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Reoperation after oesophageal cancer surgery in relation to long-term survival: a population-based cohort study

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ABSTRACT

Objectives: The influence of reoperation on longer-term prognosis is unknown. In this large population-based cohort study it was aimed to investigate the influence of a reoperation, following oesophageal cancer resection, on survival even after excluding the initial postoperative period.

Design: This was a nation-wide population-based retrospective cohort study

Setting: All hospitals performing oesophageal cancer resections during the study period (1987-2010) in Sweden

Participants: Patients operated for oesophageal cancer with curative intent in 1987-2010

Primary and secondary outcomes: Adjusted hazard ratio's (HR) of all cause, early- and late mortality up to 5-years after reoperation following oesophageal cancer resection.

Results: Some 2195 patients were identified as eligible in the study cohort. After exclusion of 373 patients (17%) where medical records were not available or where exposure data were missing, 1822 (83%) patients remained for final analysis. Among the 1484 patients who died during the entire study period, 1246 (84%) had documented tumour recurrence, which means that the all-cause mortality within 5 years closely mirrors disease-specific mortality. Compared to patients not undergoing reoperation, the 200 (11%) reoperated patients had a 27% increased hazard of death 3 months to 5 years after surgery (adjusted HR 1.27 95% CI 1.05-1.53), and the log-rank

test comparing the Kaplan Meier curves confirmed a worse prognosis (p <0.0001).

Conclusion: This large and population-based nationwide cohort study with adjustment for potential confounding factors revealed that reoperation was associated with a worse prognosis, even after the initial 3 months of the oesophageal cancer resection. This finding stresses the need to consider any actions that might prevent complications and reoperation.

STRENGTH AND LIMITATIONS OF THE STUDY

- The main strength of the study was the large cohort facilitated by the population-based design
- It was possible to adjust for important confounding factors
- Data on complications other than reoperation lacked
- The main limitation was the retrospective and observational design

INTRODUCTION

Despite recent developments in multimodal therapy, surgical tumour resection is still the mainstay of treatment for localized oesophageal cancer[1]. While postoperative mortality has decreased to less than 5% in recent years[2], oesophageal resection still carries a considerable risk for post-operative complications, some of which require reoperation[1 3 4]. Major postoperative complications are known to negatively influence short-term survival[2], but evidence of the influence of such complications on long-term survival is inconsistent[5-8]. A recent study from our group suggested that surgical complications after oesophageal cancer resection might be an independent predictor for a poorer long-term survival[9].

The potential role of reoperation is uncertain, but there are biological mechanisms by which reoperation might decrease long-term survival. The additional surgical trauma that further triggers an inflammatory response could pave the way for early recurrence from micro metastases[10], and the major surgical complications that cause the need for reoperation might directly facilitate tumour recurrence, e.g. anastomotic insufficiency might entail direct tumour spread[9 11].

Therefore, we hypothesised that reoperation within 30 days after initial oesophageal resection negatively influences long-term survival.

METHODS

Study design

This was a retrospective population-based cohort study. The study cohort has previously been presented in detail [12 13]. All patients having undergone oesophagectomy for oesophageal cancer during the period 1987-2010 in Sweden were included in the study. Eligible patients were followed up until death or end of the study (28th February 2012), whichever occurred first.

Study population

Oesophageal cancer patients were identified from the Swedish Cancer Registry, a registry with 98% nationwide coverage of oesophageal cancer patients[14 15]. Tumours of the gastric cardia were not included. Oesophageal cancer was defined by the diagnosis code 150.0, 150.8, and 150.9 in the 7th version of the International Classification of Diseases (ICD7). The identified patients were linked with the Swedish Patient Registry to include only those who underwent oesophageal resection in the final study cohort. Our group has recently reported that the Patient Registry has a positive predictive value of 99.6% for assessing oesophageal cancer resection[16]. Detailed information on tumour characteristics and surgical details were acquired through manual review of medical records from the operation charts and histopathology reports retrieved from all relevant hospitals throughout Sweden. The Patient Registry was used to obtain information on reoperations after the primary oesophageal resection and on comorbidities. Detailed information about indications for reoperation was not available. To calculate survival time after oesophagectomy, dates of death

were collected from the Swedish Causes of Death Registry. This register is complete and is updated continuously facilitating availability of accurate dates of death. The unique 10-digit Swedish personal identity number, assigned to every resident in Sweden since 1947[17], was used for linkage of individuals between registries and for identification of the patients' hospital records.

Study exposure and outcome

The exposure was defined as any open or minimally invasive reoperation within 30 days of initial oesophageal cancer resection. Exposure was defined according to the Classification of Surgical Procedures. More specifically, reoperation was categorised as: 1) Explorative laparotomy (ICD10 JAH00, JAK00), 2) explorative thoracotomy (ICD10 GAB13, GAB96, GAB10), 3) reoperation for bleeding (ICD10 JWE00, GWE00), 4) reoperation for anastomotic insufficiency (ICD10 JWF00, GWF00, DWF00, 5) reoperation for wound revision (ICD10 JWA00), or 6) reoperation for deep infection (ICD10 GWC00, GCW01, JWC00) (Table1).

The study outcome was all-cause early- and late mortality.

"Early postoperative mortality" was defined as any death occurring within 90 days of initial surgery, while "late mortality" was defined as any death between 90 days and 5 years of the primary resection. Since tumour recurrence is a less likely explanation for mortality 5 years and later after oesophageal cancer surgery, we decided to use 5 years as cut-off. The Regional Ethical Review Board in Stockholm, Sweden approved the study.

Statistical analysis

Survival was calculated using the Kaplan-Meier method, and differences in survival between the survival curves of patients with and without reoperation were evaluated using the log rank test. In a Cox proportional hazards regression model, hazard ratios (HR's) with 95% confidence intervals (CI's) were calculated, including adjustment for potential confounding factors in a multivariable model. In the Cox model the proportionality assumption was tested. The factors adjusted for were nine known prognostic factors. They were categorised as follows: 1) age (categorised into three groups: <65, 65-75, or >75 years), 2) sex, 3) comorbidity (including any of: hypertension, ischemic heart disease, cardiac failure, chronic obstructive pulmonary disease, asthma, diabetes, former cancer diagnosis, human immunodeficiency virus, liver disease and renal disease; and categorised into three groups: none, one, or two or more), 4) tumour stage (classified according to the 6th version of the Union for International Cancer Control -TNM classification; and categorised into four groups: 0-I, II, III, or IV), 5) histological type of tumour (categorised into two groups: squamous cell carcinoma or adenocarcinoma), 6) neoadjuvant therapy (yes or no), 7) surgical radicality (R0 or not R0), 8) hospital volume (<9 or ≥9 per year), and 9) calendar period (1987-1996 or 1996-2005).

Missing values in the covariates were treated as a separate group in the Cox regression model[18]. A sensitivity analysis was performed to compare the impact of categorising missing as a separate group against removing these missing values from the analysis.

All statistical analyses were done using STATA 11 for Mac (STATAcorp College Station, Texas).

RESULTS

Patients

Some 2195 patients were identified as eligible in the study cohort of oesophageal cancer patients who underwent resection in Sweden during the study period. After exclusion of 373 patients (17%) where medical records were not available or where exposure data were missing, 1822 (83%) patients remained for final analysis. Of these, 200 patients (11%) were exposed for reoperation (in total 248 reoperations) within 30 days of the primary oesophageal resection (Table 1).

Table 1. Categorisation of the 200 reoperations within 30 days after initial surgery in a cohort of 1822 patients undergoing oesophagectomy between 1987 and 2010 in Sweden, with follow-up until 28th February 2012.

Type of reoperation		Number (%)
Total number of reoperations		248 (100)
Explorative laparotomy		47 (19)
Explorative thoracotomy		11 (4)
Reoperation for bleeding		22 (9)
Reoperation for anastomotic insufficiency		43 (17)
	Laparotomy	3
	Thoracotomy	1
	Unknown/other	39
Reoperation for infection		8 (3)
Reoperation for wound revision		50 (20)
	Wound revision for bleeding	15
	Wound revision for infection	5
	Wound dehiscence	7
	Unknown	23
Other reoperations		75 (30)

There were no major differences between the groups with and without reoperation regarding the distribution of sex, age, comorbidity, tumour stage, tumour histology, neo-adjuvant therapy, hospital volume, or calendar period (Table 2). Among the 1484 patients who died during the entire study period, 1246 (84%) had documented tumour recurrence, which means that the all-cause mortality within 5 years closely mirrors disease-specific mortality. There were no missing values for reoperation (exposure) and missing values in covariates were missing at random. A sensitivity analysis was performed to compare the impact of categorising missing as a separate group against removing these missing values from the analysis, and the results were similar (data not shown). In the Cox model the proportionality assumption was tested and the model satisfied the assumption.

Table 2. Characteristics of 1822 patients undergoing oesophagectomy between 1987 and 2010 in Sweden, with follow-up until 28th February 2012

Characteristics	Number (%)		
	No reoperation	**Reoperation**	
Total	1622 (89)	200 (11)	P-value§
Sex			
Men	1211 (75)	151 (75)	0.8
Women	411 (25)	49 (25)	
Age			
≤64	754 (46)	93 (47)	0.9
65-75	615 (38)	78 (39)	
>75	253 (16)	29 (14)	
Comorbidity*			
None	832 (51)	107 (54)	0.8
1	542 (34)	63 (31)	
≥2	248 (15)	30 (15)	
Stage‡			
0-I	339 (20)	41 (20)	0.9
II	532(33)	71 (35)	
III	399 (25)	46 (23)	
IV	127(8)	13 (7)	
Missing†	225 (14)	29 (15)	
Histology			
Adenocarcinoma	645 (40)	70 (35)	0.09
Squamous cell carcinoma	880 (54)	123 (62)	
Missing†	97 (6)	7 (3)	
Neoadjuvant therapy			
None	677 (42)	85 (43)	0.4
Radiotherapy	154 (9)	26 (13)	
Chemoradiotherapy	302 (19)	35 (17)	
Missing†	489 (30)	54 (27)	
Radicality			
R0	1135 (69)	137 (68)	0.7
Not R0	251 (16)	30 (15)	
Missing †	236 (15)	33 (17)	
Hospital volume			
<9 per year	875 (54)	122 (61)	0.06
≥9 per year	747 (46)	78 (39)	
Calendar period			
1987-1990	234 (14)	34 (17)	0.2
1991-1994	302 (19)	43 (22)	
1995-1999	330 (20)	49 (25)	
2000-2005	382(24)	37 (19)	
2006-2010	374 (23)	37 (19)	

*Comorbidity included: hypertension, ischemic heart disease, cardiac failure, chronic obstructive pulmonary disease, asthma, diabetes, former cancer diagnosis, human immunodeficiency virus, liver disease, and renal disease.

† Missing values of covariates were missing at random and considered as a separate group.

‡Categorised according to the 6th version of the Union for International Cancer Control (UICC)-TNM classification.

§χ^2 of the difference between groups

Reoperation and risk of mortality

Among the 208 patients (11%) who died within 90 days of surgery, 54 (26%) underwent reoperation. Reoperation was a risk factor for 90-day mortality after adjustment for confounding factors (crude HR 3.17, adjusted HR 3.05, 95% CI 2.22-4.17). Among the 1276 (79%) patients who died between 90 days and 5 years after surgery 117 (10%) were reoperated. Among the 122 who died after 5 years of surgery 5 (4%) were reoperated. The log-rank test comparing the Kaplan-Meier survival curves of patients with and without reoperation between 90 days and 5 years after surgery revealed a statistically significantly increased mortality in the reoperated group (p<0.0001) (Figure 1, Table 3).

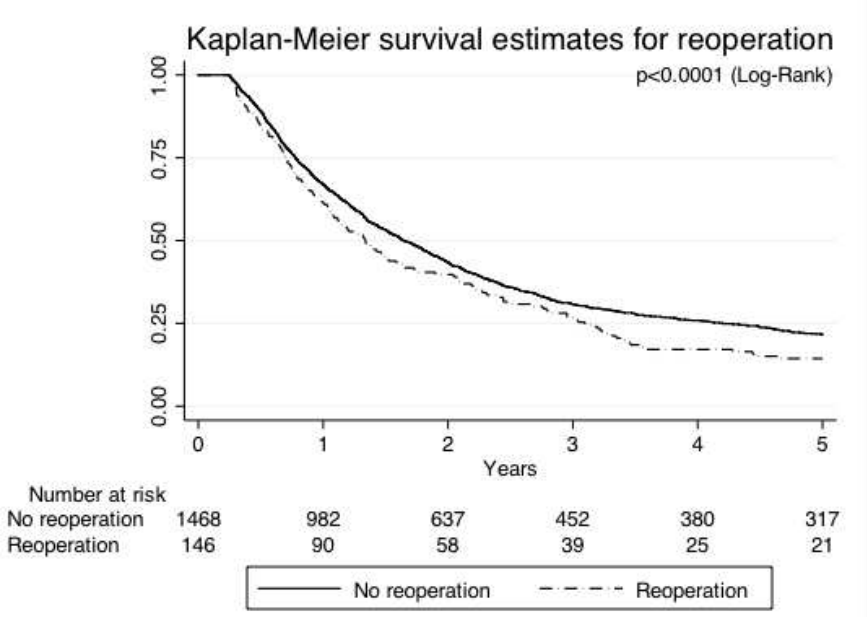

Figure 1. Kaplan-Meier survival curve for survival between 90 days and 5 years with respect to occurrence of reoperation among 1614 patients undergoing oesophageal cancer surgery in 1987-2010 in Sweden.

Table 3. Hazard ratios (HR) with 95% confidence intervals (95% CI) of mortality after oesophagectomy with respect to occurrence of reoperation, based on 1822 patients undergoing oesophageal cancer surgery in 1987-2012 in Sweden

Reoperation	Number of patients (%)	Number of events (%)‡	HR (95% CI)
All stages			
<90 days	1822 (100)	208 (11)	
Crude			3.17 (2.32-4.32)
Multivariable*,†			3.05 (2.22-4.17)
≥90 days – 5 years	1614 (89)	1276 (79)	
Crude			1.22 (1.02-1.47)
Multivariable*, †			1.27 (1.05-1.53)
>5 years	338 (19)	127 (37)	
Crude			0.51 (0.21-1.25)
Multivariable*,†			0.42 (0.17-1.07)

*Adjusted for sex, age, co-morbidities, tumour stage, histology, neoadjuvant therapy, radicality, hospital volume, and calendar period.

†Missing values of covariates were missing at random and considered as a separate group.

‡Event means death

As presented in Table 3, there was a 27% increased hazard of mortality during the period 90 days to 5 years after surgery after adjustment for all nine potential confounding factors (crude HR 1.22, adjusted HR 1.27, 95% CI 1.05-1.53). The risk of mortality after 5 years of surgery was not statistically significantly different in the two comparison groups (crude HR 0.51, adjusted HR 0.42 95% CI 0.17-1.07) (Table 3).

The proportional hazard assumption, tested using a non-zero slope, and time varying covariates were satisfied, and there were no statistically significant interaction effects with reoperation (data not shown).

DISCUSSION

This is, to the best of our knowledge, the first study addressing reoperation in relation to late mortality after primary oesophageal cancer resection, and it revealed an increased long-term mortality in patients that underwent reoperation compared to those who did not.

Among strengths of this study is the population-based design, where most patients who underwent oesophageal cancer surgery in Sweden during 1987-2010 were included. The follow-up for mortality was complete by virtue of the availability of personal identity numbers for Swedish residents, together with the fully complete Swedish Causes of Death Registry. Another major strength is the possibility to adjust for several known prognostic factors, which reduces the risk of confounding. Moreover, the exposure and outcome were predefined, which reduces the risk of chance findings and decreases the risk of systematic errors owing to misclassification. Some limitations of the study require a discussion. The retrospective clinical data collection imposes a risk of misclassification and selection bias. The researchers involved in gathering the clinical information had, however, no link with the participating hospitals and were not involved in the patient care, which decreases these risks. A risk of residual confounding by known prognostic factors or confounding by unknown factors cannot be excluded in observational research due to the lack of randomization. There was for example no access to information on pre-operative performance status and nutritional status, which might have influenced the results[19]. Another limitation was the lack of information on complications, and thus the indication for the reoperations. Moreover, information on causes of death was lacking, but the vast majority of patients

that die within 5 years after surgery for oesophageal cancer do die from recurrent disease[9], and almost all patients who died within 5 years of surgery in the current study had documented tumour recurrence. Finally, although the long study period offered good statistical power, it also entailed a risk of bias by changes in surgical techniques and standards in patients care over time. To counteract such effects, we adjusted all HRs for calendar period. The limited rate of exposure to reoperation still meant that the exposure could not be further subcategorised because of power issues.

The finding of the prognostic role of reoperations after excluding the initial postoperative period is a novel finding that should encourage further research. No previous studies have, to the best of our knowledge, addressed the influence of reoperations on long-term survival in oesophageal cancer patient. However, the main indication for reoperation is the occurrence of severe postoperative complications, and a few previous studies have assessed the role of such complications on long-term survival. These have provided conflicting results; some studies have reported a worse longer-term prognosis after surgical complications[7 9], medical complications[10], or concurrent surgical and medical complication[4], while others have not found any such effect[6 8].

One biological mechanism that might explain the decreased long-term survival after reoperation is that the additional surgical injury reduces the protection against seeding of tumour cells, including activation of natural killer cells and other anti-carcinogenic factors[20]. Furthermore, it is possible that additional surgery triggers an elevated inflammatory response that might in turn stimulate growth of micro-tumours and induce tumour recurrence and

death from recurrence[10]. Another potential mechanism considers certain complications. There is, for example, some evidence that anastomotic insufficiency entails direct tumour spread and seeding of remaining viable tumour cells in colon cancer patients[11 21].

In conclusion, this nationwide and population-based cohort study with adjustment for several potential confounding factors indicates that reoperation is associated with an increased hazard of mortality even after the initial 3 months of the oesophageal cancer resection. This finding warrants more research, but further stresses the need to consider any actions that might prevent complications requiring reoperation after the primary surgery in oesophageal cancer patients.

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Authors' individual contribution:

Dr M. van der Schaaf and J. Lagergren, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. ***Study concept and design***: M. van der Schaaf, J. Lagergren, P. Lagergren, M. Rutegård, M. Derogar. ***Acquisition of data***: P. Lagergren, J. Lagergen, M. van der Schaaf, M. Derogar. ***Analysis and interpretation of data*:** M. van der Schaaf, J. Lagergren, A. Johar. ***Drafting of the manuscript***: M. van der Schaaf, J. Lagergren. ***Critical revision of the manuscript for important intellectual content*:** J. Gossage, R. Mason, M. Rutegård, P. Lagergren. ***Statistical analysis***: A. Johar, M. Derogar. ***Obtained funding*:** J. Lagergren, P. Lagergren.

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Section/Topic	#	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
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
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	6-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
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	8,11,12
Study size	10	Explain how the study size was arrived at	9
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	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	-
		(*e*) Describe any sensitivity analyses	8
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	9
		(c) Consider use of a flow diagram	17
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential	9

		confounders	
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	9
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	10,21
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-13
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	13

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

*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.

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Reoperation after oesophageal cancer surgery in relation to long-term survival: a population-based cohort study

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ABSTRACT

Objectives: The influence of reoperation on longer-term prognosis is unknown. In this large population-based cohort study it was aimed to investigate the influence of a reoperation within 30 days of oesophageal cancer resection, on survival even after excluding the initial postoperative period.

Design*:* This was a nation-wide population-based retrospective cohort study

Setting*:* All hospitals performing oesophageal cancer resections during the study period (1987-2010) in Sweden

Participants*:* Patients operated for oesophageal cancer with curative intent in 1987-2010

Primary and secondary outcomes*:* Adjusted hazard ratio's (HR) of all cause, early- and late mortality up to 5-years after reoperation following oesophageal cancer resection.

Results: Among 1822 included patients, the 200 (11%) who were reoperated had a 27% increased HR of all-cause mortality (adjusted HR 1.27, 95% CI 1.05-1.53) and 28% increased HR of disease-specific mortality (adjusted HR 1.28, 95% CI 1.04-1.59), compared to those not reoperated. Reoperation for anastomotic insufficiency in particular was followed by an increased mortality (adjusted HR 1.82, 95% CI 1.19-2.76).

Conclusion: This large and population-based nationwide cohort study shows that reoperation within 30 days after primary oesophageal resection was

associated with a increased mortality, even after excluding the initial 3 months after surgery. This finding stresses the need to consider any actions that might prevent complications and reoperation after oesophageal cancer resection.

STRENGTH AND LIMITATIONS OF THE STUDY

- The study had a population-based cohort design
- It was possible to adjust for several confounding factors through comprehensive data collection from medical records and registries
- Data on complications other than reoperation were missing
- The retrospective design was a limitation

INTRODUCTION

Despite recent developments in multimodal therapy, surgical tumour resection is still the mainstay of treatment for localized oesophageal cancer[1]. While postoperative mortality has decreased to less than 5% in recent years[2], oesophageal resection still carries a considerable risk for post-operative complications, some of which require reoperation[1 3 4]. Major postoperative complications are known to negatively influence short-term survival[2], but evidence of the influence of such complications on long-term survival is inconsistent[5-8]. A recent study from our group suggested that surgical complications after oesophageal cancer resection might be an independent predictor for a poorer long-term survival[9]. Any potential effect of reoperation in lowering long-term survival after oesophagectomy could be mediated by several biological mechanisms, e.g. the additional surgical trauma could further trigger an inflammatory response that could lower the efficacy of bodily defence mechanisms, including destruction and removal of circulating tumour cells, and thus pave the way for early recurrence [10], and the major surgical complications that cause the need for reoperation might directly facilitate tumour recurrence, e.g. anastomotic insufficiency might entail direct tumour spread [9 11]. Therefore, we hypothesised that reoperation within 30 days after initial oesophageal resection negatively influences long-term survival.

METHODS

Study design

This was a retrospective population-based cohort study. The study cohort has previously been presented in detail [12 13]. All patients having undergone oesophagectomy for oesophageal cancer during the period 1987-2010 in Sweden were included in the study. Eligible patients were followed up until death or end of the study (28th February 2012), whichever occurred first.

Study population

Oesophageal cancer patients were identified from the Swedish Cancer Registry, a registry with 98% nationwide coverage of oesophageal cancer patients[14 15]. Tumours of the gastric cardia were not included. Oesophageal cancer was defined by the diagnosis code 150.0, 150.8, and 150.9 in the 7th version of the International Classification of Diseases (ICD7). The identified patients were linked with the Swedish Patient Registry to include only those who underwent oesophageal resection in the final study cohort. Our group has recently reported that the Patient Registry has a positive predictive value of 99.6% for assessing oesophageal cancer resection[16]. Detailed information on tumour characteristics and surgical details were acquired through manual scrutiny of medical records from the operation charts and histopathology reports, with accompanying referral notes, retrieved from all relevant hospitals throughout Sweden [12 13]. One reviewer, who was kept blinded for the study outcome to ensure objectivity, reviewed all histopathological reports according to a predefined protocol to ensure uniformity. The accuracy of the histopathological review was assessed by two

researchers who independently reviewed 100 patient records, showing high accuracy (>90% concordance).[13] The Patient Registry was used to obtain information on reoperations after the primary oesophageal resection and on comorbidities. Detailed information about indications for reoperation was not available. To calculate survival time after oesophagectomy, dates of death were collected from the Swedish Causes of Death Registry. This register is complete and is updated continuously facilitating availability of accurate dates of death. The unique 10-digit Swedish personal identity number, assigned to every resident in Sweden since 1947[17], was used for linkage of individuals between registries and for identification of the patients' hospital records.

Study exposure and outcome

The exposure was defined as any open or minimally invasive reoperation within 30 days of initial oesophageal cancer resection. Exposure was defined according to the Classification of Surgical Procedures. More specifically, reoperation was categorised as: 1) Explorative laparotomy (ICD10 JAH00, JAK00), 2) explorative thoracotomy (ICD10 GAB13, GAB96, GAB10), 3) reoperation for bleeding (ICD10 JWE00, GWE00), 4) reoperation for anastomotic insufficiency (ICD10 JWF00, GWF00, DWF00, 5) reoperation for wound revision (ICD10 JWA00), or 6) reoperation for deep infection (ICD10 GWC00, GCW01, JWC00) (Table1).

The study outcomes were was all-cause early-, late- and disease-specific mortality. "Early postoperative mortality" was defined as any death occurring within 90 days of initial surgery, while "late mortality" was defined as any death between 90 days and 5 years of the primary resection. "Disease

specific mortality" was defined as death of tumour recurrence occurring between 90-days and 5 years of surgery. If a cause of death included oesophageal cancer (diagnosis codes 150 according to ICD7) in the Swedish Causes of Death Registry, we assumed that patients died of tumour recurrence. We also analysed the impact of each of the most common types of reoperations on mortality between 90 days and 5-years of surgery in subgroup analyses. Since tumour recurrence is a less likely explanation for mortality 5 years and later after oesophageal cancer surgery, we decided to use 5 years as cut-off. The Regional Ethical Review Board in Stockholm, Sweden approved the study.

Statistical analysis

Survival was calculated using the Kaplan-Meier method, and differences in survival between the survival curves of patients with and without reoperation were evaluated using the log rank test. In a Cox proportional hazards regression model, hazard ratios (HR's) with 95% confidence intervals (CI's) were calculated, including adjustment for potential confounding factors in a multivariable model. In the Cox model the proportionality assumption was tested. The factors adjusted for were nine known prognostic factors. They were categorised as follows: 1) age (categorised into three groups: <65, 65-75, or >75 years), 2) sex, 3) comorbidity (including any of: hypertension, ischemic heart disease, cardiac failure, chronic obstructive pulmonary disease, asthma, diabetes, former cancer diagnosis, human immunodeficiency virus, liver disease and renal disease; and categorised into three groups: none, one, or two or more), 4) tumour stage (classified according to the 6th version of the

Union for International Cancer Control -TNM classification; and categorised into four groups: 0-I, II, III, or IV), 5) histological type of tumour (categorised into two groups: squamous cell carcinoma or adenocarcinoma), 6) neoadjuvant therapy (yes or no) data on the type of neo-adjuvant therapy used, i.e. chemoradiotherapy or chemotherapy, was not available, but in Sweden, the use of chemoradiotherapy has dominated whenever neo-adjuvant therapy has been used, 7) surgical radicality (R0 or not R0), 8) surgeon volume (<9 or ≥9 per year) To avoid selecting a suitable cut-off for surgeon annual volume, we simply chose to use the median as the cut-off, and 9) calendar period (1987-1996 or 1996-2005). We also considered lymph node harvest as a potential confounder, but this variable did not significantly influence the results (Chi-square p-value 0.687), and since there was a substantial rate of missing data on lymph node harvest, we decided not to include this variable in the final multivariable model. Information on comorbidities was obtained from the Swedish Patient Register, information on tumour stage and histological type of tumour, surgical radicality and neo-adjuvant treatment was extracted from histopathological records and accompanying referral notes. [16] Missing values in the covariates were treated as a separate group in the Cox regression model[18]. A sensitivity analysis was performed to compare the impact of categorising missing as a separate group against removing these missing values from the analysis. All statistical analyses were done using STATA 11 for Mac (STATAcorp College Station, Texas).

RESULTS

Patients

Some 2195 patients were identified as eligible in the study cohort of oesophageal cancer patients who underwent resection in Sweden during the study period. After exclusion of 373 patients (17%) where medical records were not available or where exposure data were missing, 1822 (83%) patients remained for final analysis. Of these, 200 patients (11%) were exposed for reoperation (in total 248 reoperations) within 30 days of the primary oesophageal resection (Table 1).

Table 1. Categorisation of the 248 reoperations within 30 days after initial surgery in a cohort of 1822 patients undergoing oesophagectomy between 1987 and 2010 in Sweden, with follow-up until 28th February 2012.

Type of reoperation		Number (%)
Total number of reoperations		248 (100)
Explorative laparotomy		47 (19)
Explorative thoracotomy		11 (4)
Reoperation for bleeding		22 (9)
Reoperation for anastomotic insufficiency		43 (17)
	Laparotomy	3
	Thoracotomy	1
	Unknown/other	39
Reoperation for infection		8 (3)
Reoperation for wound revision		50 (20)
	Wound revision for bleeding	15
	Wound revision for infection	5
	Wound dehiscence	7
	Unknown	23
Other reoperations		75 (30)

There were no major differences between the groups with and without reoperation regarding the distribution of sex, age, comorbidity, tumour stage, tumour histology, neo-adjuvant therapy, hospital volume, or calendar period (Table 2). Among the 1484 patients who died during the entire study period, 1246 (84%) had documented tumour recurrence, which means that the all-cause mortality within 5 years closely mirrors disease-specific mortality. There were no missing values for reoperation (exposure) and missing values in covariates were missing at random. A sensitivity analysis was performed to compare the impact of categorising missing as a separate group against removing these missing values from the analysis, and the results were similar (data not shown). In the Cox model the proportionality assumption was tested and the model satisfied the assumption.

Table 2. Characteristics of 1822 patients undergoing oesophagectomy between 1987 and 2010 in Sweden, with follow-up until 28th February 2012

Characteristics	Number (%)		
	No reoperation	**Reoperation**	
Total	1622 (89)	200 (11)	P-value§
Sex			
Men	1211 (75)	151 (75)	0.8
Women	411 (25)	49 (25)	
Age			
≤64	754 (46)	93 (47)	0.9
65-75	615 (38)	78 (39)	
>75	253 (16)	29 (14)	
Comorbidity*			
None	832 (51)	107 (54)	0.8
1	542 (34)	63 (31)	
≥2	248 (15)	30 (15)	
Stage‡			
0-I	339 (20)	41 (20)	0.9
II	532(33)	71 (35)	
III	399 (25)	46 (23)	
IV	127(8)	13 (7)	
Missing†	225 (14)	29 (15)	
Histology			
Adenocarcinoma	645 (40)	70 (35)	0.09
Squamous cell carcinoma	880 (54)	123 (62)	
Missing†	97 (6)	7 (3)	
Neoadjuvant therapy			
None	677 (42)	85 (43)	0.4
Radiotherapy	154 (9)	26 (13)	
Chemoradiotherapy	302 (19)	35 (17)	
Missing†	489 (30)	54 (27)	
Radicality			
R0	1135 (69)	137 (68)	0.7
Not R0	251 (16)	30 (15)	
Missing †	236 (15)	33 (17)	
Surgeon volume			
<9 per year	875 (54)	122 (61)	0.06
≥9 per year	747 (46)	78 (39)	
Calendar period			
1987-1990	234 (14)	34 (17)	0.2
1991-1994	302 (19)	43 (22)	
1995-1999	330 (20)	49 (25)	
2000-2005	382(24)	37 (19)	
2006-2010	374 (23)	37 (19)	

*Comorbidity included: hypertension, ischemic heart disease, cardiac failure, chronic obstructive pulmonary disease, asthma, diabetes, former cancer diagnosis, human immunodeficiency virus, liver disease, and renal disease.

† Missing values of covariates were missing at random and considered as a separate group.

‡Categorised according to the 6th version of the Union for International Cancer Control (UICC)-TNM classification.

§Chi-square of the difference between groups

Reoperation and risk of mortality

Among the 208 patients (11%) who died within 90 days of surgery, 54 (26%) underwent reoperation. Reoperation was a risk factor for 90-day mortality after adjustment for confounding factors (HR 3.05, 95% CI 2.22-4.17). Among the 1276 (79%) patients who died between 90 days and 5 years after surgery 117 (10%) were reoperated. Among the 122 who died after 5 years of surgery 5 (4%) were reoperated. The log-rank test comparing the Kaplan-Meier survival curves of patients with and without reoperation between 90 days and 5 years after surgery revealed a statistically significantly increased mortality in the reoperated group ($p<0.0001$) (Figure 1, Table 3).

Table 3. Hazard ratios (HR) with 95% confidence intervals (95% CI) of mortality after oesophagectomy with respect to occurrence of reoperation, based on 1822 patients undergoing oesophageal cancer surgery in 1987-2012 in Sweden

Reoperation	Number of patients (%)	Number of events (%)‡	HR (95% CI)
All stages			
<90 days	1822 (100)	208 (11)	
Crude			3.17 (2.32-4.32)
Multivariable*,†			3.05 (2.22-4.17)
≥90 days – 5 years	1614 (89)	1276 (79)	
Crude			1.22 (1.02-1.47)
Multivariable*, †			1.27 (1.05-1.53)
≥90 days – 5 years disease specific	1292 (71)	954 (74)	
Crude			1.26 (1.03-1.57)
Multivariable*, †			1.28 (1.04-1.59)

*Adjusted for sex, age, co-morbidities, tumour stage, histology, neoadjuvant therapy, radicality, surgeon volume, and calendar period.

†Missing values of covariates were missing at random and considered as a separate group.

‡Event means death

As presented in Table 3, there was a 27% increased hazard of mortality during the period 90 days to 5 years after surgery after adjustment for all nine potential confounding factors (crude HR 1.22, adjusted HR 1.27, 95% CI 1.05-1.53) (Table 3). During the follow-up period, 954 (74%) patients died of reported tumour recurrence. The disease-specific mortality within 90 days and 5 years of surgery was 28% increased among patients who were reoperated (adjusted HR 1.28, 95% CI 1.04-1.59) (Table 3). The proportional hazard assumption, tested using a non-zero slope, and time varying covariates were satisfied, and there were no statistically significant interaction effects with reoperation (data not shown).

Reoperation and risk of mortality- subgroup analyses of most common reoperations

In a subgroup analysis of the 3 most common types of reoperations, i.e. exploratory laparotomy, reoperation for anastomotic insufficiency and wound revision, the point HRs were increased for each type of reoperation (Table 4), and patients reoperated for anastomotic insufficiency in particular had a statistically significantly increased hazard of mortality (adjusted HR 1.82, 95% CI 1.19-2.76).

Table 4. Hazard ratios (HR) with 95% confidence intervals (95% CI) of mortality between 90 days and 5-years in a subgroup analyses of the most common types of reoperations after oesophagectomy, based on 1822 patients undergoing oesophageal cancer surgery in 1987-2012 in Sweden

Type of reoperation	Number of patients (%)	HR (95% CI) [*, †]

Exploratory laparotomy	47 (19)	1.17 (0.82-1.67)
Reoperation for anastomotic insufficiency	43 (17)	1.82 (1.19-2.76)
Wound revision	50 (20)	1.32 (0.87-2.00)

Adjusted for sex, age, co-morbidities, tumour stage, histology, neoadjuvant therapy, radicality, surgeon volume, and calendar period.

[†]Missing values of covariates were missing at random and considered as a separate group.

DISCUSSION

This is, to the best of our knowledge, the first study addressing reoperation in relation to late mortality after primary oesophageal cancer resection, and it revealed an increased long-term all-cause and disease-specific mortality in patients that underwent reoperation compared to those who did not. Patients that were reoperation due to anastomotic insufficiency experienced a particularly high hazard of mortality.

Among strengths of this study is the population-based design, where most patients who underwent oesophageal cancer surgery in Sweden during 1987-2010 were included. The follow-up for mortality was complete by virtue of the availability of personal identity numbers for Swedish residents, together with the fully complete Swedish Causes of Death Registry. Another major strength is the possibility to adjust for several known prognostic factors, which reduces the risk of confounding. Moreover, the exposure and outcome were predefined, which reduces the risk of chance findings and decreases the risk of systematic errors owing to misclassification. Some limitations of the study require a discussion. The retrospective clinical data collection imposes a risk of misclassification and selection bias. The researchers involved in gathering the clinical information had, however, no link with the participating hospitals and were not involved in the patient care, which decreases these risks. A risk of residual confounding by known prognostic factors or confounding by unknown factors cannot be excluded in observational research due to the lack of randomization. There was for example no access to information on pre-operative performance status and nutritional status, which might have influenced the results[19]. Another limitation was the lack of information on

complications, and thus the indication for the reoperations. Although the long study period offered good statistical power, it also entailed a risk of bias by changes in surgical techniques and standards in patients care over time. To counteract such effects, we adjusted all HRs for calendar period. The limited rate of exposure to reoperation still meant that the exposure could not be further subcategorised because of power issues. Finally, the use of a cut-off of 30 days of surgery for assessing re-operation might result in missing of later re-operations. However, we decided before the study was initiated to use a cut-off that was likely to be directly associated with the oesophagectomy, but yet not too short. Since there is no agreed upon cut-off for capturing early reoperations associated with surgery, we instead use a commonly used cut-off for short-term mortality, which is traditionally 30 days.

The finding of the prognostic role of reoperations after excluding the initial postoperative period is a novel finding that should encourage further research. It stresses the need for preventive measures to reduce the need for reoperation. In this population the 3 most common performed types of reoperation were explorative laparotomy (19%), re-operation for anastomotic leak (17%) and wound revision (20%). The results of the subgroup analyses showed that especially patients undergoing reoperation for anastomotic insufficiency had an increased risk of mortality. There is some evidence that anastomotic insufficiency entails direct tumour spread and seeding of remaining viable tumour cells in colon cancer patients[11 20]. This might explain the higher mortality in patients with reoperation for anastomotic insufficiency.

Several studies have showed that a higher surgeon or hospital volume reduces post-operative mortality and morbidity. [12 21-24] High volume surgery is facilitated by centralisation of the care for oesophageal cancer patients. Centralisation might be an effective measure for prevention of severe post-operative complications. A recent study showed that patients with comorbidity that compromises the cardiovascular status leading to a compromised perfusion of organs (e.g. hypertension, diabetes, congestive heart failure and renal failure), have a higher risk of anastomotic leak. This finding indicates that pre-operative optimisation of the cardiovascular status might also decrease the risk of severe complications requiring reoperation.[25] No previous studies have, to the best of our knowledge, addressed the influence of reoperations on long-term survival in oesophageal cancer patient. However, the main indication for reoperation is the occurrence of severe postoperative complications, and a few previous studies have assessed the role of such complications on long-term survival. These have provided conflicting results; some studies have reported a worse longer-term prognosis after surgical complications[7 9], medical complications[10], or concurrent surgical and medical complication[4], while others have not found any such effect[6 8]. These differences might be due to differences in classification of the severity of the complications and missing information on interventions.

One biological mechanism that might explain the decreased long-term survival after reoperation is that the additional surgical injury reduces the protection against seeding of tumour cells, including activation of natural killer cells and other anti-carcinogenic factors[26]. Furthermore, it is possible that

additional surgery triggers an elevated inflammatory response that might in turn stimulate growth of micro-tumours and induce tumour recurrence and death from recurrence[10]. Another potential mechanism considers certain complications. Finally, blood transfusion has been linked with a worse long-term mortality and increased cancer recurrence in different types of cancer [27-30]. Unfortunately, we did not have information on blood transfusion in this study, but it can be assumed that patients returning to theatre are more likely to receive blood transfusion, and speculatively, blood transfusion may be a mechanism that contributes to the main finding of this study.

In conclusion, this nationwide and population-based cohort study with adjustment for several potential confounding factors indicates that reoperation is associated with an increased hazard of mortality even after the initial 3 months of the oesophageal cancer resection. This finding warrants more research, but further stresses the need to consider any actions that might prevent complications requiring reoperation after the primary surgery in oesophageal cancer patients.

Figure legend:

Figure 1. Kaplan-Meier survival curve for survival between 90 days and 5 years with respect to occurrence of reoperation among 1614 patients undergoing oesophageal cancer surgery in 1987-2010 in Sweden.

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Authors' individual contribution:

Dr M. van der Schaaf and J. Lagergren, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. ***Study concept and design***: M. van der Schaaf, J. Lagergren, P. Lagergren, M. Rutegård, M. Derogar. ***Acquisition of data***: P. Lagergren, J. Lagergen, M. van der Schaaf, M. Derogar. ***Analysis and interpretation of data*****:** M. van der Schaaf, J. Lagergren, A. Johar. ***Drafting of the manuscript***: M. van der Schaaf, J. Lagergren. ***Critical revision of the manuscript for important intellectual content*****:** J. Gossage, R. Mason, M. Rutegård, P. Lagergren. ***Statistical analysis***: A. Johar, M. Derogar. ***Obtained funding*****:** J. Lagergren, P. Lagergren.

Data sharing:

"Statistical codes and dataset are available from the primary investigator Jesper Lagergren (jesper.lagergren@ki.se), at Upper GI Research Group, Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm Sweden, who will provide a permanent and citable home for the dataset"

Competing Interests:

None

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Reoperation after oesophageal cancer surgery in relation to long-term survival: a population-based cohort study

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ABSTRACT

Objectives: The influence of reoperation on longer-term prognosis is unknown. In this large population-based cohort study it was aimed to investigate the influence of a reoperation within 30 days of oesophageal cancer resection, on survival even after excluding the initial postoperative period.

Design*:* This was a nation-wide population-based retrospective cohort study

Setting*:* All hospitals performing oesophageal cancer resections during the study period (1987-2010) in Sweden

Participants*:* Patients operated for oesophageal cancer with curative intent in 1987-2010

Primary and secondary outcomes*:* Adjusted hazard ratio's (HR) of all cause, early- and late mortality up to 5-years after reoperation following oesophageal cancer resection.

Results: Among 1822 included patients, the 200 (11%) who were reoperated had a 27% increased HR of all-cause mortality (adjusted HR 1.27, 95% CI 1.05-1.53) and 28% increased HR of disease-specific mortality (adjusted HR 1.28, 95% CI 1.04-1.59), compared to those not reoperated. Reoperation for anastomotic insufficiency in particular was followed by an increased mortality (adjusted HR 1.82, 95% CI 1.19-2.76).

Conclusion: This large and population-based nationwide cohort study shows that reoperation within 30 days after primary oesophageal resection was

associated with a increased mortality, even after excluding the initial 3 months after surgery. This finding stresses the need to consider any actions that might prevent complications and reoperation after oesophageal cancer resection.

STRENGTH AND LIMITATIONS OF THE STUDY

- The study had a population-based cohort design
- It was possible to adjust for several confounding factors through comprehensive data collection from medical records and registries
- Data on complications other than reoperation were missing
- The retrospective design was a limitation

INTRODUCTION

Despite recent developments in multimodal therapy, surgical tumour resection is still the mainstay of treatment for localized oesophageal cancer[1]. While postoperative mortality has decreased to less than 5% in recent years[2], oesophageal resection still carries a considerable risk for post-operative complications, some of which require reoperation[1 3 4]. Major postoperative complications are known to negatively influence short-term survival[2], but evidence of the influence of such complications on long-term survival is inconsistent[5-8]. A recent study from our group suggested that surgical complications after oesophageal cancer resection might be an independent predictor for a poorer long-term survival[9]. Any potential effect of reoperation in lowering long-term survival after oesophagectomy could be mediated by several biological mechanisms, e.g. the additional surgical trauma could further trigger an inflammatory response that could lower the efficacy of bodily defence mechanisms, including destruction and removal of circulating tumour cells, and thus pave the way for early recurrence [10], and the major surgical complications that cause the need for reoperation might directly facilitate tumour recurrence, e.g. anastomotic insufficiency might entail direct tumour spread [9 11]. Therefore, we hypothesised that reoperation within 30 days after initial oesophageal resection negatively influences long-term survival.

METHODS

Study design

This was a retrospective population-based cohort study. The study cohort has previously been presented in detail [12 13]. All patients having undergone oesophagectomy for oesophageal cancer during the period 1987-2010 in Sweden were included in the study. Eligible patients were followed up until death or end of the study (28th February 2012), whichever occurred first.

Study population

Oesophageal cancer patients were identified from the Swedish Cancer Registry, a registry with 98% nationwide coverage of oesophageal cancer patients[14 15]. Tumours of the gastric cardia were not included. Oesophageal cancer was defined by the diagnosis code 150.0, 150.8, and 150.9 in the 7th version of the International Classification of Diseases (ICD7). The identified patients were linked with the Swedish Patient Registry to include only those who underwent oesophageal resection in the final study cohort. Our group has recently reported that the Patient Registry has a positive predictive value of 99.6% for assessing oesophageal cancer resection[16]. Detailed information on tumour characteristics and surgical details were acquired through manual scrutiny of medical records from the operation charts and histopathology reports, with accompanying referral notes, retrieved from all relevant hospitals throughout Sweden [12 13]. One reviewer, who was kept blinded for the study outcome to ensure objectivity, reviewed all histopathological reports according to a predefined protocol to ensure uniformity. The accuracy of the histopathological review was assessed by two

researchers who independently reviewed 100 patient records, showing high accuracy (>90% concordance).[13] The Patient Registry was used to obtain information on reoperations after the primary oesophageal resection and on comorbidities. Detailed information about indications for reoperation was not available. To calculate survival time after oesophagectomy, dates of death were collected from the Swedish Causes of Death Registry. This register is complete and is updated continuously facilitating availability of accurate dates of death. The unique 10-digit Swedish personal identity number, assigned to every resident in Sweden since 1947[17], was used for linkage of individuals between registries and for identification of the patients' hospital records.

Study exposure and outcome

The exposure was defined as any open or minimally invasive reoperation within 30 days of initial oesophageal cancer resection. Exposure was defined according to the Classification of Surgical Procedures. More specifically, reoperation was categorised as: 1) Explorative laparotomy (ICD10 JAH00, JAK00), 2) explorative thoracotomy (ICD10 GAB13, GAB96, GAB10), 3) reoperation for bleeding (ICD10 JWE00, GWE00), 4) reoperation for anastomotic insufficiency (ICD10 JWF00, GWF00, DWF00, 5) reoperation for wound revision (ICD10 JWA00), or 6) reoperation for deep infection (ICD10 GWC00, GCW01, JWC00) (Table1).

The study outcomes were was all-cause early-, late- and disease-specific mortality. "Early postoperative mortality" was defined as any death occurring within 90 days of initial surgery, while "late mortality" was defined as any death between 90 days and 5 years of the primary resection. "Disease

specific mortality" was defined as death of tumour recurrence occurring between 90-days and 5 years of surgery. If a cause of death included oesophageal cancer (diagnosis codes 150 according to ICD7) in the Swedish Causes of Death Registry, we assumed that patients died of tumour recurrence. We also analysed the impact of each of the most common types of reoperations on mortality between 90 days and 5-years of surgery in subgroup analyses. Since tumour recurrence is a less likely explanation for mortality 5 years and later after oesophageal cancer surgery, we decided to use 5 years as cut-off. The Regional Ethical Review Board in Stockholm, Sweden approved the study.

Statistical analysis

Survival was calculated using the Kaplan-Meier method, and differences in survival between the survival curves of patients with and without reoperation were evaluated using the log rank test. In a Cox proportional hazards regression model, hazard ratios (HR's) with 95% confidence intervals (CI's) were calculated, including adjustment for potential confounding factors in a multivariable model. In the Cox model the proportionality assumption was tested. The factors adjusted for were nine known prognostic factors. They were categorised as follows: 1) age (categorised into three groups: <65, 65-75, or >75 years), 2) sex, 3) comorbidity (including any of: hypertension, ischemic heart disease, cardiac failure, chronic obstructive pulmonary disease, asthma, diabetes, former cancer diagnosis, human immunodeficiency virus, liver disease and renal disease; and categorised into three groups: none, one, or two or more), 4) tumour stage (classified according to the 6th version of the

Union for International Cancer Control -TNM classification; and categorised into four groups: 0-I, II, III, or IV), 5) histological type of tumour (categorised into two groups: squamous cell carcinoma or adenocarcinoma), 6) neoadjuvant therapy (yes or no) data on the type of neo-adjuvant therapy used, i.e. chemoradiotherapy or chemotherapy, was not available, but in Sweden, the use of chemoradiotherapy has dominated whenever neo-adjuvant therapy has been used, 7) surgical radicality (R0 or not R0), 8) surgeon volume (<9 or ≥9 per year) To avoid selecting a suitable cut-off for surgeon annual volume, we simply chose to use the median as the cut-off, and 9) calendar period (1987-1996 or 1996-2005). We also considered lymph node harvest as a potential confounder, but this variable did not significantly influence the results (Chi-square p-value 0.687), and since there was a substantial rate of missing data on lymph node harvest, we decided not to include this variable in the final multivariable model. Information on comorbidities was obtained from the Swedish Patient Register, information on tumour stage and histological type of tumour, surgical radicality and neo-adjuvant treatment was extracted from histopathological records and accompanying referral notes. [16] Missing values in the covariates were treated as a separate group in the Cox regression model[18]. A sensitivity analysis was performed to compare the impact of categorising missing as a separate group against removing these missing values from the analysis. All statistical analyses were done using STATA 11 for Mac (STATAcorp College Station, Texas).

RESULTS

Patients

Some 2195 patients were identified as eligible in the study cohort of oesophageal cancer patients who underwent resection in Sweden during the study period. After exclusion of 373 patients (17%) where medical records were not available or where exposure data were missing, 1822 (83%) patients remained for final analysis. Of these, 200 patients (11%) were exposed for reoperation (in total 248 reoperations) within 30 days of the primary oesophageal resection (Table 1).

Table 1. Categorisation of the 248 reoperations within 30 days after initial surgery in a cohort of 1822 patients undergoing oesophagectomy between 1987 and 2010 in Sweden, with follow-up until 28th February 2012.

Type of reoperation		Number (%)
Total number of reoperations		248 (100)
Explorative laparotomy		47 (19)
Explorative thoracotomy		11 (4)
Reoperation for bleeding		22 (9)
Reoperation for anastomotic insufficiency		43 (17)
	Laparotomy	3
	Thoracotomy	1
	Unknown/other	39
Reoperation for infection		8 (3)
Reoperation for wound revision		50 (20)
	Wound revision for bleeding	15
	Wound revision for infection	5
	Wound dehiscence	7
	Unknown	23
Other reoperations		75 (30)

There were no major differences between the groups with and without reoperation regarding the distribution of sex, age, comorbidity, tumour stage, tumour histology, neo-adjuvant therapy, hospital volume, or calendar period (Table 2). Among the 1484 patients who died during the entire study period, 1246 (84%) had documented tumour recurrence, which means that the all-cause mortality within 5 years closely mirrors disease-specific mortality. There were no missing values for reoperation (exposure) and missing values in covariates were missing at random. A sensitivity analysis was performed to compare the impact of categorising missing as a separate group against removing these missing values from the analysis, and the results were similar (data not shown). In the Cox model the proportionality assumption was tested and the model satisfied the assumption.

Table 2. Characteristics of 1822 patients undergoing oesophagectomy between 1987 and 2010 in Sweden, with follow-up until 28th February 2012

Characteristics	Number (%)		
	No reoperation	**Reoperation**	
Total	1622 (89)	200 (11)	P-value§
Sex			
Men	1211 (75)	151 (75)	0.8
Women	411 (25)	49 (25)	
Age			
≤64	754 (46)	93 (47)	0.9
65-75	615 (38)	78 (39)	
>75	253 (16)	29 (14)	
Comorbidity*			
None	832 (51)	107 (54)	0.8
1	542 (34)	63 (31)	
≥2	248 (15)	30 (15)	
Stage‡			
0-I	339 (20)	41 (20)	0.9
II	532(33)	71 (35)	
III	399 (25)	46 (23)	
IV	127(8)	13 (7)	
Missing†	225 (14)	29 (15)	
Histology			
Adenocarcinoma	645 (40)	70 (35)	0.09
Squamous cell carcinoma	880 (54)	123 (62)	
Missing†	97 (6)	7 (3)	
Neoadjuvant therapy			
None	677 (42)	85 (43)	0.4
Radiotherapy	154 (9)	26 (13)	
Chemoradiotherapy	302 (19)	35 (17)	
Missing†	489 (30)	54 (27)	
Radicality			
R0	1135 (69)	137 (68)	0.7
Not R0	251 (16)	30 (15)	
Missing †	236 (15)	33 (17)	
Surgeon volume			
<9 per year	875 (54)	122 (61)	0.06
≥9 per year	747 (46)	78 (39)	
Calendar period			
1987-1990	234 (14)	34 (17)	0.2
1991-1994	302 (19)	43 (22)	
1995-1999	330 (20)	49 (25)	
2000-2005	382(24)	37 (19)	
2006-2010	374 (23)	37 (19)	

*Comorbidity included: hypertension, ischemic heart disease, cardiac failure, chronic obstructive pulmonary disease, asthma, diabetes, former cancer diagnosis, human immunodeficiency virus, liver disease, and renal disease.

† Missing values of covariates were missing at random and considered as a separate group.

‡Categorised according to the 6th version of the Union for International Cancer Control (UICC)-TNM classification.

§Chi-square of the difference between groups

Reoperation and risk of mortality

Among the 208 patients (11%) who died within 90 days of surgery, 54 (26%) underwent reoperation. Reoperation was a risk factor for 90-day mortality after adjustment for confounding factors (HR 3.05, 95% CI 2.22-4.17). Among the 1276 (79%) patients who died between 90 days and 5 years after surgery 117 (10%) were reoperated. Among the 122 who died after 5 years of surgery 5 (4%) were reoperated. The log-rank test comparing the Kaplan-Meier survival curves of patients with and without reoperation between 90 days and 5 years after surgery revealed a statistically significantly increased mortality in the reoperated group (p<0.0001) (Figure 1, Table 3).

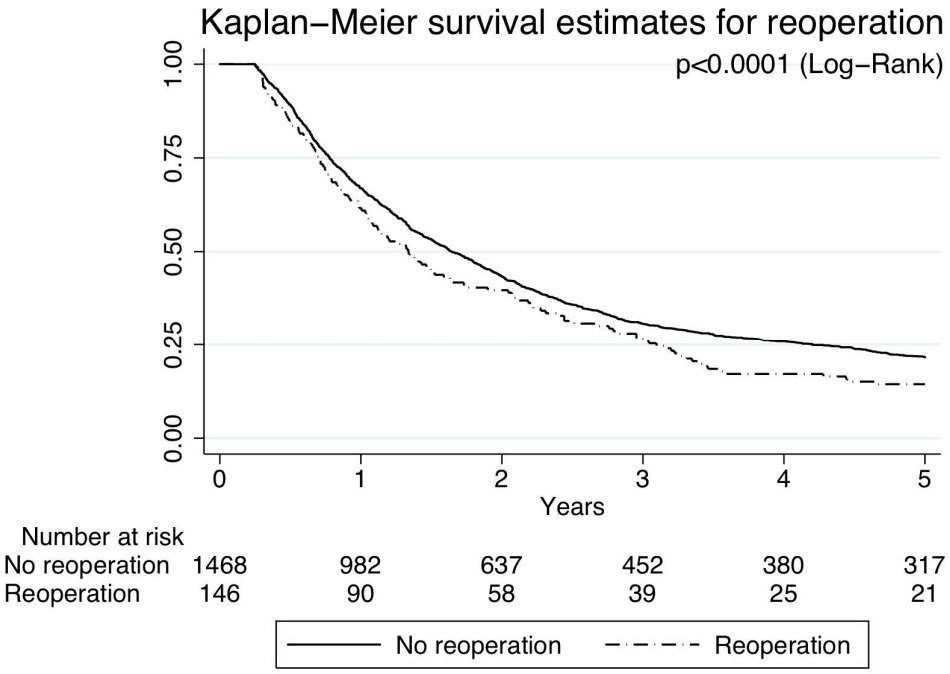

Figure 1. Kaplan-Meier survival curve for survival between 90 days and 5 years with respect to occurrence of reoperation among 1614 patients undergoing oesophageal cancer surgery in 1987-2010 in Sweden.

Table 3. Hazard ratios (HR) with 95% confidence intervals (95% CI) of mortality after oesophagectomy with respect to occurrence of reoperation, based on 1822 patients undergoing oesophageal cancer surgery in 1987-2012 in Sweden

Reoperation	Number of patients (%)	Number of events (%)‡	HR (95% CI)
All stages			
<90 days	1822 (100)	208 (11)	
Crude			3.17 (2.32-4.32)
Multivariable*,†			3.05 (2.22-4.17)
≥90 days – 5 years	1614 (89)	1276 (79)	
Crude			1.22 (1.02-1.47)
Multivariable*, †			1.27 (1.05-1.53)
≥90 days – 5 years disease specific	1292 (71)	954 (74)	
Crude			1.26 (1.03-1.57)
Multivariable*, †			1.28 (1.04-1.59)

*Adjusted for sex, age, co-morbidities, tumour stage, histology, neoadjuvant therapy, radicality, surgeon volume, and calendar period.

†Missing values of covariates were missing at random and considered as a separate group.

‡Event means death

As presented in Table 3, there was a 27% increased hazard of mortality during the period 90 days to 5 years after surgery after adjustment for all nine potential confounding factors (crude HR 1.22, adjusted HR 1.27, 95% CI 1.05-1.53) (Table 3). During the follow-up period, 954 (74%) patients died of reported tumour recurrence. The disease-specific mortality within 90 days and 5 years of surgery was 28% increased among patients who were reoperated (adjusted HR 1.28, 95% CI 1.04-1.59) (Table 3). The proportional hazard assumption, tested using a non-zero slope, and time varying covariates were satisfied, and there were no statistically significant interaction effects with reoperation (data not shown).

Reoperation and risk of mortality- subgroup analyses of most common reoperations

In a subgroup analysis of the 3 most common types of reoperations, i.e. exploratory laparotomy, reoperation for anastomotic insufficiency and wound revision, the point HRs were increased for each type of reoperation (Table 4), and patients reoperated for anastomotic insufficiency in particular had a statistically significantly increased hazard of mortality (adjusted HR 1.82, 95% CI 1.19-2.76).

Table 4. Hazard ratios (HR) with 95% confidence intervals (95% CI) of mortality between 90 days and 5-years in a subgroup analyses of the most common types of reoperations after oesophagectomy, based on 1822 patients undergoing oesophageal cancer surgery in 1987-2012 in Sweden

Type of reoperation	Number of patients (%)	HR (95% CI) [*, †]
Exploratory laparotomy	47 (19)	1.17 (0.82-1.67)
Reoperation for anastomotic insufficiency	43 (17)	1.82 (1.19-2.76)
Wound revision	50 (20)	1.32 (0.87-2.00)

*Adjusted for sex, age, co-morbidities, tumour stage, histology, neoadjuvant therapy, radicality, surgeon volume, and calendar period.

†Missing values of covariates were missing at random and considered as a separate group.

DISCUSSION

This is, to the best of our knowledge, the first study addressing reoperation in relation to late mortality after primary oesophageal cancer resection, and it revealed an increased long-term all-cause and disease-specific mortality in patients that underwent reoperation compared to those who did not. Patients that were reoperation due to anastomotic insufficiency experienced a particularly high hazard of mortality.

Among strengths of this study is the population-based design, where most patients who underwent oesophageal cancer surgery in Sweden during 1987-2010 were included. The follow-up for mortality was complete by virtue of the availability of personal identity numbers for Swedish residents, together with the fully complete Swedish Causes of Death Registry. Another major strength is the possibility to adjust for several known prognostic factors, which reduces the risk of confounding. Moreover, the exposure and outcome were predefined, which reduces the risk of chance findings and decreases the risk of systematic errors owing to misclassification. Some limitations of the study require a discussion. The retrospective clinical data collection imposes a risk of misclassification and selection bias. The researchers involved in gathering the clinical information had, however, no link with the participating hospitals and were not involved in the patient care, which decreases these risks. A risk of residual confounding by known prognostic factors or confounding by unknown factors cannot be excluded in observational research due to the lack of randomization. There was for example no access to information on pre-operative performance status and nutritional status, which might have influenced the results[19]. Another limitation was the lack of information on

complications, and thus the indication for the reoperations. Although the long study period offered good statistical power, it also entailed a risk of bias by changes in surgical techniques and standards in patients care over time. To counteract such effects, we adjusted all HRs for calendar period. The limited rate of exposure to reoperation still meant that the exposure could not be further subcategorised because of power issues. Finally, the use of a cut-off of 30 days of surgery for assessing re-operation might result in missing of later re-operations. However, we decided before the study was initiated to use a cut-off that was likely to be directly associated with the oesophagectomy, but yet not too short. Since there is no agreed upon cut-off for capturing early reoperations associated with surgery, we instead use a commonly used cut-off for short-term mortality, which is traditionally 30 days.

The finding of the prognostic role of reoperations after excluding the initial postoperative period is a novel finding that should encourage further research. It stresses the need for preventive measures to reduce the need for reoperation. In this population the 3 most common performed types of reoperation were explorative laparotomy (19%), re-operation for anastomotic leak (17%) and wound revision (20%). The results of the subgroup analyses showed that especially patients undergoing reoperation for anastomotic insufficiency had an increased risk of mortality. There is some evidence that anastomotic insufficiency entails direct tumour spread and seeding of remaining viable tumour cells in colon cancer patients[11 20]. This might explain the higher mortality in patients with reoperation for anastomotic insufficiency.

Several studies have showed that a higher surgeon or hospital volume reduces post-operative mortality and morbidity. [12 21-24] High volume surgery is facilitated by centralisation of the care for oesophageal cancer patients. Centralisation might be an effective measure for prevention of severe post-operative complications. A recent study showed that patients with comorbidity that compromises the cardiovascular status leading to a compromised perfusion of organs (e.g. hypertension, diabetes, congestive heart failure and renal failure), have a higher risk of anastomotic leak. This finding indicates that pre-operative optimisation of the cardiovascular status might also decrease the risk of severe complications requiring reoperation.[25] No previous studies have, to the best of our knowledge, addressed the influence of reoperations on long-term survival in oesophageal cancer patient. However, the main indication for reoperation is the occurrence of severe postoperative complications, and a few previous studies have assessed the role of such complications on long-term survival. These have provided conflicting results; some studies have reported a worse longer-term prognosis after surgical complications[7 9], medical complications[10], or concurrent surgical and medical complication[4], while others have not found any such effect[6 8]. These differences might be due to differences in classification of the severity of the complications and missing information on interventions.

One biological mechanism that might explain the decreased long-term survival after reoperation is that the additional surgical injury reduces the protection against seeding of tumour cells, including activation of natural killer cells and other anti-carcinogenic factors[26]. Furthermore, it is possible that

additional surgery triggers an elevated inflammatory response that might in turn stimulate growth of micro-tumours and induce tumour recurrence and death from recurrence[10]. Another potential mechanism considers certain complications. Finally, blood transfusion has been linked with a worse long-term mortality and increased cancer recurrence in different types of cancer [27-30]. Unfortunately, we did not have information on blood transfusion in this study, but it can be assumed that patients returning to theatre are more likely to receive blood transfusion, and speculatively, blood transfusion may be a mechanism that contributes to the main finding of this study.

In conclusion, this nationwide and population-based cohort study with adjustment for several potential confounding factors indicates that reoperation is associated with an increased hazard of mortality even after the initial 3 months of the oesophageal cancer resection. This finding warrants more research, but further stresses the need to consider any actions that might prevent complications requiring reoperation after the primary surgery in oesophageal cancer patients.

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Authors' individual contribution:

Dr M. van der Schaaf and J. Lagergren, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. ***Study concept and design***: M. van der Schaaf, J. Lagergren, P. Lagergren, M. Rutegård, M. Derogar. ***Acquisition of data***: P. Lagergren, J. Lagergen, M. van der Schaaf, M. Derogar. ***Analysis and interpretation of data*:** M. van der Schaaf, J. Lagergren, A. Johar. ***Drafting of the manuscript***: M. van der Schaaf, J. Lagergren. ***Critical revision of the manuscript for important intellectual content*:** J. Gossage, R. Mason, M. Rutegård, P. Lagergren. ***Statistical analysis***: A. Johar, M. Derogar. ***Obtained funding*:** J. Lagergren, P. Lagergren.

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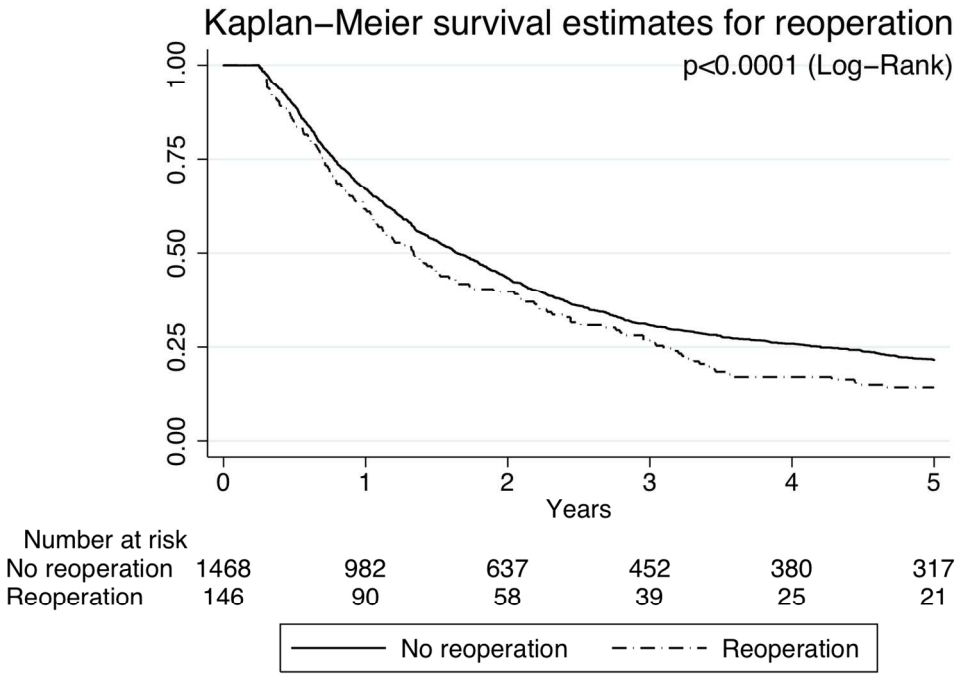

Kaplan-Meier survival curve for survival between 90 days and 5 years with respect to occurrence of reoperation among 1614 patients undergoing oesophageal cancer surgery in 1987-2010 in Sweden
139x101mm (300 x 300 DPI)