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Prognosis of oesophageal adenocarcinoma and squamous cell carcinoma following surgery or no surgery in a population-based cohort study.

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Abstract

Objectives: To assess the recent prognostic trends in oesophageal adenocarcinoma and oesophageal squamous cell carcinoma undergoing resectional surgery or no such surgery. Additionally, risk factors for death were assessed in each of these patient groups.

Design: Cohort study

Setting: A population-based, nationwide study in Sweden.

Participants: All patients diagnosed with oesophageal adenocarcinoma and oesophageal squamous cell carcinoma in Sweden from January 1, 1990 to December 31, 2013, with follow up until May 14, 2017.

Outcome measures: Observed and relative (to the background population) 1-, 3- and 5 year survival were analysed using life table method. Multivariable Cox regression provided hazard ratios (HR) with 95% confidence intervals (95%CI) for risk factors of death.

Results: Among 3794 patients with oesophageal adenocarcinoma and 4631 with oesophageal squamous cell carcinoma, 82% and 63% were men, respectively. From 1990-1994 to 2010-2013, the relative 5-year survival increased from 12% to 15% for oesophageal adenocarcinoma and from 9% to 12% for oesophageal squamous cell carcinoma. The corresponding survival following surgery increased from 27% to 45% in oesophageal adenocarcinoma and from 24% to 43% in oesophageal squamous cell carcinoma. In non-operated patients, the survival increased from 3% to 4%for oesophageal adenocarcinoma and from 3% to 6% for oesophageal squamous cell carcinoma. Women with oesophageal squamous cell carcinoma had better prognosis than men both following surgery (HR 0.71, 95%CI 0.61-0.83) and no surgery (HR 0.86, 95%CI 0.81-0.93).

Conclusions: The prognosis has improved over calendar time both in surgically treated and non-operated patients with oesophageal adenocarcinoma and oesophageal squamous-cell carcinoma in Sweden. Women appear to have better prognosis in oesophageal squamous-cell carcinoma than men, independent of treatment.

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 cancer in Sweden.
- Valid estimation of disease-specific mortality was possible with highly accurate information on oesophageal cancer histology, surgical treatment, and date of death and the calculation of relative survival rates.
- The sample size was large enough to enable robust analyses of time trends in sub-groups of patients, and to assess risk factors of mortality.
- Limitations include the unavailability some clinical variables, such as neoadjuvant or adjuvant treatment.
- Tumor stage variable was unavailable before 2004, and complete for only surgically treated patients after 2004.

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Contributors:

The authors' contributions in the study were the following: The design of the study: JHK, FM, NB, JL; Data collection and preparation for analyses: FM and JL; Data analysis: FM; Data interpretation: JHK, FM, NB, JL; Writing of first draft: JHK, revised and approved by JHK, FM, NB, JL.

Data sharing statement:

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

Introduction

Oesophageal cancer is the 6th most common cause of cancer death worldwide.[1] The overall survival is poor; only 10-22% of patients survive 5 years after diagnosis.[2-4] Most studies have reported survival for oesophageal cancer in general, but despite that oesophageal adenocarcinoma and squamous-cell carcinoma are increasingly seen as separate diseases with different aetiologies, incidence trends, and treatments.[5-9]

The 5-year survival in oesophageal cancer patients has increased in both United States and Europe until 2007.[10,11] It is not known whether and how survival in oesophageal adenocarcinoma or squamous-cell carcinoma have changed during the last few years, and even more unclear is how this might have changed specifically in operated and non-operated patients. Sweden provides an excellent setting to answer these questions, because of its accurate and complete nationwide registries.[12,13]

This nationwide Swedish study was conducted with the aim of assessing survival in oesophageal adenocarcinoma and squamous-cell carcinoma separately, and also specifically for resectional surgery (oesophagectomy) and no such surgery. Additionally, risk factors for death were assessed in each of these patient groups.

Methods

Design

This was a nationwide Swedish population-based cohort study, including all patients diagnosed with oesophageal adenocarcinoma or squamous-cell carcinoma from January 1, 1990, through December 31, 2013, with follow-up for survival until May 14, 2017. All newly diagnosed patients were identified from the Swedish Cancer Registry, while information about surgery was retrieved from the Swedish Patient Registry, and mortality from the Swedish Causes of Death Registry. The reporting to these registries is required according to Swedish law. Patient data was linked by the unique personal identity numbers assigned to each resident in Sweden, which are ideal for registry-based research.[12] The study was approved by the Regional Ethical Review Board in Stockholm, Sweden (2015/1916-31/1).

Data collection

The Swedish Cancer Registry was used to identify the study patients. The nationwide completeness for recording of oesophageal cancer was 98% and the histological confirmation was 100%.[13] The diagnosis codes 150.0, 150.8, and 150.9 in the 7th version of the International Classification of Diseases (ICD-7) were used to identify patients with oesophageal cancer. The histology codes (WHO/HS/CANC/24.1 Histology Code) were used to separate patients with oesophageal adenocarcinoma (096) and squamous cell carcinoma (146). Tumour stage has been recorded in the Swedish Cancer Registry from June 2004 onwards. The tumour stage variable is >98% concordant with patient records for operated oesophageal cancer patients.[14] The tumour stage classification in the registry was completed according to the 6th edition of the Union Internationale Contre le Cancer.[15]

The Swedish Patient Registry was used to identify all patients who underwent resectional surgery and also to assess comorbidities at the time of diagnosis.[16] The Swedish Classification of Operations and Major Procedures was used to identify the relevant operation codes (oesophagectomy codes 2820-2829 in 1990-1997 and codes JCC00-JCC97 in 1997-2014 and oesophagogastrectomy and gastrectomy codes 4411-4435 in 1990-1997 and codes JDC00-JDD96 in 1997-2014). Except for oesophagectomy codes, gastrectomy codes were included, because some surgeons tend to combine oesophagectomy with gastrectomy in locally advanced cancer. Operation codes referring to oesophagogastrectomy or gastrectomy were found in a total of 78 (0.9%) patients. The positive predictive value for oesophageal cancer resection has been estimated at 99.6% in the Swedish Patient Registry.[17]

Comorbidities were defined according to the well-validated Charlson Comorbidity Index,[18] not including the oesophageal cancer or metastatic solid tumours. The comorbidity information was retrieved from hospital admissions in the Patient Registry, which is at least 95% complete for most comorbidities,[19] up to three years before the index admission or cancer diagnosis

The Swedish Causes of Death Registry was used to obtain mortality. This registry contains 100% complete information on date of death for all deceased Swedish residents from 1952 onwards.[20]

Statistical analysis

An experienced biostatistician (F.M.) conducted all data management and statistical analysis according to a detailed and pre-defined study protocol. All analyses were conducted using SAS (version 9.4, SAS Institute Inc., Gary, NC). Observed and relative survival was

presented for survival at 1 and 5 years following a diagnosis date of oesophageal adenocarcinoma or squamous cell carcinoma. Observed survival with 95% confidence intervals (CI) was estimated using the life-table method,[21] where the event was defined as death by any cause (all-cause mortality).

To assess disease-specific mortality, relative survival with 95%CIs was calculated as the ratio of observed to the expected survival. The expected survival was derived from the survival in the general Swedish population of the same age (per year), sex, and calendar year as the patients with oesophageal cancer. Both observed and relative survival was presented as percentages (%). The survival in the general Swedish population was available from the start of the study period until the end of 2015, and for the calculation of relative survival rates for the years 2016 and 2017 the mortality rates from 2015 were used. The results were analysed for all patients independent of treatment and also stratified by resectional surgery (yes or no).

The observed survival was stratified by calendar periods (year 1990-1994, 1995-1999, 2000-2004, 2005-2009, or 2010-2013), age (<60, 60-69, 70-79, or ≥80 years), sex (male or female), and Charlson Comorbidity Index[18] score (0, 1, or ≥2). Surgically treated patients were further stratified for tumour stage (0-I, II, or III-IV) from the year 2005 onwards, when tumour stage data were available and of high completeness. Cox regression was used to calculate crude and adjusted hazard ratios (HR) with 95% CIs for each of the aforementioned stratification variables (calendar period, age, sex, Charlson Comorbidity Index score and tumour stage) with the same categorisation. The estimates were mutually adjusted for the risk factors where indicated. The missing data for tumour stage were assumed to be missing at random and were dealt with using complete case analysis.

Results

Patients

A total of 3794 patients were diagnosed with oesophageal adenocarcinoma during the study period, including 1131 (30%) who had undergone oesophagectomy. Among all 4631 patients diagnosed with oesophageal squamous cell carcinoma, 1116 (24%) had undergone oesophagectomy. Men were overrepresented in both oesophageal adenocarcinoma group (82%), and squamous cell carcinoma group (63%). The number of oesophageal adenocarcinoma patients increased throughout the study period, while the number of oesophageal squamous cell carcinoma patients decreased (Table 1). The proportion of adenocarcinoma patients who underwent oesophagectomy decreased from 38% in 1990-1994 to 27% in 2010-2013, and for squamous-cell carcinoma patients this proportion decreased from 31% in 1990-1994 to 18% in 2010-2013 (Table 1).

Survival trends in oesophageal adenocarcinoma

Because the observed survival closely mirrored the relative survival (Table 1), only the results regarding relative survival are commented on here.

All patients

The relative survival in oesophageal adenocarcinoma improved during the study period; the 1-year survival increased from 35% in 1990-1994 to 41% in 2010-2013 (with follow-up to 2017), and the corresponding 5-year survival gradually increased from 12% to 15%. (Table 1). From the year 2000 onwards, the relative 5-year survival increased by 2% (Table 1).

Surgically treated patients

The relative survival increased substantially in surgically treated patients. In the oesophagectomy group, the 1-year survival increased from 54% in 1990-1994 to 86% in 2010-2013 (with follow-up until 2017), and the corresponding 5-year survival increased from 27% to 45% (Table 1, Figure 1). From the year 2000 onwards, the relative 1-year survival increased by 11% and the 5-year survival by 12% (Table 1).

Non-operated patients

In the non-operated group, the 1-year survival increased from 24% in 1990-1994 to 25% in 2010-2013 (with follow-up to 2017), and the corresponding 5-year survival increased from 3% to 4% (Table 1, Figure 1). From 2000 onwards the 1- and 5-year survival estimates were stable (Table 1).

Survival trends in oesophageal squamous-cell carcinoma

All patients

Also the relative survival in oesophageal squamous cell carcinoma improved over time. The relative 1-year survival increased from 32% in 1990-1994 to 36% in 2010-2013 (with follow-up until 2017), and the corresponding 5-year survival increased from 9% to 12% (Table 1). From the year 2000 onwards the relative 1-year survival increased by 1%, and the 5-year survival increased by 3% (Table 1).

Surgically treated patients

The 1-year relative survival of surgically treated patients increased from 60% in 1990-1994 to 87% in 2010-2013 (with follow-up until 2017), and the corresponding 5-year survival increased from 24% to 43% (Table 1, Figure 2). From the year 2000 onwards both 1- and 5-year survival increased by 14% (Table 1).

Non-operated patients

The relative 1-year survival in non-surgically treated patients was 20% in 1990-1994 and 25% in 2010-2013 (with follow-up until 2017), and the corresponding 5-year survival doubled from 3% to 6% (Table 1, Figure 2). From the year 2000 onwards both 1-and 5-year survival increased by 2% (Table 1).

Risk factors for 5-year mortality in oesophageal adenocarcinoma

All patients

In the multivariable analysis of all oesophageal adenocarcinoma patients, the adjusted HR of mortality within 5 years of diagnosis was higher in earlier calendar periods (HR 1.17, 95%CI 1.02-1.33, first versus last calendar period), older age groups (HR 1.99, 95%CI 1.78-2.22, age ≥80 years versus <60 years), and in patients with more comorbidity (HR 1.27, 95%CI 1.15-1.40, ≥2 comorbidities versus no comorbidities), while sex did not influence the HR of mortality (Table 2).

Surgically treated patients

Among the oesophageal adenocarcinoma patients who underwent oesophagectomy, earlier calendar period (HR 2.02, 95%CI 1.56-2.61, first versus last calendar period) and older age (HR 1.98, 95%CI 1.41-2.77, age ≥80 years versus <60 years) were associated with an increased risk of mortality, while comorbidity and sex did not statistically significantly influence this risk (Table 2).

In a sub-analysis of patients diagnosed between 2005 and 2013, i.e. when tumour stage data were available and adjusted for, higher tumour stage and older age were statistically significant poor prognostic factors (Table 3).

Non-operated patients

Among the non-operated oesophageal adenocarcinoma patients, older age (HR 1.21, 95%CI 1.06-1.37, age ≥80 years versus <60 years) was the only factor associated with an increased risk of mortality (Table 2).

Risk factors for 5-year mortality in oesophageal squamous-cell carcinoma

All patients

The multivariable analysis in all oesophageal squamous cell carcinoma patients showed that risk factors for 5-year mortality were earlier calendar period (HR 1.19, 95%CI 1.07-1.31, first versus last calendar period), older age (HR 2.06, 95%CI 1.86-2.28, age ≥80 years versus <60 years), male sex (HR 0.83, 95%CI 0.78-0.89, women versus men), and comorbidity (HR 1.45, 95%CI 1.32-1.59, ≥2 comorbidities versus no comorbidities) (Table 2).

Surgically treated patients

Among the oesophageal squamous cell carcinoma patients who underwent oesophagectomy, earlier calendar period (HR 2.03, 95%CI 1.56-2.63, first versus last calendar period), older age (HR 2.06, 95%CI 1.86-2.28, age ≥80 years versus <60 years), and male sex (HR 0.71, 95%CI 0.61-0.83, women versus men) were associated with an increased risk of mortality, while comorbidity did not statistically significantly influence this risk (Table 2). In a sub-analysis of patients diagnosed between 2005 to 2013, i.e. when tumour stage data were available and adjusted for, more advanced tumour stage, earlier calendar period, older age, male sex, and more comorbidity were poor prognostic factors in oesophageal squamous cell carcinoma (Table 3).

Non-operated patients

Among the non-operated oesophageal squamous cell carcinoma patients, earlier calendar period (HR 1.24, 95%CI 1.11-1.39, first versus last calendar period), older age (HR 1.42, 95%CI 1.26-1.60, age ≥80 years versus <60 years), male sex (HR 0.86, 95%CI 0.81-0.93, women versus men), and comorbidity (HR 1.30, 95%CI 1.18-1.43, ≥2 comorbidities versus no comorbidities) were associated with an increased risk of mortality (Table 2).

Discussion

This study indicates that the overall prognosis of both oesophageal adenocarcinoma and oesophageal squamous cell carcinoma is improving over time, especially in the operated patients. Female patients with oesophageal squamous cell carcinoma had better prognosis than male patients.

Among strengths of the study is the population-based design with complete and accurate ascertainment and follow-up of all patients diagnosed with oesophageal cancer in Sweden. The assessment of the oesophageal cancer histology, surgical treatment, and date of death was highly accurate and the calculation of relative survival rates allowed valid estimation of disease-specific mortality. The sample size was large enough to enable robust analyses of time trends in sub-groups of patients, and to assess risk factors of mortality. Limitations include the unavailability of some clinical variables, such as use of neoadjuvant or adjuvant treatment. Tumour stage data were available only after 2004 and complete only in patients who had undergone surgery. However, the main purpose of the study was to evaluate time trends in survival and to separate these trends into patients who had undergone surgery or not, which was fully possible to achieve.

Previously, a registry-based study from United States showed an increase in 5-year overall survival in oesophageal cancer patients from 18% in 1990s to 22% in 2000s.[10] A European registry-based study (EUROCARE-5) also showed improvement in 5-year overall age-standardised survival rates in oesophageal cancer from 10% in 1999-2001 to 13% in 2005-2007.[11] In China, the age-standardised 5-year relative survival rate for oesophageal cancer was 21% in 2003-2005.[22] Taken together, earlier studies have shown improving prognosis in

oesophageal cancer over time. However, they reported only on earlier calendar periods, and information on histology- or treatment-specific survival were lacking.

The findings of increasing survival over time in both oesophageal adenocarcinoma and oesophageal squamous cell carcinoma despite a decreasing utilisation of oesophagectomy are encouraging. Increased awareness and diagnostic developments might explain the improved prognosis. The treatment might have been improved by centralisation of surgery,[23,24] use of neoadjuvant chemoradiotherapy[25,26] or definitive chemoradiotherapy.[27] The more clearly improved 5-year survival in patients with non-surgically managed oesophageal squamous cell carcinoma patients might be due to a higher sensitivity to chemoradiotherapy in oesophageal squamous cell carcinoma, resulting in a higher success rate of definite oncological therapy.[28,29] Additionally, careful selection of treatment for the elderly, co-morbid and frail patients by the multidisciplinary teams, preoperative optimisation of patients and improved peri- and postoperative care are likely reasons for improved survival.

The better prognosis in women with oesophageal squamous cell carcinoma was unexpected. However, some earlier population-based studies have associated female sex with favourable prognosis in oesophageal cancer,[30-32] although these studies did not separate the histological subtypes, tumour stage, or treatment strategies.[33] In the present study, female sex was a strong positive predictor of survival in both surgically and non-surgically treated patients with oesophageal squamous cell carcinoma, also after adjustment. A possible biological mechanism for a sex difference is estrogenic influence, which could inhibit cancer cell growth.[34-36] Additionally, hormone replacement therapy associates to lower risk of oesophageal squamous cell carcinoma.[37,38] The sex differences in survival after oesophageal squamous cell carcinoma might also be due to differences in socioeconomic and lifestyle

factors, which could not be adjusted for in the present study, and should be specifically examined in future studies.

The treatment of oesophageal cancer in the Swedish publicly funded healthcare system follows clinical guidelines, including neoadjuvant therapy and centralisation to fewer hospitals during the last years. Thus, the findings of the present study should be generalisable to many other countries with a similar healthcare system as in Sweden. These findings encourage careful selection of patients undergoing surgery, multidisciplinary management, centralisation of services, and use of neoadjuvant treatment in surgical candidates, and definitive chemoradiotherapy in patients ineligible for surgery.

In conclusion, this nationwide Swedish study with complete ascertainment and follow-up of patients with oesophageal cancer shows that the prognosis in both oesophageal adenocarcinoma and oesophageal squamous cell carcinoma is improving. The improved prognosis is stronger in surgically managed patients, but is also indicated in non-operated patients. Non-operated patients still have a poor prognosis. The favourable prognosis in women with oesophageal squamous cell carcinoma warrants further research.

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Table 1: Observed and relative 1- and 5-year survival across calendar periods in oesophageal adenocarcinoma and squamous cell carcinoma, stratified by treatment strategy in 1990-2013, with follow-up until 2017.

	Oesophageal adenocarcinoma						Oesophageal squamous cell carcinoma					
	Patients		Observed survival in % (95% CI)		Relative survival in % (95% CI)		Patients		Observed survival in % (95% CI)		Relative survival in % (95% CI)	
Calendar period	Number (%)	Mean age	1 year	5 year	1 year	5 year	Number (%)	Mean age	1 year	5 year	1 year	5 year
All patients												
1990-1994	332 (9)	71	33 (28-39)	10 (7-14)	35 (30-41)	12 (8-16)	1148 (25)	70	31 (28-33)	8 (6-9)	32 (29-35)	9 (7-11)
1995-1999	557 (15)	70	35 (31-39)	11 (8-13)	37 (33-41)	13 (10-16)	1014 (22)	70	32 (29-35)	10 (8-12)	33 (30-36)	12 (9-14)
2000-2004	860 (23)	70	39 (36-43)	11 (9-13)	41 (38-45)	13 (11-16)	931 (20)	70	34 (30-37)	7 (6-9)	35 (32-38)	9 (7-11)
2005-2009	1054 (28)	69	39 (36-42)	12 (10-14)	41 (38-44)	14 (12-16)	861 (19)	70	34 (30-37)	10 (8-12)	35 (32-38)	11 (9-14)
2010-2013	991 (26)	71	40 (37-43)	13 (11-15)	41 (38-45)	15 (12-17)	677 (15)	70	34 (31-38)	11 (9-13)	36 (32-39)	12 (10-15)
Surgery												
1990-1994	126 (11)	66	51 (42-60)	22 (15-29)	54 (44-63)	27 (18-36)	346 (31)	65	57 (52-62)	20 (15-24)	60 (55-66)	24 (19-29)
1995-1999	191 (17)	65	68 (61-75)	29 (22-35)	72 (65-79)	35 (27-42)	275 (25)	64	64 (59-70)	25 (20-31)	68 (62-74)	31 (24-37)
2000-2004	275 (24)	66	72 (67-78)	27 (21-32)	76 (71-82)	31 (25-37)	183 (16)	65	69 (63-76)	25 (18-31)	73 (66-80)	29 (22-36)
2005-2009	277 (24)	64	79 (75-84)	38 (32-43)	83 (78-88)	43 (36-49)	193 (17)	64	70 (64-77)	29 (23-35)	74 (67-80)	33 (26-41)
2010-2013	262 (23)	66	83 (78-87)	40 (34-46)	86 (82-91)	45 (38-51)	119 (11)	66	83 (76-90)	39 (30-48)	87 (80-94)	43 (33-54)
No surgery												
1990-1994	206 (8)	74	23 (17-29)	3 (0-5)	24 (18-30)	3 (0-6)	802 (23)	72	19 (16-22)	2 (1-3)	20 (17-23)	3 (1-4)
1995-1999	366 (14)	72	18 (14-22)	1 (0-2)	19 (15-23)	1 (0-2)	739 (21)	72	19 (17-22)	4 (2-5)	21 (18-24)	5 (3-6)
2000-2004	585 (22)	72	24 (20-27)	4 (2-6)	25 (21-29)	5 (3-7)	748 (21)	72	25 (22-28)	3 (2-5)	26 (23-29)	4 (2-5)
2005-2009	777 (29)	71	24 (21-27)	3 (2-5)	25 (22-29)	4 (2-5)	668 (19)	71	23 (20-26)	4 (3-6)	24 (21-27)	5 (3-7)
2010-2013	729 (27)	73	24 (21-27)	3 (2-5)	25 (22-29)	4 (2-5)	558 (16)	71	24 (20-27)	5 (3-7)	25 (21-29)	6 (4-8)

Table 2: Observed 5-year survival and adjusted hazard ratios (HR) with 95% confidence intervals (CI) for oesophageal adenocarcinoma and oesophageal squamous-cell carcinoma in 1990-2013, with follow-up until 2017.

		Oesophageal adenocarcinoma			Oesophageal squamous-cell carcinoma		
Covariate	Category	Patients Number (%)	5-year survival (95% CI)	HR (95% CI)*	Patients Number (%)	5-year survival (95% CI)	HR (95% CI)*
All patients							
Calendar period	1990-1994	332 (9)	10 (7-14)	1.17 (1.02-1.33)	1148 (25)	8 (6-9)	1.19 (1.07-1.31)
	1995-1999	557 (15)	11 (8-13)	1.11 (0.99-1.24)	1014 (22)	10 (8-12)	1.11 (1.00-1.23)
	2000-2004	860 (23)	11 (9-13)	1.07 (0.97-1.18)	931 (20)	7 (6-9)	1.13 (1.01-1.25)
	2005-2009	1054 (28)	12 (10-14)	1.04 (0.94-1.16)	861 (19)	10 (8-12)	1.07 (0.96-1.19)
	2010-2013	991 (26)	13 (11-15)	1 (reference)	677 (15)	11 (9-13)	1 (reference)
Age (years)	<60	686 (18)	18 (15-21)	1 (reference)	787 (17)	14 (12-17)	1 (reference)
	60-69	1079 (28)	16 (13-18)	1.05 (0.94-1.16)	1344 (29)	12 (10-14)	1.11 (1.01-1.22)
	70-79	1166 (31)	12 (10-13)	1.25 (1.13-1.39)	1588 (34)	8 (7-9)	1.38 (1.26-1.51)
	≥80	863 (23)	2 (1-3)	1.99 (1.78-2.23)	912 (20)	2 (1-2)	2.06 (1.86-2.28)
Sex	Male	3098 (82)	12 (11-13)	1 (reference)	2938 (63)	8 (7-9)	1 (reference)
	Female	696 (18)	10 (8-12)	1.04 (0.95-1.14)	1693 (37)	11 (9-12)	0.83 (0.78-0.89)
Comorbidity score	0	2096 (55)	14 (13-15)	1 (reference)	2367 (51)	11 (10-13)	1 (reference)
	1	1115 (29)	11 (9-12)	1.11 (1.03-1.20)	1598 (35)	7 (6-9)	1.15 (1.08-1.23)
	≥2	583 (15)	6 (4-8)	1.27 (1.15-1.40)	666 (14)	4 (2-5)	1.45 (1.32-1.59)
Surgery							
Calendar period	1990-1994	126 (11)	22 (15-29)	2.02 (1.56-2.61)	346 (31)	20 (15-24)	2.03 (1.56-2.63)
	1995-1999	191 (17)	29 (22-35)	1.46 (1.16-1.83)	275 (25)	25 (20-31)	1.62 (1.24-2.13)
	2000-2004	275 (24)	27 (21-32)	1.45 (1.18-1.79)	183 (16)	25 (18-31)	1.53 (1.15-2.04)
	2005-2009	277 (24)	38 (32-43)	1.07 (0.86-1.33)	193 (17)	29 (23-35)	1.41 (1.06-1.88)
	2010-2013	262 (23)	40 (34-46)	1 (reference)	119 (11)	39 (30-48)	1 (reference)
Age (years)	<60	286 (25)	40 (35-46)	1 (reference)	317 (28)	25 (20-30)	1 (reference)
	60-69	423 (37)	31 (26-35)	1.25 (1.03-1.51)	443 (40)	28 (24-32)	1.00 (0.85-1.19)
	70-79	370 (33)	30 (25-34)	1.28 (1.05-1.56)	328 (29)	24 (19-29)	1.13 (0.94-1.35)
	≥80	52 (5)	15 (5-24)	1.98 (1.41-2.77)	28 (3)	11 (-1-22)	1.61 (1.07-2.45)
Sex	Male	987 (87)	31 (28-34)	1 (reference)	729 (65)	21 (18-24)	1 (reference)
	Female	144 (13)	37 (29-45)	0.84 (0.68-1.05)	387 (35)	33 (29-38)	0.71 (0.61-0.83)
Comorbidity	0	733 (65)	33 (29-36)	1 (reference)	698 (63)	27 (24-31)	1 (reference)
	1	299 (26)	32 (27-38)	1.05 (0.89-1.23)	340 (30)	23(18-27)	1.13 (0.97-1.31)
	≥2	99 (9)	26 (18-36)	1.19 (0.93-1.53)	78 (7)	22 (12-31)	1.20 (0.92-1.57)
No surgery							
Calendar period	1990-1994	206 (8)	3 (0-5)	1.10 (0.94-1.29)	802 (23)	2 (1-3)	1.24 (1.11-1.39)
	1995-1999	366 (14)	1 (0-2)	1.14 (1.00-1.30)	739 (21)	4 (2-5)	1.15 (1.02-1.28)
	2000-2004	585 (22)	4 (2-6)	1.02 (0.91-1.13)	748 (21)	3 (2-5)	1.06 (0.95-1.19)
	2005-2009	777 (29)	3 (2-5)	1.00 (0.90-1.11)	668 (19)	4 (3-6)	1.06 (0.95-1.19)
	2010-2013	729 (27)	3 (2-5)	1 (reference)	558 (16)	5 (3-7)	1 (reference)
Age (years)	<60	400 (15)	3 (1-4)	1 (reference)	470(13)	7 (5-9)	1 (reference)
	60-69	656 (25)	6 (4-7)	0.91 (0.80-1.04)	901 (26)	4 (3-5)	1.07 (0.95-1.20)
	70-79	796 (30)	3 (2-4)	1.05 (0.93-1.19)	1260 (36)	4 (3-5)	1.19 (1.06-1.32)
	≥80	811 (30)	1 (0-2)	1.21 (1.06-1.37)	884 (25)	1 (1-2)	1.42 (1.26-1.60)
Sex	Male	2111 (79)	3 (2-4)	1 (reference)	2209 (63)	3 (2-4)	1 (reference)
	Female	552 (21)	3 (1-4)	1.00 (0.90-1.10)	1306 (37)	4 (3-5)	0.86 (0.81-0.93)
Comorbidity score	0	1363 (51)	4 (3-5)	1 (reference)	1669 (47)	5 (4-6)	1 (reference)
	1	816 (31)	3 (1-4)	1.04 (0.95-1.14)	1258 (36)	3 (2-4)	1.07 (0.99-1.15)
	≥2	484 (18)	2 (0-3)	1.08 (0.97-1.20)	588 (17)	1 (0-2)	1.30 (1.18-1.43)

* Adjusted for calendar period, age, sex and comorbidity.

Table 3: Hazard ratios (HR) with 95% confidence intervals (CI) of 5-year mortality after surgery for oesophageal adenocarcinoma and oesophageal squamous-cell carcinoma in 2005-2013, with follow-up until 2017.

	Oesophageal adenocarcinoma			**Oesophageal squamous-cell carcinoma**		
Covariates	Patients Number (%)	Crude HR (95% CI)	Adjusted HR (95% CI)*	Patients Number (%)	Crude HR (95% CI)	Adjusted HR (95% CI)*
Tumour stage†						
0-I	62 (12)	1 (Reference)	1 (Reference)	34 (11)	1 (Reference)	1 (Reference)
II	221 (41)	2.53 (1.54-4.14)	2.37 (1.44-3.90)	143 (46)	2.19 (1.25-3.83)	2.20 (1.25-3.87)
III-IV	186 (35)	4.14 (2.53-6.76)	4.04 (2.46-6.63)	98 (31)	2.71 (1.53-4.79)	2.64 (1.48-4.71)
Calendar						
2005-2009	277 (51)	1.12 (0.88-1.41)	1.04 (0.82-1.32)	193 (62)	1.42 (1.05-1.93)	1.48 (1.08-2.02)
2010-2013	262 (49)	1 (Reference)	1 (Reference)	119 (38)	1 (Reference)	1 (Reference)
Age (years)						
<60	138 (26)	1 (Reference)	1 (Reference)	79 (25)	1 (Reference)	1 (Reference)
60-69	227 (42)	1.52 (1.11-2.08)	1.41 (1.02-1.94)	137 (44)	0.88 (0.61-1.28)	0.81 (0.55-1.18)
70-79	148 (27)	1.52 (1.08-2.14)	1.47 (1.03-2.08)	86 (28)	1.23 (0.83-1.81)	1.21 (0.81-1.81)
≥80	26 (5)	3.39 (2.05-5.60)	3.58 (2.14-5.98)	10 (3)	1.57 (0.71-3.48)	1.58 (0.71-3.53)
Sex						
Male	470 (87)	1 (Reference)	1 (Reference)	210 (67)	1 (Reference)	1 (Reference)
Female	69 (13)	0.84 (0.59-1.19)	0.82 (0.57-1.18)	102 (33)	0.67 (0.49-0.93)	0.66 (0.47-0.92)
Comorbidity						
0	341 (63)	1 (Reference)	1 (Reference)	195 (63)	1 (Reference)	1 (Reference)
1	144 (27)	1.04 (0.80-1.36)	0.95 (0.73-1.25)	86 (28)	1.35 (0.98-1.87)	1.40 (1.01-1.95)
≥2	54 (10)	1.07 (0.72-1.59)	1.02 (0.68-1.52)	31 (10)	1.31 (0.82-2.12)	1.60 (0.98-2.62)

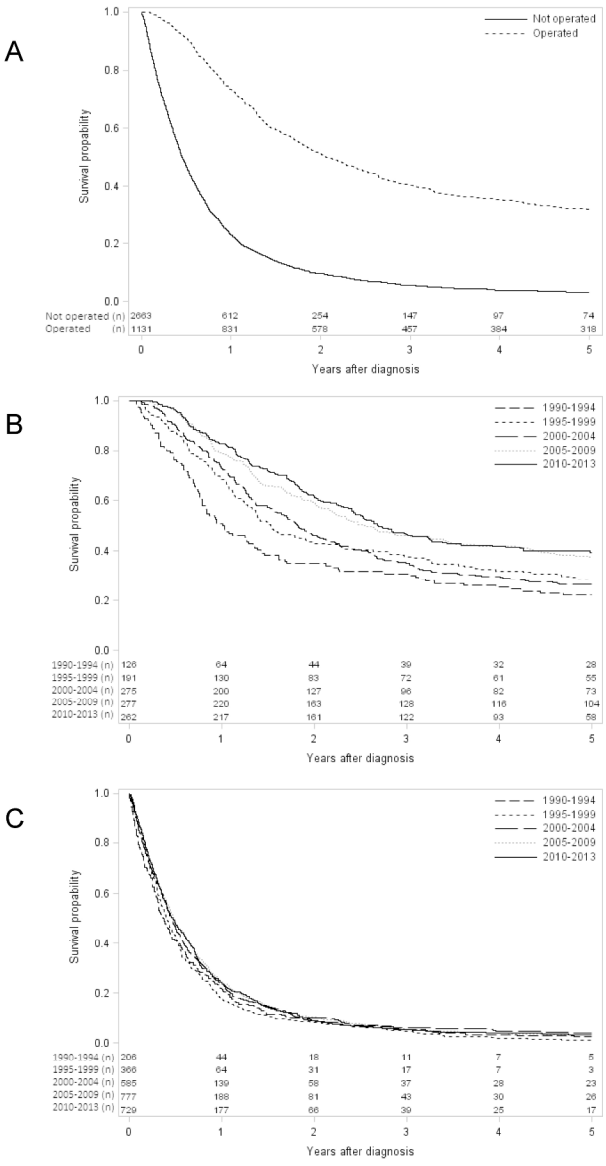
* Adjusted for calendar period, age, sex, Charlson Comorbidity Index and tumour stage.

† 70 (13%) patients with oesophageal adenocarcinoma and 37 (12%) patients with oesophageal squamous-cell carcinoma had missing tumour stage.

Figure Legends

Figure 1. Kaplan-Meier survival curves showing observed 5-year survival oesophageal adenocarcinoma (A) stratified by surgical treatment (yes or no). Patients undergoing oesophageal resection for adenocarcinoma (B) and not undergoing oesophageal resection for adenocarcinoma (C) are further stratified by calendar periods.

Figure 2. Kaplan-Meier survival curves showing observed 5-year survival oesophageal squamous cell carcinoma (A) stratified by surgical treatment (yes or no). Patients undergoing oesophageal resection for squamous cell carcinoma (B) and not undergoing oesophageal resection for squamous cell carcinoma (C) are further stratified by calendar periods.



Kaplan-Meier survival curves showing observed 5-year survival oesophageal adenocarcinoma (A) stratified by surgical treatment (yes or no). Patients undergoing oesophageal resection for adenocarcinoma (B) and not undergoing oesophageal resection for adenocarcinoma (C) are further stratified by calendar periods.

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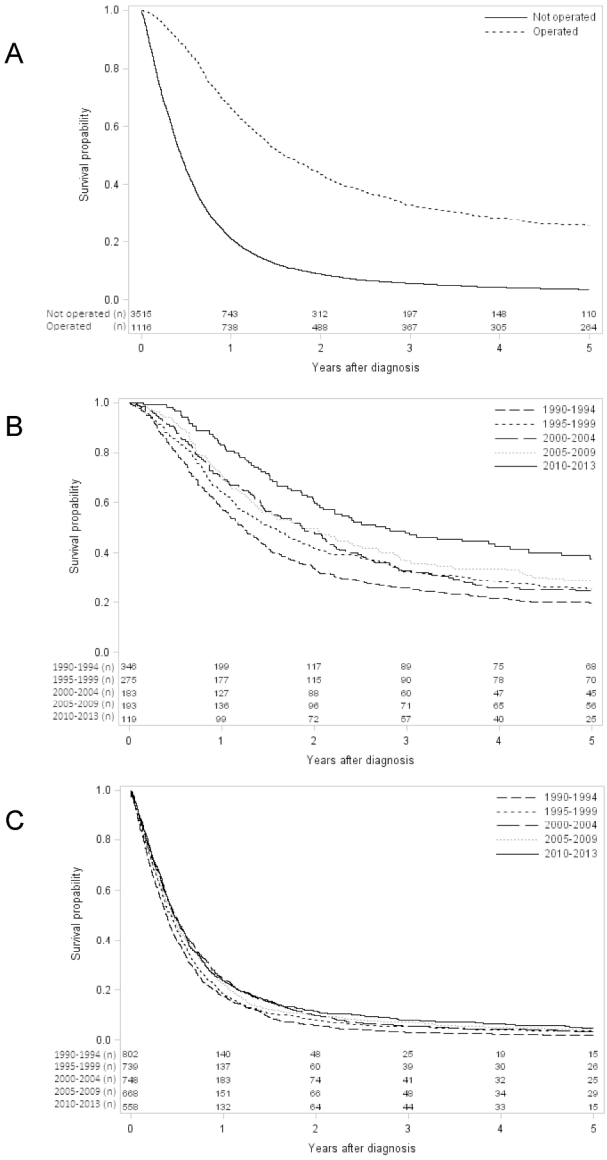

Kaplan-Meier survival curves showing observed 5-year survival oesophageal squamous cell carcinoma (A) stratified by surgical treatment (yes or no). Patients undergoing oesophageal resection for squamous cell carcinoma (B) and not undergoing oesophageal resection for squamous cell carcinoma (C) are further stratified by calendar periods.

275x397mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-8*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, 20-22
		(b) Indicate number of participants with missing data for each variable of interest	21-22
		(c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	Report numbers of outcome events or summary measures over time	9-13, 20-22
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	20-22
		(*b*) Report category boundaries when continuous variables were categorized	8, 21-22
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	20
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12, 21-22
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	4

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Prognosis of oesophageal adenocarcinoma and squamous cell carcinoma following surgery and no surgery in a nationwide Swedish cohort study

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Prognosis of oesophageal adenocarcinoma and squamous cell carcinoma following surgery and no surgery in a nationwide Swedish cohort study

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Abstract

Objectives: To assess the recent prognostic trends in oesophageal adenocarcinoma and oesophageal squamous cell carcinoma undergoing resectional surgery and no such surgery. Additionally, risk factors for death were assessed in each of these patient groups.

Design: Cohort study

Setting: A population-based, nationwide study in Sweden.

Participants: All patients diagnosed with oesophageal adenocarcinoma and oesophageal squamous cell carcinoma in Sweden from January 1, 1990 to December 31, 2013, with follow up until May 14, 2017.

Outcome measures: Observed and relative (to the background population) 1-, 3- and 5 year survival were analysed using life table method. Multivariable Cox regression provided hazard ratios (HR) with 95% confidence intervals (95%CI) for risk factors of death.

Results: Among 3794 patients with oesophageal adenocarcinoma and 4631 with oesophageal squamous cell carcinoma, 82% and 63% were men, respectively. From 1990-1994 to 2010-2013, the relative 5-year survival increased from 12% to 15% for oesophageal adenocarcinoma and from 9% to 12% for oesophageal squamous cell carcinoma. The corresponding survival following surgery increased from 27% to 45% in oesophageal adenocarcinoma and from 24% to 43% in oesophageal squamous cell carcinoma. In patients not undergoing surgery, the survival increased from 3% to 4%for oesophageal adenocarcinoma and from 3% to 6% for oesophageal squamous cell carcinoma. Women with oesophageal squamous cell carcinoma had better prognosis than men both following surgery (HR 0.71, 95%CI 0.61-0.83) and no surgery (HR 0.86, 95%CI 0.81-0.93).

Conclusions: The prognosis has improved over calendar time both in oesophageal adenocarcinoma and oesophageal squamous-cell carcinoma in Sweden that did and did not undergo surgery. Women appear to have better prognosis in oesophageal squamous-cell carcinoma than men, independent of treatment.

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 cancer in Sweden.
- Valid estimation of disease-specific mortality was possible with highly accurate information on oesophageal cancer histology, surgical treatment, and date of death and the calculation of relative survival rates.
- The sample size was large enough to enable robust analyses of time trends in sub-groups of patients, and to assess risk factors of mortality.
- Limitations include the unavailability some clinical variables, such as neoadjuvant or adjuvant treatment.
- Tumor stage variable was unavailable before 2004, and complete for only surgically treated patients after 2004.

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

Contributors:

The authors' contributions in the study were the following: The design of the study: JHK, FM, NB, JL; Data collection and preparation for analyses: FM and JL; Data analysis: FM; Data interpretation: JHK, FM, NB, JL; Writing of first draft: JHK, revised and approved by JHK, FM, NB, JL.

Data sharing statement:

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

Introduction

Oesophageal cancer is the 6th most common cause of cancer death worldwide.[1] The overall survival is poor; only 10-22% of patients survive 5 years after diagnosis in Europe, the United States, and China.[2-4] Most studies have reported survival for oesophageal cancer in general, but despite that oesophageal adenocarcinoma and squamous-cell carcinoma are increasingly seen as separate diseases with different aetiologies, incidence trends, and treatments.[5-9]

In the United States the 5-year overall survival in oesophageal cancer patients has increased from 18% in the 1990s to 22% in the 2000s,[10] whereas in Europe the survival has increased from 10% in 1999-2001 to 13% in 2005-2007.[11] The surgical technique, neoadjuvant modalities and definitive chemoradiation therapies have seen much development over the last two decades.[6 7 12] It has been acknowledged that surgeon and hospital volume are related to survival in oesophageal cancer, resulting in centralisation of oesophageal cancer treatment.[13-15] However, it is not known whether and how survival in oesophageal adenocarcinoma or squamous-cell carcinoma have changed during the last few years, and even more unclear is how this might have changed specifically in patients undergoing surgery and patients not undergoing surgery. Sweden provides an excellent setting to answer these questions, because of its accurate and complete nationwide registries.[16 17]

This nationwide Swedish study was conducted with the aim of assessing survival in oesophageal adenocarcinoma and squamous-cell carcinoma separately, and also specifically in patients undergoing resectional surgery (oesophagectomy) and those that do not undergo such surgery. Additionally, risk factors for death were assessed in each of these patient groups.

Methods

Design

This was a nationwide Swedish population-based cohort study, including all patients diagnosed with oesophageal adenocarcinoma or squamous-cell carcinoma from January 1, 1990, through December 31, 2013, with follow-up for survival until May 14, 2017. All newly diagnosed patients were identified from the Swedish Cancer Registry, while information about surgery was retrieved from the Swedish Patient Registry, and mortality from the Swedish Causes of Death Registry. The reporting to these registries is required according to Swedish law. Patient data was linked by the unique personal identity numbers assigned to each resident in Sweden, which are ideal for registry-based research.[16] The study was approved by the Regional Ethical Review Board in Stockholm, Sweden (2015/1916-31/1).

Data collection

The Swedish Cancer Registry was used to identify the study patients. The nationwide completeness for recording of oesophageal cancer was 98% and the histological confirmation was 100%.[17] The diagnosis codes 150.0, 150.8, and 150.9 in the 7th version of the International Classification of Diseases (ICD-7) were used to identify patients with oesophageal cancer. The histology codes (WHO/HS/CANC/24.1 Histology Code) were used to separate patients with oesophageal adenocarcinoma (096) and squamous cell carcinoma (146). Tumour stage has been recorded in the Swedish Cancer Registry from June 2004 onwards. The tumour stage variable is >98% concordant with patient records for operated oesophageal cancer patients.[18] The tumour stage classification in the registry was completed according to the 6th edition of the Union Internationale Contre le Cancer.[19]

The Swedish Patient Registry was used to identify all patients who underwent resectional surgery and also to assess comorbidities at the time of diagnosis.[20] The Swedish Classification of Operations and Major Procedures was used to identify the relevant operation codes (oesophagectomy codes 2820-2829 in 1990-1997 and codes JCC00-JCC97 in 1997-2014 and oesophagogastrectomy and gastrectomy codes 4411-4435 in 1990-1997 and codes JDC00-JDD96 in 1997-2014). Except for oesophagectomy codes, gastrectomy codes were included, because some surgeons tend to combine oesophagectomy with gastrectomy in locally advanced cancer. Operation codes referring to oesophagogastrectomy or gastrectomy were found in a total of 78 (0.9%) patients. The positive predictive value for oesophageal cancer resection has been estimated at 99.6% in the Swedish Patient Registry.[21]

Comorbidities were defined according to the well-validated Charlson Comorbidity Index,[22] not including the oesophageal cancer or metastatic solid tumours. The comorbidity information was retrieved from hospital admissions in the Patient Registry, which is at least 95% complete for most comorbidities,[23] up to three years before the index admission or cancer diagnosis

The Swedish Causes of Death Registry was used to obtain mortality. This registry contains 100% complete information on date of death for all deceased Swedish residents from 1952 onwards.[24]

Statistical analysis

An experienced biostatistician (F.M.) conducted all data management and statistical analysis according to a detailed and pre-defined study protocol. All analyses were conducted using SAS (version 9.4, SAS Institute Inc., Gary, NC). Observed and relative survival was

presented for survival at 1 and 5 years following a diagnosis date of oesophageal adenocarcinoma or squamous cell carcinoma. Observed survival with 95% confidence intervals (CI) was estimated using the life-table method,[25] where the event was defined as death by any cause (all-cause mortality).

To assess disease-specific mortality, relative survival with 95%CIs was calculated as the ratio of observed to the expected survival. The expected survival was derived from the survival in the general Swedish population of the same age (per year), sex, and calendar year as the patients with oesophageal cancer. Both observed and relative survival was presented as percentages (%). The survival in the general Swedish population was available from the start of the study period until the end of 2015, and for the calculation of relative survival rates for the years 2016 and 2017 the mortality rates from 2015 were used. The results were analysed for all patients independent of treatment and also stratified by resectional surgery (yes or no).

The observed survival was stratified by calendar periods (year 1990-1994, 1995-1999, 2000-2004, 2005-2009, or 2010-2013), age (<60, 60-69, 70-79, or ≥80 years), sex (male or female), and Charlson Comorbidity Index[22] score (0, 1, or ≥2). Surgically treated patients were further stratified for tumour stage (0-I, II, or III-IV) from the year 2005 onwards, when tumour stage data were available and of high completeness. Cox regression was used to calculate crude and adjusted hazard ratios (HR) with 95% CIs for each of the aforementioned stratification variables (calendar period, age, sex, Charlson Comorbidity Index score and tumour stage) with the same categorisation. The estimates were mutually adjusted for the risk factors where indicated. The missing data for tumour stage were assumed to be missing at random and were dealt with using complete case analysis.

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.

Results

Patients

A total of 3794 patients were diagnosed with oesophageal adenocarcinoma during the study period, including 1131 (30%) who had undergone oesophagectomy. Among all 4631 patients diagnosed with oesophageal squamous cell carcinoma, 1116 (24%) had undergone oesophagectomy. Men were overrepresented in both oesophageal adenocarcinoma group (82%), and squamous cell carcinoma group (63%). The number of oesophageal adenocarcinoma patients increased throughout the study period, while the number of oesophageal squamous cell carcinoma patients decreased (Table 1). The proportion of adenocarcinoma patients who underwent oesophagectomy decreased from 38% in 1990-1994 to 27% in 2010-2013, and for squamous-cell carcinoma patients this proportion decreased from 31% in 1990-1994 to 18% in 2010-2013 (Table 1).

Survival trends in oesophageal adenocarcinoma

Because the observed survival closely mirrored the relative survival (Table 1), only the results regarding relative survival are commented on here.

All patients

The relative survival in oesophageal adenocarcinoma improved during the study period; the 1-year survival increased from 35% in 1990-1994 to 41% in 2010-2013 (with follow-up to 2017), and the corresponding 5-year survival gradually increased from 12% to 15%. (Table 1). From the year 2000 onwards, the relative 5-year survival increased by 2% (Table 1).

Surgically treated patients

The relative survival increased substantially in surgically treated patients. In the oesophagectomy group, the 1-year survival increased from 54% in 1990-1994 to 86% in 2010-2013 (with follow-up until 2017), and the corresponding 5-year survival increased from 27% to 45% (Table 1, Figure 1). From the year 2000 onwards, the relative 1-year survival increased by 11% and the 5-year survival by 12% (Table 1).

Patients not undergoing surgery

In the patients not undergoing surgery, the 1-year survival increased from 24% in 1990-1994 to 25% in 2010-2013 (with follow-up to 2017), and the corresponding 5-year survival increased from 3% to 4% (Table 1, Figure 1). From 2000 onwards the 1- and 5-year survival estimates were stable (Table 1).

Survival trends in oesophageal squamous-cell carcinoma

All patients

Also the relative survival in oesophageal squamous cell carcinoma improved over time. The relative 1-year survival increased from 32% in 1990-1994 to 36% in 2010-2013 (with follow-up until 2017), and the corresponding 5-year survival increased from 9% to 12% (Table 1). From the year 2000 onwards the relative 1-year survival increased by 1%, and the 5-year survival increased by 3% (Table 1).

Surgically treated patients

The 1-year relative survival of surgically treated patients increased from 60% in 1990-1994 to 87% in 2010-2013 (with follow-up until 2017), and the corresponding 5-year survival increased from 24% to 43% (Table 1, Figure 2). From the year 2000 onwards both 1- and 5-year survival increased by 14% (Table 1).

Patients not undergoing surgery

The relative 1-year survival in patients not undergoing surgery was 20% in 1990-1994 and 25% in 2010-2013 (with follow-up until 2017), and the corresponding 5-year survival doubled from 3% to 6% (Table 1, Figure 2). From the year 2000 onwards both 1-and 5-year survival increased by 2% (Table 1).

Risk factors for 5-year mortality in oesophageal adenocarcinoma

All patients

In the multivariable analysis of all oesophageal adenocarcinoma patients, the adjusted HR of mortality within 5 years of diagnosis was higher in earlier calendar periods (HR 1.17, 95%CI 1.02-1.33, first versus last calendar period), older age groups (HR 1.99, 95%CI 1.78-2.22, age ≥80 years versus <60 years), and in patients with more comorbidity (HR 1.27, 95%CI 1.15-1.40, ≥2 comorbidities versus no comorbidities), while sex did not influence the HR of mortality (Table 2).

Surgically treated patients

Among the oesophageal adenocarcinoma patients who underwent oesophagectomy, earlier calendar period (HR 2.02, 95%CI 1.56-2.61, first versus last calendar period) and older age (HR 1.98, 95%CI 1.41-2.77, age ≥80 years versus <60 years) were associated with an increased risk of mortality, while comorbidity and sex did not statistically significantly influence this risk (Table 2).

In a sub-analysis of patients diagnosed between 2005 and 2013, i.e. when tumour stage data were available and adjusted for, higher tumour stage and older age were statistically significant poor prognostic factors (Table 3).

Patients not undergoing surgery

Among the oesophageal adenocarcinoma patients not undergoing surgery, older age (HR 1.21, 95%CI 1.06-1.37, age ≥80 years versus <60 years) was the only factor associated with an increased risk of mortality (Table 2).

Risk factors for 5-year mortality in oesophageal squamous-cell carcinoma

All patients

The multivariable analysis in all oesophageal squamous cell carcinoma patients showed that risk factors for 5-year mortality were earlier calendar period (HR 1.19, 95%CI 1.07-1.31, first versus last calendar period), older age (HR 2.06, 95%CI 1.86-2.28, age ≥80 years versus <60 years), male sex (HR 0.83, 95%CI 0.78-0.89, women versus men), and comorbidity (HR 1.45, 95%CI 1.32-1.59, ≥2 comorbidities versus no comorbidities) (Table 2).

Surgically treated patients

Among the oesophageal squamous cell carcinoma patients who underwent oesophagectomy, earlier calendar period (HR 2.03, 95%CI 1.56-2.63, first versus last calendar period), older age (HR 2.06, 95%CI 1.86-2.28, age ≥80 years versus <60 years), and male sex (HR 0.71, 95%CI 0.61-0.83, women versus men) were associated with an increased risk of mortality, while comorbidity did not statistically significantly influence this risk (Table 2). In a sub-analysis of patients diagnosed between 2005 to 2013, i.e. when tumour stage data were available and adjusted for, more advanced tumour stage, earlier calendar period, older age, male sex, and more comorbidity were poor prognostic factors in oesophageal squamous cell carcinoma (Table 3).

Patients not undergoing surgery

Among the oesophageal squamous cell carcinoma patients not undergoing surgery, earlier calendar period (HR 1.24, 95%CI 1.11-1.39, first versus last calendar period), older age (HR 1.42, 95%CI 1.26-1.60, age ≥80 years versus <60 years), male sex (HR 0.86, 95%CI 0.81-0.93, women versus men), and comorbidity (HR 1.30, 95%CI 1.18-1.43, ≥2 comorbidities versus no comorbidities) were associated with an increased risk of mortality (Table 2).

Discussion

This study indicates that the overall prognosis of both oesophageal adenocarcinoma and oesophageal squamous cell carcinoma is improving over time, especially in the groups of patients that underwent surgery. Female patients with oesophageal squamous cell carcinoma had better prognosis than male patients.

Among strengths of the study is the population-based design with complete and accurate ascertainment and follow-up of all patients diagnosed with oesophageal cancer in Sweden. The assessment of the oesophageal cancer histology, surgical treatment, and date of death was highly accurate and the calculation of relative survival rates allowed valid estimation of disease-specific mortality. The sample size was large enough to enable robust analyses of time trends in sub-groups of patients, and to assess risk factors of mortality. Limitations include the unavailability of some clinical variables, such as use of neoadjuvant or adjuvant treatment. In patients not undergoing surgery it was not possible to assess the treatment modalities used, which adds clinical heterogeneity to this group of patients. Tumour stage data were available only after 2004 and complete only in patients who had undergone surgery. However, the main purpose of the study was to evaluate time trends in survival and to separate these trends into patients who had undergone surgery or not, which was fully possible to achieve.

Previously, a registry-based study from United States showed an increase in 5-year overall survival in oesophageal cancer patients from 18% in 1990s to 22% in 2000s.[10] A European registry-based study (EUROCARE-5) also showed improvement in 5-year overall age-standardised survival rates in oesophageal cancer from 10% in 1999-2001 to 13% in 2005-2007.[11] In China, the age-standardised 5-year relative survival rate for oesophageal cancer

was 21% in 2003-2005.[26] Taken together, earlier studies have shown improving prognosis in oesophageal cancer over time. However, they reported only on earlier calendar periods, and information on histology- or treatment-specific survival were lacking.

The findings of increasing survival over time in both oesophageal adenocarcinoma and oesophageal squamous cell carcinoma despite a decreasing utilisation of oesophagectomy are encouraging. Increased awareness and diagnostic developments might explain the improved prognosis. The treatment might have been improved by centralisation of surgery,[14 15] use of neoadjuvant chemoradiotherapy[27 28] or definitive chemoradiotherapy.[29] The more clearly improved 5-year survival in patients with non-surgically managed oesophageal squamous cell carcinoma patients might be due to a higher sensitivity to chemoradiotherapy in oesophageal squamous cell carcinoma, resulting in a higher success rate of definite oncological therapy.[30 31] Additionally, careful selection of treatment for the elderly, co-morbid and frail patients by the multidisciplinary teams, preoperative optimisation of patients and improved peri- and postoperative care are likely reasons for improved survival in the patients undergoing surgery.

The better prognosis in women with oesophageal squamous cell carcinoma was unexpected. However, some earlier population-based studies have associated female sex with favourable prognosis in oesophageal cancer,[32-34] although these studies did not separate the histological subtypes, tumour stage, or treatment strategies.[35] In the present study, female sex was a strong positive predictor of survival in both surgically and non-surgically treated patients with oesophageal squamous cell carcinoma, also after adjustment. A possible biological mechanism for a sex difference is estrogenic influence, which could inhibit cancer cell growth.[36-38] Additionally, hormone replacement therapy associates to lower risk of oesophageal squamous cell carcinoma.[39 40] Healthcare-seeking patterns might also differ

between the sexes, with women more readily and more often utilizing health resources available to them, compared to men.[41 42] It is however unclear why these patterns would differ between oesophageal adenocarcinoma and squamous cell carcinoma patients, or squamous cell carcinoma patients undergoing surgery and not undergoing surgery. The sex differences in survival after oesophageal squamous cell carcinoma might also be due to differences in socioeconomic and lifestyle factors, which could not be adjusted for in the present study, and should be specifically examined in future studies.

The treatment of oesophageal cancer in the Swedish publicly funded healthcare system follows clinical guidelines, including routine neoadjuvant therapy and centralisation to fewer hospitals during the last years. Thus, the findings of the present study should be generalisable to many other countries with a similar healthcare system as in Sweden. These findings suggest that the recent changes in the Swedish healthcare system, i.e. careful selection of patients undergoing surgery, multidisciplinary management, centralisation of services, and use of neoadjuvant treatment in surgical candidates, and definitive chemoradiotherapy in patients ineligible for surgery, might result in improved prognosis of oesophageal cancer patients.

In conclusion, this nationwide Swedish study with complete ascertainment and follow-up of patients with oesophageal cancer shows that the prognosis in both oesophageal adenocarcinoma and oesophageal squamous cell carcinoma is improving. The improved prognosis is stronger in surgically managed patients, but is also indicated in non-operated patients. Non-operated patients still have a poor prognosis. The favourable prognosis in women with oesophageal squamous cell carcinoma warrants further research.

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Table 1: Observed and relative 1- and 5-year survival across calendar periods in oesophageal adenocarcinoma and squamous cell carcinoma, stratified by treatment strategy in 1990-2013, with follow-up until 2017.

	Oesophageal adenocarcinoma						Oesophageal squamous cell carcinoma					
	Patients		Observed survival in % (95% CI)		Relative survival in % (95% CI)		Patients		Observed survival in % (95% CI)		Relative survival in % (95% CI)	
Calendar period	Number (%)	Mean age	1 year	5 year	1 year	5 year	Number (%)	Mean age	1 year	5 year	1 year	5 year
All patients												
1990-1994	332 (9)	71	33 (28-39)	10 (7-14)	35 (30-41)	12 (8-16)	1148 (25)	70	31 (28-33)	8 (6-9)	32 (29-35)	9 (7-11)
1995-1999	557 (15)	70	35 (31-39)	11 (8-13)	37 (33-41)	13 (10-16)	1014 (22)	70	32 (29-35)	10 (8-12)	33 (30-36)	12 (9-14)
2000-2004	860 (23)	70	39 (36-43)	11 (9-13)	41 (38-45)	13 (11-16)	931 (20)	70	34 (30-37)	7 (6-9)	35 (32-38)	9 (7-11)
2005-2009	1054 (28)	69	39 (36-42)	12 (10-14)	41 (38-44)	14 (12-16)	861 (19)	70	34 (30-37)	10 (8-12)	35 (32-38)	11 (9-14)
2010-2013	991 (26)	71	40 (37-43)	13 (11-15)	41 (38-45)	15 (12-17)	677 (15)	70	34 (31-38)	11 (9-13)	36 (32-39)	12 (10-15)
Surgery												
1990-1994	126 (11)	66	51 (42-60)	22 (15-29)	54 (44-63)	27 (18-36)	346 (31)	65	57 (52-62)	20 (15-24)	60 (55-66)	24 (19-29)
1995-1999	191 (17)	65	68 (61-75)	29 (22-35)	72 (65-79)	35 (27-42)	275 (25)	64	64 (59-70)	25 (20-31)	68 (62-74)	31 (24-37)
2000-2004	275 (24)	66	72 (67-78)	27 (21-32)	76 (71-82)	31 (25-37)	183 (16)	65	69 (63-76)	25 (18-31)	73 (66-80)	29 (22-36)
2005-2009	277 (24)	64	79 (75-84)	38 (32-43)	83 (78-88)	43 (36-49)	193 (17)	64	70 (64-77)	29 (23-35)	74 (67-80)	33 (26-41)
2010-2013	262 (23)	66	83 (78-87)	40 (34-46)	86 (82-91)	45 (38-51)	119 (11)	66	83 (76-90)	39 (30-48)	87 (80-94)	43 (33-54)
No surgery												
1990-1994	206 (8)	74	23 (17-29)	3 (0-5)	24 (18-30)	3 (0-6)	802 (23)	72	19 (16-22)	2 (1-3)	20 (17-23)	3 (1-4)
1995-1999	366 (14)	72	18 (14-22)	1 (0-2)	19 (15-23)	1 (0-2)	739 (21)	72	19 (17-22)	4 (2-5)	21 (18-24)	5 (3-6)
2000-2004	585 (22)	72	24 (20-27)	4 (2-6)	25 (21-29)	5 (3-7)	748 (21)	72	25 (22-28)	3 (2-5)	26 (23-29)	4 (2-5)
2005-2009	777 (29)	71	24 (21-27)	3 (2-5)	25 (22-29)	4 (2-5)	668 (19)	71	23 (20-26)	4 (3-6)	24 (21-27)	5 (3-7)
2010-2013	729 (27)	73	24 (21-27)	3 (2-5)	25 (22-29)	4 (2-5)	558 (16)	71	24 (20-27)	5 (3-7)	25 (21-29)	6 (4-8)

Table 2: Observed 5-year survival and adjusted hazard ratios (HR) with 95% confidence intervals (CI) for oesophageal adenocarcinoma and oesophageal squamous-cell carcinoma in 1990-2013, with follow-up until 2017.

		Oesophageal adenocarcinoma			Oesophageal squamous-cell carcinoma		
Covariate	Category	Patients Number (%)	5-year survival (95% CI)	HR (95% CI)*	Patients Number (%)	5-year survival (95% CI)	HR (95% CI)*
All patients							
Calendar period	1990-1994	332 (9)	10 (7-14)	1.17 (1.02-1.33)	1148 (25)	8 (6-9)	1.19 (1.07-1.31)
	1995-1999	557 (15)	11 (8-13)	1.11 (0.99-1.24)	1014 (22)	10 (8-12)	1.11 (1.00-1.23)
	2000-2004	860 (23)	11 (9-13)	1.07 (0.97-1.18)	931 (20)	7 (6-9)	1.13 (1.01-1.25)
	2005-2009	1054 (28)	12 (10-14)	1.04 (0.94-1.16)	861 (19)	10 (8-12)	1.07 (0.96-1.19)
	2010-2013	991 (26)	13 (11-15)	1 (reference)	677 (15)	11 (9-13)	1 (reference)
Age (years)	<60	686 (18)	18 (15-21)	1 (reference)	787 (17)	14 (12-17)	1 (reference)
	60-69	1079 (28)	16 (13-18)	1.05 (0.94-1.16)	1344 (29)	12 (10-14)	1.11 (1.01-1.22)
	70-79	1166 (31)	12 (10-13)	1.25 (1.13-1.39)	1588 (34)	8 (7-9)	1.38 (1.26-1.51)
	≥80	863 (23)	2 (1-3)	1.99 (1.78-2.23)	912 (20)	2 (1-2)	2.06 (1.86-2.28)
Sex	Male	3098 (82)	12 (11-13)	1 (reference)	2938 (63)	8 (7-9)	1 (reference)
	Female	696 (18)	10 (8-12)	1.04 (0.95-1.14)	1693 (37)	11 (9-12)	0.83 (0.78-0.89)
Comorbidity score	0	2096 (55)	14 (13-15)	1 (reference)	2367 (51)	11 (10-13)	1 (reference)
	1	1115 (29)	11 (9-12)	1.11 (1.03-1.20)	1598 (35)	7 (6-9)	1.15 (1.08-1.23)
	≥2	583 (15)	6 (4-8)	1.27 (1.15-1.40)	666 (14)	4 (2-5)	1.45 (1.32-1.59)
Surgery							
Calendar period	1990-1994	126 (11)	22 (15-29)	2.02 (1.56-2.61)	346 (31)	20 (15-24)	2.03 (1.56-2.63)
	1995-1999	191 (17)	29 (22-35)	1.46 (1.16-1.83)	275 (25)	25 (20-31)	1.62 (1.24-2.13)
	2000-2004	275 (24)	27 (21-32)	1.45 (1.18-1.79)	183 (16)	25 (18-31)	1.53 (1.15-2.04)
	2005-2009	277 (24)	38 (32-43)	1.07 (0.86-1.33)	193 (17)	29 (23-35)	1.41 (1.06-1.88)
	2010-2013	262 (23)	40 (34-46)	1 (reference)	119 (11)	39 (30-48)	1 (reference)
Age (years)	<60	286 (25)	40 (35-46)	1 (reference)	317 (28)	25 (20-30)	1 (reference)
	60-69	423 (37)	31 (26-35)	1.25 (1.03-1.51)	443 (40)	28 (24-32)	1.00 (0.85-1.19)
	70-79	370 (33)	30 (25-34)	1.28 (1.05-1.56)	328 (29)	24 (19-29)	1.13 (0.94-1.35)
	≥80	52 (5)	15 (5-24)	1.98 (1.41-2.77)	28 (3)	11 (-1-22)	1.61 (1.07-2.45)
Sex	Male	987 (87)	31 (28-34)	1 (reference)	729 (65)	21 (18-24)	1 (reference)
	Female	144 (13)	37 (29-45)	0.84 (0.68-1.05)	387 (35)	33 (29-38)	0.71 (0.61-0.83)
Comorbidity	0	733 (65)	33 (29-36)	1 (reference)	698 (63)	27 (24-31)	1 (reference)
	1	299 (26)	32 (27-38)	1.05 (0.89-1.23)	340 (30)	23(18-27)	1.13 (0.97-1.31)
	≥2	99 (9)	26 (18-36)	1.19 (0.93-1.53)	78 (7)	22 (12-31)	1.20 (0.92-1.57)
No surgery							
Calendar period	1990-1994	206 (8)	3 (0-5)	1.10 (0.94-1.29)	802 (23)	2 (1-3)	1.24 (1.11-1.39)
	1995-1999	366 (14)	1 (0-2)	1.14 (1.00-1.30)	739 (21)	4 (2-5)	1.15 (1.02-1.28)
	2000-2004	585 (22)	4 (2-6)	1.02 (0.91-1.13)	748 (21)	3 (2-5)	1.06 (0.95-1.19)
	2005-2009	777 (29)	3 (2-5)	1.00 (0.90-1.11)	668 (19)	4 (3-6)	1.06 (0.95-1.19)
	2010-2013	729 (27)	3 (2-5)	1 (reference)	558 (16)	5 (3-7)	1 (reference)
Age (years)	<60	400 (15)	3 (1-4)	1 (reference)	470(13)	7 (5-9)	1 (reference)
	60-69	656 (25)	6 (4-7)	0.91 (0.80-1.04)	901 (26)	4 (3-5)	1.07 (0.95-1.20)
	70-79	796 (30)	3 (2-4)	1.05 (0.93-1.19)	1260 (36)	4 (3-5)	1.19 (1.06-1.32)
	≥80	811 (30)	1 (0-2)	1.21 (1.06-1.37)	884 (25)	1 (1-2)	1.42 (1.26-1.60)
Sex	Male	2111 (79)	3 (2-4)	1 (reference)	2209 (63)	3 (2-4)	1 (reference)
	Female	552 (21)	3 (1-4)	1.00 (0.90-1.10)	1306 (37)	4 (3-5)	0.86 (0.81-0.93)
Comorbidity score	0	1363 (51)	4 (3-5)	1 (reference)	1669 (47)	5 (4-6)	1 (reference)
	1	816 (31)	3 (1-4)	1.04 (0.95-1.14)	1258 (36)	3 (2-4)	1.07 (0.99-1.15)
	≥2	484 (18)	2 (0-3)	1.08 (0.97-1.20)	588 (17)	1 (0-2)	1.30 (1.18-1.43)

* Adjusted for calendar period, age, sex and comorbidity.

Table 3: Hazard ratios (HR) with 95% confidence intervals (CI) of 5-year mortality after surgery for oesophageal adenocarcinoma and oesophageal squamous-cell carcinoma in 2005-2013, with follow-up until 2017.

	Oesophageal adenocarcinoma			**Oesophageal squamous-cell carcinoma**		
Covariates	Patients Number (%)	Crude HR (95% CI)	Adjusted HR (95% CI)*	Patients Number (%)	Crude HR (95% CI)	Adjusted HR (95% CI)*
Tumour stage†						
0-I	62 (12)	1 (Reference)	1 (Reference)	34 (11)	1 (Reference)	1 (Reference)
II	221 (41)	2.53 (1.54-4.14)	2.37 (1.44-3.90)	143 (46)	2.19 (1.25-3.83)	2.20 (1.25-3.87)
III-IV	186 (35)	4.14 (2.53-6.76)	4.04 (2.46-6.63)	98 (31)	2.71 (1.53-4.79)	2.64 (1.48-4.71)
Calendar						
2005-2009	277 (51)	1.12 (0.88-1.41)	1.04 (0.82-1.32)	193 (62)	1.42 (1.05-1.93)	1.48 (1.08-2.02)
2010-2013	262 (49)	1 (Reference)	1 (Reference)	119 (38)	1 (Reference)	1 (Reference)
Age (years)						
<60	138 (26)	1 (Reference)	1 (Reference)	79 (25)	1 (Reference)	1 (Reference)
60-69	227 (42)	1.52 (1.11-2.08)	1.41 (1.02-1.94)	137 (44)	0.88 (0.61-1.28)	0.81 (0.55-1.18)
70-79	148 (27)	1.52 (1.08-2.14)	1.47 (1.03-2.08)	86 (28)	1.23 (0.83-1.81)	1.21 (0.81-1.81)
≥80	26 (5)	3.39 (2.05-5.60)	3.58 (2.14-5.98)	10 (3)	1.57 (0.71-3.48)	1.58 (0.71-3.53)
Sex						
Male	470 (87)	1 (Reference)	1 (Reference)	210 (67)	1 (Reference)	1 (Reference)
Female	69 (13)	0.84 (0.59-1.19)	0.82 (0.57-1.18)	102 (33)	0.67 (0.49-0.93)	0.66 (0.47-0.92)
Comorbidity						
0	341 (63)	1 (Reference)	1 (Reference)	195 (63)	1 (Reference)	1 (Reference)
1	144 (27)	1.04 (0.80-1.36)	0.95 (0.73-1.25)	86 (28)	1.35 (0.98-1.87)	1.40 (1.01-1.95)
≥2	54 (10)	1.07 (0.72-1.59)	1.02 (0.68-1.52)	31 (10)	1.31 (0.82-2.12)	1.60 (0.98-2.62)

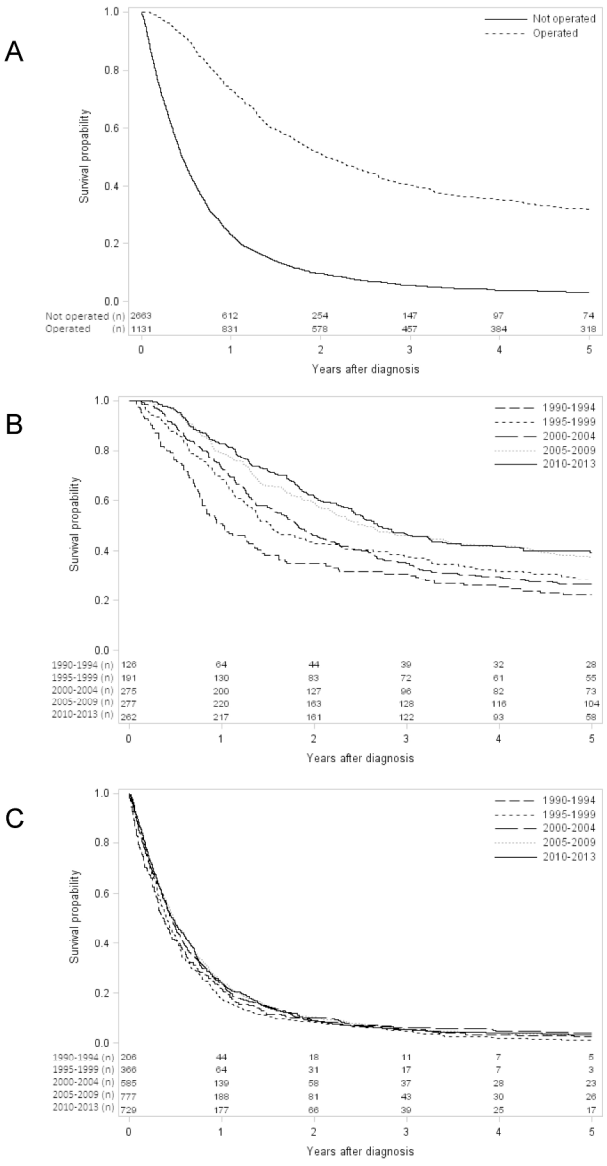
* Adjusted for calendar period, age, sex, Charlson Comorbidity Index and tumour stage.

† 70 (13%) patients with oesophageal adenocarcinoma and 37 (12%) patients with oesophageal squamous-cell carcinoma had missing tumour stage.

Figure Legends

Figure 1. Kaplan-Meier survival curves showing observed 5-year survival oesophageal adenocarcinoma (A) stratified by surgical treatment (yes or no). Patients undergoing oesophageal resection for adenocarcinoma (B) and not undergoing oesophageal resection for adenocarcinoma (C) are further stratified by calendar periods.

Figure 2. Kaplan-Meier survival curves showing observed 5-year survival oesophageal squamous cell carcinoma (A) stratified by surgical treatment (yes or no). Patients undergoing oesophageal resection for squamous cell carcinoma (B) and not undergoing oesophageal resection for squamous cell carcinoma (C) are further stratified by calendar periods.



Kaplan-Meier survival curves showing observed 5-year survival oesophageal adenocarcinoma (A) stratified by surgical treatment (yes or no). Patients undergoing oesophageal resection for adenocarcinoma (B) and not undergoing oesophageal resection for adenocarcinoma (C) are further stratified by calendar periods.

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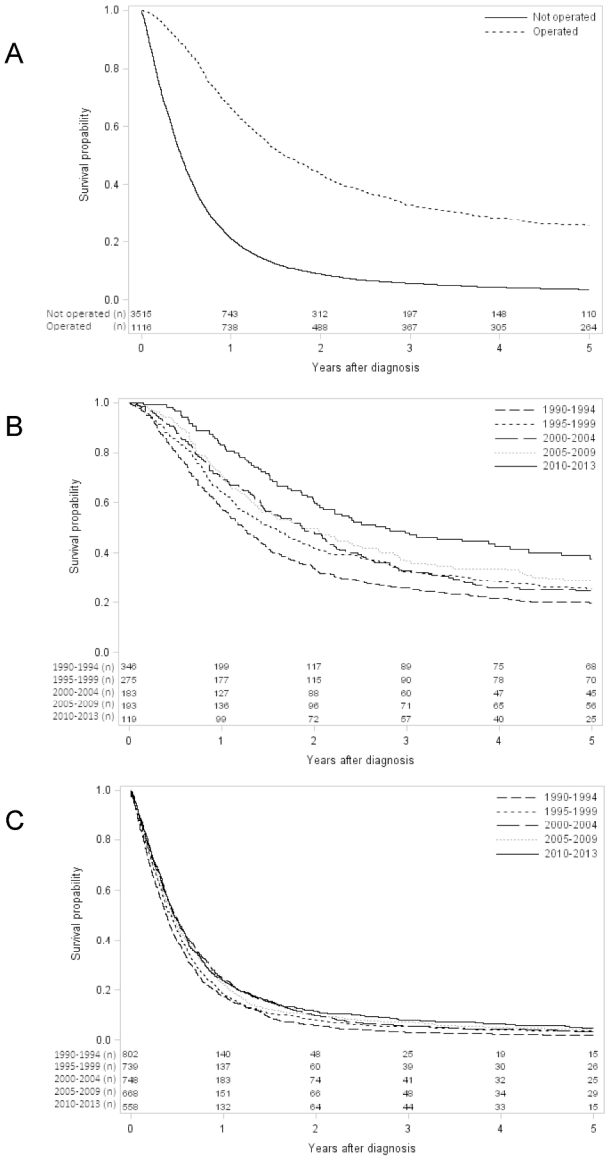

Kaplan-Meier survival curves showing observed 5-year survival oesophageal squamous cell carcinoma (A) stratified by surgical treatment (yes or no). Patients undergoing oesophageal resection for squamous cell carcinoma (B) and not undergoing oesophageal resection for squamous cell carcinoma (C) are further stratified by calendar periods.

275x397mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-8*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10, 23-25
		(b) Indicate number of participants with missing data for each variable of interest	24-25
		(c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-14, 23-25
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	23-25
		(*b*) Report category boundaries when continuous variables were categorized	8, 24-25
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	23
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-13, 24-25
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	4

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.