Original article

Geographical differences in cancer treatment and survival for patients with oesophageal and gastro-oesophageal junctional cancers

C. Jestin Hannan[1], G. Linder[1], C.-H. Kung[2,3], J. Johansson[4], M. Lindblad[2] and J. Hedberg[1]

[1]Department of Surgical Sciences, Uppsala University, Uppsala, [2]Department of Clinical Science, Intervention and Technology Karolinska Institutet, Stockholm, and Departments of Surgery, [3]Skellefteå County Hospital, Skellefteå, and [4]Skåne University Hospital, Lund, Sweden

Correspondence to: Dr C. Jestin Hannan, Department of Surgical Sciences, Uppsala University, SE-75185, Uppsala, Sweden (e-mail: christine.jestin@surgsci.uu.se; @Surgclimb)

Background: Only around one-quarter of patients with cancer of the oesophagus and the gastro-oesophageal junction (GOJ) undergo surgical resection. This population-based study investigated the rates of treatment with curative intent and resection, and their association with survival.

Methods: Patients diagnosed with oesophageal and GOJ cancer between 2006 and 2015 in Sweden were identified from the National Register for Oesophageal and Gastric Cancer (NREV). The NREV was cross-linked with several national registries to obtain information on additional exposures. The annual proportion of patients undergoing treatment with curative intent and surgical resection in each county was calculated, and the counties divided into groups with low, intermediate and high rates. Treatment with curative intent was defined as definitive chemoradiation therapy or surgery, with or without neoadjuvant oncological treatment. Overall survival was analysed using a multilevel model based on county of residence at the time of diagnosis.

Results: Some 5959 patients were included, of whom 1503 (25·2 per cent) underwent surgery. Median overall survival after diagnosis was 7·7, 8·8 and 11·1 months respectively in counties with low, intermediate and high rates of treatment with curative intent. Corresponding survival times for the surgical resection groups were 7·4, 9·3 and 11·0 months. In the multivariable analysis, a higher rate of treatment with curative intent (time ratio 1·17, 95 per cent c.i. 1·05 to 1·30; $P < 0·001$) and a higher resection rate (time ratio 1·24, 1·12 to 1·37; $P < 0·001$) were associated with improved survival after adjustment for relevant confounders.

Conclusion: Patients diagnosed in counties with higher rates of treatment with curative intent and higher rates of surgery had better survival.

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Introduction

Cancer of the oesophagus and gastro-oesophageal junction (GOJ) is the ninth most common type of cancer globally and the incidence is rising[1,2]. Most commonly the disease presents late and at an advanced stage. The 5-year overall survival rate is 10–15 per cent depending on disease stage and treatment[3,4]. Surgery has been the preferred curative treatment option for localized disease[5–7]. Definitive chemoradiotherapy (dCRT) is also given with the aim of curing the disease[8]. Over the past two decades, multimodal treatments, including neoadjuvant chemoradiotherapy or perioperative chemotherapy, have improved survival[9–12].

Many studies of survival in oesophageal and GOJ cancer are from single-centre or multi-institutional databases and include patients who undergo curative treatment. Sweden has well kept and validated national registers and, with the addition of clinical data from professional registries, information on the effects of treatment patterns in patients with cancer can be assessed. The healthcare system in Sweden is organized in 21 counties, generally with around 300 000 inhabitants each. All counties have independent healthcare systems, but patients can be referred to other counties for tertiary care if required. Swedish law states that all citizens, regardless of place of residence or income, shall receive the same level of healthcare.

Decision-making regarding treatment for cancer of the oesophagus and GOJ is complex, and is determined by patient- and tumour-related factors as well as the patient's preferences[13–15]. The recommended treatment should preferably be based on treatment guidelines, and discussed in a multidisciplinary team (MDT) meeting including a specialized surgeon, oncologist and radiologist. In 2007, less than 60 per cent of patients with oesophagogastric cancer in Sweden were discussed by a MDT, whereas 10 years later more than 90 per cent of patients were presented to one of six regional MDTs or a national MDT[16]. However, regional professional expertise and traditions may differ, reflecting differences in treatments applied and possibly in survival. The aim of this study was to assess differences in rates of curative treatment and surgery in patients with oesophageal and GOJ cancer between counties in Sweden, and to correlate this with overall survival.

Methods

This was a population-based cohort study of all patients diagnosed with oesophageal or GOJ cancer in Sweden. This study was approved by the regional ethical review board in Stockholm (2013/596-31/3 and 2016/1486-32).

In Sweden, every citizen has a unique civil registration number which gives an exclusive opportunity to cross-link data from several national registries. The selection base was the National Register for Oesophageal and Gastric cancer (NREV)[17], including all cases of adenocarcinoma and squamous cell carcinoma of the oesophagus and GOJ (C15, C16.0A, C16.0B and C16.0X) diagnosed between 1 January 2006 and 31 December 2015. Additional exposures were collected for each individual by cross-linkage to the Swedish Prescribed Drug Register[18,19], Cause of Death Register[20], Swedish Cancer Register[21] and National Patient Register (NPR). The NPR covers all inpatient care since 1987, and from 2001 it has also covered outpatient clinic visits from public as well as private caregivers[22].

Definition of exposures

The exposures were the rate of treatment with curative intent and the surgical resection rate for each county. The patient's registered home address at the time of diagnosis was used. Data on treatment with curative intent were obtained from the NREV. The decision on the recommended treatment before the patient actually starts treatment is a mandatory variable in the NREV. Treatment with curative intent includes dCRT and surgery with or without neoadjuvant or perioperative oncological treatment. Patients who underwent endoscopic surgery were also included in the surgery group.

The decision to recommend curative treatment or surgery for oesophageal and GOJ cancer has been centralized. Regional MDT meetings are recommended, and clinicians at the hospital of diagnosis in the patient's county of residence are responsible for referring the patient to a MDT and starting treatment[16]. Each county in Sweden acts as an autonomous healthcare organization. For this reason, the rate of curative intent and resection rate was calculated for each county, with an annual update. This was calculated by dividing the total number of patients with curative intent by the number of patients diagnosed with oesophageal or GOJ cancer for each county and calendar year. The rate of treatment with curative intent was divided into tertiles (low, intermediate or high) and each patient was assigned to a tertile according to the county in which the diagnosis was made. Similarly, each county's surgical resection rate was calculated as the proportion of patients with oesophageal or GOJ cancer in that county who underwent cancer resection, and the rates were divided into tertiles (low, intermediate or high).

Definition of outcome

The outcome was overall survival. Patients were followed until death, emigration or the end of follow-up (31 December 2016), whichever occurred first. Date of death was identified in the Cause of Death Register.

Co-variables and confounding factors

To identify relevant co-variables, causal directed acyclic graphs (DAGs) were used[23,24]. Sex, age, year of diagnosis, clinical stage, ASA physical status classification at time of diagnosis, education level, relevant co-morbidities and the proportion of patients with intended curative oncological treatment were identified as potential co-variables and included in the multivariable models. The number of patients intended to receive dCRT was extracted from the NREV and used to calculate the percentage of patients planned for dCRT. The percentage of patients planned for dCRT per county was included in the multivariable analysis. Data on all co-variables, except education level and co-morbidities, were obtained from the NREV.

Clinical disease stage, including tumour category (cT), regional lymph node metastasis (cN), and distant metastasis (cM), was generally evaluated by CT of the chest and abdomen, endoscopy and, in some patients also by endoscopic ultrasonography as well as other radiological modalities according to local routines. PET–CT was used for staging mainly during the later years of the study. The eighth edition of the TNM classification[25] was used to

define clinical disease stages based on cT, cN and cM recorded in the NREV according to the TNM system in place at the time of diagnosis.

The patient's education level was extracted from Statistics Sweden and classified as: low, 9 years or less, equivalent to compulsory primary school; intermediate, 10–12 years, equivalent to fulfilled primary school and partly or fully fulfilled secondary school; and high, more than 12 years, equivalent to university or other academic studies.

Relevant co-morbidities identified as possible co-variables in the DAG analysis were: pharmaceutically treated diabetes, chronic obstructive pulmonary disease (COPD), heart disease, peripheral vascular disease, and malignancy other than oesophageal or GOJ cancer. Accurate and recent information on co-morbidities up to the time of oesophageal and GOJ cancer diagnosis was obtained from the NPR and the Prescribed Drug Register[26]. Diagnostic codes from ICD-10 and Anatomical Therapeutic Chemical Classification System medication codes were used. Diabetes was defined as a co-morbidity if the patient had been prescribed insulin (A10A) and/or diabetes drugs excluding insulin (A10B). Patients with COPD comprised all those with a prescription for medication related to obstructive pulmonary disease (R03A, R03B, R03C), as well as patients with a diagnosis of COPD (J44) in the inpatient register. Heart disease was defined as a diagnosis of heart failure (I50) or coronary disease (I21). Peripheral vascular disease was identified by diagnosis (I73.9), drugs for vascular disease (B01AC06) and drugs for hypertension (C03, C07, C08, C09). Malignancies included all earlier or current malignancies (C00–C96), excluding oesophageal and GOJ cancer (C15, C16.0A, C16.0B, C16.0X) as well as non-melanoma skin cancer (C44).

Statistical analysis

Baseline characteristics are presented as numbers with percentages, with analysis by means of the χ^2 test. Overall survival was analysed using a two-level mixed-effects parametric survival model with a log logistic parametric distribution. In addition to modelling fixed effects for the co-variables described, county was modelled at a second level with a random intercept. Separate models were fitted for surgery and treatment with curative intent. Log logistic parameterization was used because it provided a better model according to the Aikaike information criterion compared with other distributions (exponential, log normal and Weibull) and is generally superior when the hazard rises to a peak and then falls (non-monotonic). The coefficients were exponentiated and expressed as time ratios, that is the proportion of difference in survival time added for each co-variable. Other variables in the model were: sex, age (less than 60, 60–69, 70–79, or 80 years or more), year of diagnosis (2006–2015), clinical stage according to the eighth edition of the TNM classification (0–IVb)[25], ASA grade (I–II, III or more), level of education (low, intermediate or high), pharmaceutically treated diabetes (yes or no), COPD (yes or no), heart disease (yes or no), peripheral vascular disease (yes or no), malignancy other than oesophageal or GOJ cancer (yes or no), whether the patient had been discussed at a MDT meeting (yes or no), and annual proportion of intended curative oncological treatment per county (not included in the resection rate analysis). The total risk of events was illustrated in Kaplan–Meier plots, with analysis using the log rank test. The time course of increased hazards for the two exposures was analysed and displayed graphically.

Subgroup analyses were undertaken, with exclusion of all patients with clinical stage T4b and M1 disease, and overall survival was analysed using the same type of model co-variables as in the main analysis.

The exposure resection rate was set in relation to the proportion of patients who underwent surgery. As these patients had, by definition, not died before surgery, a risk of introduction of immortal time bias was identified. To explore the effect of immortal time bias, analyses of the effect of resection rate on survival were performed with the index date 120 days after diagnosis.

The correlation between rate of treatment with curative intent and rate of surgery was analysed using Pearson's correlation coefficient. No imputation was used. The majority of missing data related to clinical stage. Patients with missing data on clinical stage were also analysed separately.

All statistical analysis was done using Stata® version 14.2 (StataCorp, College Station, Texas, USA) and R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

Results

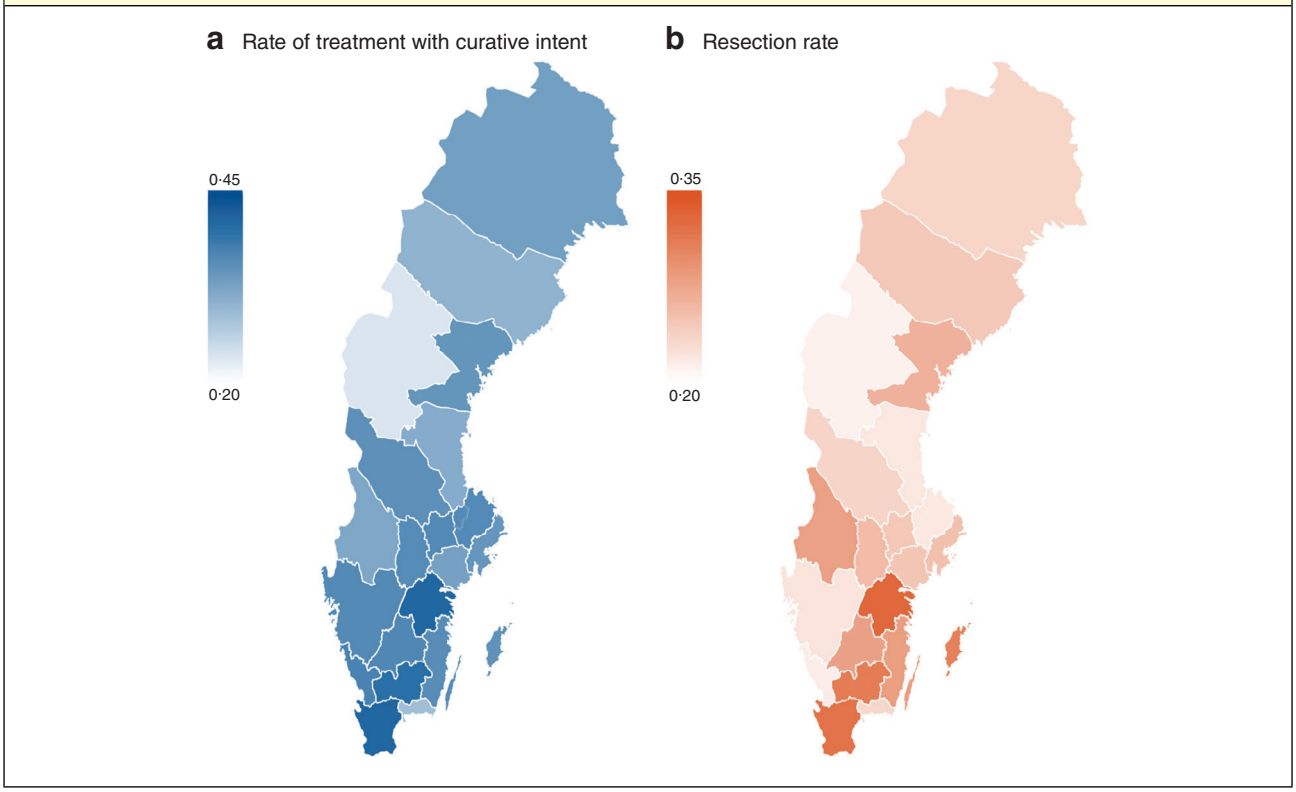
In total, 5959 patients were included in the study (*Table 1*), of whom 2364 (39·7 per cent) had treatment with curative intent. A total of 1503 patients (25·2 per cent) underwent surgery, and 852 (56·7 per cent) of these received neoadjuvant treatment. There was variation in the percentage of patients proposed for treatment with curative intent among the 21 counties, with rates ranging from 24·4 to 47·8 per cent (*Fig. 1a*). There was also variation in the percentage of patients undergoing surgical resection, from 21·4 to 35·9 per cent, depending on the county of residence (*Fig. 1b*).

Table 1 Baseline data of patients according to tertiles of treatment with curative intent and surgical resection

	Treatment with curative intent				Surgical resection			
	Low ($n = 2005$)	Intermediate ($n = 2022$)	High ($n = 1932$)	P†	Low ($n = 2010$)	Intermediate ($n = 2052$)	High ($n = 1897$)	P†
Person-years follow-up	2963	3184	3070		2619	3184	3414	
Age at diagnosis (years)				< 0·001				< 0·001
< 60	307 (15·3)	307 (15·2)	365 (18·9)		309 (15·4)	313 (15·3)	357 (18·8)	
60–69	613 (30·6)	673 (33·3)	598 (31·0)		577 (28·7)	680 (33·1)	627 (33·1)	
70–79	595 (29·7)	600 (29·7)	595 (30·8)		625 (31·1)	618 (30·1)	547 (28·8)	
≥ 80	490 (24·4)	442 (21·9)	374 (19·4)		499 (24·8)	441 (21·5)	366 (19·3)	
Sex				0·812				0·143
M	1485 (74·1)	1494 (73·9)	1444 (74·7)		1470 (73·1)	1515 (73·8)	1438 (75·8)	
F	520 (25·9)	528 (26·1)	488 (25·3)		540 (26·9)	537 (26·2)	459 (24·2)	
Histology				0·013				0·507
Adenocarcinoma	1466 (73·1)	1398 (69·1)	1398 (72·4)		1459 (72·6)	1459 (71·1)	1344 (70·8)	
Squamous cell carcinoma	527 (26·3)	609 (30·1)	519 (26·9)		541 (26·9)	574 (28·0)	540 (28·5)	
Missing	12 (0·6)	15 (0·7)	15 (0·8)		10 (0·5)	19 (0·9)	13 (0·7)	
Clinical stage				< 0·001				< 0·001
0	63 (3·1)	65 (3·2)	54 (2·8)		64 (3·2)	58 (2·8)	60 (3·2)	
I	70 (3·5)	62 (3·1)	66 (3·4)		67 (3·3)	66 (3·2)	65 (3·4)	
II	213 (10·6)	250 (12·4)	284 (14·7)		182 (9·1)	250 (12·2)	315 (16·6)	
III	392 (19·6)	527 (26·1)	510 (26·4)		458 (22·8)	554 (27·0)	417 (22·0)	
IVA	115 (5·7)	129 (6·4)	165 (8·5)		135 (6·7)	145 (7·1)	129 (6·8)	
IVB	689 (34·3)	597 (29·5)	514 (26·6)		672 (33·4)	598 (29·1)	530 (27·9)	
Missing	463 (23·1)	392 (19·4)	339 (17·5)		432 (21·5)	381 (18·6)	381 (20·1)	
Diabetes treatment				0·381				0·624
No	1734 (86·5)	1758 (86·9)	1651 (85·5)		1745 (86·8)	1760 (85·8)	1638 (86·3)	
Yes	271 (13·5)	264 (13·1)	281 (14·5)		265 (13·2)	292 (14·2)	259 (13·7)	
COPD				0·250				0·731
No	1672 (83·4)	1705 (84·3)	1591 (82·3)		1672 (83·2)	1704 (83·0)	1592 (83·9)	
Yes	333 (16·6)	317 (15·7)	341 (17·7)		338 (16·8)	348 (17·0)	305 (16·1)	
Heart disease				0·068				0·133
No	1715 (85·5)	1718 (85·0)	1689 (87·4)		1724 (85·8)	1744 (85·0)	1654 (87·2)	
Yes	290 (14·5)	304 (15·0)	243 (12·6)		286 (14·2)	308 (15·0)	243 (12·8)	
Peripheral vascular disease				0·715				0·049
No	771 (38·5)	777 (38·4)	764 (39·5)		774 (38·5)	762 (37·1)	776 (40·9)	
Yes	1234 (61·5)	1245 (61·6)	1168 (60·5)		1236 (61·5)	1290 (62·9)	1121 (59·1)	
Malignancy*				0·034				0·049
No	1534 (76·5)	1573 (77·8)	1544 (79·9)		1548 (77·0)	1586 (77·3)	1517 (80·0)	
Yes	471 (23·5)	449 (22·2)	388 (20·1)		462 (23·0)	466 (22·7)	380 (20·0)	
Education level				0·302				0·630
Low	719 (35·9)	719 (35·6)	740 (38·3)		723 (36·0)	766 (37·3)	689 (36·3)	
Intermediate	680 (33·9)	754 (37·3)	775 (40·1)		719 (35·8)	787 (38·4)	703 (37·1)	
High	277 (13·8)	331 (16·4)	307 (15·9)		277 (13·8)	339 (16·5)	299 (15·8)	
Missing	329 (16·4)	218 (10·8)	110 (5·7)		291 (14·5)	160 (7·8)	206 (10·9)	
ASA fitness grade				< 0·001				< 0·001
I–II	1094 (54·6)	1199 (59·3)	1266 (65·5)		1152 (57·3)	1210 (59·0)	1197 (63·1)	
≥ III	739 (36·9)	763 (37·7)	603 (31·2)		744 (37·0)	764 (37·2)	597 (31·5)	
Missing	172 (8·6)	60 (3·0)	63 (3·3)		114 (5·7)	78 (3·8)	103 (5·4)	
MDT assessment				< 0·001				< 0·001
No	643 (32·1)	413 (20·4)	385 (19·9)		588 (29·3)	444 (21·6)	409 (21·6)	
Yes	1198 (59·8)	1577 (78·0)	1527 (79·0)		1329 (66·1)	1569 (76·5)	1404 (74·0)	
Missing	164 (8·2)	32 (1·6)	20 (1·0)		93 (4·6)	39 (1·9)	84 (4·4)	
Planned dCRT				< 0·001				0·044
No	1938 (96·7)	1876 (92·8)	1772 (91·7)		1872 (93·1)	1914 (93·3)	1800 (94·9)	
Yes	67 (3·3)	146 (7·2)	160 (8·3)		138 (6·9)	138 (6·7)	97 (5·1)	

Values in parentheses are percentages. *Other than oesophageal or gastro-oesophageal junctional cancer. COPD, chronic obstructive pulmonary disease; MDT, multidisciplinary team; dCRT, definitive chemoradiotherapy. †Pearson's χ^2 test.

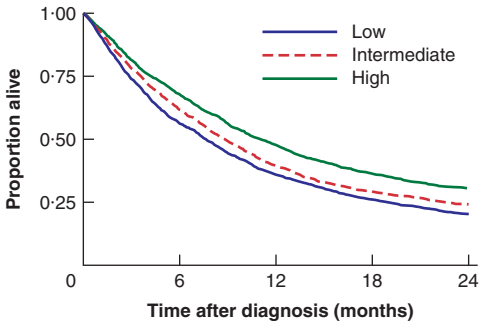
Fig. 1 Rates of recommended treatment with curative intent and resection by county, 2006–2015



a Treatment with curative intent and **b** resection. Figures are based on the mean value for each county for the whole study interval.

The annual rates of treatment with curative intent per county ranged from 0 to 88 (5–95th centile 22–57) per cent. The tertiles of treatment with curative intent were defined as low (0–35·2 per cent), intermediate (35·3–44·4 per cent) and high (45·0–87·5 per cent), with 2005, 2022 and 1932 patients respectively in each group. The annual surgery rates per county varied between 0 and 71 (14–44) per cent. The tertiles were defined as low (0–22·2 per cent), intermediate (22·6–31·6 per cent) and high (31·8–71·4 per cent), with 2010, 2052 and 1897 patients in each group. The groups were well matched for age, education level and most co-morbidities. There were differences for age, clinical stage, histology, ASA grade, curative oncological treatment, whether the patient was discussed by a MDT, and certain co-morbidities. These differences were adjusted for in the two-level mixed-effects parametric survival model.

Fig. 2 Kaplan–Meier plot showing overall survival according to tertiles of rate of treatment with curative intent for all patients in county of residence at year of diagnosis



No. at risk					
Low	2001	1131	719	514	397
Intermediate	2018	1245	794	562	437
High	1926	1311	918	623	476

$P < 0·001$ (log rank test).

Overall survival

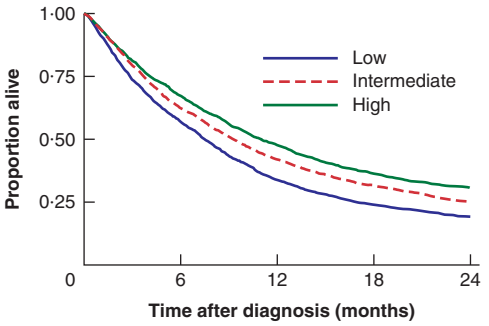
Median overall survival after diagnosis was 7·7, 8·8 and 11·1 months in the groups with low, intermediate and high rates of treatment with curative intent respectively (*Fig. 2*). In the two-level mixed-effects parametric survival model, a higher rate of treatment with curative intent was associated with improved survival (time ratio 1·17, 95 per cent c.i. 1·05 to 1·30; $P < 0·005$) (*Table 2*).

Table 2 Time ratios from multilevel mixed-effects parametric survival models for the outcome overall survival

	Rate of treatment with curative intent		Resection rate	
	Time ratio*	*P*	Time ratio*	*p*
Exposure group				
Low	1·00 (reference)		1·00 (reference)	
Intermediate	0·99 (0·90, 1·10)	0·876	1·05 (0·96, 1·16)	0·284
High	1·17 (1·05, 1·30)	0·005	1·24 (1·12, 1·37)	< 0·001
Age at diagnosis (years)				
< 60	1·00 (reference)		1·00 (reference)	
60–69	0·93 (0·83, 1·03)	0·181	0·93 (0·83, 1·03)	0·157
70–79	0·71 (0·63, 0·80)	< 0·001	0·71 (0·64, 0·80)	< 0·001
≥ 80	0·51 (0·44, 0·58)	< 0·001	0·50 (0·44, 0·58)	< 0·001
Sex				
F	1·00 (reference)		1·00 (reference)	
M	1·01 (0·92, 1·10)	0·897	1·01 (0·92, 1·10)	0·885
Year of diagnosis				
2006	1·00 (reference)		1·00 (reference)	
Per additional year	0·98 (0·97, 1·00)	0·013	0·98 (0·97, 1·00)	0·035
Clinical stage				
0	1·00 (reference)		1·00 (reference)	
I	0·47 (0·34, 0·64)	< 0·001	0·47 (0·34, 0·64)	< 0·001
II	0·28 (0·21, 0·36)	< 0·001	0·28 (0·21, 0·36)	< 0·001
III	0·18 (0·14, 0·23)	< 0·001	0·18 (0·14, 0·23)	< 0·001
IVA	0·11 (0·08, 0·14)	< 0·001	0·11 (0·08, 0·14)	< 0·001
IVB	0·06 (0·04, 0·07)	< 0·001	0·06 (0·05, 0·07)	< 0·001
Histology				
Adenocarcinoma	1·00 (reference)		1·00 (reference)	
Squamous cell carcinoma	0·73 (0·67, 0·80)	< 0·001	0·73 (0·67, 0·80)	< 0·001
Diabetes				
No	1·00 (reference)		1·00 (reference)	
Yes	0·87 (0·78, 0·97)	0·016	0·87 (0·78, 0·98)	0·018
COPD				
No	1·00 (reference)		1·00 (reference)	
Yes	0·87 (0·79, 0·96)	0·007	0·87 (0·79, 0·96)	0·007
Heart disease				
No	1·00 (reference)		1·00 (reference)	
Yes	1·05 (0·93, 1·18)	0·460	1·04 (0·93, 1·17)	0·494
Peripheral vascular disease				
No	1·00 (reference)		1·00 (reference)	
Yes	1·01 (0·92, 1·09)	0·902	1·01 (0·93, 1·10)	0·865
Malignancy†				
No	1·00 (reference)		1·00 (reference)	
Yes	0·85 (0·77, 0·93)	< 0·001	0·85 (0·78, 0·93)	0·001
Education level				
Low	1·00 (reference)		1·00 (reference)	
Intermediate	1·09 (1·01, 1·19)	0·035	1·09 (1·01, 1·19)	0·032
High	1·20 (1·08, 1·34)	0·001	1·20 (1·08, 1·34)	0·001
ASA fitness grade				
I–II	1·00 (reference)		1·00 (reference)	
≥ III	0·59 (0·54, 0·64)	< 0·001	0·59 (0·54, 0·64)	< 0·001
MDT assessment				
No	1·00 (reference)		1·00 (reference)	
Yes	1·77 (1·58, 1·97)	< 0·001	1·75 (1·57, 1·95)	< 0·001
Planned dCRT (per additional %)	0·99 (0·99, 1·00)	0·199		

Values in parentheses are 95 per cent confidence intervals. *Factor for time to event (death) for each level of co-variable; a value above 1·00 indicates improved survival. †Other than oesophageal or gastro-oesophageal junctional cancer. COPD, chronic obstructive pulmonary disease; MDT, multidisciplinary team; dCRT, definitive chemoradiotherapy.

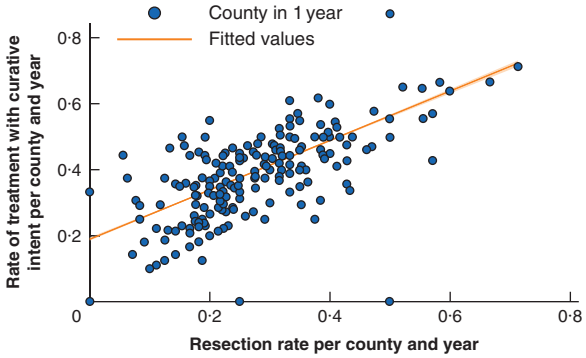
Fig. 3 Kaplan–Meier plot showing overall survival according to tertiles of total resection rate for all patients in county of residence at year of diagnosis



No. at risk					
Low	2008	1141	675	456	342
Intermediate	2045	1274	856	600	454
High	1892	1272	900	643	514

$P < 0{\cdot}001$ (log rank test).

Fig. 4 Scatterplot showing correlation between rate of treatment with curative intent and total resection rate



Each point represents a county over 1 year (between 2006 and 2015) in Sweden. The shaded area represents the 95 per cent confidence interval for the fitted values.

Overall median survival after diagnosis was 7·4, 9·3 and 11·0 months in the groups with low, intermediate and high rates of surgical resection respectively (*Fig. 3*). The two-level mixed-effects parametric survival model demonstrated an association between higher resection rate and improved survival (time ratio 1·24, 1·12 to 1·37; $P < 0{\cdot}001$) (*Table 2*).

In addition to rates of treatment with curative intent and resection being significant predictors of survival, lower ASA grade, younger age, less advanced clinical stage, adenocarcinoma, higher education level, whether the patient was discussed by a MDT, and absence of diabetes treatment, COPD or other malignancy, were all associated with statistically significant differences in survival.

After excluding patients with M1 or T4b disease, a higher rate of treatment with curative intent (time ratio 1·21, 1·05 to 1·41; $P = 0{\cdot}009$) or of surgical resection (time ratio 1·36, 1·18 to 1·55; $P < 0{\cdot}001$) was associated with better survival (*Table S1*, supporting information).

Timing of hazard difference

All models showed that the differences in hazard were highest in the first year, after which the three groups (low, intermediate and high rate) had more similar hazard profiles (*Figs S1* and *S2*, supporting information).

Curative intention *versus de facto* resection

The correlation between rate of treatment with curative intent and rate of surgical resection was 67·6 per cent (Pearson's correlation) (*Fig. 4*).

Sensitivity analysis

There were no statistically significant changes between the three groups in the Kaplan–Meier survival analysis after excluding all patients with clinical stage IVb disease, meaning all patients with metastatic disease, and patients diagnosed in counties with fewer than ten cases of oesophageal or GOJ cancer annually. Most patients with incomplete data had clinical stage missing (1194 patients). Baseline characteristics of these patients were similar to those of the rest of the cohort (*Table S2*, supporting information), except for older age and lower percentage of patients presented to a MDT among the group with clinical stage missing.

In addition to the risk of hidden confounding, the risk of immortal time bias affecting the results of resection rate on survival was explored. With the analysis changed to start the observation 120 days (median time to surgery) after diagnosis, there were no substantial differences in the main results. Median survival time was 8·0, 10·6 and 12·8 in the groups with a low, medium and high resection rate, compared with 7·4, 9·3 and 11·0 months without adjustment for immortal time bias.

Discussion

This study showed that survival was better for patients diagnosed with oesophageal or GOJ cancer in a county in which a higher proportion of patients was allocated to treatment with curative intent. This also translated into a higher proportion of cancer resections, as the two were shown to correlate to a large extent.

An important reason for choosing the rate of treatment with curative intent is that the NREV demands a statement

on the intention of treatment when patients are entered into the database. Intention of treatment is based on a variety of factors: patient and tumour characteristics, physician-dependent factors (personal preference and expertise) and guidelines all play a role. Differences in referral of patients for curative treatment have previously been linked to survival in oesophageal and junctional cancer by Koëter and colleagues[27], who showed that a higher total resection rate was associated with improved survival. Likewise, van Putten and colleagues[28] reported variation in the probability of receiving curative treatment for oesophageal cancer depending on the hospital of diagnosis in the Netherlands. Being diagnosed in a hospital with a lower probability of offering potentially curative treatment was associated with worse overall survival. During the present study interval, there was ongoing centralization of care, which is why the patient's county of residence was chosen as a yearly updated exposure. Other studies[29–31] of total resection rate, and especially the effect of centralization, in pancreatic and gastric cancer also reported associations between a higher total resection rate and survival benefit.

Age is a well known predictor for the likelihood of undergoing curative surgery[32]. Likewise, clinical tumour stage is central to the decision whether a patient would benefit from resection[7]. Both age and clinical stage differed between the three volume categories for treatment with curative intent and surgical resection. However, there were only minor differences in co-morbidities between the groups. By identifying relevant co-morbidities from the NPR and the Swedish Prescribed Drug registry, with 100 per cent coverage, the risk of missing or inaccurate data was reduced.

The exact proportion of patients who would benefit from surgery is unknown. The resection rate may also vary over time as new oncological treatments, including surgical approaches, evolve[33]. In the present study, this may have occurred within each county, especially during a period when centralization of care was taking place in addition to normal variation over time. Changes in medical personnel, such as clinical practitioners, surgeons and oncologists, at hospitals within each county may also have played a role. By assigning each county a rate of treatment with curative intent and surgical resection per year, effects of other time-dependent changes were diminished, making the results more generalizable.

The multivariable analysis showed better survival for counties with a higher resection rate. This does not mean that the association is infinite, without an upper limit, but this could not be determined from the present data. Counties with a higher resection rate are also more likely to refer patients for surgical evaluation and may strive to give the patient curative treatment. Referring patients also often means that they will be discussed by a MDT, which has been shown to have a positive effect on survival in previous studies[10,34]. Even though the analysis was adjusted for educational level, remaining socioeconomic differences, such as the variable availability of healthcare to patients in more remote areas, might have influenced the results. Another possible explanation for the association between survival and resection rate is more accurate diagnosis and, as a consequence, a lower probability of overstaging. Differences in clinical staging between counties, especially overstaging, could explain some of the differences in this study. For example, some counties had more patients with higher disease stages who were not eligible for curative treatment. Possible differences in diagnosis and treatment are the reason why the whole population was included in this study and not only selected disease stages. Furthermore, the prominent peak in hazard differences during the first year after diagnosis implies that differences in cancer care, rather than inherent patient factors, probably explain the outcomes.

The NREV has recently been updated to provide complete and comprehensive data on all aspects of oncological treatment. In this study, only data on the intention of treatment at the time of diagnosis were available, and not the completed treatment. Patients receiving dCRT constituted only a small proportion of all patients, and were included in the multivariable analysis with rate of treatment with curative intent as exposure.

The major strength of this study is the use of population-based data from several validated national registries[17–22], minimizing selection bias and misclassification. Some limitations are inherent to the retrospective study design, such as the risk of recall bias, where information was reported late, and confounding. A causal DAG full model was used for choosing co-variables. If a method using sample-based variation among variables in the database is used (stepwise or other), causal relationships between variables are not considered[35].

The risk of immortal time bias was explored in the analysis of resection rates, as the exposure was defined as the proportion of patients undergoing surgery. However, no change in the results was observed when the index date was changed to 120 days after surgery, and immortal time bias is therefore unlikely to explain the differences in survival.

There were more missing values in the counties with low rates of treatment with curative intent and surgery. This is to be expected as more information on treatment, outcomes and additional surveys will be collected

and reported to the registry when a patient is receiving treatment with curative intent, resulting in fewer missing data. No imputation of missing data was performed and information on many co-variables was available for all patients (co-morbidity and survival status). Moreover, even though clinical stage was available as a co-variable for the majority of patients, there may have been coding and radiological discrepancies; this was one of the reasons why T4b and M1 disease stages were included in the main analysis. A subgroup analysis excluding patients with clinical stage T4b or M1 disease showed similar results, supporting the view that county has an impact on survival, irrespective of disease stage.

The healthcare system in Sweden aims to provide equal care for the whole population, regardless of place of residence, income, education or other socioeconomic factors. The present results suggest that this is not being achieved. This opens up a discussion on possible reasons for the differences and, more importantly, how to overcome them. The results of this study may be valid for other countries with a similar healthcare system to that in Sweden, where most oncological care is provided by the government and the dominant histological subtype is adenocarcinoma[36]. The choice of treatment and outcomes may differ in countries where squamous cell carcinoma is the predominant subtype[37].

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.