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Short title: Cancer surgery during holiday periods

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Research Article

Novelty and impact:

Surgery is the mainstay curative treatment in most solid cancer types. This study found that cancer surgery performed during holiday periods is associated with worse prognosis than for non-holiday periods for several cancer sites, particularly for cancer of the breast and liver-pancreas-bile ducts, and in sub-groups of cancer of the colon-rectum, head-and-neck, prostate, kidney-urine bladder, and thyroid. These findings highlight the importance of maintaining sufficient surgical expertise for certain cancer procedures during holiday periods.

Abstract

Surgery is the mainstay curative treatment in most cancer. We aimed to test the new hypothesis that cancer surgery performed during holiday periods is associated with worse long-term prognosis than for non-holiday periods. This nationwide Swedish population-based cohort study included 228,927 patients during 1997-2014 who underwent elective resectional surgery for a cancer where the annual number of resections was over 100. The 16 eligible cancer sites were grouped into 10 cancer groups. The exposure, holiday periods, was classified as wide (14-weeks) or narrow (7-weeks). Surgery conducted inside versus outside holiday periods was compared regarding overall disease-specific (main outcome) and overall all-cause (secondary outcome) mortality. Cox regression provided hazard ratios (HR) with 95% confidence intervals (CI) adjusted for age, sex, comorbidity, hospital volume, calendar period, and tumor stage. Surgery conducted during wide and narrow holiday periods were associated with increased HRs of disease-specific mortality for cancer of the breast (HR 1.08, 95% CI 1.03-1.13 and HR 1.06, 95% CI 1.01-1.12) and possibly of cancer of the liver-pancreas-bile ducts (HR 1.09, 95% CI 0.99-1.20 and HR 1.12, 95% CI 0.99-1.26). Sub-groups with cancer of the colon-rectum, head-and-neck, prostate, kidney-urine bladder, and thyroid also experienced statistically significantly worse prognosis following surgery conducted during holiday periods. No influence of surgery during holiday was detected for cancer of the esophagus-stomach, lung, or ovary-uterus. All-cause HRs were similar to the disease-specific HRs. The prognosis following cancer surgery might not be fully maintained during holiday periods for all cancer sites.

Introduction

Cancer is a major public health concern and the overall cancer incidence is increasing.[1] Despite all efforts to add and improve non-surgical cancer treatments, surgery remains the primary curative treatment for most solid carcinomas.[2] Of the 15.2 million individuals diagnosed with cancer in 2015 worldwide, over 80% needed surgery.[2] Cancer surgical research has often focused on short-term outcomes, and the 30-day mortality rate has reduced to <5% even for extensive cancer procedures. The vast majority of patients who die within 5 years of cancer surgery die from tumor recurrence, however, and in terms of saved lives in cancer there is much to gain from improving the long-term prognosis. It is known that annual surgery volume strongly influences the prognosis of some cancers,[3, 4] but otherwise, research examining opportunities for improvements in surgical strategies is limited. The hypothesis of the present study was that the timing of cancer surgery within holiday periods negatively influences long-term prognosis. To the best of our knowledge there are no previous studies that have tested this hypothesis. During holiday periods the availability of surgeons with expertise and experience in certain cancer procedures might be limited or absent in some hospitals, which may result in worse outcomes after cancer surgery. In Sweden, the holiday periods (mid-June to end of August and mid-December to mid-January) are more distinct than in most other countries, making this country an ideal base for the present study. With the aim of evaluating the association between the timing of major cancer surgery regarding holiday periods and long-term prognosis, we therefore conducted a nationwide Swedish study including all common cancer groups where surgery is the primary therapy.

Methods

Design

This was a population-based nationwide Swedish cohort study conducted during the period January 1, 1997 to December 31, 2014. We followed a detailed study protocol finalized before initiation of any analyses. The study exposure was the timing of cancer surgery within or outside holiday periods. The main outcome was overall disease-specific mortality, while overall all-cause mortality was the secondary outcome. Included in the cohort were patients who had undergone elective resectional surgery for cancer sites where surgery is the primary treatment. The data sources were high-quality and complete nationwide Swedish registers for cancer (Cancer Registry), all diagnoses and surgical procedures (Patient Registry), and mortality (Causes of Death Registry). Accurate linkage of each participant's information between registers was possible through the unique 10-digit personal identity number given to all Swedish residents upon birth or immigration. This identifier has been validated as a highly robust tool for linkages in register-based research.[5] The study was approved by the Regional Ethical Review Board in Stockholm (2015/1916-31/1).

Cohort

Selected as cohort members were adult patients (at least 18 years) who had undergone elective (planned) surgical resection corresponding in site and time with the primary cancer diagnosis. Only carcinomas of sites where a yearly average of at least 100 operations was conducted in Sweden during the study period were included. Resectional surgery was identified from the Swedish Patient Registry and cancer diagnoses were retrieved from the Swedish Cancer Registry. The operations were defined by codes in the Swedish Classification of Surgical Procedures from 1997 onwards. Sixteen eligible cancer sites were identified:

esophagus, stomach, liver, pancreas, bile ducts, colon, rectum, head-and-neck, lung, thyroid, breast, kidney, urine bladder, prostate, ovary, and uterus. These were further combined into 10 cancer groups on the basis of anatomical proximity, shared clinical characteristics (diagnostic procedures, treatment, and prognosis), and surgical sub-specialty performing the operations: esophagus-stomach, liver-pancreas-bile ducts, colon-rectum, head-and-neck, lung, thyroid, breast, kidney-urine bladder, prostate, and ovary-uterus.

Exposure

The study exposure was the timing of surgery within or outside holiday periods. We considered two holiday periods, one representing a 14-week "wide holiday period" from June 16 to August 31 and December 16 to January 7, and one representing a 7-week "narrow holiday period", from June 25 to August 15. The narrow holiday period corresponded to a holiday period in Sweden when most healthcare staff members have holidays, i.e. representing the most 'under-staffed period', while the wide holiday period corresponded to a time period when many healthcare staff members in Sweden have holiday, but the under-staffing is not as heavy as during the narrow holiday period. In other words, the narrow holiday period is supposed to represent an exposure of higher specificity and lower sensitivity, while the wide holiday period is meant to represent an exposure period of lower specificity and higher sensitivity. Data on the exposure (date of surgery) were retrieved from the Patient Registry.

Outcomes

The main study outcome was overall disease-specific mortality, defined as a death where the tumor diagnosis of the same type as the one operated for was listed as a cause of death

from surgery to end of study period. The secondary outcome was overall all-cause mortality, defined as the date of death from any cause during the same period of follow-up. Data on the outcomes were retrieved from the Swedish Causes of Death Registry.

Covariates

Six well-established prognostic factors were considered as potential confounders: age, sex, comorbidity, annual hospital volume, calendar year of surgery, and tumor stage. Information about age and sex were available in all registers. Comorbidities were defined and categorized according to the most updated version of the well-validated Charlson comorbidity index.[6] Data on comorbidity, annual hospital volume, and calendar year of surgery were collected from the Patient Registry. The seventh version of the Union for International Cancer Control TNM-classification was used for tumor staging.[7] Tumor stage was available from the year 2004 onwards in the Cancer Registry.

Validity of the data sources

The Swedish Cancer Registry was initiated in 1958. The completeness of recording all new cancers in this registry is 96%,[8] and is nearly 100% in patients who undergo surgery. Data on tumor stage have excellent completeness (98%) and concordance (98%) for surgically resected cancer.[9]

The Swedish Patient Registry contains data on all in-hospital diagnoses and surgical procedures in Sweden since 1987.[10] The variables representing dates and types of cancer surgery have almost 100% positive predictive values compared to operation charts.[11, 12] The

diagnoses defining comorbidities in the Charlson comorbidity index have excellent nationwide coverage and positive predictive values of up to 95%.[10]

The Swedish Causes of Death Registry has 99% completeness for causes of deaths and 100% completeness of dates of deaths for all deceased Swedish residents since 1952.[13]

Statistical analysis

Surgery conducted during wide and narrow holiday periods (with dates presented above) was analyzed in relation to risk of mortality, using non-holiday periods as the reference category. Each of the 10 cancer groups was analyzed separately. Cox regression analysis provided crude and multivariable adjusted hazard ratios (HR) with 95% confidence intervals (CI). The prognostic factors included in the full model (with categorizations) were: age at surgery (continuous variable), sex (male or female), comorbidity (Charlson comorbidity index 0, 1-2, or ≥3), hospital volume (in quartiles for each cancer group), and calendar period of surgery (1997-2002, 2003- 2008, or 2009-2014). Additionally, tumor stage (I-II or III-IV) was added to the multivariable model in a sensitivity analysis for the period 2004-2014 when this variable was available. Missing data on tumor stage were managed by complete case analysis. Stratified analyses were performed for the five covariates with complete data, which were dichotomized to preserve statistical power as: age <65 years and ≥65 years, male and female sex, Charlson comorbidity index 0 and ≥1, hospital volume quartiles 1-2 and 3-4, and calendar year 1997-2005 and 2006-2014. There were no losses to follow-up. Kaplan-Meier curves showing crude survival data were plotted for selected tumors. An experienced biostatistician (FM) conducted all data management and statistical analyses, and used the statistical software SAS version 9.4 (SAS Institute, Cary, NC).

Results

Patients

The study included 228,927 patients who underwent cancer surgery. Of these, 49,897 patients (21.8%) had their surgery during the wide holiday period. Characteristics of the study participants are presented in Table 1. There were no major differences in the distribution of age, sex, comorbidity score, annual hospital volume, or calendar period of surgery for patients operated during and outside of wide holiday periods in any of the 10 cancer groups.

Esophago-gastric cancer

Surgery conducted during wide or narrow holiday periods were not associated with any increased mortality in esophago-gastric cancer in the overall analyses, compared to surgery outside holiday periods (Table 2 and 3). The adjusted disease-specific HR was 1.00 (95% CI 0.93-1.07) for wide holiday periods and 0.98 (95% CI 0.89-1.07) for narrow holiday periods. Similarly, the stratified analyses showed no associations (Table 4).

Liver-pancreas-biliary cancer

Surgery for liver-pancreas-biliary cancer during holiday periods was associated with an increased HRs of mortality of borderline statistical (Table 2 and 3, Supplementary Figure 1). The adjusted disease-specific HR was 1.09 (95% CI 0.99-1.20) for wide holiday periods and 1.12 (95% CI 0.99-1.26) for narrow holiday periods. The corresponding HRs for disease-specific mortality were increased in men (HR 1.22, 95% CI 1.08-1.39 and HR 1.21, 95% CI 1.02-1.43, respectively) and in patients with comorbidity (HR 1.17, 1.02-1.35 and HR 1.25, 95% CI 1.05-1.48) (Table 4).

Colorectal cancer

Surgery conducted during wide and narrow holiday periods was not associated with increased HRs of mortality in colorectal cancer in the overall analyses (Table 2 and 3), with adjusted disease-specific HR of 1.02 (95% CI 0.99-1.05) for wide holiday periods and 1.00 (95% CI 0.96-1.04) for narrow holiday periods. However, the stratified analyses of surgery conducted during narrow holiday periods showed increased HRs of disease-specific mortality in patients with comorbidity (HR 1.08, 95% CI 1.01-1.15) and in those operated during the later calendar period (HR 1.08, 95% CI 1.01-1.15) (Table 4).

Head-neck cancer

Surgery conducted during wide and narrow holiday periods was not associated with increased HRs of mortality in head-and-neck cancer in the overall analyses (Table 2 and 3). The adjusted disease-specific HR was 1.05 (95% CI 0.93-1.18) for wide holiday periods and 1.02 (95% CI 0.88-1.19) for narrow holiday periods. However, in hospitals with lower annual volume the disease-specific HRs were increased for surgery conducted during wide (HR 1.31, 95% CI 1.09-1.56) and narrow (HR 1.25, 95% CI 1.01-1.57) holiday periods (Table 4).

Lung cancer

Surgery conducted during wide and narrow holiday periods was not associated with increased HRs of mortality in lung cancer in the overall analyses, although all HRs were above 1.0 (Table 2 and 3). The adjusted disease-specific HR was 1.10 (95% CI 0.97-1.26) for wide holiday periods and 1.07 (95% CI 0.91-1.25) for narrow holiday periods. Similarly, the

stratified analyses revealed no statistically significant associations, although all HRs were above 1.0 (Table 4).

Thyroid cancer

Surgery conducted during wide and narrow holiday periods was not associated with increased HRs of mortality in thyroid cancer in the overall analyses, although all HRs were above 1.0 (Table 2 and 3). The adjusted disease-specific HR was 1.19 (95% CI 0.95-1.48) for wide holiday periods and 1.27 (95% CI 0.95-1.69) for narrow holiday periods. The stratified analyses showed an increased disease-specific HR following surgery during the narrow holiday period in patients without comorbidity (HR 1.44, 95% CI 1.01-2.06), and all other point HRs were above 1.0 (Table 4).

Breast cancer

Surgery for breast cancer during holiday periods was associated with increased HRs of mortality in the overall analyses (Table 2 and 3, Supplementary Figure 2). The adjusted disease-specific HR was 1.08 (95% CI 1.03-1.13) for wide holiday periods and 1.06 (95% CI 1.01-1.12) for narrow holiday periods. The associations were similar between stratification variable categories (Table 4).

Kidney-bladder cancer

Surgery conducted during wide and narrow holiday periods was not associated with increased HRs of mortality in kidney-bladder cancer in the overall analyses (Table 2 and 3). The adjusted disease-specific HR was 1.10 (95% CI 1.01-1.20) for wide holiday periods and 1.05 (95% CI 0.94-1.17) for narrow holiday periods. The stratified analyses revealed

increased HRs of disease-specific mortality in men (HR 1.14, 95% CI 1.02-1.27), in hospitals of higher annual volume (HR 1.22, 95% CI 1.09-1.37), and in surgery performed during a later calendar period (HR 1.27, 95% CI 1.11-1.44) (Table 4).

Prostate cancer

Surgery conducted during wide and narrow holiday periods was not associated with increased HRs of mortality in prostate cancer in the overall analyses (Table 2 and 3). The adjusted disease-specific HR was 0.97 (95% CI 0.78-1.20) for wide holiday periods and 1.10 (95% CI 0.83-1.46) for narrow holiday periods. The only statistically significant association in the stratified analyses was an increased HR of disease-specific mortality following surgery conducted in wide holiday periods during the calendar period 2006-2014 (HR 1.63, 95% CI 1.07-2.47) (Table 4).

Ovary-uterus cancer

Surgery conducted during wide and narrow holiday periods was not associated with increased HRs of mortality in ovary-uterus cancer in the overall analyses (Table 2 and 3). The adjusted HR of disease-specific mortality was 1.02 (95% CI 0.97-1.08) for wide holiday periods and 0.96 (95% CI 0.90-1.03) for narrow holiday periods. The stratified analyses did not reveal any statistically significant associations (Table 4).

Sensitivity analyses for tumor stage

In analyses of the sub-group of patients with data on tumor stage, the HRs were very similar with and without adjustment for tumor stage for all 10 cancer groups (data not shown).

Discussion

This study indicates that surgery performed during holiday periods increases the overall mortality in cancer of the breast and of the liver-pancreas-bile ducts, but also in sub-groups of patients with cancer of the colon-rectum, head-neck, prostate, kidney-urine bladder, and thyroid. No associations were found for surgery for cancer of the esophagus-stomach, lung, or ovary-uterus.

The population-based design with inclusion of virtually all patients in Sweden who underwent elective surgery of common cancers during the study period counteracted selection bias, made it possible to compare results between cancer groups, and provided large sample sizes. The personal identity numbers available for all Swedish residents enabled complete follow-up of all patients. The distinct holiday periods in Sweden provided a good exposure classification, and the accurate and objective assessment of both the exposure (timing of surgery) and outcome (mortality) also counteracted information bias. Confounding is a source of error in observational studies in general, but might of less concern in this study because cancer surgery is conducted without unnecessary delays and there is no factor that would obviously influence whether the surgery is conducted outside or inside holiday periods. Nevertheless, the results were adjusted for six prognostic factors resulting in negligible changes, documenting absence of confounding by these factors. The many tests performed increase the risk of chance errors (type I). Therefore, we reduced the number of tests by combining cancer sites into fewer groups, a strategy that also improved the statistical precision. Yet, it is possible that some of the increased HRs of the sub-group analyses are chance findings, but no single HR of mortality was statistically significantly

decreased for cancer surgery conducted during holiday periods, indicating consistency of the findings.

The increased mortality associated with the timing of certain cancer procedures during holiday periods might suggest that the expertise of the available surgeons and other healthcare staff is decreased for some procedures during these periods, at least in Sweden. However, it was not possible to measure the level of availability of surgical expertise in this study. These results might not be readily generalizable to other populations, at least not to countries where the healthcare is organized in a different fashion from Sweden. To the best of our knowledge, there is only one previous study examining how cancer surgery conducted during holiday periods influences the prognosis, i.e. our study examining esophageal cancer in a different cohort study, which found no association,[14] which is in agreement with the results of esophago-gastric cancer in the present study. Thus, further studies on this topic within other populations are warranted before any general clinical recommendations can be considered. If confirmed in future studies, however, these findings highlight a need for careful holiday planning for surgeons whose expertise cannot be easily replaced.

There is a need for studies examining the mechanisms behind the findings of this study. We can only speculate about explanations. Mammography screening may be less intense during holiday periods, and screen detected breast tumors are more likely to be of earlier stages with better prognosis, while symptomatic breast cancers with worse prognosis may more often undergo surgery during holiday periods. However, the association remained in analyses adjusted for tumor stage, which argue against this mechanism. Regarding cancer of the liver-pancreas-biliary tract, and also other tumors where associations were indicated,

more advanced tumors with worse prognosis might need to undergo surgery during holiday periods, while less advanced cases may more often be able to wait until after holiday periods. But again, the association remained after adjustment for tumor stage arguing against this explanation. Another potential explanation for the differences in prognosis between certain cancers is differences in how the surgical sub-specialites deal with the potential "holiday problem". Less experienced surgeons might be allowed to take on procedures for some cancer types without the optimal support, e.g. breast cancer, and not in others, e.g. cancer of the oesophagus and stomach. We know from own experience that an systematic collaboration to ascertain the surgical competence in surgery for esophageal cancer during holiday periods is in place in Sweden. Patients are readily referred to another hospital whenever the optimal surgical expertise is not available.[14] Regarding cancer of the liver-pancreas-biliary tract the differences in prognosis might be due to surgeons with less extensive surgical training in these specific procedures still may need to conduct some of these operations without the support from the most experienced surgeons. Regarding the decreased prognosis in some sub-groups of other cancer types, variations in surgeons' experience and the lack of the optimal expertise during holiday periods might help explain these findings. The findings of this study indicate that an organized collaboration between hospitals might be warranted for cancer surgery in general, and particularly for cancer of the breast and liver-pancreas-bile ducts. An alternative strategy might be to ask surgeons with the appropriate experience and expertise to conduct or assist the operation at another hospital.

In conclusion, this population-based study of nearly a quarter of a million patients who underwent surgery for cancer in Sweden indicates that the timing of surgery during holiday

periods might negatively influence the prognosis for cancer of the breast and possibly also for cancer of the liver-pancreas-bile ducts. Sub-groups of patients with cancer of the colon-rectum, head-neck, prostate, kidney-urine bladder, and thyroid might also be at increased risk of increased mortality, while no associations were found for cancer of the esophagus-stomach, lung, or ovary-uterus. If confirmed in future research, these findings might indicate the importance of maintaining sufficient surgical expertise for certain cancer procedures during holiday periods.

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Table 1. Characteristics of 228,927 patients who underwent surgery for 10 common cancer groups in 1997-2014 in Sweden.

Cancer	Wide holiday period *	Total	Age	Sex		Charlson comorbidity score			Hospital volume (quartiles)				Calendar period		
			Mean (SD)†	Male N (%)	Female N (%)	0 N (%)	1 N (%)	≥2 N (%)	I N (%)	II N (%)	III N (%)	IV N (%)	1997-2002 N (%)	2003-2008 N (%)	2009-2014 N (%)
Esophago-gastric	No	4656	68 (11)	3076 (77)	1580 (75)	2759 (76)	1167 (77)	730 (75)	1159 (77)	1144 (73)	974 (77)	1379 (77)	1595 (75)	1516 (76)	1545 (77)
	Yes	1468	69 (11)	941 (23)	527 (25)	883 (24)	346 (23)	239 (25)	356 (23)	415 (27)	296 (23)	401 (23)	520 (25)	477 (24)	471 (23)
Liver-pancreas-biliary	No	3102	65 (10)	1622 (77)	1480 (75)	1641 (76)	921 (76)	540 (77)	777 (78)	694 (77)	592 (75)	1039 (76)	594 (76)	872 (76)	1636 (76)
	Yes	971	65 (10)	473 (23)	498 (25)	519 (24)	291 (24)	161 (23)	223 (22)	212 (23)	200 (25)	336 (24)	185 (24)	271 (24)	515 (24)
Colorectal	No	45667	71 (11)	23547 (75)	22120 (75)	27298 (75)	10977 (75)	7392 (76)	11217 (76)	11593 (75)	10621 (75)	12236 (74)	12428 (75)	14769 (75)	18470 (75)
	Yes	15232	71 (11)	7809 (25)	7423 (25)	9179 (25)	3657 (25)	2396 (24)	3626 (24)	3851 (25)	3453 (25)	4302 (26)	4169 (25)	4834 (25)	6229 (25)
Head-neck	No	4076	63 (13)	2526 (76)	1550 (78)	2635 (76)	905 (77)	536 (77)	818 (77)	1068 (76)	456 (77)	1734 (77)	931 (76)	1301 (78)	1844 (76)
	Yes	1247	64 (13)	808 (24)	439 (22)	816 (24)	269 (23)	162 (23)	250 (23)	340 (24)	134 (23)	523 (23)	301 (24)	368 (22)	578 (24)
Lung	No	1877	65 (9)	938 (73)	939 (75)	1033 (75)	529 (72)	315 (74)	406 (75)	405 (73)	549 (74)	517 (73)	486 (73)	585 (75)	806 (74)
	Yes	660	65 (9)	349 (27)	311 (25)	346 (25)	202 (28)	112 (26)	133 (25)	149 (27)	190 (26)	188 (27)	177 (27)	196 (25)	287 (26)
Thyroid	No	3843	52 (17)	1045 (81)	2798 (82)	3035 (82)	542 (80)	266 (83)	964 (85)	993 (82)	665 (80)	1221 (80)	804 (81)	1065 (83)	1974 (82)
	Yes	848	54 (18)	239 (19)	609 (18)	660 (18)	135 (20)	53 (17)	164 (15)	219 (18)	169 (20)	296 (20)	184 (19)	216 (17)	448 (18)
Breast	No	61050	63 (13)	-	61050 (77)	47502 (77)	9491 (78)	4057 (77)	15032 (79)	14704 (77)	13751 (77)	17563 (76)	16998 (77)	19384 (78)	24668 (77)
	Yes	17774	63 (13)	-	17774 (23)	13809 (23)	2724 (22)	1241 (23)	4033 (21)	4316 (23)	4000 (23)	5425 (24)	5018 (23)	5548 (22)	7208 (23)
Kidney-bladder	No	7026	66 (11)	4208 (77)	2818 (78)	4213 (77)	1775 (78)	1038 (79)	1608 (79)	1748 (78)	1674 (76)	1996 (78)	1866 (77)	2303 (77)	2857 (78)
	Yes	2018	66 (11)	1225 (23)	793 (22)	1262 (23)	487 (22)	269 (21)	425 (21)	493 (22)	526 (24)	574 (22)	544 (23)	684 (23)	790 (22)
Prostate	No	23911	63 (5)	23911 (84)	-	18822 (84)	4046 (85)	1043 (83)	5727 (85)	5821 (85)	5395 (84)	6968 (83)	2263 (83)	8479 (85)	13169 (83)
	Yes	4570	63 (6)	4570 (16)	-	3635 (16)	725 (15)	210 (17)	1028 (15)	1056 (15)	1046 (16)	1440 (17)	455 (17)	1476 (15)	2639 (17)
Ovary-uterus	No	21804	64 (13)	-	21804 (75)	16432 (76)	3744 (74)	1628 (74)	5241 (77)	5093 (75)	5565 (75)	5905 (75)	6071 (75)	7168 (75)	8565 (75)
	Yes	7127	64 (13)	-	7127 (25)	5281 (24)	1283 (26)	563 (26)	1592 (23)	1673 (25)	1875 (25)	1987 (25)	2007 (25)	2337 (25)	2783 (25)

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

†Standard deviation.

Table 2. Wide holiday period (14-week period, 16th June to 31st August and 16th December to 7th January) of cancer surgery and risk of overall mortality, expressed as hazard ratio (HR) with 95% confidence interval (CI).

Cancer	Wide holiday period	Patients Number (%)	Disease-specific mortality		All-cause mortality	
			Crude HR (95% CI)	Adjusted HR (95% CI)*	Crude HR (95% CI)	Adjusted HR (95% CI)*
Esophago-gastric	No	4656 (76)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Yes	1468 (24)	1.01 (0.93-1.08)	1.00 (0.93-1.07)	1.01 (0.95-1.09)	1.00 (0.94-1.07)
Liver-pancreas-biliary	No	3102 (76)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Yes	971 (24)	1.08 (0.99-1.19)	1.09 (0.99-1.20)	1.07 (0.98-1.17)	1.08 (0.99-1.18)
Colorectal	No	45667 (75)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Yes	15232 (25)	1.02 (0.99-1.06)	1.02 (0.99-1.05)	1.02 (1.00-1.05)	1.02 (0.99-1.05)
Head-neck	No	4076 (77)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Yes	1247 (23)	1.03 (0.92-1.17)	1.05 (0.93-1.18)	1.02 (0.92-1.12)	1.04 (0.94-1.15)
Lung	No	1877 (74)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Yes	660 (26)	1.13 (0.99-1.28)	1.10 (0.97-1.26)	1.09 (0.96-1.23)	1.06 (0.94-1.20)
Thyroid	No	3843 (82)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Yes	848 (18)	1.46 (1.17-1.81)	1.19 (0.95-1.48)	1.33 (1.12-1.59)	1.08 (0.91-1.29)
Breast	No	61050 (77)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Yes	17774 (23)	1.07 (1.02-1.12)	1.08 (1.03-1.13)	1.04 (1.01-1.08)	1.05 (1.01-1.08)
Kidney-bladder	No	7026 (78)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Yes	2018 (22)	1.09 (1.00-1.19)	1.10 (1.01-1.20)	1.05 (0.98-1.13)	1.08 (1.00-1.16)
Prostate	No	23911 (84)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Yes	4570 (16)	0.96 (0.77-1.19)	0.97 (0.78-1.20)	0.96 (0.85-1.10)	0.98 (0.86-1.12)
Ovary-uterus	No	21804 (75)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Yes	7127 (25)	1.04 (0.98-1.10)	1.02 (0.97-1.08)	1.05 (1.01-1.10)	1.03 (0.98-1.08)

* Multivariable adjustment for age at surgery (continuous variable), sex (male or female), comorbidity (Charlson index 0, 1, or ≥2), hospital volume (in quartiles for each cancer group), and calendar year of surgery (1997-2002, 2003- 2008, or 2009-2014).

Table 3. Timing of cancer surgery within the narrow holiday period (7-wek period, 25th June to 15th August) and risk of mortality, expressed as hazard ratio (HR) with 95% confidence interval (CI).

Cancer	Narrow holiday period	Patients Number (%)	Disease-specific mortality		All-cause mortality	
			Crude HR (95% CI)	Adjusted HR (95% CI)*	Crude HR (95% CI)	Adjusted HR (95% CI)*
Esophago-gastric	No	5333 (87)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Yes	791 (13)	1.00 (0.91-1.10)	0.98 (0.89-1.07)	0.99 (0.91-1.08)	0.97 (0.89-1.06)
Liver-pancreas-biliary	No	3585 (88)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Yes	488 (12)	1.12 (0.99-1.26)	1.12 (0.99-1.26)	1.10 (0.98-1.24)	1.11 (0.99-1.24)
Colorectal	No	52321 (86)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Yes	8578 (14)	1.01 (0.97-1.05)	1.00 (0.96-1.04)	1.02 (0.99-1.06)	1.02 (0.98-1.05)
Head-neck	No	4633 (87)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Yes	690 (13)	1.03 (0.89-1.21)	1.02 (0.88-1.19)	1.03 (0.91-1.17)	1.02 (0.90-1.16)
Lung	No	2170 (86)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Yes	367 (14)	1.09 (0.93-1.28)	1.07 (0.91-1.25)	1.06 (0.91-1.23)	1.03 (0.89-1.20)
Thyroid	No	4276 (91)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Yes	415 (9)	1.53 (1.16-2.03)	1.27 (0.95-1.69)	1.38 (1.10-1.74)	1.12 (0.89-1.42)
Breast	No	69014 (88)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Yes	9810 (12)	1.06 (1.01-1.12)	1.06 (1.01-1.12)	1.03 (0.99-1.08)	1.02 (0.98-1.07)
Kidney-bladder	No	7934 (88)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Yes	1110 (12)	1.03 (0.92-1.15)	1.05 (0.94-1.17)	0.99 (0.90-1.09)	1.03 (0.93-1.13)
Prostate	No	26410 (93)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Yes	2071 (7)	1.11 (0.84-1.47)	1.10 (0.83-1.46)	0.99 (0.83-1.19)	0.98 (0.82-1.18)
Ovary-uterus	No	24993 (86)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Yes	3938 (14)	0.99 (0.92-1.06)	0.96 (0.90-1.03)	1.03 (0.97-1.09)	0.99 (0.94-1.05)

* Multivariable adjustment for age at surgery (continuous variable), sex (male or female), comorbidity (Charlson index 0, 1, or ≥2), hospital volume (in quartiles for each cancer group), and calendar year of surgery (1997-2002, 2003- 2008, or 2009-2014).

Table 4. Timing of surgery within wide and narrow holiday periods and disease-specific mortality, stratified by dichotomized covariates, expressed as adjusted hazard ratio (HR) with 95% confidence interval (CI).

Cancer	Covariate		Wide holiday period†		Narrow holiday period§	
			No	Yes	No	Yes
			HR (95 % CI)	HR (95 % CI)*	HR (95 % CI)	HR (95 % CI)*
Esophago-gastric	**Age (years)**	<65	1.00 (reference)	0.98 (0.86-1.12)	1.00 (reference)	1.03 (0.87-1.21)
		≥65	1.00 (reference)	1.01 (0.92-1.10)	1.00 (reference)	0.95 (0.85-1.07)
	Sex	Male	1.00 (reference)	1.00 (0.91-1.10)	1.00 (reference)	0.94 (0.84-1.06)
		Female	1.00 (reference)	0.99 (0.87-1.13)	1.00 (reference)	1.04 (0.89-1.22)
	Comorbidity score	0	1.00 (reference)	1.01 (0.92-1.12)	1.00 (reference)	1.02 (0.90-1.15)
		≥1	1.00 (reference)	0.97 (0.87-1.09)	1.00 (reference)	0.92 (0.79-1.06)
	Hospital volume (quartiles)	1+2	1.00 (reference)	1.00 (0.91-1.11)	1.00 (reference)	0.94 (0.82-1.06)
		3+4	1.00 (reference)	0.99 (0.89-1.11)	1.00 (reference)	1.03 (0.89-1.18)
	Calendar period	1997-2005	1.00 (reference)	0.99 (0.90-1.09)	1.00 (reference)	0.95 (0.84-1.07)
		2006-2014	1.00 (reference)	1.04 (0.92-1.17)	1.00 (reference)	1.06 (0.92-1.23)
Liver-pancreas-biliary	**Age (years)**	<65	1.00 (reference)	1.06 (0.91-1.23)	1.00 (reference)	1.06 (0.87-1.28)
		≥65	1.00 (reference)	1.10 (0.98-1.24)	1.00 (reference)	1.16 (0.99-1.35)
	Sex	Male	1.00 (reference)	1.22 (1.08-1.39)	1.00 (reference)	1.21 (1.02-1.43)
		Female	1.00 (reference)	0.97 (0.85-1.11)	1.00 (reference)	1.04 (0.88-1.23)
	Comorbidity score	0	1.00 (reference)	1.03 (0.91-1.17)	1.00 (reference)	1.02 (0.87-1.21)
		≥1	1.00 (reference)	1.17 (1.02-1.35)	1.00 (reference)	1.25 (1.05-1.48)
	Hospital volume (quartiles)	1+2	1.00 (reference)	1.06 (0.94-1.21)	1.00 (reference)	1.08 (0.92-1.27)
		3+4	1.00 (reference)	1.12 (0.98-1.28)	1.00 (reference)	1.17 (0.98-1.39)
	Calendar period	1997-2005	1.00 (reference)	1.07 (0.92-1.23)	1.00 (reference)	1.13 (0.94-1.36)
		2006-2014	1.00 (reference)	1.11 (0.98-1.25)	1.00 (reference)	1.12 (0.95-1.31)
Colorectal	**Age (years)**	<65	1.00 (reference)	1.06 (0.99-1.13)	1.00 (reference)	1.03 (0.95-1.12)
		≥65	1.00 (reference)	1.01 (0.98-1.05)	1.00 (reference)	1.00 (0.95-1.04)
	Sex	Male	1.00 (reference)	1.01 (0.96-1.05)	1.00 (reference)	1.00 (0.94-1.05)
		Female	1.00 (reference)	1.03 (0.98-1.08)	1.00 (reference)	1.01 (0.95-1.07)
	Comorbidity score	0	1.00 (reference)	1.00 (0.96-1.04)	1.00 (reference)	0.95 (0.90-1.00)
		≥1	1.00 (reference)	1.05 (1.00-1.10)	1.00 (reference)	1.08 (1.02-1.15)
	Hospital volume (quartiles)	1+2	1.00 (reference)	0.98 (0.94-1.03)	1.00 (reference)	0.97 (0.91-1.02)
		3+4	1.00 (reference)	1.05 (1.01-1.10)	1.00 (reference)	1.04 (0.98-1.10)
	Calendar period	1997-2005	1.00 (reference)	0.99 (0.95-1.03)	1.00 (reference)	0.96 (0.91-1.01)
		2006-2014	1.00 (reference)	1.07 (1.02-1.12)	1.00 (reference)	1.08 (1.01-1.15)
Head-neck	**Age (years)**	<65	1.00 (reference)	1.05 (0.87-1.26)	1.00 (reference)	0.91 (0.71-1.17)
		≥65	1.00 (reference)	1.05 (0.89-1.23)	1.00 (reference)	1.11 (0.91-1.35)
	Sex	Male	1.00 (reference)	1.07 (0.92-1.24)	1.00 (reference)	0.97 (0.80-1.18)
		Female	1.00 (reference)	1.01 (0.82-1.25)	1.00 (reference)	1.13 (0.87-1.47)
	Comorbidity score	0	1.00 (reference)	1.06 (0.91-1.24)	1.00 (reference)	1.01 (0.83-1.23)
		≥1	1.00 (reference)	1.02 (0.84-1.24)	1.00 (reference)	1.04 (0.82-1.33)
	Hospital	1+2	1.00 (reference)	1.31 (1.09-1.56)	1.00 (reference)	1.25 (1.01-1.57)

	volume (quartiles)	3+4	1.00 (reference)	0.87 (0.73-1.03)	1.00 (reference)	0.85 (0.69-1.06)
	Calendar period	1997-2005	1.00 (reference)	1.02 (0.86-1.20)	1.00 (reference)	0.94 (0.76-1.16)
		2006-2014	1.00 (reference)	1.08 (0.91-1.30)	1.00 (reference)	1.12 (0.90-1.40)
Lung	**Age (years)**	<65	1.00 (reference)	1.08 (0.89-1.32)	1.00 (reference)	1.04 (0.81-1.34)
		≥65	1.00 (reference)	1.12 (0.94-1.33)	1.00 (reference)	1.08 (0.88-1.34)
	Sex	Male	1.00 (reference)	1.07 (0.91-1.26)	1.00 (reference)	1.11 (0.90-1.36)
		Female	1.00 (reference)	1.16 (0.94-1.42)	1.00 (reference)	1.00 (0.77-1.30)
	Comorbidity score	0	1.00 (reference)	1.09 (0.92-1.30)	1.00 (reference)	1.09 (0.88-1.35)
		≥1	1.00 (reference)	1.11 (0.92-1.36)	1.00 (reference)	1.03 (0.80-1.33)
	Hospital volume (quartiles)	1+2	1.00 (reference)	1.08 (0.90-1.31)	1.00 (reference)	1.05 (0.83-1.33)
		3+4	1.00 (reference)	1.11 (0.93-1.33)	1.00 (reference)	1.08 (0.86-1.35)
	Calendar period	1997-2005	1.00 (reference)	1.16 (0.98-1.37)	1.00 (reference)	1.11 (0.90-1.36)
		2006-2014	1.00 (reference)	1.04 (0.84-1.28)	1.00 (reference)	1.03 (0.79-1.34)
Thyroid	**Age (years)**	<65	1.00 (reference)	1.25 (0.78-2.00)	1.00 (reference)	1.35 (0.74-2.46)
		≥65	1.00 (reference)	1.28 (1.00-1.64)	1.00 (reference)	1.33 (0.96-1.83)
	Sex	Male	1.00 (reference)	1.18 (0.82-1.70)	1.00 (reference)	1.25 (0.79-2.00)
		Female	1.00 (reference)	1.20 (0.91-1.58)	1.00 (reference)	1.28 (0.89-1.83)
	Comorbidity score	0	1.00 (reference)	1.29 (0.98-1.69)	1.00 (reference)	1.44 (1.01-2.06)
		≥1	1.00 (reference)	1.04 (0.71-1.51)	1.00 (reference)	1.04 (0.65-1.67)
	Hospital volume (quartiles)	1+2	1.00 (reference)	1.06 (0.76-1.47)	1.00 (reference)	1.18 (0.76-1.82)
		3+4	1.00 (reference)	1.32 (0.98-1.78)	1.00 (reference)	1.35 (0.93-1.97)
	Calendar period	1997-2005	1.00 (reference)	1.05 (0.78-1.42)	1.00 (reference)	1.17 (0.80-1.71)
		2006-2014	1.00 (reference)	1.41 (1.02-1.96)	1.00 (reference)	1.41 (0.92-2.17)
Breast	**Age (years)**	<65	1.00 (reference)	1.06 (0.99-1.13)	1.00 (reference)	1.07 (0.99-1.16)
		≥65	1.00 (reference)	1.09 (1.03-1.16)	1.00 (reference)	1.06 (0.98-1.14)
	Comorbidity score	0	1.00 (reference)	1.07 (1.02-1.13)	1.00 (reference)	1.08 (1.01-1.15)
		≥1	1.00 (reference)	1.09 (1.01-1.19)	1.00 (reference)	1.02 (0.92-1.14)
	Hospital volume (quartiles)	1+2	1.00 (reference)	1.08 (1.02-1.14)	1.00 (reference)	1.09 (1.01-1.17)
		3+4	1.00 (reference)	1.07 (1.00-1.14)	1.00 (reference)	1.03 (0.94-1.12)
	Calendar period	1997-2005	1.00 (reference)	1.08 (1.02-1.13)	1.00 (reference)	1.05 (0.99-1.13)
		2006-2014	1.00 (reference)	1.09 (1.00-1.18)	1.00 (reference)	1.09 (0.99-1.20)
Kidney-bladder	**Age (years)**	<65	1.00 (reference)	1.12 (0.97-1.28)	1.00 (reference)	1.08 (0.90-1.28)
		≥65	1.00 (reference)	1.08 (0.96-1.20)	1.00 (reference)	1.01 (0.88-1.16)
	Sex	Male	1.00 (reference)	1.14 (1.02-1.27)	1.00 (reference)	1.12 (0.98-1.29)
		Female	1.00 (reference)	1.04 (0.90-1.21)	1.00 (reference)	0.93 (0.77-1.12)
	Comorbidity score	0	1.00 (reference)	1.10 (0.99-1.23)	1.00 (reference)	0.99 (0.86-1.14)
		≥1	1.00 (reference)	1.10 (0.95-1.27)	1.00 (reference)	1.15 (0.97-1.38)
	Hospital volume (quartiles)	1+2	1.00 (reference)	0.96 (0.84-1.10)	1.00 (reference)	0.85 (0.72-1.01)
		3+4	1.00 (reference)	1.22 (1.09-1.37)	1.00 (reference)	1.25 (1.08-1.44)
	Calendar period	1997-2005	1.00 (reference)	0.99 (0.88-1.11)	1.00 (reference)	0.92 (0.79-1.07)
		2006-2014	1.00 (reference)	1.27 (1.11-1.44)	1.00 (reference)	1.25 (1.06-1.47)

Prostate	**Age (years)**	<65	1.00 (reference)	0.84 (0.61-1.15)	1.00 (reference)	0.83 (0.53-1.30)
		≥65	1.00 (reference)	1.09 (0.81-1.45)	1.00 (reference)	1.36 (0.94-1.96)
	Comorbidity score	0	1.00 (reference)	0.93 (0.73-1.19)	1.00 (reference)	1.02 (0.73-1.43)
		≥1	1.00 (reference)	1.11 (0.73-1.71)	1.00 (reference)	1.36 (0.80-2.31)
	Hospital volume (quartiles)	1+2	1.00 (reference)	1.00 (0.74-1.36)	1.00 (reference)	0.91 (0.59-1.40)
		3+4	1.00 (reference)	0.95 (0.70-1.28)	1.00 (reference)	1.32 (0.91-1.92)
	Calendar period	1997-2005	1.00 (reference)	0.89 (0.67-1.17)	1.00 (reference)	0.85 (0.58-1.26)
		2006-2014	1.00 (reference)	1.15 (0.82-1.63)	1.00 (reference)	1.63 (1.07-2.47)
Ovary-uterus	**Age (years)**	<65	1.00 (reference)	1.02 (0.94-1.11)	1.00 (reference)	0.93 (0.84-1.04)
		≥65	1.00 (reference)	1.02 (0.96-1.10)	1.00 (reference)	0.99 (0.90-1.08)
	Comorbidity score	0	1.00 (reference)	1.02 (0.96-1.09)	1.00 (reference)	0.94 (0.86-1.02)
		≥1	1.00 (reference)	1.02 (0.92-1.13)	1.00 (reference)	1.03 (0.91-1.16)
	Hospital volume (quartiles)	1+2	1.00 (reference)	0.99 (0.92-1.07)	1.00 (reference)	0.96 (0.87-1.06)
		3+4	1.00 (reference)	1.05 (0.98-1.13)	1.00 (reference)	0.97 (0.88-1.07)
	Calendar period	1997-2005	1.00 (reference)	1.02 (0.95-1.09)	1.00 (reference)	0.91 (0.84-1.00)
		2006-2014	1.00 (reference)	1.03 (0.94-1.12)	1.00 (reference)	1.03 (0.93-1.15)

* Multivariable adjustment for age at surgery (continuous variable), sex (male or female), comorbidity (Charlson index 0, 1, or ≥2), hospital volume (in quartiles for each cancer group), and calendar year of surgery (1997-2002, 2003- 2008, or 2009-2014).
†Wide holiday period is period from 16th June to 31st August and 16th December to 7th January.
§ Narrow holiday period is period from 25th June to 15th August.

Figure legends

Supplementary Figure 1. Kaplan-Meier curves of the crude disease-specific mortality in cancer of the liver-pancreas-biliary tract following surgery conducted during wide holiday periods (1A) and narrow holiday periods (1B).

Supplementary Figure 2. Kaplan-Meier curves of the crude disease-specific mortality in cancer of the breast following surgery conducted during wide holiday periods (2A) and narrow holiday periods (2B).