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Surgery during holiday periods and prognosis in oesophageal cancer

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Surgery during holiday periods and prognosis in oesophageal cancer

Running head: Holiday periods and oesophagectomy prognosis

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ABSTRACT (word count 203)

Objective: Previous studies indicate an increased short- and long-term mortality from major cancer surgery performed towards the end of the working week or during the weekend. We hypothesised that the prognosis after major cancer surgery is also negatively influenced by surgery conducted during holiday periods.

Setting: Population-based nationwide Swedish cohort study

Participants: Patients undergoing oesophagectomy for oesophageal cancer between 1987 and 2010. Among 1820 included patients, 206 (11.3%) and 373 (20.5%) patients were operated on during narrow and wide holiday periods, respectively.

Interventions: Narrow (7 weeks) and wide (14 weeks) Swedish holiday periods.

Primary and Secondary Outcome measures: 90-day all-cause, 5-year all-cause and 5-year disease-specific mortality.

Results: Narrow holiday period did not increase all-cause 90-day (HR=0.84, 95% CI 0.53–1.33), all-cause 5-year (HR=1.01, 95% CI 0.85–1.21) or disease-specific 5-year mortality (HR=1.04, 95% CI 0.87–1.26). Similarly, wide holiday period did not increase the risk of 90-day (HR=0.79, 95% CI 0.55–1.13), all-cause 5-year (HR=0.96, 95% CI 0.84–1.1) or disease-specific 5-year mortality (HR=1.03, 95% CI 0.89–1.19).

Conclusions: No measurable effects of holiday periods upon short- or longer term mortality following surgery for oesophageal cancer were observed in this population-based study, indicating that an adequate surgical experience was maintained during holiday periods.

Trial registration: Not applicable

STRENGTHS AND LIMITATIONS

Strengths:

- The population-based design with virtually complete inclusion of all eligible patients in Sweden.
- The large sample size, complete follow-up of all patients, and the adjustment for all relevant confounding factors are other advantages.
- The Swedish system with personal identity numbers of all residents and a nationwide population registry for dates and causes of death enabled complete assessment of mortality, without loss to follow-up.

Limitations

- Retrospective observational in design

INTRODUCTION

Large studies from the UK and US of various elective surgical procedures have shown increased 30-day mortality if the procedures were carried out on Friday or a weekend.[1,2] These results may be attributable to lower staffing density and experience during weekends, and have led to a call for a 7-day working week in the UK healthcare. Other studies have suggested that short- and long-term mortality from major cancer surgery is influenced by both the hospital and surgeon volume,[3–6] and the resources available to the centre to rescue the patient following a major complication.[7] In a recent study, we found an intriguing increased long-term mortality with each later weekday of oesophageal cancer surgery during the weekdays Monday to Friday, particularly for earlier tumour stages.[8] In the present study, we hypothesised that surgical timing with respect to calendar period may also influence the prognosis following major cancer surgery. During holiday periods the experience and density of the surgeons and staff may be lower, which may contribute to worse outcomes. Oesophagectomy for cancer represents the ideal procedure to test this hypothesis, as it is a high-risk elective surgical procedure with a significant rate of measureable short- and long-term mortality and has a stronger association with the experience of the hospital and surgeon than most other procedures.[4] Sweden was considered an ideal country for this study because of its distinct holiday periods. We tested the new hypothesis that major cancer surgery conducted during holiday periods is followed by worse prognosis in a nationwide Swedish study of oesophageal cancer surgery.

METHODS

Study design

The design of this population-based cohort study has been described in detail elsewhere.[9] In brief, this Swedish nationwide cohort study included 98% of all patients with oesophageal cancer treated with curative intended surgery between 1987 and 2010 with follow-up until November 2014. From the Swedish Cancer Registry, patients with a diagnosis of oesophageal cancer (150.0, 150.8, or 150.9) were identified according to the 7th edition of the International Classification of Diseases (ICD7). This Cancer Registry has 98% nationwide coverage of oesophageal cancer.[10,11] Oesophageal cancer patients who underwent oesophagectomy were identified from the Swedish Patient Registry, which has an excellent positive identification rate (99.6%) for oesophageal cancer surgery.[12] The Patient Registry also provided data pertaining to patient medical comorbidities.[12] The comorbidities were classified according to the well-validated Charlson comorbidity index, and we did not count the oesophageal cancer diagnosis.[13] The Swedish Causes of Death Registry provided accurate data for date and causes of death. This Registry has 100% coverage. If the diagnosis oesophageal cancer was listed as a cause of death, this mortality was defined as disease-specific. The Swedish personal identity number, assigned to each Swedish resident at birth or immigration, was used to link individuals' data between registries and to identify their medical records. The clinical data collection was facilitated by a nationwide Swedish clinical network established in the mid-1990s.[14] Medical records containing operation notes and histopathology reports of the cohort members were retrieved from all Swedish hospitals where oesophageal cancer surgery was performed during the

study period. Data concerning neoadjuvant therapy, surgical therapy, names of the surgeons, pathological tumour stage and histological type were obtained from these individual patient records. The histopathological review has been demonstrated for its high accuracy.[15] Neoadjuvant therapy was predominantly used in more recent years, and when used was typically a combination of chemotherapy and radiotherapy. Tumour stage was classified according to the TNM classification of the Union Internationale Contre le Cancer (UICC).[16] Open transthoracic oesophageal resection with intrathoracic anastomosis was the dominating surgical procedure (95%). The Regional Ethical Review Board in Stockholm, Sweden approved the study.

Exposures, outcomes and covariates

The exposures tested were a 7-week "narrow holiday period" (25th June to 15th August) and a 14-week "wide holiday period" (16th December to 7th January and 16th June to 31st August). The outcomes were all-cause 90-day and 5-year mortality as well as disease-specific 5-year mortality. Covariates considered as potential confounding factors were age (continuous variable), pathological TNM stage (0, I, II, III, or IV), Charlson comorbidity index (0, I, or ≥I), neoadjuvant therapy (yes or no), histological type (adenocarcinoma or squamous cell carcinoma), and cumulative surgeon volume of oesophagectomies during study period (≤6, 7–16, or 17–46).

Statistical analysis

Kaplan Meier survival analysis was conducted to visualize crude long-term all-cause and disease-specific mortality. The holiday periods were analysed in relation to mortality using a multivariable Cox-proportional hazards model, providing hazard

ratios (HRs) with 95% confidence intervals (CIs), adjusted for the seven potential confounding factors with categorizations as described above. These factors were included in the multivariable model because of their known prognostic influence. To manage missing data (0.8%), a complete case analysis was carried out. The patients who underwent surgery during the narrow holiday period were compared both with patients outside the narrow holiday period and with those outside the wide holiday period. Since the study period was long, we added a stratified analysis for an earlier calendar period (1987–1999) and a later calendar period (2000–2010). Follow-up ended at the date of death or end of study period, whichever occurred first. The statistical software SPSS 22.0 (Statistical Package for the Social Sciences software, Version 22, SPSS Chicago (IL), USA) was used for the data management and statistical analysis.

RESULTS

Patients

During the study period from 1987 to 2010, 1820 patients who underwent surgery for oesophageal cancer were included. Characteristics of these patients are presented in Table 1. The average age was 65.1 years, with the majority of patients (58.5%) having a Charlson comorbidity index of 0. The incidences of 90-day all-cause, 5-year all-cause and 5-year disease-specific mortality were 11.4%, 74.7% and 79.7%, respectively. In total, 206 (11.3%) and 373 (20.5%) patients were operated on during narrow and wide holiday periods, respectively. Comparison of patient demographics of operated on inside and outside of holiday periods, showed no major differences, except for an increased proportion of patients with Charlson comorbidity index >1 within the holiday periods (Table 1).

Table 1: Characteristics of study patients undergoing surgery for oesophageal cancer in Sweden in 1987–2010.

Variable	Total Number (%)	Narrow holiday period Number (%)		Wide holiday periods Number (%)	
		No (%) (n=1447)	Yes (%) (n=206)	No (%) (n=1447)	Yes (%) (n=373)
Mean age (standard deviation)	65.1 (9.6)	65.1 (9.7)	64.9 (9.0)	65.1 (9.7)	65.2 (9.1)
Charlson comorbidity index					
0	1064 (58.5)	863 (59.6)	108 (52.4)	863 (59.6)	201 (53.9)
1	375 (20.6)	301 (20.8)	45 (21.8)	301 (20.8)	74 (19.8)
>1	381 (20.9)	283 (19.6)	53 (25.7)	283 (19.6)	98 (26.3)
Tumour stage					
0 – I	422 (23.4)	339 (23.6)	52 (25.4)	339 (23.6)	83 (22.3)
II	662 (36.7)	523 (36.5)	76 (37.1)	523 (36.5)	139 (37.4)
III – IV	722 (40.0)	572 (39.9)	77 (37.6)	572 (39.9)	150 (40.3)
Tumour histology					
Adenocarcinoma	792 (43.6)	639 (44.3)	83 (40.5)	639 (44.3)	153(41.1)
Squamous cell carcinoma	1024 (56.4)	805 (55.7)	122 (59.5)	805 (55.7)	219 (58.9)
Neoadjuvant therapy					
No	1231 (67.7)	986 (68.2)	131 (63.6)	986 (68.2)	245 (65.7)
Yes	587 (32.3)	459 (31.8)	75 (36.4)	459 (31.8)	128 (34.3)
Cumulative surgeon volume					
≤6	1108 (63.0)	880 (62.8)	127 (64.8)	880 (62.8)	228 (63.5)
7 – 16	569 (32.3)	455 (32.5)	60 (30.6)	455 (32.5)	114 (31.8)
17 – 46	83 (4.7)	66 (4.7)	9 (4.6)	66 (4.7)	17 (4.7)
Calendar period					
1987 – 1999	992 (54.5)	790 (54.6)	112 (54.4)	790 (54.6)	202 (54.2)
2000 – 2010	828 (45.5)	657 (45.4)	94 (45.6)	657 (45.4)	171 (45.8)

*Patients who underwent surgery during the narrow holiday period were compared both with patients outside the narrow holiday period and with those outside the wide holiday period.

Narrow holiday period and mortality

Kaplan-Meier survival analysis showed that oesophagectomy during the narrow holiday period did not affect all-cause 90-day (P=0.84), all-cause 5-year (P=0.97) (Figure 1) or disease-specific 5-year mortality (P=0.79). Regression analysis with adjustment for potential confounders further showed that narrow holiday period did not increase the risk of all-cause 90-day (HR=0.84, 95% CI 0.53–1.33), all-cause 5-year (HR=1.01, 95% CI 0.85–1.21) or disease-specific 5-year mortality (HR=1.04, 95% CI 0.87–1.26) (Table 2). Stratified analysis for earlier and later calendar periods showed no association between surgery during narrow holiday period and the risk of all-cause 90-day, all-cause 5-year or disease-specific 5-year mortality (data not shown).

Table 2: Oesophageal cancer surgery during narrow holiday period (7 weeks) and hazard ratios (HR) with 95% confidence intervals (CI) of mortality.

	90-day all-cause mortality	5-year all-cause mortality	5-year disease-specific mortality
Variable	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Narrow holiday period$^{\Psi}$*			
No	1 (reference)	1 (reference)	1 (reference)
Yes	0.84 (0.53 – 1.33)	1.01 (0.85 – 1.21)	1.04 (0.87 – 1.26)
Wide holiday period$^{\Psi}$**			
No	1 (reference)	1 (reference)	1 (reference)
Yes	0.79 (0.55 – 1.13)	0.96 (0.84 – 1.1)	1.03 (0.89 – 1.19)

$^{\Psi}$ Adjusted for age, tumour stage, tumour histology, Charlson comorbidity score, neoadjuvant therapy, surgeon volume and narrow/wide holiday period.

* Narrow holiday period is period of 7 weeks from 25th June to 15th August.

** Wide holiday period is period of 14 weeks from 16th December to 7th January and 16th June to 31st August.

Wide holiday period and mortality

Kaplan-Meier survival analysis showed that oesophagectomy during wide holiday periods did not affect all-cause 90-day (P=0.43), all-cause 5-year (P=0.77) (Figure 2) or disease-specific 5-year mortality (P=0.90). Regression analysis with adjustment for relevant confounders further showed no increased risk of all-cause 90-day (HR=0.79, 95% CI 0.55–1.13), all-cause 5-year (HR=0.96, 95% CI 0.84–1.1) or disease-specific 5-year mortality (HR=1.03, 95% CI 0.89–1.19) (Table 2). The analysis stratified for calendar periods showed no association between surgery during wide holiday period and the risk of all-cause 90-day, all-cause 5-year and disease-specific 5-year mortality (data not shown).

DISCUSSION

The results of this study disprove the hypothesis that oesophageal cancer surgery conducted during holiday periods increases the risk of short- or long-term mortality.

The population-based design with virtually complete inclusion of all eligible patients in Sweden is a major strength of the study. The large sample size, complete follow-up of all patients, and the adjustment for all relevant confounding factors are other advantages. There are also limitations associated with retrospective observational studies such as this. However, the cohort utilised for this study has high accuracy in the correct identification of patients undergoing oesophagectomy for cancer, and the clinical data were collected from extensive review of medical records, which made it possible to have accurate and detailed information on exposures and covariates, not the least on key variables like date of surgery, surgeons' names and tumour stage. Finally, the Swedish system with personal identity numbers of all residents and a nationwide population registry for dates and causes of death enabled complete assessment of mortality, without loss to follow-up.

The present study shows that during narrow and wider holiday periods when staffing levels are potentially less experienced and somewhat depleted, there is no effect upon postoperative short- or long-term mortality. In view of the strong association between surgeon volume of oesophagectomies and mortality,[4–6] these results reassuringly indicate that the experience of the surgeons is well maintained during holiday periods, at least in Sweden. This might be due to good planning of procedures to when the experienced surgeons are available during holiday periods

and to well-working referral systems of patients to other hospitals where the required expertise is available even during holiday periods.

To the best of our knowledge, this is the first study to examine the effect of cancer surgery during holiday periods on mortality. Thus, more research is needed and one should be cautious when considering any administrative or structural recommendations based upon the findings of this single study. It would be of interest to consider an alternative population where the presence of surgical experience during the holiday period might be lower, to further investigate this hypothesis.

The negative results of the present study might be generalizable to other cancer surgical procedures. In the absence of any effect of surgery during holiday periods of for oesophageal cancer on mortality, it seems unlikely that any such effect would exist for cancer procedures where the influence of surgeon volume is absent or weaker.

In conclusion, this large national study has demonstrated no worse mortality following major cancer surgery, in this study exemplified by oesophageal cancer surgery, during holiday periods. The benefit of ensuring a strategy for maintaining an adequate surgical experience even during holiday periods is recommended.

Contributorship statement

Sheraz R. Markar; conception and design, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript.

Karl Wahlin; data analysis and interpretation, manuscript writing and final approval of manuscript.

Fredrik Mattsson; data analysis and interpretation, manuscript writing and final approval of manuscript.

Pernilla Lagergren; conception and design, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript.

Jesper Lagergren; conception and design, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript.

Competing interests

No support from any organisation for the submitted work; no financial relationships with any organisations that might have an interested in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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Data sharing statement

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REFERENCES

1. Aylin P, Alexandrescu R, Jen MH, et al. Day of week of procedure and 30 day mortality for elective surgery: retrospective analysis of hospital episode statistics. BMJ (Clinical research ed 2013;346:f2424.
2. Zare MM, Itani KM, Schifftner TL, et al. Mortality after nonemergent major surgery performed on Friday versus Monday through Wednesday. Annals of surgery 2007;246:866-74.
3. Markar SR, Karthikesalingam A, Thrumurthy S, et al. Volume-outcome relationship in surgery for esophageal malignancy: systematic review and meta-analysis 2000 – 2011. J Gastrointest Surg 2012; 16: 1055 – 1063.
4. Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. N Engl J Med 2011; 364: 2128 – 2137.
5. Brusselaers N, Mattsson F, Lagergren J. Hospital and surgeon volume in relation to long-term survival after oesophagectomy: systematic review and meta-analysis. Gut 2014; 63: 1393–1400.
6. Derogar M, Sadr-Azodi O, Johar A, et al. Hospital and surgeon volume in relation to survival after esophageal cancer surgery in a population-based study. J Clin Oncol 2013; 311: 551–557.
7. Almoudaris A, Mamidanna R, Bottle A, et al. Failure to rescue patients after reintervention in gastroesophageal cancer surgery in England. JAMA Surg 2013; 148: 272 – 276.
8. Lagergren J, Mattsson F, Lagergren P. Weekday of oesophageal cancer surgery and its relation to prognosis. Annals of surgery 2015;in press.
9. van der Schaaf M, Johar A, Wijnhoven B, et al. Extent of lymph node removal during esophageal cancer surgery and survival. J Natl Cancer Inst 2015; 107: djv043

10. Barlow L, Westergren K, Holmberg L, et al. The completeness of the Swedish cancer register: a sample survey for year 1998; Acta Oncol 2009; 48: 27–33.
11. Lindblad M, Ye W, Lindgren A, et al. Disparities in the classification of esophageal and cardia adenocarcinomas and their influence on reported incidence rates. Ann Surg 2006; 243: 479–485.
12. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011; 11: 450.
13. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40: 373-83.
14. Lagergren J, Bergstrom R, Lindgren A, et al. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999; 340: 825–831.
15. Rouvelas I, Zeng W, Lindblad M, et al. Survival after surgery for oesophageal cancer: a population-based study. Lancet Oncol. 2005; 6: 864–870.
16. Sobin LH, Gospodarowicz MK, Wittekind C. UICC TNM classification of malignant tumors, 7th edition. Wiley Blackwell; 2009.

FIGURE LEGENDS

Figure 1: Kaplan-Meier survival curve for the effect of surgery of oesophageal cancer during a narrow holiday period (7 weeks) upon all-cause 5-year survival.

Figure 2: Kaplan-Meier survival curve for the effect of surgery for oesophageal cancer during a wide holiday period (14 weeks) upon all-cause 5-year survival.

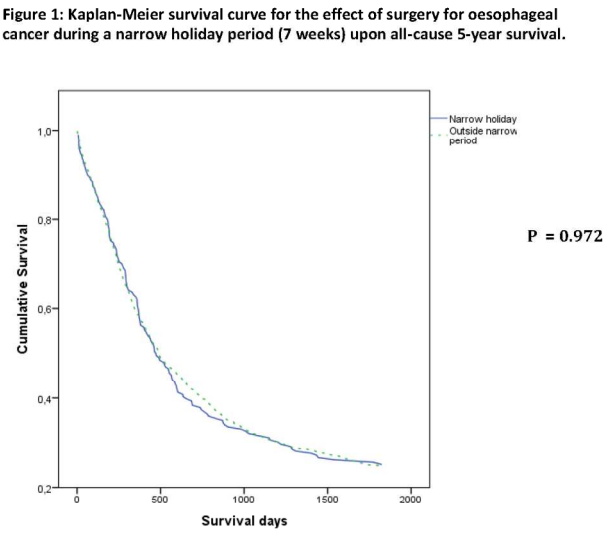

Figure 1: Kaplan-Meier survival curve for the effect of surgery of oesophageal cancer during a narrow holiday period (7 weeks) upon all-cause 5-year survival.

209x297mm (200 x 200 DPI)

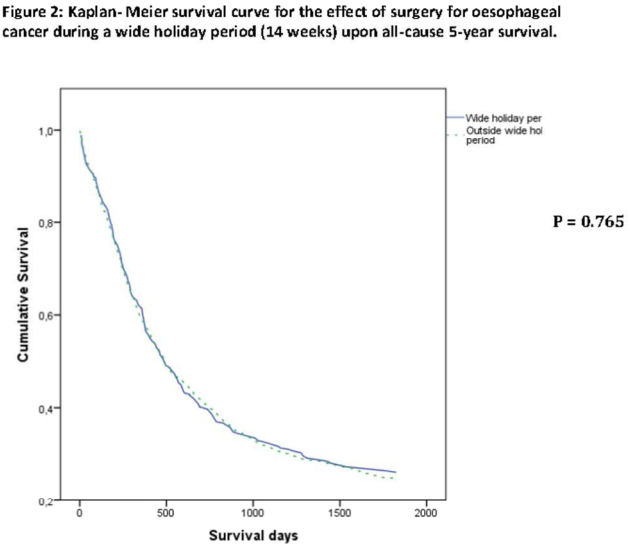

Figure 2: Kaplan-Meier survival curve for the effect of surgery for oesophageal cancer during a wide holiday period (14 weeks) upon all-cause 5-year survival.

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Secondary Subject Heading:	Health policy, Health services research, Oncology
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Surgery during holiday periods and prognosis in oesophageal cancer – a population-based nationwide Swedish cohort study

Running head: Holiday periods and oesophagectomy prognosis

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Setting: Population-based nationwide Swedish cohort study

Participants: Patients undergoing oesophagectomy for oesophageal cancer between 1987 and 2010. Among 1820 included patients, 206 (11.3%) and 373 (20.5%) patients were operated on during narrow and wide holiday periods, respectively.

Interventions: Narrow (7 weeks) and wide (14 weeks) Swedish holiday periods.

Primary and Secondary Outcome measures: 90-day all-cause, 5-year all-cause and 5-year disease-specific mortality.

Results: Narrow holiday period did not increase all-cause 90-day (HR=0.84, 95% CI 0.53–1.33), all-cause 5-year (HR=1.01, 95% CI 0.85–1.21) or disease-specific 5-year mortality (HR=1.04, 95% CI 0.87–1.26). Similarly, wide holiday period did not increase the risk of 90-day (HR=0.79, 95% CI 0.55–1.13), all-cause 5-year (HR=0.96, 95% CI 0.84–1.1) or disease-specific 5-year mortality (HR=1.03, 95% CI 0.89–1.19).

Conclusions: No measurable effects of holiday periods upon short- or longer term mortality following surgery for oesophageal cancer were observed in this population-based study, indicating that an adequate surgical experience was maintained during holiday periods.

Trial registration: Not applicable

STRENGTHS AND LIMITATIONS

Strengths:

- The population-based design with virtually complete inclusion of all eligible patients in Sweden.
- The large sample size, complete follow-up of all patients, and the adjustment for all relevant confounding factors are other advantages.
- The Swedish system with personal identity numbers of all residents and a nationwide population registry for dates and causes of death enabled complete assessment of mortality, without loss to follow-up.

Limitations

- Retrospective observational in design

INTRODUCTION

Large studies from the UK and US of various elective surgical procedures have shown increased 30-day mortality if the procedures were carried out on Friday or a weekend.[1,2] These results may be attributable to lower staffing density and experience during weekends, and have led to a call for a 7-day working week in the UK healthcare. Other studies have suggested that short- and long-term mortality from major cancer surgery is influenced by both the hospital and surgeon volume,[3–6] and the resources available to the centre to rescue the patient following a major complication.[7] In a recent study, we found an intriguing increased long-term mortality with each later weekday of oesophageal cancer surgery during the weekdays Monday to Friday, particularly for earlier tumour stages.[8] In the present study, we hypothesised that surgical timing with respect to calendar period may also influence the prognosis following major cancer surgery. During holiday periods the experience and density of the surgeons and staff may be lower, which may contribute to worse outcomes. Oesophagectomy for cancer represents the ideal procedure to test this hypothesis, as it is a high-risk elective surgical procedure with a significant rate of measureable short- and long-term mortality and has a stronger association with the experience of the hospital and surgeon than most other procedures.[4] Sweden was considered an ideal country for this study because of its distinct holiday periods. We tested the new hypothesis that major cancer surgery conducted during holiday periods is followed by worse prognosis in a nationwide Swedish study of oesophageal cancer surgery.

METHODS

Study design

The design of this population-based cohort study has been described in detail elsewhere.[9] In brief, this Swedish nationwide cohort study included 98% of all patients with oesophageal cancer treated with curative intended surgery between 1987 and 2010 with follow-up until November 2014. From the Swedish Cancer Registry, patients with a diagnosis of oesophageal cancer (150.0, 150.8, or 150.9) were identified according to the 7th edition of the International Classification of Diseases (ICD7). This Cancer Registry has 98% nationwide coverage of oesophageal cancer.[10,11] Oesophageal cancer patients who underwent oesophagectomy were identified from the Swedish Patient Registry, which has an excellent positive identification rate (99.6%) for oesophageal cancer surgery.[12] The Patient Registry also provided data pertaining to patient medical comorbidities.[12] The comorbidities were classified according to the well-validated Charlson comorbidity index, and we did not count the oesophageal cancer diagnosis.[13] The Swedish Causes of Death Registry provided accurate data for date and causes of death. This Registry has 100% coverage. If the diagnosis oesophageal cancer was listed as a cause of death, this mortality was defined as disease-specific. The Swedish personal identity number, assigned to each Swedish resident at birth or immigration, was used to link individuals' data between registries and to identify their medical records. The clinical data collection was facilitated by a nationwide Swedish clinical network established in the mid-1990s.[14] Medical records containing operation notes and histopathology reports of the cohort members were retrieved from all Swedish hospitals where oesophageal cancer surgery was performed during the

study period. Data concerning neoadjuvant therapy, surgical therapy, names of the surgeons, pathological tumour stage and histological type were obtained from these individual patient records. The histopathological review has been demonstrated for its high accuracy.[15] Neoadjuvant therapy was predominantly used in more recent years, and when used was typically a combination of chemotherapy and radiotherapy. Tumour stage was classified according to the TNM classification of the Union Internationale Contre le Cancer (UICC).[16] Open transthoracic oesophageal resection with intrathoracic anastomosis was the dominating surgical procedure (95%). The Regional Ethical Review Board in Stockholm, Sweden approved the study.

Exposures, outcomes and covariates

The exposures tested were a 7-week "narrow holiday period" (25th June to 15th August) and a 14-week "wide holiday period" (16th December to 7th January and 16th June to 31st August). The outcomes were all-cause 90-day and 5-year mortality as well as disease-specific 5-year mortality. Covariates considered as potential confounding factors were age (continuous variable), pathological TNM stage (0, I, II, III, or IV), Charlson comorbidity index (0, I, or ≥I), neoadjuvant therapy (yes or no), histological type (adenocarcinoma or squamous cell carcinoma), and cumulative surgeon volume of oesophagectomies during study period (≤6, 7–16, or 17–46).

Statistical analysis

Kaplan Meier survival analysis was conducted to visualize crude long-term all-cause and disease-specific mortality. The holiday periods were analysed in relation to mortality using a multivariable Cox-proportional hazards model, providing hazard

ratios (HRs) with 95% confidence intervals (CIs), adjusted for the seven potential confounding factors with categorizations as described above. These factors were included in the multivariable model because of their known prognostic influence. To manage missing data (0.8%), a complete case analysis was carried out. The patients who underwent surgery during the narrow holiday period were compared both with patients outside the narrow holiday period and with those outside the wide holiday period. Since the study period was long, we added a stratified analysis for an earlier calendar period (1987–1999) and a later calendar period (2000–2010). Follow-up ended at the date of death or end of study period, whichever occurred first. The statistical software SPSS 22.0 (Statistical Package for the Social Sciences software, Version 22, SPSS Chicago (IL), USA) was used for the data management and statistical analysis.

RESULTS

Patients

During the study period from 1987 to 2010, 1820 patients who underwent surgery for oesophageal cancer were included. Characteristics of these patients are presented in Table 1. The average age was 65.1 years, with the majority of patients (58.5%) having a Charlson comorbidity index of 0. The incidences of 90-day all-cause, 5-year all-cause and 5-year disease-specific mortality were 11.4%, 74.7% and 79.7%, respectively. In total, 206 (11.3%) and 373 (20.5%) patients were operated on during narrow and wide holiday periods, respectively. Comparison of patient demographics of operated on inside and outside of holiday periods, showed no major differences, except for an increased proportion of patients with Charlson comorbidity index >1 within the holiday periods (Table 1).

Table 1: Characteristics of study patients undergoing surgery for oesophageal cancer in Sweden in 1987–2010.

Variable	Total Number (%)	Narrow holiday period Number (%)		Wide holiday periods Number (%)	
		No (%) (n=1447)	Yes (%) (n=206)	No (%) (n=1447)	Yes (%) (n=373)
Mean age (standard deviation)	65.1 (9.6)	65.1 (9.7)	64.9 (9.0)	65.1 (9.7)	65.2 (9.1)
Charlson comorbidity index					
0	1064 (58.5)	863 (59.6)	108 (52.4)	863 (59.6)	201 (53.9)
1	375 (20.6)	301 (20.8)	45 (21.8)	301 (20.8)	74 (19.8)
>1	381 (20.9)	283 (19.6)	53 (25.7)	283 (19.6)	98 (26.3)
Tumour stage					
0 – I	422 (23.4)	339 (23.6)	52 (25.4)	339 (23.6)	83 (22.3)
II	662 (36.7)	523 (36.5)	76 (37.1)	523 (36.5)	139 (37.4)
III – IV	722 (40.0)	572 (39.9)	77 (37.6)	572 (39.9)	150 (40.3)
Tumour histology					
Adenocarcinoma	792 (43.6)	639 (44.3)	83 (40.5)	639 (44.3)	153(41.1)
Squamous cell carcinoma	1024 (56.4)	805 (55.7)	122 (59.5)	805 (55.7)	219 (58.9)
Neoadjuvant therapy					
No	1231 (67.7)	986 (68.2)	131 (63.6)	986 (68.2)	245 (65.7)
Yes	587 (32.3)	459 (31.8)	75 (36.4)	459 (31.8)	128 (34.3)
Cumulative surgeon volume					
≤6	1108 (63.0)	880 (62.8)	127 (64.8)	880 (62.8)	228 (63.5)
7 – 16	569 (32.3)	455 (32.5)	60 (30.6)	455 (32.5)	114 (31.8)
17 – 46	83 (4.7)	66 (4.7)	9 (4.6)	66 (4.7)	17 (4.7)
Calendar period					
1987 – 1999	992 (54.5)	790 (54.6)	112 (54.4)	790 (54.6)	202 (54.2)
2000 – 2010	828 (45.5)	657 (45.4)	94 (45.6)	657 (45.4)	171 (45.8)

*Patients who underwent surgery during the narrow holiday period were compared both with patients outside the narrow holiday period and with those outside the wide holiday period.

Narrow holiday period and mortality

Kaplan-Meier survival analysis showed that oesophagectomy during the narrow holiday period did not affect all-cause 90-day (P=0.84), all-cause 5-year (P=0.97) (Figure 1) or disease-specific 5-year mortality (P=0.79). Regression analysis with adjustment for potential confounders further showed that narrow holiday period did not increase the risk of all-cause 90-day (HR=0.84, 95% CI 0.53–1.33), all-cause 5-year (HR=1.01, 95% CI 0.85–1.21) or disease-specific 5-year mortality (HR=1.04, 95% CI 0.87–1.26) (Table 2). Stratified analysis for earlier and later calendar periods showed no association between surgery during narrow holiday period and the risk of all-cause 90-day, all-cause 5-year or disease-specific 5-year mortality (data not shown).

Table 2: Oesophageal cancer surgery during narrow holiday period (7 weeks) and hazard ratios (HR) with 95% confidence intervals (CI) of mortality.

	90-day all-cause mortality	5-year all-cause mortality	5-year disease-specific mortality
Variable	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Narrow holiday period$^{\Psi}$*			
No	1 (reference)	1 (reference)	1 (reference)
Yes	0.84 (0.53 – 1.33)	1.01 (0.85 – 1.21)	1.04 (0.87 – 1.26)
Wide holiday period$^{\Psi}$**			
No	1 (reference)	1 (reference)	1 (reference)
Yes	0.79 (0.55 – 1.13)	0.96 (0.84 – 1.1)	1.03 (0.89 – 1.19)

$^{\Psi}$ Adjusted for age, tumour stage, tumour histology, Charlson comorbidity score, neoadjuvant therapy, surgeon volume and narrow/wide holiday period.

* Narrow holiday period is period of 7 weeks from 25th June to 15th August.

** Wide holiday period is period of 14 weeks from 16th December to 7th January and 16th June to 31st August.

Wide holiday period and mortality

Kaplan-Meier survival analysis showed that oesophagectomy during wide holiday periods did not affect all-cause 90-day (P=0.43), all-cause 5-year (P=0.77) (Figure 2) or disease-specific 5-year mortality (P=0.90). Regression analysis with adjustment for relevant confounders further showed no increased risk of all-cause 90-day (HR=0.79, 95% CI 0.55–1.13), all-cause 5-year (HR=0.96, 95% CI 0.84–1.1) or disease-specific 5-year mortality (HR=1.03, 95% CI 0.89–1.19) (Table 2). The analysis stratified for calendar periods showed no association between surgery during wide holiday period and the risk of all-cause 90-day, all-cause 5-year and disease-specific 5-year mortality (data not shown).

DISCUSSION

The results of this study disprove the hypothesis that oesophageal cancer surgery conducted during holiday periods increases the risk of short- or long-term mortality.

The population-based design with virtually complete inclusion of all eligible patients in Sweden is a major strength of the study. The large sample size, complete follow-up of all patients, and the adjustment for all relevant confounding factors are other advantages. There are also limitations associated with retrospective observational studies such as this. However, the cohort utilised for this study has high accuracy in the correct identification of patients undergoing oesophagectomy for cancer, and the clinical data were collected from extensive review of medical records, which made it possible to have accurate and detailed information on exposures and covariates, not the least on key variables like date of surgery, surgeons' names and tumour stage. Finally, the Swedish system with personal identity numbers of all residents and a nationwide population registry for dates and causes of death enabled complete assessment of mortality, without loss to follow-up.

The present study shows that during narrow and wider holiday periods when staffing levels are potentially less experienced and somewhat depleted, there is no effect upon postoperative short- or long-term mortality. In view of the strong association between surgeon volume of oesophagectomies and mortality,[4–6] these results reassuringly indicate that the experience of the surgeons is well maintained during holiday periods, at least in Sweden. This might be due to good planning of procedures to when the experienced surgeons are available during holiday periods

and to well-working referral systems of patients to other hospitals where the required expertise is available even during holiday periods.

To the best of our knowledge, this is the first study to examine the effect of cancer surgery during holiday periods on mortality. Thus, more research is needed and one should be cautious when considering any administrative or structural recommendations based upon the findings of this single study. It would be of interest to consider an alternative population where the presence of surgical experience during the holiday period might be lower, or in a centralised cancer service like the United Kingdom, to further investigate this hypothesis. In a modern era with a low rate of perioperative mortality further studies may also include assessment of more subtle outcomes from oesophagectomy including complications, length of hospital stay and hospital transfer.

The negative results of the present study might be generalizable to other cancer surgical procedures. In the absence of any effect of surgery during holiday periods of for oesophageal cancer on mortality, it seems unlikely that any such effect would exist for cancer procedures where the influence of surgeon volume is absent or weaker.

In conclusion, this large national study has demonstrated no worse mortality following major cancer surgery, in this study exemplified by oesophageal cancer surgery, during holiday periods. The benefit of ensuring a strategy for maintaining an adequate surgical experience even during holiday periods is recommended.

Contributorship statement

Sheraz R. Markar; conception and design, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript.

Karl Wahlin; data analysis and interpretation, manuscript writing and final approval of manuscript.

Fredrik Mattsson; data analysis and interpretation, manuscript writing and final approval of manuscript.

Pernilla Lagergren; conception and design, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript.

Jesper Lagergren; conception and design, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript.

Competing interests

No support from any organisation for the submitted work; no financial relationships with any organisations that might have an interested in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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Data sharing statement

Statistical codes and the dataset are available from the senior investigator JL (jesper.lagergren@ki.se) at the research group Upper Gastrointestinal Surgery, Department of Molecular medicine and Surgery, Karolinska Institutet, Stockholm Sweden, who will provide a permanent and citable home for the dataset.

REFERENCES

1. Aylin P, Alexandrescu R, Jen MH, et al. Day of week of procedure and 30 day mortality for elective surgery: retrospective analysis of hospital episode statistics. BMJ (Clinical research ed 2013;346:f2424.
2. Zare MM, Itani KM, Schifftner TL, et al. Mortality after nonemergent major surgery performed on Friday versus Monday through Wednesday. Annals of surgery 2007;246:866-74.
3. Markar SR, Karthikesalingam A, Thrumurthy S, et al. Volume-outcome relationship in surgery for esophageal malignancy: systematic review and meta-analysis 2000 – 2011. J Gastrointest Surg 2012; 16: 1055 – 1063.
4. Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. N Engl J Med 2011; 364: 2128 – 2137.
5. Brusselaers N, Mattsson F, Lagergren J. Hospital and surgeon volume in relation to long-term survival after oesophagectomy: systematic review and meta-analysis. Gut 2014; 63: 1393–1400.
6. Derogar M, Sadr-Azodi O, Johar A, et al. Hospital and surgeon volume in relation to survival after esophageal cancer surgery in a population-based study. J Clin Oncol 2013; 311: 551–557.
7. Almoudaris A, Mamidanna R, Bottle A, et al. Failure to rescue patients after reintervention in gastroesophageal cancer surgery in England. JAMA Surg 2013; 148: 272 – 276.
8. Lagergren J, Mattsson F, Lagergren P. Weekday of oesophageal cancer surgery and its relation to prognosis. Annals of surgery 2015;in press.
9. van der Schaaf M, Johar A, Wijnhoven B, et al. Extent of lymph node removal during esophageal cancer surgery and survival. J Natl Cancer Inst 2015; 107: djv043

10. Barlow L, Westergren K, Holmberg L, et al. The completeness of the Swedish cancer register: a sample survey for year 1998; Acta Oncol 2009; 48: 27–33.

11. Lindblad M, Ye W, Lindgren A, et al. Disparities in the classification of esophageal and cardia adenocarcinomas and their influence on reported incidence rates. Ann Surg 2006; 243: 479–485.

12. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011; 11: 450.

13. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40: 373-83.

14. Lagergren J, Bergstrom R, Lindgren A, et al. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999; 340: 825–831.

15. Rouvelas I, Zeng W, Lindblad M, et al. Survival after surgery for oesophageal cancer: a population-based study. Lancet Oncol. 2005; 6: 864–870.

16. Sobin LH, Gospodarowicz MK, Wittekind C. UICC TNM classification of malignant tumors, 7th edition. Wiley Blackwell; 2009.

FIGURE LEGENDS

Figure 1: Kaplan-Meier survival curve for the effect of surgery of oesophageal cancer during a narrow holiday period (7 weeks) upon all-cause 5-year survival.

Figure 2: Kaplan-Meier survival curve for the effect of surgery for oesophageal cancer during a wide holiday period (14 weeks) upon all-cause 5-year survival.

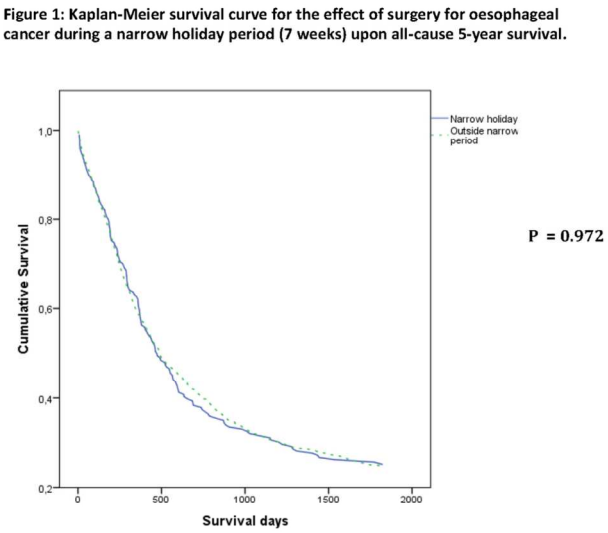

Figure 1: Kaplan-Meier survival curve for the effect of surgery of oesophageal cancer during a narrow holiday period (7 weeks) upon all-cause 5-year survival.

127x180mm (300 x 300 DPI)

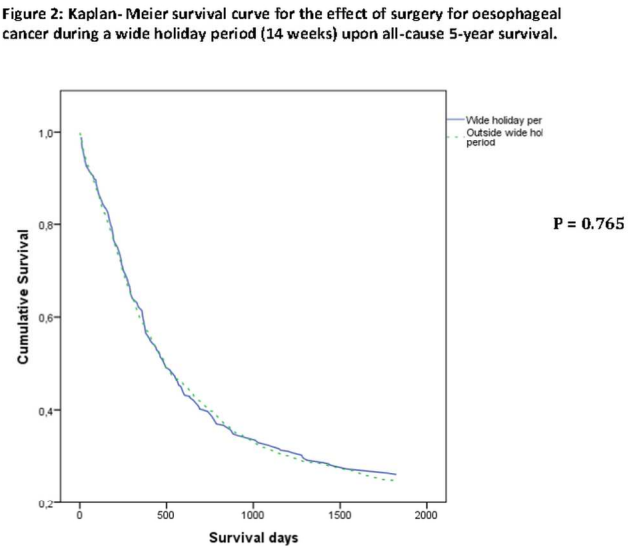

Figure 2: Kaplan-Meier survival curve for the effect of surgery for oesophageal cancer during a wide holiday period (14 weeks) upon all-cause 5-year survival.

127x180mm (300 x 300 DPI)