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Original Article

Impact of surgical resection rate on survival in gastric cancer: nationwide study

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Abstract

Background: There are marked geographical variations in the proportion of patients undergoing resection for gastric cancer. This study investigated the impact of resection rate on survival.

Methods: All patients with potentially curable gastric cancer between 2006 and 2017 were identified from the Swedish National Register of Oesophageal and Gastric Cancer. The annual resection rate was calculated for each county per year. Resection rates in all counties for all years were grouped into tertiles and classified as low, intermediate or high. Survival was analysed using the Cox proportional hazards model.

Results: A total of 3465 patients were diagnosed with potentially curable gastric cancer, and 1934 (55.8 per cent) were resected. Resection rates in the low (1261 patients), intermediate (1141) and high (1063) tertiles were 0–50.0, 50.1–62.5 and 62.6–100 per cent respectively. The multivariable Cox analysis revealed better survival for patients diagnosed in counties during years with an intermediate *versus* low resection rate (hazard ratio (HR) 0.81, 95 per cent c.i. 0.74 to 0.90; $P < 0.001$) and high *versus* low resection rate (HR 0.80, 0.73 to 0.88; $P < 0.001$).

Conclusion: This national register study showed large regional variation in resection rates for gastric cancer. A higher resection rate appeared to be beneficial with regard to overall survival for the entire population.

Introduction

Gastric cancer is the fifth most common malignancy worldwide and accounts for the third highest cancer-related mortality rate[1]. Modern treatment of gastric cancer has evolved with the development of specialist multidisciplinary teams and wider use of surgical resection in conjunction with other therapies as standard of care. Perioperative chemotherapy is most commonly used in Europe, adjuvant chemoradiotherapy in North America, and adjuvant chemotherapy in eastern Asia[2–11].

Despite recent advances, surgical resection of the primary tumour and regional lymph node stations remains the principal treatment for potentially curable disease. Better diagnostics and greater staging accuracy, as well as improved understanding of patient co-morbidities and functional status, have all contributed to improvements in outcome. There is, however, large variation in the proportion of patients undergoing curative resection between and within countries. Historically, in a review of non-Japanese studies up to 1990[12], the average surgical exploration rate of all studies, involving 80738 patients, was 74.1 per cent, but the resection rate was only 35.2 per cent, and the rate of resections deemed radical was 17.8 per cent. A more recent study from the Netherlands[13] also found marked variation in resection rates depending on where, and during what time period, treatment was undertaken. Surgery for gastric cancer designed to cure was performed historically in almost all hospitals with surgical capacity in Sweden. Over the past 20 years, resectional surgery for gastric cancer has gradually been centralized to specialized units, whereas diagnostics, preoperative investigation, some limited palliative procedures, and some oncological therapies are still usually performed at the hospital of diagnosis.

The aim of the present study was to identify any differences in resection rates by county and see whether this was related to survival. An optimized curative resection rate should be of value for the entire population of patients with potentially curative gastric cancer.

Methods

This was a national register-based cohort study based on the National Register of Oesophageal and Gastric Cancer (NREV). The register has detailed data on all patients with gastric cancer in Sweden, including baseline characteristics, operative details, and postoperative complications. The register has previously been validated and holds data of excellent quality with high

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completeness[14]. Data from NREV were cross-matched with the Swedish Patient Register, Prescribed Drug Register, Cause of Death Register, Total Population Register and Education Register to obtain additional patient exposure and outcome information, as described previously[15,16]. The study was approved by the regional ethics committee (EPN Stockholm Dnr 2016/1486-32 and 2013/596-31/3).

Study population

All patients in Sweden diagnosed with gastric cancer and gastro-oesophageal junction cancer, Siewert type III, in 2006–2017 were considered for inclusion. Only patients with registry data indicating potentially curable disease were included, thereby excluding patients registered with clinical metastatic disease (cM1) or unknown metastatic status (cMx).

Regions and regional multidisciplinary team conference

The healthcare system of Sweden is organized in 21 counties that have independent responsibility for the provision of healthcare to their population. Most counties have several hospitals, providing general healthcare. Neighbouring counties are organized into larger regions that offer highly specialized care, resulting in six regions that each have one tertiary referral centre, each covering a population from around 900 000 to roughly over 2 million. The two last decades of gradual centralization of gastric resectional surgery have resulted in regional referral to the tertiary centre for each region, but referral to other regions is possible in selected cases. Individual patient treatment recommendations are typically made in each of the six regional multidisciplinary team (MDT) conferences, held at least weekly by video conference, connecting hospitals in the counties of each region. Referral to the regional MDT conference is at the discretion of each diagnosing hospital.

Exposure

For every patient, the county of residence at the time of diagnosis was registered. Each county had its resection rate for gastric cancer calculated for each year during the study period by dividing the number of patients undergoing resection for gastric cancer with the total number of patients diagnosed in that county. All patients, irrespective of resection or not, were assigned a resection rate exposure, corresponding to the resection rate of their county of residence for the particular year in which they were diagnosed. The resection rate of all patients was grouped into tertiles (low, intermediate and high).

Outcome

The primary outcome was overall survival from time of diagnosis to death from any cause, emigration, or censorship date of 11 March 2018, whichever came first.

Statistical analysis

Data are presented as mean(s.d.) values and actual counts with percentages. Continuous variables were analysed with ANOVA, and categorical variables with the χ^2 test. Survival was presented using the Kaplan–Meier method with the log rank test, and multivariable assessment of survival was performed with the Cox proportional hazards model. The multivariable model included only variables with information on both resected and non-resected patients, thereby excluding perioperative chemotherapy. The model included resection rate (categorized into low, intermediate and high tertiles), age (per year increment), sex (male or female), ASA grade (categorized as I–II, III–IV and missing), clinical tumour stage according to TNM 8 (categorized as I, II, III, IVa and missing), Charlson Co-morbidity Index (CCI) (categorized as a score of 0–1, 2, and 3 or more), educational level (categorized as 9 years or less, 10–12 years, more than 12 years, and missing) and decision-making in the MDT conference (yes or no). The variables were chosen based on clinical importance, and the model was decided upon *a priori*. Sensitivity analyses were done for survival when resection rates were calculated: by use of 2-, 4- and 6-year periods instead of annually; in an extended study population including all patients with cM disease; and in a modified population that excluded non-resected patients who died within the median time frame from diagnosis to surgery of resected patients, to adjust for immortal time bias. Missing data were handled by the missing-indicator method. All statistical analyses were performed with IBM SPSS® Statistics version 26 (IBM, Armonk, NY, USA).

Results

A total of 3465 patients diagnosed with clinically non-metastatic gastric adenocarcinoma were included in the analysis. Patient selection is shown in *Fig. 1*. Of these patients, 1934 (55.8 per cent) had a resection. The annual county-specific resection rate varied from 0 to 100 (5th to 95th percentile 25.0–85.7) per cent. The resection rate was 0–50.0 per cent in the low tertile (1261 patients), 50.1–62.5 per cent in the intermediate tertile (1141 patients), and 62.6–100 per cent in the high tertile (1063 patients). Baseline characteristics of the patients are shown in *Table 1*. In general, patients in intermediate and high resection rate tertiles had a lower ASA grade, less advanced tumour stage, and less co-morbidity than those in the low resection rate tertile.

Among the 1934 resected patients, 621 patients (32.1 per cent) received preoperative chemotherapy: 164 (33.6 per cent) of 488 patients in the low resection rate tertile, 259 (39.3 per cent) of 659 in the intermediate tertile, and 198 (25.2 per cent) of 787 in the high tertile.

The mean resection rate for each county during the entire study period showed a large variation, ranging from approximately 43.0 to 71.4 per cent. The annual resection rate within each county also varied during the study period, so that all counties, depending on year of analysis, had patients in all resection rate tertiles (*Fig. 2*).

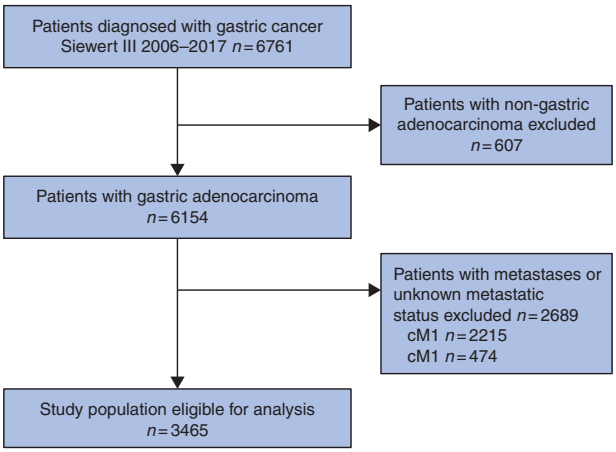

Fig. 1 Flow diagram of patient selection for the study

Table 1 Baseline characteristics of patients diagnosed with non-metastatic gastric adenocarcinoma in Sweden, 2006–2017, by resection rate tertiles

	Resection rate				
	Low (0–50.0%) (*n* = 1261)	Intermediate (50.1–62.5%) (*n* = 1141)	High (62.6–100%) (*n* = 1063)	All patients (*n* = 3465)	*P*†
Age (years)*	73(12)	72(12)	72(12)	72(12)	0.064‡
Sex					0.554
M	747 (59.2)	652 (57.1)	613 (57.7)	2012 (58.1)	
F	514 (40.8)	489 (42.9)	450 (42.3)	1453 (41.9)	
ASA grade					<0.001
I–II	729 (57.8)	741 (65.0)	676 (63.6)	2146 (61.9)	
III–IV	382 (30.3)	371 (32.5)	322 (30.3)	1075 (31.0)	
Missing	150 (11.9)	29 (2.5)	65 (6.1)	244 (7.0)	
Clinical tumour stage					<0.001
I	237 (18.8)	289 (25.3)	304 (28.6)	830 (24.0)	
II	356 (28.2)	329 (28.8)	283 (26.6)	968 (27.9)	
III	242 (19.2)	234 (20.5)	182 (17.1)	658 (19.0)	
IVa	18 (1.4)	7 (0.6)	3 (0.3)	28 (0.8)	
Missing	408 (32.4)	282 (24.7)	291 (27.4)	981 (28.3)	
CCI score					0.003
0–1	424 (33.6)	362 (31.7)	385 (36.2)	1171 (33.8)	
2	177 (14.0)	202 (17.7)	192 (18.1)	571 (16.5)	
≥3	660 (52.3)	577 (50.6)	486 (45.7)	1723 (49.7)	
Educational level (years)					<0.001
≤9 years	519 (41.2)	430 (37.7)	414 (38.9)	1363 (39.3)	
10–12	465 (36.9)	431 (37.8)	341 (32.1)	1237 (35.7)	
>12	188 (14.9)	186 (16.3)	139 (13.1)	513 (14.8)	
Missing	89 (7.1)	94 (8.2)	169 (15.9)	352 (10.2)	
MDT conference					<0.001
No	487 (38.6)	295 (25.9)	439 (41.3)	1221 (35.2)	
Yes	764 (60.6)	828 (72.6)	570 (53.6)	2162 (62.4)	
Missing	10 (0.8)	18 (1.6)	54 (5.1)	82 (2.4)	
Tumour location					<0.001
GOJ, Siewert III	118 (9.4)	103 (9.0)	63 (5.9)	284 (8.2)	
Upper	66 (5.2)	52 (4.6)	53 (5.0)	171 (4.9)	
Middle	364 (28.9)	362 (31.7)	371 (34.9)	1097 (31.7)	
Lower	421 (33.4)	419 (36.7)	419 (39.4)	1259 (36.3)	
Whole	40 (3.2)	36 (3.2)	30 (2.8)	106 (3.1)	
Missing	252 (20.0)	169 (14.8)	127 (11.9)	548 (15.8)	
Resection					<0.001
No	773 (61.3)	482 (42.2)	276 (26.0)	1531 (44.2)	
Yes	488 (38.7)	659 (57.8)	787 (74.0)	1934 (55.8)	

Values in parentheses are percentages unless indicated otherwise; * values are mean(s.d.). CCI, Charlson Co-morbidity Index; MDT, multidisciplinary therapy; GOJ, gastro-oesophageal junction. †χ^2 test, except. ‡ANOVA.

Survival

Overall median survival for the whole cohort was 18.4 months, with median overall survival of 14.2, 20.9 and 21.9 months for the low, intermediate and high resection rate tertiles respectively. Corresponding 5-year survival rates were 19.0, 26.9 and 27.8 per cent respectively ($P < 0.001$) (*Fig. 3*).

Multivariable assessment revealed improved survival for individuals diagnosed in a county during a year with an intermediate or high resection rate *versus* a low resection rate: hazard ratio (HR) 0.81, 95 per cent c.i. 0.74 to 0.90 ($P < 0.001$) and HR 0.80, 0.73 to 0.88 ($P < 0.001$) respectively. Age, ASA grade, tumour stage and decision taken in an MDT setting were also independently associated with survival, whereas sex, educational level and co-morbidity had no such impact (*Table 2*).

Sensitivity analysis

Sensitivity analyses showed that when 2-, 4- and 6-year periods were used for the resection rate instead of annual periods for the individual counties, similar results were obtained to those in the main analysis (*Table 3*). When adjusting for immortal time bias, the results also showed no differences from the main analysis.

Discussion

This national register study revealed large variation between different counties in resection rates among patients with non-metastatic gastric adenocarcinoma. Intermediate and high resection rates were associated with survival benefit for the entire population compared with low resection rates. The factors associated with improved survival were lower age, lower ASA grade, lower clinical tumour stage and treatment decision taken after an MDT conference.

As resection of the tumour is the main element in therapy aimed at cure for gastric adenocarcinoma, it is not surprising that a high resection rate would correlate with improved survival. This has been reported previously in a Dutch population-based study[13]. Resection rates for gastric cancer vary between Western European countries, ranging from 21.6 to 41.9 per cent in all

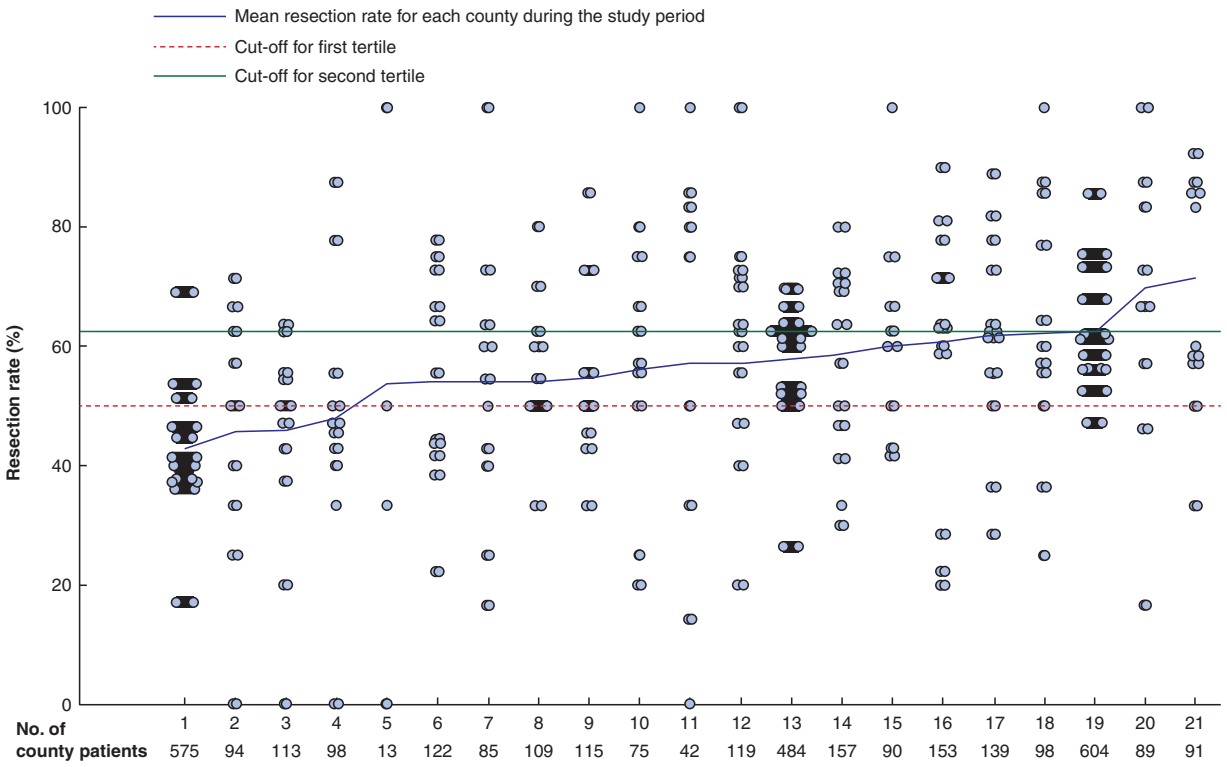

Fig. 2 Range of resection rates for all counties over the study period

The width of stacked markers represents the number of cases per annual resection rate.

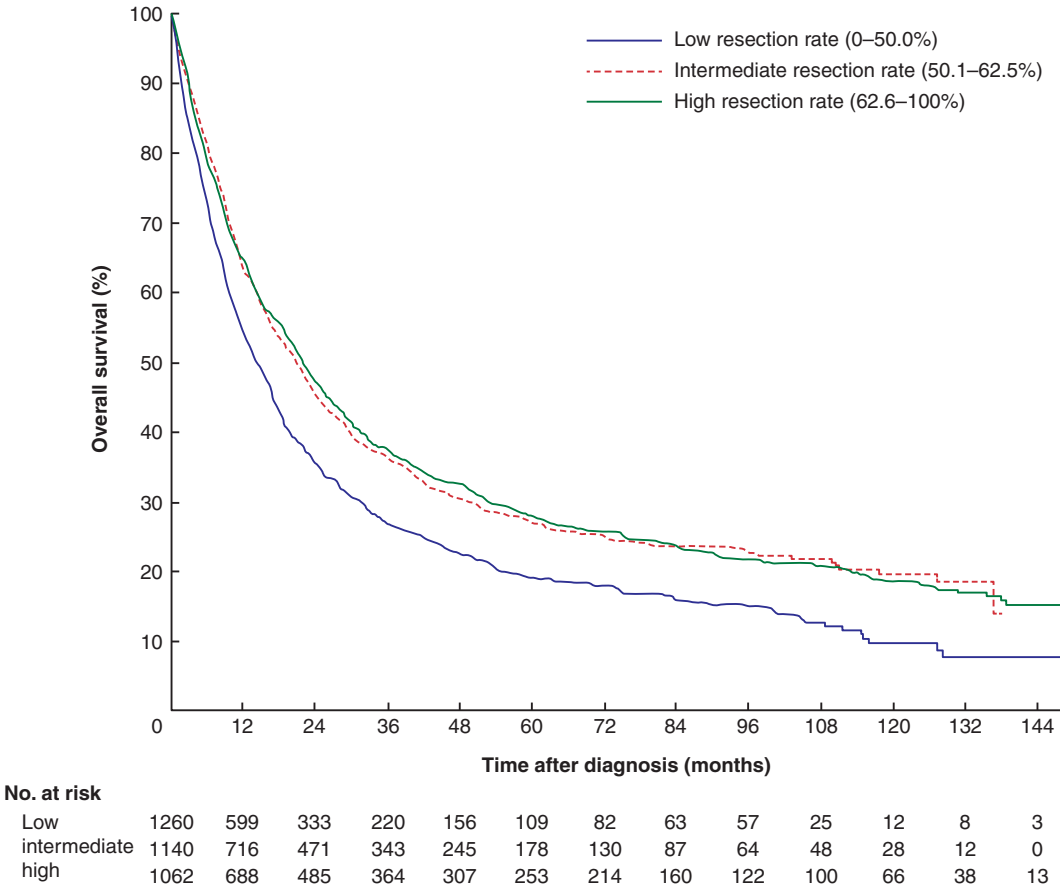

Fig. 3 Kaplan–Meier analysis of overall survival of patients diagnosed with non-metastatic gastric adenocarcinoma in Sweden, 2006–2017, by resection rate tertiles

$P<0.001$ (log rank test).

Table 2 Cox proportional hazards analysis of overall survival in patients with non-metastatic gastric adenocarcinoma diagnosed in Sweden, 2006–2017

	Univariable analysis		Multivariable analysis	
	Hazard ratio	*P*	Hazard ratio	*P*
Resection rate				
Low (0–50.0%)	1.00 (reference)		1.00 (reference)	
Intermediate (50.1–62.5%)	0.75 (0.68, 0.83)	<0.001	0.81 (0.74, 0.90)	<0.001
High (62.6–100%)	0.74 (0.68, 0.82)	<0.001	0.80 (0.73, 0.88)	<0.001
Age (per year increment)	1.04 (1.03, 1.04)	<0.001	1.03 (1.02, 1.03)	<0.001
Sex				
M	1.00 (reference)		1.00 (reference)	–
F	0.98 (0.91, 1.06)	0.624	1.02 (0.94, 1.10)	0.683
ASA grade				
I–II	1.00 (reference)		1.00 (reference)	–
III–IV	1.93 (1.78, 2.10)	<0.001	1.52 (1.39, 1.66)	<0.001
Missing	1.20 (1.00, 1.46)	0.055	1.12 (0.91, 1.37)	0.289
Clinical tumour stage				
I	1.00 (reference)		1.00 (reference)	
II	1.79 (1.59, 2.01)	<0.001	1.92 (1.71, 2.17)	<0.001
III	2.54 (2.24, 2.88)	<0.001	2.96 (2.60, 3.36)	<0.001
IVa	4.50 (2.96, 6.85)	<0.001	4.95 (3.22, 7.63)	<0.001
Missing	2.28 (2.04, 2.56)	<0.001	1.98 (1.76, 2.22)	<0.001
CCI score				
0–1	1.00 (reference)		1.00 (reference)	
2	1.01 (0.90, 1.14)	0.821	0.98 (0.87, 1.10)	0.709
≥3	1.21 (1.11, 1.32)	<0.001	1.04 (0.95, 1.14)	0.353
Educational level (years)				
≤9	1.00 (reference)		1.00 (reference)	
10–12	0.84 (0.77, 0.92)	<0.001	0.98 (0.90, 1.08)	0.720
>12	0.71 (0.63, 0.81)	<0.001	0.96 (0.84, 1.09)	0.511
Missing	1.44 (1.27, 1.63)	<0.001	1.20 (1.05, 1.37)	0.006
MDT conference				
No	1.00 (reference)	–	1.00 (reference)	
Yes	0.66 (0.61, 0.71)	<0.001	0.77 (0.71, 0.84)	<0.001
Missing	0.66 (0.51, 0.84)	0.001	0.90 (0.69, 1.17)	0.425

Values in parentheses are 95 per cent confidence intervals. CCI, Charlson Co-morbidity Index; MDT, multidisciplinary therapy.

Table 3 Sensitivity analysis for Cox proportional hazards model of survival

	Hazard ratio	*P*
Main analysis		
Low	1.00 (reference)	
Intermediate	0.81 (0.74, 0.90)	<0.001
High	0.80 (0.73, 0.88)	<0.001
Rate calculated from a 2-year interval mean		
Low	1.00 (reference)	
Intermediate	0.88 (0.80, 0.97)	0.010
High	0.82 (0.74, 0.90)	<0.001
Rate calculated from a 4-year interval mean		
Low	1.00 (reference)	
Intermediate	0.95 (0.86, 1.05)	0.330
High	0.89 (0.81, 0.99)	0.024
Rate calculated from a 6-year interval mean		
Low	1.00 (reference)	
Intermediate	0.91 (0.83, 1.01)	0.082
High	0.92 (0.83, 1.01)	0.080
Rate calculated including all patients with metastases or unknown metastatic status		
Low	1.00 (reference)	
Intermediate	1.06 (0.99, 1.13)	0.118
High	0.89 (0.83, 0.95)	0.001
Rate calculated regarding immortal time bias		
Low	1.00 (reference)	
Intermediate	0.82 (0.74, 0.91)	<0.001
High	0.82 (0.73, 0.91)	<0.001

Values in parentheses are 95 per cent confidence intervals.

patients diagnosed with gastric cancer[17]. In this study population of non-metastatic gastric cancers, the overall resection rate was 55.8 per cent.

This study found that resection rates also varied greatly between the different counties in Sweden. More advanced tumour stage, greater age, more and severe co-morbidity (higher CCI and ASA grade) were associated with worse survival, as expected. Studies in colorectal and pancreatic cancer[18,19] have also shown hospital variation in resection rates within a nation. Multiple factors are likely to influence the decision to proceed with surgery, including contiguous organ invasion, extent of lymphatic spread, and response to preoperative chemotherapy, as well as age, co-morbidity, performance status and patients' wishes. Variations between counties and different years in the resection rate might reflect differences in the quality of investigation and evaluation of these tumour- and patient-related factors; thus, performance of the MDT conference is likely to have a large impact on the treatment recommendation, resulting in differences geographically between counties and time periods.

Stage migration may be a factor influencing survival in favour of the intermediate and high resection rate groups if there were changes in the diagnostic accuracy of cM categorization during the course of the study. The use of PET–CT and diagnostic laparoscopy is likely to increase the accuracy of cM categorization and could bias the results. Data were not included regarding the availability and introduction of these diagnostic tools during the study, and they were not included in the multivariable Cox

proportional hazards model. Instead, a sensitivity analysis on an extended study population including patients with cM1 and cMx status was carried out, with similar results to the those in the main analysis. To investigate any residual baseline differences between the county populations, they were expanded to larger groups by extending the time period from an annual rate to 2-, 4- and 6-year intervals. As seen in *Table 3*, expanding the time interval modified the results slightly, but the overall interpretation was the same.

A strength of nationwide register studies is the inclusion of the entire population. As all patients, regardless of age or co-morbidity, were included, decision-making processes and outcomes for subgroups of patients that are often excluded from participation in clinical trials can be studied. Inherently, given its observational design, this study has some weaknesses that need to be addressed. As patients were not randomized to different counties, selection bias, as well as residual confounding, could occur. However, for these data, the risk of bias relating to patient or doctor delay, diagnostic capacity and healthcare availability, resulting in more advanced tumour stage and inability to resect owing to inoperable metastatic disease, should be limited, as the study included only potentially curable patients with non-metastatic disease. Additionally, adjustments were made in the regression models for important potentially confounding factors including age, co-morbidity and severity of co-morbidity, although important data such as WHO performance status and tobacco smoking status were not available. To some extent, ASA and CCI grades as variables that describe functional class and co-morbidity might make up for the absence of WHO performance status. Most studies suffer from missing values and, importantly, in the present study some were not evenly distributed between the tertiles. There were fewer missing values for ASA grade and clinical tumour stage among patients with an intermediate or high resection rate compared with the low resection rate tertile. Patients in the high tertile more frequently had missing values for whether a therapy decision was taken in an MDT conference or not, and for educational level.

Chemotherapy as an adjuvant or perioperative treatment to curative surgical resection was not included in this analysis, even though chemotherapy is known to affect survival. There are some data on preoperative chemotherapy in resected patients in the existing register, but this is presently incomplete.

Geographical variation in the rate of resection for gastric cancer in Sweden appears to result in survival differences between counties. A higher resection rate improved survival for the entire population of potentially curable, non-metastatic gastric cancer. There still seems to be room for improvement in standardizing MDT decision-making in order to offer as many patients as possible a curative resection of gastric cancer.

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