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Weekday of oesophageal cancer surgery and early postoperative outcomes

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Title: Weekday of oesophageal cancer surgery and early postoperative outcomes

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Keywords: Oesophageal neoplasm; Day of surgery; Short-term outcomes, Postoperative reoperation; 30-day mortality.

Abstract

Objectives: Later weekday of surgery for oesophageal cancer seems to increases 5-year mortality, but the mechanisms are unclear. We hypothesised that early postoperative reoperations and mortality might explain this association, since reoperation after oesophagectomy decreases long-term prognosis and later weekday of elective surgery increases 30-day mortality.

Design: This was a population-based cohort study during the study period 1987-2014.

Setting: All Swedish hospitals conducting elective surgery for oesophageal cancer in Sweden.

Participants: Included were 1,748 patients, representing almost all (98%) patients who underwent elective surgery for oesophageal cancer in Sweden during 1987-2010, with follow-up until 2014.

Primary and secondary outcome measures: The risk of reoperation or mortality within 30 days of oesophageal cancer surgery was assessed in relation to weekday of surgery by calculating odds ratios (ORs) with 95% confidence intervals (CIs) using multivariable logistic regression. ORs were adjusted for age, co-morbidity, tumour stage, histology, neoadjuvant therapy, and surgeon volume.

Results: Surgery Wednesday-Friday did not increase the risk of reoperation or mortality compared to surgery Monday-Tuesday (OR=0.99, 95% CI 0.75-1.31). A decreased point estimate of reoperation (OR=0.88, 95% CI 0.64-1.21) was counteracted by an increased point estimate of mortality (OR=1.28, 95% CI 0.83-1.99). ORs did not increase from Monday to Friday when each weekday was analysed separately. There was no association between weekday of surgery and reoperation specifically for anastomotic leak, laparotomy, or wound infection. Stratification for surgeon volume did not reveal any clear associations between weekday of surgery and risk of 30-day reoperation or mortality.

Conclusions: Weekday of oesophageal cancer surgery does not seem to influence the risk of reoperation or mortality within 30 days of surgery, and thus cannot explain the association between weekday of surgery and long-term prognosis.

Strengths and limitations

Strengths:

- Large and population-based study with high participation rate
- Accurate assessment of the exposure, outcomes and confounders
- Complete follow-up

Weaknesses:

- Competing events
- Retrospective data collection

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Competing interests: There are no competing interests.

Introduction

In a recent Swedish cohort study, we found increased 5-year all-cause and disease-specific 5-year mortality following surgery for oesophageal cancer later in the week compared to earlier weekdays, and the association seemed to increase for each weekday (1). The mechanism explaining these associations remains to be identified. Another study from our group revealed that patients who require reoperation within 30 days of oesophageal cancer surgery are at an increased risk of all-cause and disease-specific 5-year mortality, also after excluding mortality occurring within the initial 3 months of surgery (2). Moreover, later weekday of surgery for various elective procedures has been shown to increase the *r*isk of severe postoperative complications, including 30-day mortality (3, 4). Therefore, we hypothesised that occurrence of early and severe postoperative complications requiring reoperation or resulting in mortality explains the association between weekday of surgery and long-term prognosis in oesophageal cancer. This hypothesis was tested in a nationwide Swedish cohort study.

Methods

Design

This was a nationwide Swedish population-based cohort study conducted between 1987 and 2010. Earlier versions of this cohort have been published elsewhere (1, 5-7). The study exposure was the day of the week on which the operation was conducted and the study outcome was reoperations or mortality occurring within 30 days of the oesophagectomy. By including both these outcomes as the main outcome, we avoided errors from competing risks from the fact that those who died within 30 days of surgery could not be recorded with reoperations. The participating patients represented 98% of all oesophageal cancer patients who underwent surgery in Sweden between January 1, 1987 and December 31, 2010. Eligible patients were identified from national Swedish healthcare registers. Clinical data were extracted from medical records, retrieved through our Swedish network of clinicians, established in the mid-1990s as part of a prospective and nationwide case-control study (8). Linkages of data from individuals between registers and the identification of their medical records were enabled by the personal identity number, an individual 10-digit identifier assigned to each Swedish resident upon birth or immigration (9). The study was approved by the Ethical Review Board in Stockholm, Sweden.

Registry data

The Swedish Cancer Registry was used to identify all patients in Sweden with oesophageal cancer, represented by the diagnosis codes 150.0, 150.8, or 150.9 according to the 7th version of the International Classification of Diseases. This register records all cancer diagnoses in Sweden since 1958, and has 98% nationwide coverage of oesophageal cancer (10, 11).

The Swedish Patient Registry provided data on oesophagectomy, co-morbidities, and hospital admittances. This register records all surgical procedures and diagnoses within in-hospital care in Sweden since 1987 (12). The positive predictive value for the recording of oesophageal cancer surgery in this register is 99.6% according to a validation study (13).

The Swedish Causes of Death Registry provided causes and dates of death. This register is nationwide since 1961 and highly complete.

Medical records data

The *medical records* of all participating patients were continuously collected from the operating hospitals, including surgical charts and pathological reviews of the resected specimens. Based on this data collection, we assessed weekday of oesophagectomy, co-morbidity, tumour stage, location, and histology, neoadjuvant therapy, surgery, and annual surgeon volume of oesophagectomies. The reviewers of the medical records were kept blinded from the study outcomes and filled in a predefined protocol. Co-morbidity was assessed according to the well validated Charlson co-morbidity index scoring system (14). Tumour stage was classified according to the TNM classification of the Union Internationale Contre le Cancer (UICC) (15). Neoadjuvant therapy was infrequently used in Sweden during the study period, which was due to the limited support of such treatment until more recently (16).

When used, the neoadjuvant therapy of choice was a combination of chemotherapy and radiotherapy. The dominating (95%) surgical procedure throughout the study period was open transthoracic oesophageal resection with intra-thoracic anastomosis. The preferred

oesophageal substitute was a pulled-up gastric tube, anastomosed to the proximal esophago in the thorax or neck. The surgeon volume variable was created based on a previously described algorithm, where the names of the individual surgeons were used to assign the operation to the most experienced surgeon whenever more than one surgeon conducted the procedure (6).

Statistical analysis

The weekday variable was analysed in two ways. First, surgery during Monday or Tuesday was compared with surgery during Wednesday-Friday. Second, each of the 5 weekdays was analysed as separate categories with Monday as reference. Potential differences in reoperation or mortality within 30 days of surgery between exposure groups were analysed using a multivariable logistic regression, providing odds ratios (ORs) with 95% confidence intervals (CIs) adjusted for potential confounding variables. Seven pre-defined variables were included in the multivariable model: 1) age (continuous variable), 2) sex, 3) co-morbidity (Charlson index score 0, 1, or >1), 4) tumour stage (0-I, II, or III-IV), 5) tumour histology (adenocarcinoma or squamous cell carcinoma), 6) neoadjuvant treatment (yes or no), and 7) annual surgeon volume of oesophagectomies (<17 or ≥17, median number). Furthermore we evaluated if the effect of weekday was modified by surgeon volume by including an interaction term in the model. Thereafter, we derived the ORs for weekday variable within each stratum for surgeon volume. To manage limited missing data (2.8%), a complete case analysis was performed. The statistical software SAS 9.4 (SAS Institute, Cary, NC) was used for the data management and statistical analysis.

Results

Patients

The 1,799 patients who underwent elective surgery for oesophageal cancer during the weekdays Monday to Friday in 1987-2010 represented 98% of all such procedures in Sweden. Of these, 51 (2.8%) were excluded due to missing data in any of the covariates. Table 1 presents characteristics of the final 1,748 study participants, grouped into those with and without reoperation or mortality within 30 days of surgery. There were no major differences in distribution of age, sex, tumour stage, tumour histology or use of neoadjuvant therapy comparing the groups with and without reoperation or mortality within 30 days of surgery, while lower annual surgeon volume was found in the group with poor short-term outcomes.

Risk of postoperative reoperation or mortality

The comparison of surgery later in the week (Wednesday-Friday) with earlier in the week (Monday-Tuesday) showed no increased risk of death or reoperation within 30 days of surgery (adjusted OR=0.99, 95% CI 0.75-1.31) (Table 2). When weekday of surgery was categorised into each of the 5 weekdays, the ORs did not increase from Monday to Friday. A slightly decreased point estimate of reoperation (OR 0.88, 95% CI 0.64-1.21) following later weekday of surgery was counteracted by an increased point estimate of mortality (OR 1.28, 95% CI 0.83-1.99). There was no increased OR of reoperation for anastomotic leak, laparotomy or wound infection associated with later weekday of surgery (Table 2).

The analyses evaluating effect modification by annual surgeon volume did not reveal any statistically significant associations between weekday of surgery and risk of reoperation or mortality within 30 days of surgery for oesophageal cancer (Table 3).

Discussion

This study provides no evidence of an association between later weekday of surgery for oesophageal cancer and risk of early postoperative reoperation or mortality.

Strengths of the present study include the population-based cohort design, accurate assessment of the exposure (weekday of surgery) and outcome (postoperative reoperation or mortality), complete follow-up, adjustment for several potential confounding factors, and the large sample size. A weakness is that the long study period might introduce confounding by changes in treatment or patient selection over time. However, it is unlikely that these changes would influence choice of weekday of surgery, which means that these changes would not act as confounders (17). The results should be generalisable to other western populations of Caucasian origin. A methodological issue is that reoperation and mortality are competing events, since death occurring before any potential later reoperation is not accounted for. Therefore, the combined reoperation/mortality outcome was selected as the main study outcome, while the results regarding the separate reoperation outcomes should be interpreted more cautiously. An observational study can never rule out residual confounding, but the risk of confounding should be counteracted by the fact that we adjusted the risk estimates for the key potential confounding variables. The retrospective collection of data from medical records might introduce bias, but we avoided such error by keeping the researchers collecting and introducing the medical records data without being aware of the study outcome. Finally, the occurrence of the study outcomes was low, which resulted in limited statistical power to detect weak differences, particularly in stratified sub-group analyses.

To the best of our knowledge, there is no previous study addressing weekday of oesophageal cancer surgery in relation to reoperation or short-term mortality. However, large cohort studies evaluating various types of elective surgery have found an increased risk of 30-day mortality associated with a later weekday of surgery (3, 4). This was not found in this study, which might be due to a more limited statistical power compared to the studies addressing many types of surgical procedures. However, it is unlikely that any potentially weakly increased risk of reoperation or short-term mortality would explain the substantially increased long-term mortality associated with later weekdays of oesophageal cancer surgery recently reported (1). This suggests that the weekday effect on long-term prognosis is due to other reasons than poor short-term outcomes, e.g. increased likelihood of tumour recurrence.

In conclusion, this population-based and nationwide Swedish cohort study found no influence of weekday of oesophageal cancer surgery on risk of reoperations or mortality within 30 days of surgery. Thus, poor short-term outcomes do not seem to contribute to the association between later weekday of oesophageal cancer surgery and increased 5-year mortality.

Author contributions:

Jesper Lagergren: Substantial contributions to the conception and design, and acquisition and interpretation of the data; Drafting of the paper; Final approval of the version to be published; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Fredrik Mattsson: Substantial contributions to the conception and design, and analysis and interpretation of the data; Revising the paper critically for important intellectual content; Final approval of the version to be published; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Pernilla Lagergren: Substantial contributions to the conception and design, and acquisition and interpretation of the data; Revising the paper critically for important intellectual content; Final approval of the version to be published; Final approval of the version to be published; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data sharing statement:

Statistical codes and dataset are available upon request from the corresponding author.

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Table 1. Characteristics of 1748 study patients who underwent surgical resection for oesophageal cancer in Sweden in 1987-2010, with follow-up until 2014.

		No death/reoperation within 30 days of surgery	Death/reoperation within 30 days of surgery
		Number (%)	Number (%)
Total		1490 (100)	258 (100)
Age (years): Mean (standard deviation)		65 (10)	67 (9)
Sex	Male	1110 (74)	195 (76)
	Female	380 (26)	63 (24)
Charlson co-morbidity index	0	870 (58)	145 (56)
	1	306 (21)	57 (22)
	>1	314 (21)	56 (22)
Tumour stage	0-I	357 (24)	54 (21)
	II	535 (36)	104 (40)
	III-IV	598 (40)	100 (39)
Tumour histology	Adenocarcinoma	675 (45)	93 (36)
	Squamous carcinoma	815 (55)	165 (64)
Neoadjuvant therapy	No	1013 (68)	170 (66)
	Yes	477 (32)	88 (34)
Annual surgeon volume	<17	719 (48)	155 (60)
	≥17	771 (52)	103 (40)

Table 2. Risk of death or reoperation within 30 days of surgery for oesophageal cancer. Results presented as odds ratio (OR) with 95% confidence interval (CI).

Weekday of surgery	Death/reoperation (n=258)	Death (n=93)	Reoperation (n=191)	Reoperation for anastomotic leak (n=34)	Reoperation with laparotomy (n=54)	Reoperation for wound infection (n=38)
	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*
Monday-Tuesday	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Wednesday-Friday	0.99 (0.75-1.31)	1.28 (0.83-1.99)	0.88 (0.64-1.21)	0.98 (0.47-2.02)	0.75 (0.42-1.34)	1.44 (0.75-2.79)
Monday	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Tuesday	0.98 (0.69-1.38)	0.61 (0.33-1.11)	1.00 (0.68-1.46)	0.62 (0.26-1.46)	0.92 (0.47-1.80)	0.96 (0.39-2.41)
Wednesday	1.20 (0.81-1.78)	1.16 (0.64-2.11)	1.05 (0.67-1.65)	1.47 (0.62-3.49)	0.74 (0.33-1.69)	1.33 (0.50-3.53)
Thursday	0.86 (0.55-1.34)	0.82 (0.42-1.61)	0.81 (0.49-1.34)	0.15 (0.02-1.17)	0.96 (0.42-2.20)	1.54 (0.58-4.14)
Friday	0.66 (0.34-1.29)	1.04 (0.44-2.44)	0.54 (0.24-1.23)	0.42 (0.05-3.37)	NA	1.33 (0.35-5.13)

*Adjusted for age, sex, Charlson co-morbidity index, tumour stage, tumour histology, neoadjuvant therapy, and surgeon volume.

Table 3. Risk of death or reoperation within 30 days of surgery for oesophageal cancer, stratified for surgeon volume. Results presented as odds ratio (OR) with 95% confidence interval (CI).

Weekday of surgery	Surgeon volume	Death/reoperation (n=258)	Death (n=93)	Reoperation (n=191)	Anastomotic (n=34)	Laparotomy (n=54)	Wound within 30 days (n=38)
		OR (95 % CI)*	OR (95 % CI)*	OR (95 % CI)*	OR (95 % CI)*	OR (95 % CI)*	OR (95 % CI)*
Monday-Tuesday	<17	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Wednesday-Friday	<17	1.02 (0.72-1.46)	1.31 (0.78-2.20)	0.88 (0.58-1.34)	0.64 (0.19-2.16)	0.73 (0.36-1.48)	1.55 (0.69-3.50)
Monday-Tuesday	≥17	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Wednesday-Friday	≥17	0.94 (0.60-1.47)	1.22 (0.54-2.75)	0.87 (0.54-1.42)	1.26 (0.52-3.05)	0.79 (0.28-2.24)	1.25 (0.40-3.87)
Monday	<17	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Tuesday	<17	0.87 (0.54-1.39)	0.55 (0.25-1.17)	0.90 (0.52-1.54)	0.94 (0.23-3.84)	1.55 (0.65-3.67)	0.53 (0.15-1.84)
Wednesday	<17	1.27 (0.78-2.05)	1.24 (0.63-2.45)	1.11 (0.63-1.93)	0.98 (0.22-4.47)	1.29 (0.50-3.33)	1.26 (0.43-3.71)
Thursday	<17	0.74 (0.41-1.32)	0.72 (0.31-1.63)	0.72 (0.37-1.43)	0.43 (0.05-3.90)	0.82 (0.24-2.75)	1.16 (0.35-3.79)
Friday	<17	0.58 (0.25-1.33)	0.92 (0.34-2.49)	0.32 (0.09-1.09)	NA	NA	0.96 (0.19-4.86)
Monday	≥17	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Tuesday	≥17	1.12 (0.67-1.87)	0.73 (0.27-2.00)	1.11 (0.64-1.92)	0.50 (0.17-1.47)	0.36 (0.11-1.20)	2.34 (0.47-11.80)
Wednesday	≥17	1.00 (0.50-2.02)	0.78 (0.20-3.05)	0.89 (0.41-1.94)	1.89 (0.66-5.39)	NA	1.09 (0.10-12.17)
Thursday	≥17	1.06 (0.54-2.05)	1.10 (0.35-3.49)	0.92 (0.44-1.92)	NA	1.14 (0.37-3.53)	2.95 (0.48-18.16)
Friday	≥17	0.85 (0.28-2.59)	1.48 (0.29-7.43)	1.03 (0.33-3.16)	0.85 (0.10-7.18)	NA	2.89 (0.25-33.07)

*Adjusted for age, sex, Charlson co-morbidity index, tumour stage, tumour histology, neoadjuvant therapy, and surgeon volume.

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

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*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	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
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	5-6
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	7
		(*e*) Describe any sensitivity analyses	NA
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	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8 + 13
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	8
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	8 + 14 + 15
		(*b*) Report category boundaries when continuous variables were categorized	8 + 14 + 15
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8 + 14 + 15
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
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	3

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

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

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Keywords: Oesophageal neoplasm; Day of surgery; Short-term outcomes, Postoperative reoperation; 30-day mortality.

Abstract

Objectives: Later weekday of surgery for oesophageal cancer seems to increases 5-year mortality, but the mechanisms are unclear. We hypothesised that early postoperative reoperations and mortality might explain this association, since reoperation after oesophagectomy decreases long-term prognosis and later weekday of elective surgery increases 30-day mortality.

Design: This was a population-based cohort study during the study period 1987-2014.

Setting: All Swedish hospitals conducting elective surgery for oesophageal cancer in Sweden.

Participants: Included were 1,748 patients, representing almost all (98%) patients who underwent elective surgery for oesophageal cancer in Sweden during 1987-2010, with follow-up until 2014.

Primary and secondary outcome measures: The risk of reoperation or mortality within 30 days of oesophageal cancer surgery was assessed in relation to weekday of surgery by calculating odds ratios (ORs) with 95% confidence intervals (CIs) using multivariable logistic regression. ORs were adjusted for age, co-morbidity, tumour stage, histology, neoadjuvant therapy, and surgeon volume.

Results: Surgery Wednesday-Friday did not increase the risk of reoperation or mortality compared to surgery Monday-Tuesday (OR=0.99, 95% CI 0.75-1.31). A decreased point estimate of reoperation (OR=0.88, 95% CI 0.64-1.21) was counteracted by an increased point estimate of mortality (OR=1.28, 95% CI 0.83-1.99). ORs did not increase from Monday to Friday when each weekday was analysed separately. There was no association between weekday of surgery and reoperation specifically for anastomotic leak, laparotomy, or wound infection. Stratification for surgeon volume did not reveal any clear associations between weekday of surgery and risk of 30-day reoperation or mortality.

Conclusions: Weekday of oesophageal cancer surgery does not seem to influence the risk of reoperation or mortality within 30 days of surgery, and thus cannot explain the association between weekday of surgery and long-term prognosis.

Strengths and limitations

Strengths:

- Large and population-based study with high participation rate
- Accurate assessment of the exposure, outcomes and confounders
- Complete follow-up

Weaknesses:

- Competing events
- Retrospective data collection

Introduction

In a recent Swedish cohort study, we found increased 5-year all-cause and disease-specific 5-year mortality following surgery for oesophageal cancer later in the week compared to earlier weekdays, and the association seemed to increase for each weekday (1). The mechanism explaining these associations remains to be identified. Another study from our group revealed that patients who require reoperation within 30 days of oesophageal cancer surgery are at an increased risk of all-cause and disease-specific 5-year mortality, also after excluding mortality occurring within the initial 3 months of surgery (2). Moreover, later weekday of surgery for various elective procedures has been shown to increase the *r*isk of severe postoperative complications, including 30-day mortality (3, 4). Therefore, we hypothesised that occurrence of early and severe postoperative complications requiring reoperation or resulting in mortality explains the association between weekday of surgery and long-term prognosis in oesophageal cancer. This hypothesis was tested in a nationwide Swedish cohort study.

Methods

Design

This was a nationwide Swedish population-based cohort study conducted between 1987 and 2010. Earlier versions of this cohort have been published elsewhere (1, 5-7). The study exposure was the day of the week on which the operation was conducted and the study outcome was reoperations or mortality occurring within 30 days of the oesophagectomy. By including both these outcomes as the main outcome, we avoided errors from competing risks from the fact that those who died within 30 days of surgery could not be recorded with reoperations. The participating patients represented 98% of all oesophageal cancer patients who underwent surgery in Sweden between January 1, 1987 and December 31, 2010. Eligible patients were identified from national Swedish healthcare registers. Clinical data were extracted from medical records, retrieved through our Swedish network of clinicians, established in the mid-1990s as part of a prospective and nationwide case-control study (8). Linkages of data from individuals between registers and the identification of their medical records were enabled by the personal identity number, an individual 10-digit identifier assigned to each Swedish resident upon birth or immigration (9). The study was approved by the Ethical Review Board in Stockholm, Sweden.

Registry data

The Swedish Cancer Registry was used to identify all patients in Sweden with oesophageal cancer, represented by the diagnosis codes 150.0, 150.8, or 150.9 according to the 7th version of the International Classification of Diseases. This register records all cancer diagnoses in Sweden since 1958, and has 98% nationwide coverage of oesophageal cancer (10, 11).

The Swedish Patient Registry provided data on oesophagectomy, co-morbidities, and hospital admittances. This register records all surgical procedures and diagnoses within in-hospital care in Sweden since 1987 (12). The positive predictive value for the recording of oesophageal cancer surgery in this register is 99.6% according to a validation study (13).

The Swedish Causes of Death Registry provided causes and dates of death. This register is nationwide since 1961 and highly complete.

Medical records data

The *medical records* of all participating patients were continuously collected from the operating hospitals, including surgical charts and pathological reviews of the resected specimens. Based on this data collection, we assessed weekday of oesophagectomy, co-morbidity, tumour stage, location, and histology, neoadjuvant therapy, surgery, and annual surgeon volume of oesophagectomies. The reviewers of the medical records were kept blinded from the study outcomes and filled in a predefined protocol. Co-morbidity was assessed according to the well validated Charlson co-morbidity index scoring system (14). Tumour stage was classified according to the TNM classification of the Union Internationale Contre le Cancer (UICC) (15). Neoadjuvant therapy was infrequently used in Sweden during the study period, which was due to the limited support of such treatment until more recently (16).

When used, the neoadjuvant therapy of choice was a combination of chemotherapy and radiotherapy. The dominating (95%) surgical procedure throughout the study period was open transthoracic oesophageal resection with intra-thoracic anastomosis. The preferred

oesophageal substitute was a pulled-up gastric tube, anastomosed to the proximal esophago in the thorax or neck. The surgeon volume variable was created based on a previously described algorithm, where the names of the individual surgeons were used to assign the operation to the most experienced surgeon whenever more than one surgeon conducted the procedure (6).

Statistical analysis

The weekday variable was analysed in two ways. First, surgery during Monday or Tuesday was compared with surgery during Wednesday-Friday. Second, each of the 5 weekdays was analysed as separate categories with Monday as reference. Potential differences in reoperation or mortality within 30 days of surgery between exposure groups were analysed using a multivariable logistic regression, providing odds ratios (ORs) with 95% confidence intervals (CIs) adjusted for potential confounding variables. Seven pre-defined variables were included in the multivariable model: 1) age (continuous variable), 2) sex, 3) co-morbidity (Charlson index score 0, 1, or >1), 4) tumour stage (0-I, II, or III-IV), 5) tumour histology (adenocarcinoma or squamous cell carcinoma), 6) neoadjuvant treatment (yes or no), and 7) annual surgeon volume of oesophagectomies (<17 or ≥17, median number). Furthermore we evaluated if the effect of weekday was modified by surgeon volume by including an interaction term in the model. Thereafter, we derived the ORs for weekday variable within each stratum for surgeon volume. To manage limited missing data (2.8%), a complete case analysis was performed. The statistical software SAS 9.4 (SAS Institute, Cary, NC) was used for the data management and statistical analysis.

Results

Patients

The 1,799 patients who underwent elective surgery for oesophageal cancer during the weekdays Monday to Friday in 1987-2010 represented 98% of all such procedures in Sweden. Of these, 51 (2.8%) were excluded due to missing data in any of the covariates. Table 1 presents characteristics of the final 1,748 study participants, grouped into those with and without reoperation or mortality within 30 days of surgery. There were no major differences in distribution of age, sex, tumour stage, tumour histology or use of neoadjuvant therapy comparing the groups with and without reoperation or mortality within 30 days of surgery, while lower annual surgeon volume was found in the group with poor short-term outcomes.

Risk of postoperative reoperation or mortality

The total rate of reoperation and mortality were 10.9% (n=191) and 5.3% (n=93), respectively. The comparison of surgery later in the week (Wednesday-Friday) with earlier in the week (Monday-Tuesday) showed no increased risk of death or reoperation within 30 days of surgery (adjusted OR=0.99, 95% CI 0.75-1.31) (Table 2). When weekday of surgery was categorised into each of the 5 weekdays, the ORs did not increase from Monday to Friday. A slightly decreased point estimate of reoperation (OR 0.88, 95% CI 0.64-1.21) following later weekday of surgery was counteracted by an increased point estimate of mortality (OR 1.28, 95% CI 0.83-1.99). There was no increased OR of reoperation for anastomotic leak, laparotomy or wound infection associated with later weekday of surgery (Table 2).

The analyses evaluating effect modification by annual surgeon volume did not reveal any statistically significant associations between weekday of surgery and risk of reoperation or mortality within 30 days of surgery for oesophageal cancer (Table 3).

Discussion

This study provides no evidence of an association between later weekday of surgery for oesophageal cancer and risk of early postoperative reoperation or mortality.

Strengths of the present study include the population-based cohort design, accurate assessment of the exposure (weekday of surgery) and outcome (postoperative reoperation or mortality), complete follow-up, adjustment for several potential confounding factors, and the large sample size. A weakness is that the long study period might introduce confounding by changes in treatment or patient selection over time. However, it is unlikely that these changes would influence choice of weekday of surgery, which means that these changes would not act as confounders (17). The results should be generalisable to other western populations of Caucasian origin. A methodological issue is that reoperation and mortality are competing events, since death occurring before any potential later reoperation is not accounted for. Therefore, the combined reoperation/mortality outcome was selected as the main study outcome, while the results regarding the separate reoperation outcomes should be interpreted more cautiously. An observational study can never rule out residual confounding, but the risk of confounding should be counteracted by the fact that we adjusted the risk estimates for the key potential confounding variables. The retrospective collection of data from medical records might introduce bias, but we avoided such error by keeping the researchers collecting and introducing the medical records data without being aware of the study outcome. Finally, the occurrence of the study outcomes was low, which resulted in limited statistical power to detect weak differences, particularly in stratified sub-group analyses.

To the best of our knowledge, there is no previous study addressing weekday of oesophageal cancer surgery in relation to reoperation or short-term mortality. However, large cohort studies evaluating various types of elective surgery have found an increased risk of 30-day mortality associated with a later weekday of surgery (3, 4). This was not found in this study, which might be due to a more limited statistical power compared to the studies addressing many types of surgical procedures. However, it is unlikely that any potentially weakly increased risk of reoperation or short-term mortality would explain the substantially increased long-term mortality associated with later weekdays of oesophageal cancer surgery recently reported (1). This suggests that the weekday effect on long-term prognosis is due to other reasons than poor short-term outcomes, e.g. increased likelihood of tumour recurrence.

Our previous findings of an association between later weekday of surgery and increased risk of long-term mortality and tumour recurrence do not seem to be explained by worse short-term outcomes linked with weekday of surgery (1). It is possible that the tumour dissection is negatively influenced by surgeon fatigue, while this factor does not influence the short-term outcomes. Another hypothesis is that surgery later in the week is associated with a lower lymph node harvest. However, in a separate paper from the same cohort, we have found no prognostic role of lymph node harvest (7). A potential role of non-radical resection in relation to weekday of surgery and long-term survival is another hypothesis worthy of a separate study.

In conclusion, this population-based and nationwide Swedish cohort study found no influence of weekday of oesophageal cancer surgery on risk of reoperations or mortality

within 30 days of surgery. Thus, poor short-term outcomes do not seem to contribute to the association between later weekday of oesophageal cancer surgery and increased 5-year mortality.

Author contributions:

Jesper Lagergren: Substantial contributions to the conception and design, and acquisition and interpretation of the data; Drafting of the paper; Final approval of the version to be published; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Fredrik Mattsson: Substantial contributions to the conception and design, and analysis and interpretation of the data; Revising the paper critically for important intellectual content; Final approval of the version to be published; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Pernilla Lagergren: Substantial contributions to the conception and design, and acquisition and interpretation of the data; Revising the paper critically for important intellectual content; Final approval of the version to be published; Final approval of the version to be published; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing interests: There are no competing interests.

Data sharing statement:

Statistical codes and dataset are available upon request from the corresponding author.

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Table 1. Characteristics of 1748 study patients who underwent surgical resection for oesophageal cancer in Sweden in 1987-2010, with follow-up until 2014.

		No death/reoperation within 30 days of surgery	Death/reoperation within 30 days of surgery
		Number (%)	Number (%)
Total		1490 (100)	258 (100)
Age (years): Mean (standard deviation)		65 (10)	67 (9)
Sex	Male	1110 (74)	195 (76)
	Female	380 (26)	63 (24)
Charlson co-morbidity index	0	870 (58)	145 (56)
	1	306 (21)	57 (22)
	>1	314 (21)	56 (22)
Tumour stage	0-I	357 (24)	54 (21)
	II	535 (36)	104 (40)
	III-IV	598 (40)	100 (39)
Tumour histology	Adenocarcinoma	675 (45)	93 (36)
	Squamous carcinoma	815 (55)	165 (64)
Neoadjuvant therapy	No	1013 (68)	170 (66)
	Yes	477 (32)	88 (34)
Annual surgeon volume	<17	719 (48)	155 (60)
	≥17	771 (52)	103 (40)

Table 2. Risk of death or reoperation within 30 days of surgery for oesophageal cancer. Results presented as odds ratio (OR) with 95% confidence interval (CI).

Weekday of surgery	Death/reoperation (n=258)	Death (n=93)	Reoperation (n=191)	Reoperation for anastomotic leak (n=34)	Reoperation with laparotomy (n=54)	Reoperation for wound infection (n=38)
	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*
Monday-Tuesday	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Wednesday-Friday	0.99 (0.75-1.31)	1.28 (0.83-1.99)	0.88 (0.64-1.21)	0.98 (0.47-2.02)	0.75 (0.42-1.34)	1.44 (0.75-2.79)
Monday	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Tuesday	0.98 (0.69-1.38)	0.61 (0.33-1.11)	1.00 (0.68-1.46)	0.62 (0.26-1.46)	0.92 (0.47-1.80)	0.96 (0.39-2.41)
Wednesday	1.20 (0.81-1.78)	1.16 (0.64-2.11)	1.05 (0.67-1.65)	1.47 (0.62-3.49)	0.74 (0.33-1.69)	1.33 (0.50-3.53)
Thursday	0.86 (0.55-1.34)	0.82 (0.42-1.61)	0.81 (0.49-1.34)	0.15 (0.02-1.17)	0.96 (0.42-2.20)	1.54 (0.58-4.14)
Friday	0.66 (0.34-1.29)	1.04 (0.44-2.44)	0.54 (0.24-1.23)	0.42 (0.05-3.37)	NA	1.33 (0.35-5.13)

*Adjusted for age, sex, Charlson co-morbidity index, tumour stage, tumour histology, neoadjuvant therapy, and surgeon volume.

Table 3. Risk of death or reoperation within 30 days of surgery for oesophageal cancer, stratified for surgeon volume. Results presented as odds ratio (OR) with 95% confidence interval (CI).

Weekday of surgery	Surgeon volume	Death/reoperation (n=258)	Death (n=93)	Reoperation (n=191)	Anastomotic (n=34)	Laparotomy (n=54)	Wound within 30 days (n=38)
		OR (95 % CI)*	OR (95 % CI)*	OR (95 % CI)*	OR (95 % CI)*	OR (95 % CI)*	OR (95 % CI)*
Monday-Tuesday	<17	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Wednesday-Friday	<17	1.02 (0.72-1.46)	1.31 (0.78-2.20)	0.88 (0.58-1.34)	0.64 (0.19-2.16)	0.73 (0.36-1.48)	1.55 (0.69-3.50)
Monday-Tuesday	≥17	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Wednesday-Friday	≥17	0.94 (0.60-1.47)	1.22 (0.54-2.75)	0.87 (0.54-1.42)	1.26 (0.52-3.05)	0.79 (0.28-2.24)	1.25 (0.40-3.87)
Monday	<17	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Tuesday	<17	0.87 (0.54-1.39)	0.55 (0.25-1.17)	0.90 (0.52-1.54)	0.94 (0.23-3.84)	1.55 (0.65-3.67)	0.53 (0.15-1.84)
Wednesday	<17	1.27 (0.78-2.05)	1.24 (0.63-2.45)	1.11 (0.63-1.93)	0.98 (0.22-4.47)	1.29 (0.50-3.33)	1.26 (0.43-3.71)
Thursday	<17	0.74 (0.41-1.32)	0.72 (0.31-1.63)	0.72 (0.37-1.43)	0.43 (0.05-3.90)	0.82 (0.24-2.75)	1.16 (0.35-3.79)
Friday	<17	0.58 (0.25-1.33)	0.92 (0.34-2.49)	0.32 (0.09-1.09)	NA	NA	0.96 (0.19-4.86)
Monday	≥17	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Tuesday	≥17	1.12 (0.67-1.87)	0.73 (0.27-2.00)	1.11 (0.64-1.92)	0.50 (0.17-1.47)	0.36 (0.11-1.20)	2.34 (0.47-11.80)
Wednesday	≥17	1.00 (0.50-2.02)	0.78 (0.20-3.05)	0.89 (0.41-1.94)	1.89 (0.66-5.39)	NA	1.09 (0.10-12.17)
Thursday	≥17	1.06 (0.54-2.05)	1.10 (0.35-3.49)	0.92 (0.44-1.92)	NA	1.14 (0.37-3.53)	2.95 (0.48-18.16)
Friday	≥17	0.85 (0.28-2.59)	1.48 (0.29-7.43)	1.03 (0.33-3.16)	0.85 (0.10-7.18)	NA	2.89 (0.25-33.07)

*Adjusted for age, sex, Charlson co-morbidity index, tumour stage, tumour histology, neoadjuvant therapy, and surgeon volume.

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

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*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	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
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	5-6
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	7
		(*e*) Describe any sensitivity analyses	NA
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	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8 + 13
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	8
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	8 + 14 + 15
		(*b*) Report category boundaries when continuous variables were categorized	8 + 14 + 15
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8 + 14 + 15
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
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	3

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

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