Original article

Impact of co-morbidity on mortality after oesophageal cancer surgery

L. Backemar[1], P. Lagergren[1], A. Johar[1] and J. Lagergren[2,3]

[1]Surgical Care Science and [2]Upper Gastrointestinal Surgery, Department of Molecular Medicine and Surgery, Karolinska Institute, Stockholm, Sweden, and [3]Division of Cancer Studies, King's College London, London, UK

Correspondence to: Miss L. Backemar, Surgical Care Science, Department of Molecular Medicine and Surgery, NS 67, 2nd Floor, Karolinska Institute, 171 76 Stockholm, Sweden (e-mail: lovisa.backemar@ki.se)

Background: There is limited knowledge of how co-morbidities influence survival after surgery for oesophageal cancer. This population-based cohort study investigated how Charlson co-morbidity index and specific co-morbidities influenced all-cause and disease-specific mortality.

Methods: Data from all patients who underwent oesophageal cancer surgery in Sweden in 1987–2010, with follow-up until 2012, came from histopathology records, operation charts and nationwide registers. Associations between co-morbidities (Charlson co-morbidity index) and mortality were analysed using Cox proportional hazard regression with adjustment for potential confounding, and presented as hazard ratio (HR) with 95 per cent c.i.

Results: Among 1822 patients there were 1474 deaths (80·9 per cent), of which 1139 (77·3 per cent) occurred between 91 days and 5 years after surgery. Overall all-cause mortality was increased in patients with a Charlson score of 2 or more (HR 1·24, 95 per cent c.i. 1·08 to 1·42), and those with a history of myocardial infarction (HR 1·23, 1·01 to 1·49) or congestive heart failure (HR 1·31, 1·04 to 1·67). Patients with squamous cell carcinoma had increased overall all-cause mortality if they had been diagnosed with cerebrovascular disease (HR 1·35, 1·00 to 1·83) or other cancers (HR 1·36, 1·09 to 1·71), whereas those with adenocarcinoma did not. A Charlson score of 1 or exposure to the co-morbidity groups peripheral vascular disease, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, diabetes and liver disease did not increase mortality. The disease-specific results were generally similar to the all-cause mortality data.

Conclusion: Co-morbidity with a Charlson score of 2 or more, previous myocardial infarction and congestive heart failure were associated with increased mortality after oesophageal cancer surgery undertaken with curative intent.

Paper accepted 9 April 2015
Published online 8 June 2015 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.9854

Introduction

Oesophageal cancer is the eighth most common cancer globally, and the poor prognosis (5-year survival rate less than 15 per cent) makes it the sixth most common cancer death[1,2]. Attempted curative treatment usually involves oesophageal resection, with a population-based 5-year survival rate of 30 per cent[3]. Although early postoperative mortality rates have decreased during recent years as a result of the development of surgical techniques and perioperative care[4–6], they are still as high as 4–14 per cent[4,7]. Owing to advanced tumour stage and co-morbidity, only 20–35 per cent of all patients with oesophageal cancer are considered suitable for surgery[8]. The lack of clinical standards regarding how to include co-morbidities in preoperative decision-making can make the selection for surgery difficult and subjective[9,10]. Several studies have identified preoperative factors that predict mortality, but only a limited number of studies have investigated how co-morbidities predict prognosis after oesophageal cancer surgery. Regarding short-term mortality, co-morbidities in general seem to increase the risk[4,7,11–15], but analyses of specific conditions are lacking. The literature on long-term survival is sparse, and yet any influence of co-morbidities on overall prognosis would be highly relevant in view of the poor long-term survival rates.

Two previous studies[3,16] analysing co-morbidity in relation to mortality prompted the present study. In a cohort study[3] of patients undergoing oesophageal cancer

surgery in Sweden in 1987–2000, co-morbidity in general increased the risk of overall mortality by approximately 60 per cent. In another Swedish cohort study[16], including 609 patients with cancer of the oesophagus or cardia who underwent surgery in 2001–2005, the long-term prognosis was not influenced by co-morbidity, although the limited sample size was a concern. By expanding the nationwide Swedish cohort and adding more clinical data, the present study sought to investigate how the Charlson co-morbidity index and specific co-morbidities might influence overall all-cause and disease-specific mortality.

Methods

This was a nationwide, population-based cohort study investigating the influence of co-morbidities on mortality among all patients in Sweden who underwent surgery with curative intent for oesophageal cancer between 1 January 1987 and 31 December 2010, with follow-up until February 2012. Data were collected by manual review of histopathology records and operation charts, in combination with linkage of data retrieved from the Swedish Cancer Registry, National Patient Registry, Swedish Causes of Death Registry and Swedish Registry of the Total Population. The assessment of medical records and registry data for all patients was possible through the unique ten-digit identification number assigned to each Swedish resident upon birth or immigration.

Data sources

Histopathology reports and operation charts were evaluated to assess tumour stage, location, histology and surgical approach for each patient. Data were collected from all hospitals where oesophageal cancer surgery had been conducted in Sweden since 1987. The assessment of clinical data was validated in a random sample of 100 records, which showed over 90 per cent agreement between three independent researchers regarding stage, location and histology of the tumour, as well as the surgical approach. Throughout all updates of this cohort, the same study protocol has been used to ensure uniformity. All investigators were kept blinded to the patients' survival time as the date of death was linked to the data only after the medical charts had been reviewed.

The Swedish Cancer Registry was used to identify all patients with a diagnosis of primary oesophageal cancer, defined by the diagnosis code 150 in ICD version 7 (ICD-7). All cancer diagnosis codes in this registry are translated to ICD-7 codes[17]. Only tumours of the main histological types, adenocarcinoma and squamous cell carcinoma, were included. The Swedish Cancer Registry was established in 1958 and it is compulsory by law for every healthcare provider (both clinicians and pathologists) to report all newly detected cancers. A validation study showed that the Swedish Cancer Registry is 98 per cent complete regarding the reporting of oesophageal cancer[18].

The National Patient Registry was used to identify all patients with oesophageal cancer who had undergone surgical resection, as well as to assess data on co-morbidities. This registry contains ICD codes for diagnoses, including co-morbidities, and surgical procedures on all in-hospital care in Sweden since 1987. All ICD codes are registered by the patient's physician or consultant, and always countersigned by the consultant, ensuring that correct diagnosis and surgical procedures are recorded. Regarding diagnosis codes, ICD-8 was used before 1987, ICD-9 between 1987 and 1996, and ICD-10 since 1997. All hospitals are obliged by law to report all inpatient care. The drop-out rate has been estimated at less than 1 per cent, and the overall positive predictive value of recorded diagnoses at 85–95 per cent[19]. Between 1987 and 1996, the sixth edition of the Swedish Classification of Operations was used to define oesophageal resection (2820, 2821, 2822, 2829)[20], and from 1997 the Swedish Classification of Operations and Major Procedures (JCC00, JCC10, JCC11, JCC20, JCC30, JCC96, JCC97)[21]. A recent validation study of oesophageal cancer surgery in 1987–2005 showed a positive predictive value of 99·6 per cent of operations recorded in the National Patient Registry compared with operation charts[22].

The Swedish Registry of the Total Population and the Swedish Causes of Death Registry were used to assess date and causes of death. The population registry is 100 per cent complete and accurate, and continuously updated regarding dates of death. All physicians have been obliged to report causes of death to the Causes of Death Registry since 1961, and the completeness is over 99 per cent[23]. Causes of death were used to analyse disease-specific mortality.

Co-morbidities

Co-morbidity was defined as any major chronic disease recorded before or at the time of surgery, and retrieved from the National Patient Registry. Co-morbidities were categorized according to the Charlson co-morbidity index[24]. Only a slight modification was made by excluding oesophageal cancer, gastric cancer and metastatic cancer because oesophageal cancer could be misclassified as gastric cancer before surgery and metastatic cancer could include oesophageal cancer. Transformation from ICD codes to Charlson co-morbidities was done retrospectively according to a well validated system[25–27]. If fewer than ten patients had a co-morbidity, either they were grouped

with a similar co-morbidity (for example leukaemia, malignant lymphoma and solid tumours comprised the cancer group) or a new group was created (including dementia, chronic kidney disease, hemiplegia and acquired immune deficiency syndrome (AIDS)), and used only as an adjustment variable in the analysis. Finally, patients were divided into 11 co-morbidity groups: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease (including chronic bronchitis, emphysema, chronic obstructive pulmonary disorder, asthma, bronchiectasis, pneumoconiosis and chronic lung manifestations caused by chemicals, gases, smoke, radiation or drugs), connective tissue disease, peptic ulcer disease, diabetes (uncomplicated and with end-organ damage), liver disease (mild to severe), other cancers (leukaemia, malignant lymphoma and solid tumours excluding oesophageal and gastric cancer) and others (dementia, chronic kidney disease, hemiplegia and AIDS). The Charlson co-morbidity index was calculated and patients were divided into three groups depending on the score: 0, 1, or 2 or more. This grouping is common practice in the surgical literature because patients with severe co-morbid conditions do not undergo high-risk surgical procedures such as oesophageal resection. The age-related Charlson co-morbidity score was calculated (by adding scores as follows: age less than 40 years, 0 points; 41–50 years, 1 point; 51–60 years, 2 points; 61–70 years; 3 points; over 70 years, 4 points) and divided into five groups: 0–1, 2–3, 4–5, 6–7, and 8 or more.

Outcome

The main outcome was all-cause mortality and three mortality time categories after surgery were analysed: from date of surgery to end of follow-up, from 91 days after surgery to 5 years, and from date of surgery to 90 days after surgery. The secondary outcome was disease-specific mortality, represented by patients with oesophageal cancer listed as a cause of death in the Swedish Causes of Death Registry. Disease-specific mortality was analysed using the first two categories outlined for all-cause mortality. Short-term mortality was not assessed as disease-specific death is rare within 90 days of surgery.

Statistical analysis

Differences in mortality between patients with and without co-morbidity were analysed using a Cox proportional hazard regression model, which provided hazard ratios (HRs) as an estimate of relative risk, with 95 per cent c.i. Reference categories were a Charlson score of 0 in the analyses of Charlson co-morbidity index, and lack of a specific co-morbidity in the analyses of specific co-morbidity groups. Adjustments were made for potential confounding using all seven established prognostic factors: age (less than 55, 55–65, 66–75 or over 75 years), sex (male or female), tumour stage (0–I, II, III or IV), tumour histology (adenocarcinoma or squamous cell carcinoma), neoadjuvant therapy (yes or no), surgical volume (cumulative volume fewer than 6, 6–15, 16–46 or more than 46 operations) and calendar period of surgery (1987–1990, 1991–1994, 1995–1999, 2000–2004 or 2005–2010). Stratified analyses were conducted for calendar time of surgery and histological type of cancer. The calendar periods 1987–1999 and 2000–2010 were analysed separately to take into account changes in surgical technique and treatment regimens. Stratification for histological type was done because adenocarcinoma and squamous cell carcinoma are increasingly being considered as separate diseases that might respond differently to therapy. An analysis with age-related Charlson co-morbidity score was conducted in addition to analysis using the standard Charlson co-morbidity score. Missing values were used as separate categories in the Cox regression model because a sensitivity analysis comparing these models with models excluding all missing data showed similar results. All statistical analyses were completed using the statistical software Stata® version 12 for Windows® (StataCorp, College Station, Texas, USA).

Results

Among 2195 patients recorded as having undergone oesophageal cancer surgery, 373 (17·0 per cent) were excluded owing to missing medical records or because they had another histological type of oesophageal cancer, leaving 1822 study patients. Characteristics of patients with and without co-morbidities are presented in *Table 1*. Patients aged 65 years or less had a lower proportion of co-morbidities and the proportion of patients with co-morbidity increased with calendar time period. Groups were similar regarding tumour stage, histology, treatment with neoadjuvant therapy and surgeon volume. However, when stratified by tumour stage, among those with stage 0–II disease, neoadjuvant therapy was administered less frequently to patients with a Charlson co-morbidity score of 1 (36·9 per cent) and 2 or more (40·4 per cent) than to those with a score of 0 (47·1 per cent). No such difference was seen among patients with tumour stage III–IV.

A total of 756 patients (41·5 per cent) had a Charlson score of at least 1 at baseline, and among these 375 (20·6 per cent) had a score of 1, 228 (12·5 per cent) a score of 2, 102 (5·6 per cent) a score of 3, 32 (1·8 per cent) a score of 4, 13 (0·7 per cent) a score of 5 and 6 (0·3 per cent) a

Table 1 Patient and tumour characteristics of 1822 patients with oesophageal cancer who had surgery with curative intent in Sweden during 1987–2010

	Total ($n = 1822$)	Charlson score 0 ($n = 1066$)	Charlson score 1 ($n = 375$)	Charlson score ≥ 2 ($n = 381$)
Age (years)				
< 55	258 (14·2)	189 (17·7)	34 (9·1)	35 (9·2)
55–65	659 (36·2)	406 (38·1)	135 (36·0)	118 (31·0)
66–75	685 (37·6)	353 (33·1)	153 (40·8)	179 (47·0)
> 75	220 (12·1)	118 (11·1)	53 (14·1)	49 (12·9)
Sex				
M	1362 (74·8)	785 (73·6)	292 (77·9)	285 (74·8)
F	460 (25·2)	281 (26·4)	83 (22·1)	96 (25·2)
Tumour stage				
0–I	380 (20·9)	208 (19·5)	82 (21·9)	90 (23·6)
II	603 (33·1)	336 (31·5)	132 (35·2)	135 (35·4)
III	445 (24·4)	273 (25·6)	79 (21·1)	93 (24·4)
IV	140 (7·7)	92 (8·6)	27 (7·2)	21 (5·5)
Missing*	254 (13·9)	157 (14·7)	55 (14·7)	42 (11·0)
Tumour histology				
Adenocarcinoma	715 (39·2)	386 (36·2)	163 (43·5)	166 (43·6)
Squamous cell carcinoma	1003 (55·0)	620 (58·2)	195 (52·0)	188 (49·3)
Missing*	104 (5·7)	60 (5·6)	17 (4·5)	27 (7·1)
Neoadjuvant therapy				
Yes	576 (31·6)	351 (32·9)	108 (28·8)	117 (30·7)
No	1165 (63·9)	662 (62·1)	254 (67·7)	249 (65·4)
Missing*	81 (4·4)	53 (5·0)	13 (3·5)	15 (3·9)
Surgeon volume				
< 6	490 (26·9)	311 (29·2)	100 (26·7)	79 (20·7)
6–15	396 (21·7)	229 (21·5)	87 (23·2)	80 (21·0)
16–46	443 (24·3)	248 (23·3)	90 (24·0)	105 (27·6)
> 46	433 (23·8)	239 (22·4)	88 (23·5)	106 (27·8)
Missing*	60 (3·3)	39 (3·7)	10 (2·7)	11 (2·9)
Time of surgery				
1987–1990	268 (14·7)	183 (17·2)	49 (13·1)	36 (9·4)
1991–1994	345 (18·9)	222 (20·8)	60 (16·0)	63 (16·5)
1995–1999	379 (20·8)	241 (22·6)	73 (19·5)	65 (17·1)
2000–2004	399 (21·9)	209 (19·6)	103 (27·5)	87 (22·8)
2005–2010	431 (23·7)	211 (19·8)	90 (24·0)	130 (34·1)

Values in parentheses are percentages. *Missing values of co-variables were missing at random and considered as separate groups.

score of at least 6. The most common co-morbidities were other cancers (10·5 per cent), chronic pulmonary disease (10·4 per cent) and myocardial infarction (8·2 per cent).

There were 1474 deaths (80·9 per cent) in the cohort during the entire study period; 1139 (77·3 per cent) of these occurred between 91 days and 5 years after surgery. Some 1176 patients (79·8 per cent of all deaths) died from a documented oesophageal cancer recurrence, and the vast majority of these disease-specific deaths (954, 81·1 per cent) occurred between 91 days and 5 years after surgery. The 90-day mortality rate was 11·4 per cent (208 patients).

Co-morbidity and risk of all-cause mortality

The median survival for patients without co-morbidity was 15·5 months, whereas it was 19·3 months for patients with a Charlson score of 1, and 14·6 months for those with a Charlson score of at least 2. The shortest median survival was found for patients with connective tissue disease (13·2 months), myocardial infarction (13·6 months) and congestive heart failure (13·6 months). Patients with a Charlson score of 2 or more had a 24 per cent increased risk of overall mortality (HR 1·24, 95 per cent c.i. 1·08 to 1·42) (*Table 2*). This pattern was strengthened by including the age component in the Charlson co-morbidity score; for patients with a score of 2–3, 4–5, 6–7 and 8 or more the HR for overall mortality was 1·46 (1·15 to 1·86), 1·70 (1·34 to 2·16), 1·89 (1·43 to 2·50) and 2·53 (1·64 to 3·90) respectively. The corresponding HRs for mortality between 91 days and 5 years were 1·44 (1·10 to 1·88), 1·49 (1·13 to 1·95), 1·45 (1·05 to 2·00) and 1·91 (1·15 to 3·18). Among specific groups of co-morbidity, statistically significantly increased HRs for overall mortality were seen for patients with a history of myocardial infarction (HR 1·23,

Table 2 Co-morbidities and risk of all-cause mortality after surgery with curative intent for oesophageal cancer in 1822 patients

		Hazard ratio†‡			
	No. of patients*	91 days to 5 years	≤ 90 days	> 90 days	Overall
Charlson score 1§	375 (20·6)	0·96 (0·83, 1·12)	1·13 (0·77, 1·68)	1·01 (0·87, 1·16)	1·04 (0·91, 1·18)
Charlson score ≥ 2§	381 (20·9)	1·13 (0·96, 1·32)	1·18 (0·77, 1·61)	1·19 (1·02, 1·38)	1·24 (1·08, 1·42)
Myocardial infarction	150 (8·2)	1·05 (0·83, 1·33)	1·87 (1·10, 3·17)	1·08 (0·87, 1·35)	1·23 (1·01, 1·49)
Congestive heart failure	88 (4·8)	1·16 (0·87, 1·54)	1·28 (0·70, 2·36)	1·21 (0·92, 1·58)	1·31 (1·04, 1·67)
Peripheral vascular disease	61 (3·3)	1·15 (0·89, 1·60)	1·24 (0·58, 2·63)	1·11 (0·80, 1·55)	1·18 (0·88, 1·59)
Cerebrovascular disease	109 (6·0)	1·08 (0·85, 1·38)	1·03 (0·54, 1·96)	1·08 (0·85, 1·37)	1·06 (0·85, 1·49)
Chronic pulmonary disease	189 (10·4)	0·86 (0·69, 1·06)	0·98 (0·60, 1·59)	0·85 (0·70, 1·04)	0·93 (0·78, 1·11)
Connective tissue disease	44 (2·4)	1·02 (0·69, 1·50)	1·01 (0·39, 2·62)	1·04 (0·72, 1·49)	1·06 (0·76, 1·49)
Peptic ulcer disease	88 (4·8)	0·90 (0·68, 1·19)	0·60 (0·29, 1·23)	0·90 (0·69, 1·17)	0·88 (0·69, 1·12)
Diabetes	135 (7·4)	1·05 (0·83, 1·33)	0·98 (0·53, 1·84)	1·07 (0·85, 1·33)	1·12 (0·91, 1·38)
Liver disease	43 (2·4)	1·02 (0·68, 1·51)	0·97 (0·43, 2·16)	1·10 (0·76, 1·59)	1·20 (0·86, 1·66)
Other cancers	192 (10·5)	1·11 (0·91, 1·35)	0·70 (0·41, 1·19)	1·18 (0·98, 1·41)	1·14 (0·96, 1·35)

Values in parentheses are *percentages and †95 per cent c.i. ‡Adjusted for age, sex, tumour stage, tumour histology, neoadjuvant therapy, surgeon volume and calendar period of surgery. Hazard ratios are shown for presence *versus* absence of specific co-morbidity, except §Charlson score 1 or ≥ 2 *versus* score 0.

Table 3 Co-morbidities and risk of disease-specific mortality after surgery with curative intent for oesophageal cancer in 1822 patients

		Hazard ratio†‡			
	No. of patients*	91 days to 5 years	≤ 90 days	> 90 days	Overall
Charlson score 1§	375 (20·6)	0·95 (0·81, 1·13)	1·02 (0·67, 1·56)	0·97 (0·82, 1·14)	1·00 (0·86, 1·16)
Charlson score ≥ 2§	381 (20·9)	1·12 (0·93, 1·33)	1·08 (0·74, 1·59)	1·15 (0·96, 1·36)	1·19 (1·02, 1·39)
Myocardial infarction	150 (8·2)	1·05 (0·81, 1·37)	1·62 (0·91, 2·90)	1·08 (0·83, 1·40)	1·22 (0·97, 1·53)
Congestive heart failure	88 (4·8)	1·02 (0·73, 1·43)	1·40 (0·73, 2·67)	1·02 (0·73, 1·42)	1·16 (0·88, 1·54)
Peripheral vascular disease	61 (3·3)	1·15 (0·80, 1·66)	1·31 (0·58, 2·91)	1·13 (0·78, 1·62)	1·22 (0·88, 1·68)
Cerebrovascular disease	109 (6·0)	1·03 (0·78, 1·36)	1·16 (0·58, 2·32)	1·00 (0·76, 1·32)	0·97 (0·76, 1·25)
Chronic pulmonary disease	189 (10·4)	0·89 (0·70, 1·13)	0·94 (0·55, 1·59)	0·89 (0·71, 1·12)	0·97 (0·79, 1·19)
Connective tissue disease	44 (2·4)	1·06 (0·69, 1·63)	1·02 (0·38, 2·73)	1·05 (0·69, 1·60)	1·12 (0·77, 1·64)
Peptic ulcer disease	88 (4·8)	0·85 (0·61, 1·19)	0·53 (0·24, 1·16)	0·87 (0·63, 1·19)	0·84 (0·63, 1·13)
Diabetes	135 (7·4)	1·03 (0·78, 1·35)	0·85 (0·41, 1·75)	1·03 (0·79, 1·34)	1·05 (0·82, 1·33)
Liver disease	43 (2·4)	0·81 (0·51, 1·31)	1·03 (0·43, 2·43)	0·88 (0·56, 1·38)	1·00 (0·68, 1·48)
Other cancers	192 (10·5)	1·13 (0·90, 1·41)	0·84 (0·49, 1·45)	1·17 (0·95, 1·46)	1·15 (0·94, 1·40)

Values in parentheses are *percentages and †95 per cent c.i. ‡Adjusted for age, sex, tumour stage, tumour histology, neoadjuvant therapy, surgeon volume and calendar period of surgery. Hazard ratios are shown for presence *versus* absence of specific co-morbidity, except §Charlson score 1 or ≥ 2 *versus* score 0.

1·01 to 1·49) and congestive heart failure (HR 1·31, 1·04 to 1·67). The HRs were slightly attenuated in the analyses of death between 91 days and 5 years, and after 90 days. Myocardial infarction was also associated with increased 90-day postoperative mortality (HR 1·87, 1·10 to 3·17). Patients with peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, diabetes, liver disease or other cancers did not have statistically significantly increased HRs for all-cause mortality, independent of the time of death (*Table 2*).

Co-morbidity and risk of disease-specific mortality

The HRs for disease-specific mortality were generally similar to those for all-cause mortality, but the positive associations were slightly attenuated (*Table 3*). Disease-specific mortality was increased among patients with a Charlson score of 2 or more (HR 1·19, 1·02 to 1·39). The HR among patients with history of myocardial infarction also indicated increased mortality of similar strength to the all-cause mortality (HR 1·22, 0·97 to 1·53), whereas the HR among patients with congestive heart failure was attenuated; however, neither of these HRs was statistically significant. No other statistically significant associations were identified, independent of time of death.

Co-morbidity and risk of death by calendar period

A Charlson score of at least 2 was associated with a significantly increased risk of overall all-cause mortality during 1987–1999 (HR 1·28, 1·06 to 1·53) but not in 2000–2010 (HR 1·22, 0·99 to 1·49) (*Table 4*). Among patients with a history of myocardial infarction, the HR was also higher during the earlier period (HR 1·38, 1·04 to 1·83), whereas it was higher among patients with congestive heart failure

Table 4 Co-morbidities and risk of all-cause mortality after surgery with curative intent for oesophageal cancer in 1822 patients, stratified by calendar period

		Hazard ratio†‡			
		91 days to 5 years		Overall	
	No. of patients*	1987–1999 ($n = 840$)	2000–2010 ($n = 774$)	1987–1999 ($n = 992$)	2000–2010 ($n = 830$)
Charlson score 1§	375 (20·6)	1·01 (0·82, 1·24)	0·91 (0·72, 1·16)	1·09 (0·92, 1·30)	0·96 (0·78, 1·19)
Charlson score ≥ 2§	381 (20·9)	1·18 (0·94, 1·47)	1·14 (0·91, 1·43)	1·28 (1·06, 1·53)	1·22 (0·99, 1·49)
Myocardial infarction	150 (8·2)	1·19 (0·83, 1·71)	1·06 (0·77, 1·46)	1·38 (1·04, 1·83)	1·17 (0·89, 1·55)
Congestive heart failure	88 (4·8)	1·23 (0·81, 1·86)	1·18 (0·80, 1·76)	1·29 (0·91, 1·84)	1·44 (1·04, 2·01)
Peripheral vascular disease	61 (3·3)	1·03 (0·64, 1·67)	1·20 (0·74, 1·94)	1·15 (0·77, 1·71)	1·16 (0·75, 1·80)
Cerebrovascular disease	109 (6·0)	1·14 (0·80, 1·62)	1·00 (0·70, 1·42)	1·06 (0·78, 1·44)	1·03 (0·75, 1·41)
Chronic pulmonary disease	189 (10·4)	1·08 (0·80, 1·46)	0·74 (0·55, 1·01)	1·08 (0·84, 1·39)	0·84 (0·65, 1·10)
Connective tissue disease	44 (2·4)	0·91 (0·55, 1·52)	1·24 (0·67, 2·30)	1·02 (0·67, 1·56)	1·18 (0·67, 2·08)
Peptic ulcer disease	88 (4·8)	0·80 (0·55, 1·16)	1·04 (0·67, 1·61)	0·80 (0·58, 1·09)	0·95 (0·63, 1·42)
Diabetes	135 (7·4)	1·02 (0·67, 1·55)	1·06 (0·78, 1·43)	1·10 (0·80, 1·53)	1·09 (0·83, 1·44)
Liver disease	43 (2·4)	1·00 (0·57, 1·74)	0·96 (0·54, 1·72)	1·00 (0·62, 1·63)	1·36 (0·85, 2·18)
Other cancers	192 (10·5)	1·13 (0·86, 1·49)	1·11 (0·83, 1·48)	1·17 (0·93, 1·47)	1·10 (0·84, 1·43)

Values in parentheses are *percentages and †95 per cent c.i. ‡Adjusted for age, sex, tumour stage, tumour histology, neoadjuvant therapy and surgeon volume. Hazard ratios are shown for presence *versus* absence of specific co-morbidity, except §Charlson score 1 or ≥ 2 *versus* score 0.

Table 5 Co-morbidities and risk of all-cause mortality after surgery with curative intent for oesophageal cancer in 1822 patients, stratified by tumour histology

		Hazard ratio†‡			
		91 days to 5 years		Overall	
	No. of patients*	Adenocarcinoma ($n = 645$)	Squamous cell carcinoma ($n = 872$)	Adenocarcinoma ($n = 715$)	Squamous cell carcinoma ($n = 1003$)
Charlson score 1§	375 (20·6)	1·00 (0·79, 1·28)	0·96 (0·78, 1·17)	1·06 (0·85, 1·32)	1·05 (0·88, 1·25)
Charlson score ≥ 2§	381 (20·9)	0·96 (0·74, 1·23)	1·29 (1·04, 1·60)	1·14 (0·91, 1·41)	1·37 (1·14, 1·65)
Myocardial infarction	150 (8·2)	1·07 (0·75, 1·52)	1·16 (0·82, 1·63)	1·28 (0·96, 1·73)	1·30 (0·99, 1·73)
Congestive heart failure	88 (4·8)	1·24 (0·83, 1·89)	0·93 (0·60, 1·43)	1·43 (1·01, 2·02)	1·12 (0·79, 1·60)
Peripheral vascular disease	61 (3·3)	1·71 (0·96, 3·07)	0·94 (0·61, 1·46)	1·58 (0·95, 2·65)	1·02 (0·70, 1·49)
Cerebrovascular disease	109 (6·0)	0·88 (0·62, 1·26)	1·31 (0·92, 1·86)	0·82 (0·60, 1·14)	1·35 (1·00, 1·83)
Chronic pulmonary disease	189 (10·4)	0·85 (0·60, 1·21)	0·88 (0·67, 1·17)	1·04 (0·78, 1·38)	0·89 (0·70, 1·14)
Connective tissue disease	44 (2·4)	1·20 (0·68, 2·13)	0·69 (0·38, 1·28)	1·40 (0·86, 2·28)	0·74 (0·44, 1·23)
Peptic ulcer disease	88 (4·8)	0·91 (0·58, 1·42)	0·83 (0·56, 1·23)	0·78 (0·52, 1·17)	0·91 (0·66, 1·25)
Diabetes	135 (7·4)	0·96 (0·70, 1·31)	1·20 (0·79, 1·83)	1·06 (0·81, 1·40)	1·24 (0·87, 1·77)
Liver disease	43 (2·4)	0·83 (0·38, 1·79)	1·21 (0·73, 2·00)	1·10 (0·60, 1·99)	1·41 (0·92, 2·16)
Other cancers	192 (10·5)	0·91 (0·65, 1·28)	1·38 (1·06, 1·79)	0·99 (0·74, 1·33)	1·36 (1·09, 1·71)

Values in parentheses are *percentages and †95 per cent c.i. ‡Adjusted for age, sex, tumour stage, neoadjuvant therapy, surgeon volume and calendar period of surgery. Hazard ratios are shown for presence *versus* absence of specific co-morbidity, except §Charlson score 1 or ≥ 2 *versus* score 0.

during the later period (HR 1·44, 1·04 to 2·01). Otherwise, the results were generally similar between the time intervals. The HR for mortality 91 days to 5 years after surgery was similar to that for overall mortality (*Table 4*), and the disease-specific mortality results were similar to the corresponding all-cause mortality results (data not shown).

Co-morbidity and risk of death by tumour histology

Patients with squamous cell carcinoma with a Charlson score of 2 or more had a greater risk of overall all-cause mortality (HR 1·37, 1·14 to 1·65) than patients with adenocarcinoma (HR 1·14, 0·91 to 1·41) (*Table 5*). The increased HRs following a diagnosis of myocardial infarction were similar for the two histological tumour types. Congestive heart failure was a slightly stronger risk factor for mortality in patients with adenocarcinoma (HR 1·43, 1·01 to 2·02) than among those with squamous cell carcinoma (HR 1·12, 0·79 to 1·60). Patients with squamous cell carcinoma also had increased overall all-cause mortality if they had had a diagnosis of cerebrovascular disease (HR 1·35, 1·00 to 1·83) or other cancers (HR 1·36, 1·09 to 1·71), which was not found for adenocarcinoma. Squamous cell

carcinoma was the predominant histological type among patients with a history of head and neck cancer (26 of 30), lung cancer (8 of 8) and breast or genital cancer in women (26 of 37). The HRs for mortality 91 days to 5 years after surgery were generally similar to those for overall mortality. The disease-specific mortality results were similar to the all-cause mortality results.

Discussion

This study suggests a worse prognosis (all-cause and disease-specific mortality) after attempted curative oesophageal cancer surgery in patients with pre-existing co-morbidities who have a Charlson score of 2 or more, and specifically in patients with a history of myocardial infarction, congestive heart failure or other cancers (the latter only among patients with squamous cell carcinoma). Other co-morbidities studied, that is peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, diabetes and liver disease, did not individually have a significant influence on prognosis.

The complete nationwide and population-based design, including all patients who had oesophageal cancer surgery between 1987 and 2010 in Sweden, is a methodological strength of the study that counteracts selection bias and facilitates generalizability. Additionally, the complete follow-up of all patients and the adjustment for potential confounding by all known prognostic factors are important features. The fact that the medical records were reviewed blinded to the patients' survival time prevents information bias. The variables of interest and outcomes were predefined, and followed well validated strategies, to reduce the risk of chance findings and misclassification. Despite a thorough assessment of clinical variables, a level of misclassification cannot be excluded, although this should be at random; it would only dilute risk estimates and not explain the positive associations in the present study. The registries used are recognized to be complete and well validated, although not 100 per cent perfect[18,22]. The retrospective design introduces a risk of misclassification and selection biases, but to minimize these risks the data were collected by researchers with no involvement with the hospitals or patients. The lack of detailed information on the severity of co-morbidities is a weakness. Patients selected for surgery, despite having co-morbidities, may have had better performance status than those with these co-morbidities who were not selected. However, the Charlson co-morbidity index has been developed to take the severity of co-morbidity into account by giving higher scores to more severe diseases, and the index has been tested and well validated to accomplish this[24,26,27]. Another potential drawback was the lack of data on adjuvant treatment, which might influence mortality. As postoperative treatment for oesophageal cancer is not recommended according to Swedish national clinical guidelines[28] and was used only rarely during the study interval, this is unlikely to have influenced the results. The long study period allows good statistical power, but might also have introduced bias owing to changes in treatment standards and surgical techniques. Calendar time of surgery was therefore adjusted for in the statistical model, along with a stratified analysis to evaluate effects of calendar period.

The proportion of patients with co-morbidity selected for surgery seemed to increase in recent times. This in turn might influence the selection of patients for surgery based on co-morbidities. This potential problem has been highlighted previously, indicating that decisions leading to patients with co-morbid conditions being less likely to receive surgical treatment than patients with minimal co-morbidity might not always be justified[29].

The present study indicated an increased risk of overall mortality in patients with a Charlson score of 2 or more, in line with some other investigations[3,4,15,30], including a Swedish study[3] based on an earlier version of this cohort. Another Swedish study[16], which used another database of 609 patients who underwent surgery for oesophageal or cardia cancer in 2001–2005, did not show increased mortality in patients with co-morbidities in general or in patients with cardiovascular disease, hypertension or pulmonary disease. That study collected information about co-morbidities from medical charts, whereas the present analysis used ICD codes in the National Patient Registry. The earlier study also included patients with cardia cancer, which was not the case here. Most importantly, the statistical power was substantially lower in the earlier study.

A history of myocardial infarction or congestive heart failure was associated with increased overall mortality after oesophageal cancer surgery in the present study. Similarly, a single-centre study[15] from the Netherlands including 1950 patients showed a 22 per cent increased disease-specific 5-year mortality rate among patients with ischaemic heart disease, hypertension and myocardial infarction. These two studies taken together indicate that even careful preoperative assessment and intervention might benefit patients with oesophageal cancer who have a history of cardiac disease.

The present study showed no reduced impact on prognosis related to diabetes, confirming the findings of a previous Swedish study[16]. Diabetes has been reported, however, to increase the risk of death in patients with cancer in general[31], and a single-centre study[32] from the USA, which

included 510 patients with oesophageal or cardia cancer, found a 30 per cent increased overall mortality among diabetic patients. Follow-up, however, was short in the latter study (data collected between 1996 and 2001 with follow-up until 2002), it included patients with cardia cancer and the single-centre design is not entirely comparable with a population-based study.

Patients with squamous cell carcinoma who had a history of another cancer had an increased risk of death after surgery, whereas those with adenocarcinoma did not. Both tobacco smoking and alcohol consumption are well established risk factors for oesophageal squamous cell carcinoma[2,33], and smoking-related cancers, specifically those of the head and neck, lung, and breast and genitalia in women, were over-represented in the squamous cell carcinoma group in the present sample. Tobacco smoking might be an explanation for this increased mortality. Similarly, the higher HR for mortality among patients with squamous cell carcinoma and a Charlson score of 2 or more, compared with patients with adenocarcinoma, might be explained by lifestyle factors (tobacco smoking, alcohol abuse, low socioeconomic status) that are known risk factors for both squamous cell cancer and mortality[33].

The stratified analysis for year of surgery revealed only a slightly worse prognosis for patients with a Charlson score of 2 or more operated on in 1987–1999, compared with 2000–2010, and for death between 91 days and 5 years there was no difference. The fact that more patients with co-morbidities underwent surgery during the later interval might neutralize the potential beneficial effect of better surgical strategies (such as centralization) and perioperative management.

This large and population-based cohort study with adjustment for all established prognostic factors indicated that patients with oesophageal cancer and a Charlson co-morbidity score of at least 2 or a history of myocardial infarction or congestive heart failure might need more evaluation and intervention before undergoing surgery, or may not benefit from surgery at all. Patients with lower Charlson scores or other co-morbidities should not be excluded from surgery merely on the presence of these co-morbidities.

Acknowledgements

The project was funded by the Swedish Research Council (SIMSAM) and the Swedish Cancer Society.
Disclosure: The authors declare no conflict of interest.

References

1 Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69–90.
2 Enzinger PC, Mayer RJ. Esophageal cancer. *N Engl J Med* 2003; **349**: 2241–2252.
3 Rouvelas I, Zeng W, Lindblad M, Viklund P, Ye W, Lagergren J. Survival after surgery for oesophageal cancer: a population-based study. *Lancet Oncol* 2005; **6**: 864–870.
4 Steyerberg EW, Neville BA, Koppert LB, Lemmens VE, Tilanus HW, Coebergh JW *et al*. Surgical mortality in patients with esophageal cancer: development and validation of a simple risk score. *J Clin Oncol* 2006; **24**: 4277–4284.
5 Stein HJ, Siewert JR. Improved prognosis of resected esophageal cancer. *World J Surg* 2004; **28**: 520–525.
6 Law S. Esophagectomy without mortality: what can surgeons do? *J Gastrointest Surg*; **14**(Suppl 1): S101–S107.
7 Ra J, Paulson EC, Kucharczuk J, Armstrong K, Wirtalla C, Rapaport-Kelz R *et al*. Postoperative mortality after esophagectomy for cancer: development of a preoperative risk prediction model. *Ann Surg Oncol* 2008; **15**: 1577–1584.
8 Lagergren J, Lagergren P. Oesophageal cancer. *BMJ* 2010; **341**: c6280.
9 D'Amico TA. Outcomes after surgery for esophageal cancer. *Gastrointest Cancer Res* 2007; **1**: 188–196.
10 Wu PC, Posner MC. The role of surgery in the management of oesophageal cancer. *Lancet Oncol* 2003; **4**: 481–488.
11 Atkins BZ, Shah AS, Hutcheson KA, Mangum JH, Pappas TN, Harpole DH Jr *et al*. Reducing hospital morbidity and mortality following esophagectomy. *Ann Thorac Surg* 2004; **78**: 1170–1176.
12 Sauvanet A, Mariette C, Thomas P, Lozac'h P, Segol P, Tiret E *et al*. Mortality and morbidity after resection for adenocarcinoma of the gastroesophageal junction: predictive factors. *J Am Coll Surg* 2005; **201**: 253–262.
13 McCulloch P, Ward J, Tekkis PP. Mortality and morbidity in gastro-oesophageal cancer surgery: initial results of ASCOT multicentre prospective cohort study. *BMJ* 2003; **327**: 1192–1197.
14 Bailey SH, Bull DA, Harpole DH, Rentz JJ, Neumayer LA, Pappas TN *et al*. Outcomes after esophagectomy: a ten-year prospective cohort. *Ann Thorac Surg* 2003; **75**: 217–222.
15 Cijs TM, Verhoef C, Steyerberg EW, Koppert LB, Tran TC, Wijnhoven BP *et al*. Outcome of esophagectomy for cancer in elderly patients. *Ann Thorac Surg* 2010; **90**: 900–907.
16 Backemar L, Djärv T, Wikman A, Johar A, Ross P, Lagergren P *et al*. The role of diabetes and other co-morbidities on survival after esophageal cancer surgery in a population-based study. *Am J Surg* 2013; **206**: 539–543.
17 National Board of Health and Welfare. *Cancer Incidence in Sweden 2010*; 2011. www.socialstyrelsen.se [accessed 30 April 2015].
18 Lindblad M, Ye W, Lindgren A, Lagergren J. Disparities in the classification of esophageal and cardia adenocarcinomas and their influence on reported incidence rates. *Ann Surg* 2006; **243**: 479–485.
19 Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C *et al*. External review and validation of the

Swedish national inpatient register. *BMC Public Health* 2011; **11**: 450.
20 National Board of Health and Welfare. *Klassifikation av operationer, sjätte upplagan*. National Board of Health and Welfare: Stockholm, 1993.
21 National Board of Health and Welfare. *Classification of Surgical Procedures*. National Board of Health and Welfare: Stockholm, 2004.
22 Lagergren K, Derogar M. Validation of oesophageal cancer surgery data in the Swedish Patient Registry. *Acta Oncol* 2012; **51**: 65–68.
23 *National Board of Health and Welfare: Causes of Death 2012*; 2013. www.socialstyrelsen.se [accessed 30 April 2015].
24 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40**: 373–383.
25 Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992; **45**: 613–619.
26 Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P *et al*. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol* 2011; **173**: 676–682.
27 Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC *et al*. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005; **43**: 1130–1139.
28 *Esofagus- och ventrikelcancer, Nationellt vårdprogram*; 2012. www.cancercentrum.se [accessed 30 April 2015].
29 Paulson EC, Ra J, Armstrong K, Wirtalla C, Spitz F, Kelz RR. Underuse of esophagectomy as treatment for resectable esophageal cancer. *Arch Surg* 2008; **143**: 1198–1203.
30 Pultrum BB, Bosch DJ, Nijsten MW, Rodgers MG, Groen H, Slaets JP *et al*. Extended esophagectomy in elderly patients with esophageal cancer: minor effect of age alone in determining the postoperative course and survival. *Ann Surg Oncol* 2010; **17**: 1572–1580.
31 Liu X, Ji J, Sundquist K, Sundquist J, Hemminki K. The impact of type 2 diabetes mellitus on cancer-specific survival: a follow-up study in Sweden. *Cancer* 2012; **118**: 1353–1361.
32 Rizk NP, Bach PB, Schrag D, Bains MS, Turnbull AD, Karpeh M *et al*. The impact of complications on outcomes after resection for esophageal and gastroesophageal junction carcinoma. *J Am Coll Surg* 2004; **198**: 42–50.
33 Secretan B, Straif K, Baan R, Grosse Y, El Ghissassi F, Bouvard V *et al*. A review of human carcinogens – Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. *Lancet Oncol* 2009; **10**: 1033–1034.

Snapshot quiz

Snapshot quiz 15/8

Answer: This woman presented with a 1-month history of abdominal swelling and discomfort. She was otherwise healthy with regular menstruation. CT revealed a large (32 × 24 × 13 cm) unilocular cystic intra-abdominal mass. Differentials included either a mesenteric, ovarian or peritoneal inclusion cyst. At laparoscopy, the cyst was arising from the right ovary. The cyst was decompressed laparoscopically and resected along with the right ovary. The specimen was retrieved via a Pfannenstiel incision.