma			Adenocarcinoma		
	Number	Men HR (95% CI) Reference	Women HR (95% CI)	Number	Men HR (95% CI) Reference	Women HR (95% CI)
Overall all-cause mortality (main outcome)						
Stage 0-I						
Crude	210	1.00	0.56 (0.39–0.79)	212	1.00	1.25 (0.77–2.02)
Adjusted*	194	1.00	0.54 (0.37–0.79)	209	1.00	1.17 (0.71–1.93)
Stage II						
Crude	415	1.00	0.77 (0.63–0.95)	247	1.00	0.83 (0.52–1.32)
Adjusted*	379	1.00	0.74 (0.59–0.93)	230	1.00	0.81 (0.48–1.35)
Stage III-IV						
Crude	393	1.00	0.80 (0.64–0.99)	329	1.00	0.76 (0.53–1.09)
Adjusted*	362	1.00	0.79 (0.63–1.00)	314	1.00	0.81 (0.56–1.20)
90-day all-cause mortality						
Stage 0-I						
Crude	210	1.00	0.32 (0.09–1.10)	212	1.00	1.91 (0.52–7.04)
Adjusted*	194	1.00	0.36 (0.10–1.27)	209	1.00	1.81 (0.42–7.73)
Stage II						
Crude	415	1.00	0.71 (0.41–1.23)	247	1.00	0.38 (0.05–2.86)
Adjusted*	379	1.00	0.64 (0.35–1.16)	230	1.00	—†
Stage III-IV						
Crude	393	1.00	0.49 (0.25–0.98)	329	1.00	1.71 (0.79–3.70)
Adjusted*	362	1.00	0.55 (0.27–1.12)	314	1.00	1.86 (0.80–4.31)
5-year all-cause mortality						
Stage 0-I						
Crude	210	1.00	0.53 (0.35–0.81)	212	1.00	1.32 (0.72–2.40)
Adjusted*	194	1.00	0.55 (0.35–0.87)	209	1.00	1.22 (0.65–2.30)
Stage II						
Crude	415	1.00	0.78 (0.63–0.98)	247	1.00	0.94 (0.59–1.52)
Adjusted*	379	1.00	0.76 (0.60–0.96)	230	1.00	0.96 (0.56–1.65)
Stage III-IV						
Crude	393	1.00	0.77 (0.62–0.97)	329	1.00	0.81 (0.57–1.16)
Adjusted*	362	1.00	0.77 (0.60–0.98)	314	1.00	0.86 (0.59–1.26)
5-year disease-specific mortality						
Stage 0-I						
Crude	210	1.00	0.52 (0.33–0.83)	212	1.00	1.35 (0.68–2.68)
Adjusted*	194	1.00	0.54 (0.33–0.89)	209	1.00	1.30 (0.63–2.70)
Stage II						
Crude	415	1.00	0.81 (0.65–1.02)	247	1.00	0.74 (0.42–1.31)
Adjusted*	379	1.00	0.77 (0.60–0.99)	230	1.00	0.73 (0.37–1.41)

Stage III-IV						
Crude	393	1.00	0.81 (0.64–1.02)	329	1.00	0.83 (0.56–1.23)
Adjusted*	362	1.00	0.80 (0.63–1.02)	314	1.00	0.83 (0.54–1.27)

*Adjusted for calendar period, age, education level, comorbidity, neoadjuvant therapy, and surgeon volume; †could not be calculated due to low number of cases.

Figure legends

Figure 1. Observed overall all-cause mortality curves comparing men and women who underwent surgery for esophageal squamous cell carcinoma. The curves were compared with a log-rank test (n=1024, p<0.001).



Number at risk										
Years	0	1	2	3	4	5		10	15	20
Male	669	349	214	156	128	110		46	22	8
Female	355	215	153	120	104	95		51	27	7