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Annual hospital volume of surgery for gastrointestinal cancer in relation to prognosis

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ABSTRACT

Background: Studies examining hospital volume for surgery for various gastrointestinal (GI) cancer types have shown conflicting results regarding the influence on long-term prognosis. The aim of this study was to examine annual hospital volume in relation to long-term survival after elective surgery for all GI cancers (esophagus, stomach, liver, pancreas, bile ducts, small bowel, colon, and rectum).
Methods: Population-based cohort study including all 45,908 patients who underwent elective surgery for GI cancers in Sweden in 2005–2013. Follow-up was until 2016 for disease-specific 5-year mortality (main outcome) and 2018 for all-cause 5-year mortality (secondary outcome). Hospitals were divided into quartiles for each GI cancer according to a 4-year average annual volume of the year of surgery and three years earlier. Multivariable Cox regression provided hazard ratios (HRs) with 95% confidence intervals (CIs), adjusted for relevant confounders.
Results: Higher hospital volume was associated with a survival benefit in the large group of patients (n = 26,688) who underwent colon cancer resection, with HR 0.89 (95% CI 0.84–0.96) for disease-specific 5-year mortality comparing the highest with the lowest quartile. Higher hospital volume improved 5-year mortality in sub-groups of patients who underwent surgery for cancer of the esophagus, pancreas, and rectum. No such improvements were found for cancer of the stomach, liver, bile ducts, or small bowel.
Conclusion: Long-term survival was improved at higher volume hospitals for some GI cancers (colon, esophagus, pancreas, rectum), but not for others (stomach, liver, bile ducts, small bowel).

Introduction

Gastrointestinal cancers, including cancer of the esophagus, stomach, liver, pancreas, bile ducts, small bowel, colon and rectum, account for over 3.4 million deaths globally each year [1]. The primary curative treatment for gastrointestinal cancers is surgery, sometimes combined with chemotherapy or chemo-radiotherapy [2–8]. Research has consistently shown that short-term mortality after some gastrointestinal cancer procedures is lower at high-volume hospitals, especially for the most complex procedures such as esophagectomies and pancreatectomies [9,10], whereas this association is weaker for other gastrointestinal cancer resections [9]. Studies examining how hospital volume influences long-term survival are fewer and the findings are less conclusive, with some studies supporting a prognostic role [11–14], and others not [12,15–20]. Yet, because short-term survival following cancer surgery has improved greatly during the last decades, long-term survival has become an increasingly important outcome in surgical research [21–23]. To facilitate the decision-making whether and how to centralize gastrointestinal cancer surgical procedures, there is an advantage of directly comparing the prognosis after these procedures in the same study. Yet, to the best of our knowledge, no original study has assessed hospital volume in relation to long-term survival in all types of gastrointestinal cancers.

This study aimed to assess how hospital volume influences long-term survival after elective surgery in all gastrointestinal cancers in

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a well-defined population with long and complete follow-up. The hypothesis was a prognostic benefit of higher annual hospital volume of surgery for more complex procedures (esophageal and pancreatic resections) and a smaller benefit for other procedures.

Materials and methods

Design

This was a nationwide Swedish population-based cohort study examining how annual hospital volume (exposure) influences disease-specific 5-year mortality (main outcome) and all-cause 5-year mortality (secondary outcome) in patients who have undergone surgery for any of eight gastrointestinal cancer locations separately. The cancer locations belonged to three main groups: upper gastrointestinal cancers (esophagus and stomach), hepato-pancreatico-biliary cancers (liver, pancreas, and bile ducts), and lower gastrointestinal cancers (small bowel, colon, and rectum). The operations were conducted between January 1, 2005 and December 31, 2013 and the follow-up ended on December 31, 2016 for disease-specific mortality and on April 30, 2018 for all-cause mortality (latest available updates). Thus, not all patients were followed up for 5 years. Data were retrieved from high-quality nationwide Swedish health data registries that contain information on cancer, other diagnoses, surgical procedures, and mortality (described below). Each participant's data were linked between registries using the personal identity numbers assigned to each Swedish resident at birth or immigration [24]. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden (2015/1916-31/1).

Data collection

The Swedish Cancer Registry was used to identify all patients with a gastrointestinal cancer diagnosis in 2005–2013 according to the 7th edition of the International Classification of Diseases (ICD-7) (Supplementary Table 1) [25]. Only histologically verified invasive carcinomas were included (Supplementary Table 2). Pathological tumor stage data were recorded according to the TNM classification of the Union for International Cancer Control (UICC), and were available from 2005 onwards (Supplementary Table 2) [26]. Validation studies have shown the Cancer Registry to be 96% complete for newly diagnosed cancers [27], and tumor stage data to be above 98% accurate for operated esophageal cancer [28].

The Swedish National Patient Registry provided data on all elective surgical resections conducted in 2005–2013 among gastrointestinal cancer patients. The surgical procedures were defined according to the Swedish version of the Nordic Medico-Statistical Committee Classification of Surgical Procedures (NCSP-S) Version 1.9 (Supplementary Table 1) [29]. Information regarding operating hospital, year of surgery, and medical comorbidities (according to the most recent and well-validated Charlson Comorbidity Index scoring system) was also retrieved [30,31]. The Patient Registry has 100% positive predictive values for esophageal cancer surgery [32], and between 85 and 95% for comorbidities [33].

The Swedish Cause of Death Registry provided information about date and causes of death in the cohort until the dates presented above (Design) [34]. The Cause of Death Registry is above 98% complete for causes of death and 100% complete for date of death [34].

Annual hospital volume exposure

The exposure was annual hospital volume for planned resectional surgery for each of the eight gastrointestinal cancer locations under study. Hospital volume was categorized into four about equal-sized groups (quartiles) separately for each cancer type. Hospitals with the 25% lowest annual surgery volume constituted the 1st quartile, and hospitals with the highest 25% annual surgery volume were in the 4th quartile, whereas quartiles 2 and 3 were inbetween. This pre-defined categorization was used to avoid arbitrary cut-offs. To account for temporary fluctuations in annual hospital volume between calendar years and to incorporate the experience achieved during the last few years prior to each operation, hospital volume was calculated using a 4-year moving average number of operations for each cancer procedure at each hospital, starting in 2002 (3 years before the first study year) and ending in 2013 (last study year). Thus, each patient was allocated the moving average of hospital volume for the year of their operation plus 3 years earlier. For example, for an operation conducted in 2005, the exposure was the average hospital volume of that procedure at that hospital during the 4 years 2002, 2003, 2004 and 2005.

Mortality outcomes

The main outcome was disease-specific mortality within 5 years of surgery, i.e. with the cancer location under study being recorded as the main or contributing cause of death. The secondary outcome was all-cause mortality within 5 years of surgery, i.e. deaths occurring independent of the cause of death.

Statistical analysis

Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using multivariable Cox proportional hazards models. The HRs were adjusted for five well-established prognostic factors shared by gastrointestinal cancers (with categorizations in brackets): age (continuous), sex (male or female), comorbidity (Charlson comorbidity score 0, 1 or $\geq$2, excluding any cancer) [30], calendar year of surgery (continuous), and pathological tumor stage (0-II or III-IV).

Information was complete for all variables, except for tumor stage. To manage missing data for tumor stage, both complete case analysis and multiple imputation analysis were conducted. The number of imputed datasets was 20 and the monotone logistic method in PROC MI was used based on the assumption that missing occurred randomly (MAR) [35]. The seven variables included in the imputation analysis were age (continuous), sex (male and female), comorbidity (Charlson comorbidity score 0, 1, or $\geq$2), calendar year of surgery (continuous), follow-up time (until death or maximum 5 years), disease-specific 5-year mortality, and hospital volume (quartiles). Furthermore, PROC MIANALYZE was used to combine the results from the analyses of the 20 datasets.

A sensitivity analysis was conducted in which patients with any cancer diagnosis prior to the gastrointestinal cancer under study were excluded. To evaluate effect modification, an interaction term was included for each of the five above mentioned prognostic factors and hospital volume one by one. Thereafter HRs with 95% CIs were calculated for the association for each category of the prognostic factor. Each prognostic factor was categorized as above, except for age and calendar year of surgery which were categorized as below and above the median.

An experienced biostatistician (FM) conducted all data management and statistical analyses according to a pre-defined study protocol. All analyses were conducted using SAS Statistical Package (version 9.4, SAS Institute Inc., Gary, NC).

Table 1
Characteristics of patients who have undergone resectional surgery for gastrointestinal cancers in Sweden in 2005–2013.

	Cancer localization							
	Esophagus (N = 1,534)	Stomach (N = 1,957)	Liver (N = 514)	Pancreas (N = 1,631)	Bile ducts (N = 363)	Small bowel (N = 1,257)	Colon (N = 26,688)	Rectum (N = 11,964)
	Number (%)							
Age, median (interquartile range)	65 (59–72)	72 (63–79)	68 (60–74)	67 (60–73)	66 (58–73)	67 (59–76)	74 (65–81)	70 (62–77)
Sex								
Male	1,227 (80.0)	1,115 (57.0)	313 (60.9)	826 (50.6)	130 (35.8)	673 (53.5)	12,786 (47.9)	7,114 (59.5)
Female	307 (20.0)	842 (43.0)	201 (39.1)	805 (49.4)	233 (64.2)	584 (46.5)	13,902 (52.1)	4,850 (40.5)
Charlson comorbidity score								
0	912 (59.5)	1,157 (59.1)	181 (35.2)	932 (57.1)	242 (66.7)	783 (62.3)	15,615 (58.5)	7,911 (66.1)
1	384 (25.0)	459 (23.5)	200 (38.9)	476 (29.2)	76 (20.9)	299 (23.8)	6,459 (24.2)	2,618 (21.9)
≥2	238 (15.5)	341 (17.4)	133 (25.9)	223 (13.7)	45 (12.4)	175 (13.9)	4,614 (17.3)	1,435 (12.0)
Calendar year of surgery, median (interquartile range)	2009 (2007–2012)	2009 (2007–2011)	2010 (2008–2012)	2010 (2007–2012)	2010 (2007–2012)	2009 (2007–2011)	2009 (2007–2011)	2009 (2007–2012)
Tumor stage								
0-II	855 (55.7)	1,132 (57.8)	402 (78.2)	740 (45.4)	245 (67.5)	238 (18.9)	12,458 (46.7)	6,809 (56.9)
III-IV	595 (38.8)	705 (36.0)	51 (9.9)	714 (43.8)	82 (22.6)	535 (42.6)	13,141 (49.2)	4,653 (38.9)
Missing	84 (5.5)	120 (6.1)	61 (11.9)	177 (10.9)	36 (9.9)	484 (38.5)	1,089 (4.1)	502 (4.2)
Previous cancer diagnosis	167 (10.9)	269 (13.8)	76 (14.8)	210 (12.9)	39 (10.7)	208 (16.6)	4177 (15.7)	1405 (11.7)
Outcomes								
Disease-specific 5-year mortality	800 (52.2)	1,104 (56.4)	213 (41.4)	1,092 (67.0)	186 (51.2)	232 (18.5)	7,820 (29.3)	2,556 (21.4)
All-cause 5-year mortality	999 (65.1)	1,290 (65.9)	315 (61.3)	1,214 (74.4)	243 (66.9)	469 (37.3)	10,998 (41.2)	3,943 (33.0)

Results

Patients

The study included 45,908 patients who had undergone resectional surgery for any of the eight studied gastrointestinal cancer locations. Patients' characteristics by cancer location are presented in Table 1. Most patients had colon cancer (n = 26,688) and the fewest had bile duct cancer (n = 363). The median age was between 65 and 74 years in the various cancer groups. Male sex was most prevalent in esophageal cancer (80.0%) and least prevalent in bile duct cancer (35.8%). A Charlson comorbidity score ≥1 was most common in patients with liver cancer (64.8%) and least common in bile duct cancer patients (33.3%). The highest proportion with advanced tumor stage (III-IV) was in patients with colon cancer (49.2%) and the lowest proportion in liver cancer patients (9.9%). Tumor stage was missing for 4.1–11.9% for all cancer locations, except for a higher rate in small bowel cancer (38.5%). The disease-specific 5-year mortality was >50% in cancer of the esophagus, stomach, pancreas, or bile ducts (Table 1).

Risk of 5-year mortality

The HRs of disease-specific 5-year mortality and all-cause 5-year mortality were similar in the complete-case and imputated analyses. Therefore, only the HRs based on multiple imputation are presented. The sensitivity analysis excluding patients with any previous cancer yielded similar results to those where these patients were included, thus only the latter results are presented.

Upper gastrointestinal cancers

Esophageal cancer

Higher hospital volume of esophageal cancer surgery did not decrease the risk of mortality in most overall analyses, and the disease-specific 5-year mortality was 1.01 (95% CI 0.82–1.24) when comparing the highest hospital volume quartile with the lowest (Table 2). However, a decreased all-cause 5-year mortality was found in the 3rd quartile of hospital volume category compared to the 1st quartile (adjusted HR 0.82, 95% CI 0.68–0.99) (Table 2), and the effect modification analyses indicated a decreased disease-

Table 2
Hospital volume (in quartiles) for upper gastrointestinal cancer in relation to 5-year mortality.

Cancer type	Hospital volume	Average annual volume	Number of patients (%)	Disease-specific 5-year mortality		All-cause 5-year mortality	
				Hazard ratio (95% confidence interval)[a]			
				Crude	Adjusted	Crude	Adjusted
Esophagus	Quartile I	5	277 (18.1)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Quartile II	12	331 (21.6)	0.94 (0.75–1.17)	0.86 (0.68–1.07)	0.91 (0.74–1.11)	0.82 (0.67–1.01)
	Quartile III	25	443 (28.9)	0.93 (0.75–1.15)	0.84 (0.68–1.05)	0.91 (0.75–1.09)	0.82 (0.68–0.99)
	Quartile IV	39	483 (31.5)	1.06 (0.86–1.30)	1.01 (0.82–1.24)	1.05 (0.88–1.26)	0.99 (0.83–1.19)
Stomach	Quartile I	4	344 (17.6)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Quartile II	7	436 (22.2)	1.09 (0.90–1.31)	1.11 (0.91–1.34)	1.03 (0.87–1.23)	1.04 (0.88–1.24)
	Quartile III	10	538 (27.5)	1.11 (0.92–1.33)	1.10 (0.91–1.32)	1.05 (0.89–1.24)	1.04 (0.88–1.23)
	Quartile IV	26	639 (32.7)	0.99 (0.83–1.19)	1.01 (0.85–1.21)	0.96 (0.81–1.13)	0.98 (0.83–1.16)

[a] Adjusted for age, sex, comorbidity, calendar year of surgery and tumor stage.

Table 3
Hospital volume (in quartiles) for hepato-pancreatico-biliary cancer in relation to 5-year mortality.

Cancer type	Hospital group	Average annual volume	Number of patients (%)	Disease-specific 5-year mortality		All-cause 5-year mortality	
				Hazard ratio (95% confidence interval)[a]			
				Crude	Adjusted	Crude	Adjusted
Liver	Quartile I	4	82 (16.0)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Quartile II	6	97 (18.9)	1.49 (0.94–2.34)	1.71 (1.07–2.74)	1.27 (0.88–1.84)	1.37 (0.94–2.02)
	Quartile III	10	167 (32.5)	1.30 (0.85–2.00)	1.38 (0.89–2.14)	1.20 (0.86–1.69)	1.27 0.90–1.79)
	Quartile IV	22	168 (32.7)	0.91 (0.58–1.43)	0.92 (0.58–1.46)	0.85 0.60–1.21)	0.88 (0.61–1.27)
Pancreas	Quartile I	4	221 (13.5)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Quartile II	10	386 (23.7)	1.23 (1.01–1.50)	1.12 (0.91–1.37)	1.25 (1.03–1.51)	1.13 (0.93–1.38)
	Quartile III	21	471 (28.9)	0.94 (0.77–1.15)	0.96 (0.79–1.18)	0.98 (0.81–1.18)	0.99 (0.82–1.20)
	Quartile IV	51	553 (33.9)	0.98 (0.81–1.19)	0.94 (0.77–1.15)	1.04 (0.87–1.25)	1.00 (0.82–1.20)
Bile ducts	Quartile I	3	53 (14.6)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Quartile II	5	49 (13.5)	0.53 (0.29–0.98)	0.58 (0.31–1.08)	0.63 (0.38–1.04)	0.67 (0.40–1.12)
	Quartile III	7	142 (39.1)	1.01 (0.65–1.57)	1.02 (0.65–1.60)	0.88 (0.60–1.29)	0.90 (0.60–1.33)
	Quartile IV	15	119 (32.8)	1.18 (0.75–1.86)	1.22 (0.75–1.99)	1.20 (0.82–1.77)	1.26 (0.84–1.91)

[a] Adjusted for age, sex, comorbidity, calendar year of surgery and tumor stage.

specific 5-year mortality in all higher hospital volume quartiles compared to the 1st quartile in patients with tumor stage III-IV; particularly pronounced in the 3rd quartile (adjusted HR 0.70, 95% CI 0.51–0.95) (Table 5).

Gastric cancer

Higher hospital volume of surgery for gastric cancer did not decrease any of the 5-year mortality outcomes (Table 2). The disease-specific 5-year mortality was similar when comparing the 4th and 1st quartile volume hospitals (adjusted HR 1.01, 95% CI 0.85–1.21), and the effect modification analyses revealed no statistically significant associations (Table 5).

Hepato-pancreatico-biliary cancers

Liver cancer

Higher hospital volume of liver cancer surgery did not decrease the 5-year mortality outcomes (Table 3). The adjusted HR of disease-specific 5-year mortality comparing the 4th and 1st hospital volume quartiles was 0.92 (95% CI 0.58–1.46), and the effect modification analyses revealed no statistically significantly decreased HRs (Table 5).

Pancreatic cancer

Higher hospital volume for pancreatic cancer surgery did not decrease the 5-year mortality outcomes in most analyses (Table 3). When comparing the 4th and 1st hospital volume categories, the adjusted HR for disease-specific 5-year mortality was 0.94 (95% CI 0.77–1.15). However, the effect modification analyses suggested decreased disease-specific 5-year mortality in patients with a Charlson comorbidity score ≥2 when higher volume hospitals were compared with the 1st quartile (Table 3), and a statistically significant decrease was found for the 4th quartile hospitals (adjusted HR 0.55, 95% CI 0.33–0.90). Although not statistically significant, the disease-specific 5-year mortality was possibly decreased for patients with tumor stage III-IV when comparing the 4th and 1st hospital volume quartiles (adjusted HR 0.82, 95% CI 0.62–1.07) (Table 5).

Bile duct cancer

Higher hospital volume of surgery for bile duct cancer did not decrease the 5-year mortality (Table 3). The comparison of the 4th and 1st hospital volume quartiles showed an adjusted HR of disease-specific 5-year mortality of 1.22 (95% CI 0.75–1.99). The effect modification analyses revealed no statistically significant associations (Table 5).

Lower gastrointestinal cancers

Small bowel cancer

Higher hospital volume for small bowel cancer surgery did not decrease the 5-year mortality outcomes (Table 4). For disease-

Table 4
Hospital volume (in quartiles) for lower gastrointestinal cancer in relation to 5-year mortality.

Cancer type	Hospital group	Average annual volume	Number of patients (%)	Disease-specific 5-year mortality		All-cause 5-year mortality	
				Hazard ratio (95% confidence interval)[a]			
				Crude	Adjusted	Crude	Adjusted
Small bowel	Quartile I	2	181	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Quartile II	3	330	1.31 (0.85–2.02)	1.38 (0.89–2.15)	1.16 (0.87–1.55)	1.25 (0.93–1.68)
	Quartile III	7	322	1.28 (0.83–1.98)	1.14 (0.73–1.77)	1.07 (0.80–1.44)	1.00 (0.74–1.35)
	Quartile IV	19	424	0.86 (0.55–1.33)	0.87 (0.56–1.36)	0.76 (0.57–1.03)	0.82 (0.61–1.11)
Colon	Quartile I	34	4,276	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Quartile II	58	5,983	0.95 (0.88–1.02)	0.93 (0.87–1.00)	0.93 (0.88–0.99)	0.92 (0.87–0.98)
	Quartile III	83	7,953	0.87 (0.81–0.93)	0.88 (0.82–0.94)	0.90 (0.85–0.96)	0.91 (0.86–0.96)
	Quartile IV	185	8,476	0.92 (0.86–0.98)	0.89 (0.84–0.96)	0.93 (0.88–0.98)	0.91 (0.86–0.96)
Rectum	Quartile I	17	1,891	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Quartile II	31	2,720	0.96 (0.84–1.08)	0.96 (0.85–1.09)	0.91 (0.82–1.00)	0.92 (0.83–1.02)
	Quartile III	43	3,188	0.86 (0.76–0.97)	0.89 (0.79–1.01)	0.86 (0.78–0.95)	0.90 (0.81–0.99)
	Quartile IV	115	4,165	0.89 (0.79–1.00)	0.92 (0.82–1.04)	0.91 (0.83–1.00)	0.97 (0.88–1.07)

[a] Adjusted for age, sex, comorbidity, calendar year of surgery and tumor stage.

specific 5-year mortality, the adjusted HR comparing the 4th and 1st quartiles of hospital volume was 0.87 (95% CI 0.56–1.36), and the effect modification analyses revealed no statistically significant associations (Table 5).

Colon cancer

Higher hospital volume of colon cancer surgery was associated with a decreased risk of 5-year mortality outcomes (Table 4). Comparing the 4th and 1st quartile volume hospitals showed an adjusted HR of 0.89 (95% CI 0.84–0.96) for disease-specific 5-year mortality. This association was more pronounced in patients aged ≥74 years, with more comorbidity, and with more advanced tumor stage (Table 5).

Rectal cancer

Higher hospital volume of rectal cancer surgery did not decrease the 5-year mortality in most analyses (Table 4). The HR for disease-specific 5-year mortality was not statistically significantly decreased when comparing the 4th and 1st quartile of volume hospitals (adjusted HR 0.92, 95% CI 0.82–1.04). However, there was a decreased risk of all-cause 5-year mortality in the 3rd quartile volume hospitals compared to the 1st (HR 0.90, 95% CI 0.81–0.99), and the effect modification analyses indicated a decreased disease-specific 5-year mortality at higher volume hospitals compared to the 1st quartile in female and older patients (Table 5).

Discussion

This study indicates a long-term prognostic benefit of higher hospital volume in colon cancer, especially in patients of older age, more comorbidity, and more advanced tumor stage. A survival benefit of higher hospital volume was also indicated in subgroups of patients with cancer of the esophagus, pancreas, and rectum. Hospital volume did not influence the survival in cancer of the stomach, liver, bile ducts, or small bowel.

Strengths of this study include the population-based cohort design and the long and complete follow-up. Additionally, the data on cancer diagnoses, hospital volume, mortality, and confounders were complete and accurate. The statistical power for assessing the survival in colon cancer was high. Among limitations is the fact that Sweden has a relatively low incidence of some of the studied tumours, and surgery of some tumours is still conducted at many hospitals. Thus, the hospital volume of some tumours was lower than in many other countries. There is also uncertainty of how hospital volume should ideally be defined to reflect reality. The moving average for assessing hospital volume took into account recent experiences regarding the specific type of surgery under investigation, which would seem justified. The use of quartiles counteracted arbitrary cut-offs, but it is possible that the highest quartile did not represent surgery of high enough volume to identify associations. Experience of other similar cancer procedures than the one under study might also influence the performance, which is difficult to assess. Another limitation is possible residual confounding, e.g. from tumor stage because of missing data. This problem was especially large for small bowel tumours, where 38% of tumour stage data was missing. However, the complete case and imputation analyses showed similar results, indicating that missing tumor stage data may not have influenced the results. One tumor stage classification was used for all cancers with rough categorization which might have introduced misclassification and residual confounding. Although the study was nationwide, there was limited precision for some tumours, particularly in the smallest patient groups, i.e. those with cancer of the liver, bile ducts, and small bowel. Thus, some true associations might not have been identified because of type II errors. In other words, lack of associations may to some degree be due to limited statistical power, rather than lack of true associations. The patients operated during the latest date of the study period could have maximum 3 years of follow up for disease-specific mortality and approximately 4,5 years for all-cause mortality. However, this was only the case for a minority of all patients in the whole cohort, and should not explain the risk estimates, but only reduce the statistical power. Also, although the evaluation of several tumors in one study makes it possible to compare results, it also introduces a risk of chance findings due to multiple testing. Therefore, the positive findings from the subgroup analyses should be interpreted with caution.

The study hypothesis of a stronger survival benefit of high-volume hospitals of more complex procedures and less so for other operations, was not supported by the findings. Instead long-term survival after colon cancer surgery was consistently improved by higher hospital volume. This might partly be explained by the superior statistical power in the colon cancer analyses, showing statistical significance for relatively weak associations. The finding regarding colon cancer surgery is in conflict with a recent systematic review and meta-analysis of 11,978 patients, reporting no association between increased hospital volume and improved 5-year survival [36], but the meta-analysis included fewer than half of those in the present study. In this study, it was also possible to assess effect modification, which was not conducted in the meta-analysis, and interestingly the associations were more prominent in patients of older age, more comorbidity, and more advanced tumor stage. Centralization of such patients groups might be justified if a tailored centralization is warranted.

Regarding esophageal cancer surgery, a recent systematic review and meta-analysis found that higher hospital volume was associated with improved 5-year survival [37]. The present study partly support those findings, because an improved survival was found in patients who had undergone esophagectomy in the 3rd quartile of hospital volume and in patients with more advanced tumor stage.

Higher hospital volume of pancreatic cancer surgery was associated with improved long-term survival in a systematic review and meta-analysis [38]. These results are in line with some subgroup analyses in the present study, which revealed improved survival for higher volume hospitals in patients with more comorbidity and possibly also in patients with more advanced tumor stage.

For rectal cancer surgery, a recent systematic review and meta-analysis did not find any association between higher hospital volume and long-term survival [36], which is supported by the main analyses of the present study. However, the current study indicated an improved survival in subgroups of patients who underwent surgery at higher volume hospitals, which suggests a need for more studies with stratified analyses.

The present study found no associations between higher hospital volume for surgery of cancer of the stomach, liver, bile ducts, or small bowel and 5-year mortality. For gastric cancer surgery, the negative findings are supported by some previous studies [12], but not by all [11]. Regarding liver cancer, the negative findings are contradicted by a previous study, but that study did not adjust for tumor stage [39]. The lack of association between higher hospital volume for bile duct cancer is in line with other studies [40]. Studies on small bowel cancer are scarce, and the present study had limited power and substantial missing data on tumor stage, thus more research is needed before a prognostic role of higher hospital volume can be dismissed.

Increased hospital volume of surgery can be achieved by centralizing procedures to fewer hospitals. However, some studies have indicated that surgeon volume for colorectal and esophageal cancer is more important than hospital volume [13,37,41]. It is possible that individual surgeons receive more training at smaller

Table 5
Hospital volume (in quartiles) for gastrointestinal cancers in relation to disease-specific 5-year mortality in effect modification analyses.

Prognostic factor		Quartile I	Quartile II	Quartile III	Quartile IV
		Hazard ratio (95% confidence interval)[a]			
Esophageal cancer					
Age (years)	<65	1.00 (reference)	0.91 (0.64–1.30)	0.85 (0.61–1.18)	1.04 (0.74–1.45)
	≥65	1.00 (reference)	0.80 (0.59–1.08)	0.79 (0.59–1.05)	1.01 (0.77–1.33)
Sex	Male	1.00 (reference)	0.88 (0.69–1.13)	0.80 (0.63–1.01)	0.96 (0.76–1.21)
	Female	1.00 (reference)	0.67 (0.36–1.25)	0.90 (0.52–1.55)	1.36 (0.81–2.30)
Charlson comorbidity score	0	1.00 (reference)	0.80 (0.59–1.08)	0.72 (0.54–0.96)	1.03 (0.78–1.36)
	1	1.00 (reference)	0.72 (0.45–1.15)	0.96 (0.63–1.46)	0.84 (0.54–1.29)
	≥2	1.00 (reference)	1.26 (0.74–2.15)	0.85 (0.50–1.45)	1.29 (0.78–2.12)
Calendar year of surgery	<2009	1.00 (reference)	1.07 (0.76–1.50)	0.72 (0.51–1.02)	1.03 (0.75–1.42)
	≥2009	1.00 (reference)	0.70 (0.51–0.96)	0.86 (0.65–1.14)	1.01 (0.76–1.34)
Tumor stage	0-II	1.00 (reference)	0.83 (0.60–1.15)	0.92 (0.68–1.24)	1.21 (0.92–1.59)
	III-IV	1.00 (reference)	0.81 (0.58–1.13)	0.70 (0.51–0.95)	0.80 (0.58–1.11)
Gastric cancer					
Age (years)	<72	1.00 (reference)	1.24 (0.92–1.67)	1.08 (0.81–1.44)	1.06 (0.80–1.40)
	≥72	1.00 (reference)	1.09 (0.85–1.41)	1.17 (0.92–1.48)	0.96 (0.75–1.23)
Sex	Male	1.00 (reference)	1.07 (0.83–1.38)	1.07 (0.83–1.36)	0.95 (0.75–1.21)
	Female	1.00 (reference)	1.28 (0.95–1.72)	1.20 (0.91–1.59)	1.08 (0.82–1.43)
Charlson comorbidity score	0	1.00 (reference)	1.11 (0.86–1.43)	1.06 (0.83–1.35)	1.05 (0.83–1.32)
	1	1.00 (reference)	1.02 (0.68–1.53)	1.16 (0.81–1.68)	1.01 (0.69–1.46)
	≥2	1.00 (reference)	1.51 (0.94–2.43)	1.31 (0.82–2.09)	0.89 (0.55–1.43)
Calendar year of surgery	<2009	1.00 (reference)	1.21 (0.92–1.60)	0.96 (0.74–1.26)	0.93 (0.71–1.22)
	≥2009	1.00 (reference)	1.10 (0.84–1.44)	1.30 (1.01–1.68)	1.08 (0.84–1.38)
Tumor stage	0-II	1.00 (reference)	1.15 (0.87–1.52)	1.02 (0.77–1.34)	1.08 (0.83–1.41)
	III-IV	1.00 (reference)	1.16 (0.88–1.52)	1.22 (0.95–1.56)	0.95 (0.74–1.22)
Liver cancer					
Age (years)	<68	1.00 (reference)	2.04 (0.92–4.53)	1.43 (0.67–3.05)	0.93 (0.43–2.02)
	≥68	1.00 (reference)	1.50 (0.79–2.85)	1.15 (0.64–2.07)	0.82 (0.45–1.50)
Sex	Male	1.00 (reference)	2.00 (1.02–3.90)	1.52 (0.81–2.85)	1.19 (0.63–2.24)
	Female	1.00 (reference)	1.32 (0.62–2.80)	0.95 (0.48–1.87)	0.53 (0.25–1.09)
Charlson comorbidity score	0	1.00 (reference)	1.00 (0.46–2.17)	0.65 (0.30–1.37)	0.85 (0.40–1.78)
	1	1.00 (reference)	2.69 (1.03–7.02)	1.90 (0.78–4.64)	0.87 (0.34–2.24)
	≥2	1.00 (reference)	1.99 (0.83–4.79)	1.74 (0.79–3.82)	0.95 (0.42–2.18)
Calendar year of surgery	<2010	1.00 (reference)	1.65 (0.92–2.96)	1.25 (0.67–2.36)	0.81 (0.41–1.59)
	≥2010	1.00 (reference)	1.91 (0.52–7.01)	1.28 (0.64–2.56)	0.90 (0.44–1.83)
Tumor stage	0-II	1.00 (reference)	1.76 (1.00–3.08)	1.32 (0.79–2.21)	0.78 (0.45–1.34)
	III-IV	1.00 (reference)	1.44 (0.48–4.34)	0.88 (0.29–2.65)	1.45 (0.52–4.04)
Pancreatic cancer					
Age (years)	<67	1.00 (reference)	1.14 (0.83–1.57)	0.82 (0.59–1.13)	0.78 (0.57–1.07)
	≥67	1.00 (reference)	1.12 (0.85–1.48)	1.02 (0.77–1.34)	0.93 (0.71–1.23)
Sex	Male	1.00 (reference)	1.06 (0.77–1.45)	0.84 (0.62–1.15)	0.76 (0.56–1.03)
	Female	1.00 (reference)	1.18 (0.89–1.56)	1.00 (0.75–1.33)	0.96 (0.73–1.27)
Charlson comorbidity score	0	1.00 (reference)	1.22 (0.93–1.62)	0.89 (0.68–1.18)	0.86 (0.65–1.13)
	1	1.00 (reference)	1.36 (0.91–2.03)	1.20 (0.81–1.79)	1.10 (0.75–1.64)
	≥2	1.00 (reference)	0.57 (0.33–0.97)	0.63 (0.38–1.06)	0.55 (0.33–0.90)
Calendar year of surgery	<2010	1.00 (reference)	1.23 (0.94–1.62)	1.05 (0.78–1.41)	0.99 (0.72–1.35)
	≥2010	1.00 (reference)	1.02 (0.73–1.42)	0.81 (0.60–1.09)	0.76 (0.57–1.01)
Tumor stage	0-II	1.00 (reference)	1.44 (1.07–1.93)	1.02 (0.76–1.37)	0.85 (0.62–1.18)
	III-IV	1.00 (reference)	0.90 (0.67–1.21)	0.84 (0.63–1.14)	0.82 (0.62–1.07)
Bile duct cancer					
Age (years)	<66	1.00 (reference)	1.63 (0.54–4.90)	2.00 (0.77–5.20)	2.22 (0.85–5.80)
	≥66	1.00 (reference)	0.43 (0.18–1.03)	0.88 (0.48–1.62)	1.12 (0.60–2.12)
Sex	Male	1.00 (reference)	0.67 (0.19–2.44)	1.33 (0.54–3.26)	1.23 (0.51–2.98)
	Female	1.00 (reference)	0.73 (0.34–1.56)	1.09 (0.59–1.98)	1.57 (0.82–3.00)
Charlson comorbidity score	0	1.00 (reference)	0.61 (0.26–1.42)	1.18 (0.63–2.19)	1.25 (0.64–2.42)
	1	1.00 (reference)	0.66 (0.17–2.53)	1.13 (0.36–3.49)	1.27 (0.37–4.33)
	≥2	1.00 (reference)	1.73 (0.34–8.79)	1.02 (0.26–4.04)	2.06 (0.58–7.27)
Calendar year of surgery	<2010	1.00 (reference)	0.80 (0.35–1.82)	1.48 (0.76–2.88)	1.44 (0.65–3.17)
	≥2010	1.00 (reference)	0.65 (0.22–1.97)	0.79 (0.36–1.74)	1.17 (0.56–2.41)

Table 5 (*continued*)

Prognostic factor		Quartile I	Quartile II	Quartile III	Quartile IV
		Hazard ratio (95% confidence interval)[a]			
Tumor stage	0-II	1.00 (reference)	0.81 (0.38–1.73)	1.21 (0.65–2.25)	1.59 (0.82–3.07)
	III-IV	1.00 (reference)	0.47 (0.10–2.31)	1.07 (0.45–2.55)	1.08 (0.46–2.57)
Small bowel cancer					
Age (years)	<67	1.00 (reference)	0.65 (0.27–1.60)	1.26 (0.56–2.84)	0.72 (0.32–1.63)
	≥67	1.00 (reference)	2.11 (1.12–3.98)	1.40 (0.71–2.76)	1.02 (0.51–2.03)
Sex	Male	1.00 (reference)	1.55 (0.75–3.20)	1.79 (0.88–3.66)	1.24 (0.60–2.55)
	Female	1.00 (reference)	1.27 (0.62–2.64)	1.02 (0.48–2.17)	0.64 (0.30–1.38)
Charlson comorbidity score	0	1.00 (reference)	2.16 (1.03–4.52)	2.13 (1.00–4.52)	1.35 (0.63–2.88)
	1	1.00 (reference)	0.78 (0.26–2.34)	0.77 (0.26–2.29)	0.79 (0.27–2.29)
	≥2	1.00 (reference)	1.12 (0.40–3.10)	1.00 (0.36–2.78)	0.37 (0.12–1.19)
Calendar year of surgery	<2009	1.00 (reference)	1.51 (0.80–2.86)	1.38 (0.72–2.63)	1.18 (0.60–2.32)
	≥2009	1.00 (reference)	1.32 (0.56–3.13)	1.42 (0.59–3.44)	0.68 (0.29–1.60)
Tumor stage	0-II	1.00 (reference)	1.50 (0.40–5.54)	1.10 (0.28–4.41)	1.56 (0.39–6.26)
	III-IV	1.00 (reference)	1.44 (0.83–2.53)	1.46 (0.83–2.57)	0.86 (0.48–1.52)
Colon cancer					
Age (years)	<74	1.00 (reference)	0.99 (0.89–1.11)	0.88 (0.79–0.98)	0.91 (0.81–1.01)
	≥74	1.00 (reference)	0.90 (0.82–0.99)	0.84 (0.76–0.92)	0.86 (0.78–0.94)
Sex	Male	1.00 (reference)	0.92 (0.83–1.02)	0.82 (0.75–0.91)	0.87 (0.79–0.96)
	Female	1.00 (reference)	0.96 (0.87–1.07)	0.88 0.80–0.98)	0.88 (0.80–0.97)
Charlson comorbidity score	0	1.00 (reference)	1.01 (0.92–1.12)	0.93 (0.84–1.02)	0.93 (0.85–1.03)
	1	1.00 (reference)	0.88 (0.76–1.01)	0.77 (0.67–0.88)	0.83 (0.73–0.95)
	≥2	1.00 (reference)	0.84 (0.71–0.99)	0.80 (0.68–0.93)	0.80 (0.68–0.92)
Calendar year of surgery	<2009	1.00 (reference)	0.94 (0.85–1.05)	0.81 (0.73–0.89)	0.86 (0.78–0.95)
	≥2009	1.00 (reference)	0.94 (0.85–1.04)	0.90 (0.82–0.99)	0.89 (0.81–0.98)
Tumor stage	0-II	1.00 (reference)	0.99 (0.84–1.16)	0.90 (0.77–1.05)	0.93 (0.80–1.09)
	III-IV	1.00 (reference)	0.93 (0.85–1.01)	0.84 (0.78–0.91)	0.86 (0.80–0.93)
Rectal cancer					
Age (years)	<70	1.00 (reference)	1.03 (0.83–1.28)	0.95 (0.77–1.18)	0.94 (0.77–1.15)
	≥70	1.00 (reference)	0.92 (0.79–1.08)	0.89 (0.76–1.04)	0.91 (0.78–1.06)
Sex	Male	1.00 (reference)	0.98 (0.83–1.16)	0.95 (0.81–1.12)	0.96 (0.82–1.11)
	Female	1.00 (reference)	0.92 (0.75–1.14)	0.85 (0.69–1.04)	0.86 (0.71–1.04)
Charlson comorbidity score	0	1.00 (reference)	1.00 (0.85–1.19)	0.92 (0.78–1.09)	0.94 (0.80–1.10)
	1	1.00 (reference)	0.87 (0.68–1.13)	0.85 (0.66–1.09)	0.85 (0.67–1.08)
	≥2	1.00 (reference)	0.96 (0.70–1.32)	0.98 (0.73–1.32)	0.95 (0.71–1.27)
Calendar year of surgery	<2009	1.00 (reference)	0.99 (0.83–1.20)	0.84 (0.69–1.01)	0.93 (0.78–1.10)
	≥2009	1.00 (reference)	0.93 (0.77–1.11)	0.98 (0.82–1.16)	0.91 (0.78–1.08)
Tumor stage	0-II	1.00 (reference)	1.00 (0.80–1.26)	0.90 (0.72–1.12)	0.84 (0.68–1.05)
	III-IV	1.00 (reference)	0.94 (0.80–1.10)	0.92 (0.79–1.07)	0.95 (0.83–1.10)

[a] Adjusted for age, sex, comorbidity, calendar year of surgery and tumor stage.

hospitals due to fewer operating surgeons, compared to larger hospitals. This could explain some of the heterogeneity in results between studies examining hospital volume and long-term survival. Also, high-volume surgeons might have performed surgery at low-volume hospitals from time to time, which could attenuate associations between hospital volume and long-term prognosis. Differences in results between studies might also be due to differences in methodology, cut-offs for hospital volume, populations, and healthcare systems.

In conclusion, this nationwide and population-based cohort study of all gastrointestinal cancer locations found decreased disease-specific and all-cause 5-year mortality after higher volume surgery for patients with cancer of the colon, particularly in patients of older age, more comorbidity, and advanced tumor stage, and possibly also in groups of patients with cancer of the esophagus, pancreas, or rectum. No such prognostic benefits were found for patients with cancer of the stomach, liver, bile ducts, or small bowel. However, these result need to be interpretated with caution, as the power for tumours other than colon was limited.

Conflicts of interest

No conflicts of interest to declare.

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Appendix A. Supplementary data

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