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ORIGINAL ARTICLE

Survival trends of patients with non-metastatic gastric adenocarcinoma in the US and European countries: the impact of decreasing resection rates

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Abstract

Background: We previously observed decreasing resection rates of non-metastatic gastric adenocarcinoma (GaC) in the US and some European countries. If and to what extent these trends affect the trends in overall survival (OS) of patients with non-metastatic GaC at the population level remain unclear. This large international population-based cohort study aimed to assess the impact of the previously observed decreasing resection rates on multivariable-adjusted trends in the long-term OS of patients with non-metastatic GaC.

Abbreviations: GC, gastric cancer; GaC, gastric adenocarcinoma; OS, overall survival; HR, hazard ratio; SEER, Surveillance, Epidemiology, and End Results; DCO, death certificate only; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; ASA, American Society of Anesthesiologists; AJCC/UICC, American Joint Committee on Cancer/Union for International Cancer Control.

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Methods: Individual-level data of patients with non-metastatic GaC were obtained from the national cancer registries of the Netherlands, Belgium, Sweden, Norway, and Slovenia, and the US Surveillance, Epidemiology, and End Results database. We analyzed data for each country separately. Associations between year of diagnosis and OS were assessed using Cox proportional hazards regression model with adjustment for multiple prognostic variables, with and without including resection and chemotherapy as potential explanatory variables.

Results: A total of 66,398 non-metastatic GaC patients diagnosed in 2003-2016 were analyzed, with an accumulated follow-up of 172,357 person-years. Without adjustment for resection, OS was improved only slightly in the US [hazard ratio $(HR)_{per\ year} = 0.99$; $HR_{\geq\ vs.\ <2010} = 0.96$], and no improvement was observed in the investigated European countries, with OS even worsening in Sweden ($HR_{per\ year} = 1.03$; $HR_{\geq\ vs.\ <2010} = 1.17$). After adjusting for resection, the increasing OS trend became stronger in the US ($HR_{per\ year} = 0.98$; $HR_{\geq\ vs.\ <2010} = 0.88$), and the temporal trend became insignificant in Sweden. In Slovenia ($HR_{per\ year} = 0.99$; $HR_{\geq\ vs.\ <2010} = 0.92$) and Norway ($HR_{per\ year} = 0.97$; $HR_{\geq\ vs.\ <2010} = 0.86$), improved OS over time emerged after resection adjustment. Improved OS in patients undergoing resection was observed in the US, the Netherlands, and Norway. Adjustment for chemotherapy did not alter the observed associations. Stratified analyses by tumor location showed mostly similar results with the findings in all patients with non-metastatic GaCs regarding the associations between year of diagnosis and survival.

Conclusions: OS of patients with non-metastatic GaC mostly did not improve in selected European countries and was even worsened in Sweden, while it was slightly increased in the US in the early 21st century. Progress in OS of patients with non-metastatic GaC seems to have been impeded to a large extent by decreasing rates of resection.

KEYWORDS
gastric adenocarcinoma, resection rate, adjusted overall survival, temporal trend, prognostic factors, international population-based cohort study

1 | BACKGROUND

Gastric cancer (GC), the majority of which is gastric adenocarcinoma (GaC), remains a significant global cancer burden. Worldwide, there is an estimate of ~1,100,000 new GC cases and ~800,000 GC-associated deaths in 2020, ranking GC as the 5th most often diagnosed malignancy and the 4th leading cause of cancer-associated death [1].

Resection is the only curative management for early-stage non-metastatic GaC. Also, it is the most important type of treatment for cure in non-early non-metastatic GaC, which should be managed by multi-modal therapy. Non-metastatic GaC accounts for approximately 56%-70% of all patients with GaC [2–6]. In our previous study [2], based on cancer registry data from the US and six European countries, we observed significantly decreasing age-standardized rates of resection for non-metastatic GaC over calendar years in all of these countries (by 4%-24%). After adjustment for multiple variables, the rates of resection for non-metastatic GaC remained decreasing with prevalence ratio of 0.97-0.995 per year, and the decreasing trends were consistently observed in various subgroups. If and to what extent these trends affect the trends in overall survival (OS) of patients with non-metastatic GaC at the population level remain unclear as population-based

cancer survival studies typically did not account for changes in treatment patterns [7–9].

OS adjusting for prognostic factors at the population level remains largely unexplored in most Western countries in the early 21st century with various therapeutic advances. Studies on population-based OS trends are mostly available for overall patients without multivariable adjustment for important prognostic factors, including treatment and tumor stage [7–9]. While crude survival improvement has been reported in GC [7–9], the unadjusted trend could have been influenced by treatment application, particularly the decreasing resection rates and increasing non-surgical therapy use [2]. International analyses of adjusted OS patterns and trends could aid in detecting disparities and potentially improvable areas in clinical practice, and guiding health resource allocation and policymaking.

In this international population-based study using individual-level data from the US and some European countries, we assessed trends in multivariable-adjusted long-term OS of patients with non-metastatic GaC with and without adjustment for resection and chemotherapy.

2 | PATIENTS AND METHODS

2.1 | Patients

Nationwide population-based registries eligible for this international real-world observational study were extensively searched, and the selection of contacted European registries with reasons for exclusion is listed in Supplementary Table S1. Individual-level data of patients with GC from the national cancer registries of the Netherlands, Belgium, Sweden, Slovenia and Norway, and the Surveillance, Epidemiology, and End Results (SEER)-18 database of the US were included finally (Supplementary Table S2). The participating European countries, located in Western, Central, and Northern Europe, respectively, were those able to contribute eligible high-quality data, especially on TNM stage, treatment, and survival, following a standard uniform data-request sheet to guarantee the robustness of the findings. All variables were consistently and uniformly (re)coded throughout countries. The characteristics of the participating registries were previously described in details, and the data generally had high quality [10]. The Ethics Committee of the Medical Faculty Heidelberg approved this study.

Coding of morphology and tumor location was in accordance with the International Classification of Diseases for Oncology, 3rd Edition (http://codes.iarc.fr/) [11]. Only patients with primary invasive adenocarcinomas of the stomach (C16) confirmed microscopically without distant metastases and registered in 2003-2017 were eligible. Cardia and non-cardia cancers were both included. Patients with non-invasive benign/precancerous/in situ tumors, non-gastric tumors affecting the stomach, squamous cell carcinomas, sarcomas/gastrointestinal stromal tumors, carcinoids/neuroendocrine tumors, germ-cell tumors, or lymphomas (Supplementary Table S3) were excluded, as were patients diagnosed based on autopsy or death certificate only (DCO) and those who had unknown follow-up duration or OS status. Individuals were also excluded if they had cancers with distant metastasis, which is considered mostly contraindicative to resection, or if metastasis status was unclear.

The data on patients (year of diagnosis, age, and sex), tumor (microscopic confirmation, location, histology, differentiation grade, and TNM stage), treatment (resection, chemotherapy, and radiotherapy), and follow-up parameters (OS status and time) were retrieved. Non-surgical treatment was under-ascertained with low sensitivity in the US SEER database [12]; i.e., the patients who were classified not to have received non-surgical treatment in the SEER database could include some patients who did actually receive such treatment. Neoadjuvant and adjuvant treatment could not be mutually differentiated in the Norwegian registry, and data on adjuvant treatment were not available in the Swedish registry. Data on type of hospital (the Netherlands, Belgium, and Sweden), volume of hospital (the Netherlands and Sweden), Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score (Sweden and Belgium), American Society of Anesthesiologists (ASA) score (Sweden), comorbidities (the Netherlands and Belgium), previous cancer (the US, the Netherlands, and Belgium), tumor size (the US), resection type (the US, the Netherlands, and Sweden), resection margin (the Netherlands, Sweden, and Slovenia), and harvested node number (the US, the Netherlands, and Sweden) were only available in certain registries.

We defined resection as the removal of the primary tumor regardless of being curative or palliative, of the type, extent, and radicality of excision and lymphadenectomy, and of the approach, method, technique, and procedure of treatment. This definition included endoscopic resection, which was majorly performed for only a few non-metastatic GaCs with invasion within lamina propria/submucosa and without lymph node metastasis, considering its cancer-directed resectional nature.

We derived cancer local invasion and lymph node involvement from the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) TNM staging system, and reclassified them into categories that were consistent throughout the study periods during which the 7th or 6th edition was in effect. Cancer stage was (re)coded according to the 8th AJCC TNM

edition, which was the same with the 7th edition for defining T and N stages in gastric cancer. Mortality follow-up of patients was performed by record linkage with national death registrations and/or population registers.

2.2 | Statistics

Given the possible heterogeneities across countries, we analyzed and presented data for each country separately without pooling. OS was defined as the time interval from diagnosis until last follow-up or death of any cause. Unadjusted OS in overall patients with non-metastatic GaCs and patients with resected cancers was computed using the Kaplan-Meier method. We used multivariable Cox proportional hazards regression to quantify the associations of year of diagnosis [alternatively entered as continuous variable or as dichotomous variable (≥ *vs.* <2010)] with OS, with adjustment for age, sex, tumor location, differentiation, local invasion, and positive lymph node for overall and resected non-metastatic GaCs in main analyses. The year 2010 was used as a cut since nearly half of the patients were diagnosed in 2010 or later across countries (43.6% to 61.2%; Table 1). In a subsequent step, resection was added to the multivariable models to assess if and to what extent the trends in resection rates might explain the observed temporal trends in OS. Changes in perioperative mortality per year in patients with resected non-metastatic GaCs were shown by depicting the temporal trends in multivariable-adjusted 1-month OS rate in all patients with resected non-metastatic GaCs, and further association analyses for patients with resected non-metastatic GaCs were conditioned to those surviving > 1 month to minimize the influence of possible heterogeneities in surgical quality and perioperative factors. For detailed assessment of temporal trends in OS, year of diagnosis was included as a categorical variable with 2010 as reference in the main multivariable models. We verified the proportional hazards assumption by plotting the logarithm of the negative logarithm of the OS function against the logarithm of OS time for all variables before analyses [13]. To account for missing data, especially M stage data, whose potential temporal proportion change might affect OS trends during case selection, we performed multiple imputations using the *MICE* package in R software (version, 3.4.1; http://www.rproject.org) and applied the following variables: year of diagnosis, age, sex, tumor location, morphology, differentiation, T, N, and M stages (based on the 8th AJCC TNM classification for GaC), resection, chemotherapy, radiotherapy, and OS time and status.

In additional analyses, we also added chemotherapy to the multivariable models to assess if and to what extent the temporal trends in OS might be explained by changes in frequency of such therapy over time. Chemotherapy was included in multivariable modeling either as a static or time-dependent variable, based on the availability and sensitivity of the recording of these variables and of the time intervals between diagnosis/resection and non-surgical management. In further sensitivity analyses, only patients with cancer stage greater than T1N0, which is identically defined in both the six and seventh editions of the TNM staging, or with tumor invading beyond submucosa were included to rule out the application of endoscopic resection. Stratified analyses by tumor location (cardia and non-cardia cancers) were further performed. We evaluated the associations with additional variables (e.g., tumor size, hospital volume and type, ECOG PS and ASA scores, and comorbidity type and number) for overall patients by adding them one by one into the main models additionally adjusting for resection in countries where such data were available. We used the SAS software (version, 9.4; Cary, NC, USA) and defined statistical significance by 2-sided $P < 0.05$.

3 | RESULTS

3.1 | Patient characteristics

Together, 134,894 patients with GC were initially included (the initial cohort; Supplementary Table S2). Patients with autopsy/DCO-based diagnosis (0.7%), without eligible or microscopically-confirmed pathology (11.4%), with non-invasive tumors (0.9%), without information on distant metastasis status (7.5%), with metastatic cancers (30.2%), and with unknown survival time and/or status (<0.1%) were excluded. Finally, 66,398 patients with non-metastatic GaC were analyzed (the final cohort). In the initial cohort, excluding those without pathologically diagnosed or eligible cancers reduced median OS by only 0-3 months, and excluding those without known metastasis status increased median OS by only 0-3 months (Supplementary Table S4).

Patient characteristics of the final cohort are shown in Table 1. The accumulated follow-up time was 172,357 person-years for all patients in the final cohort and 149,902 person-years for patients who underwent resection (the resection cohort).

In the final cohort, 43.6% (Belgium) to 61.2% (Sweden) were diagnosed in 2010 or later. Male proportions were 62.5% (Norway) to 66.1% (Belgium). Mean ages were 69-72 years, and most patients were ≥70 years [53.7% (the US) to 61.8% (Norway)]. Most cancers were located at the gastric cardia [26.8% (Slovenia) to 54.9% (Belgium)] or antrum/pylorus [31.8% (Belgium) to 46.5% (Slovenia)], poorly-differentiated/undifferentiated [57.2%

TABLE 1 Demographic and clinical characteristics of patients with non-metastatic gastric adenocarcinoma in the final cohort and the resection cohort*

	The US, 2004-2015		Netherlands, 2005-2016		Belgium, 2004-2013		Sweden, 2006-2016		Slovenia, 2003-2015		Norway, 2003-2014	
Variable	**Total**	**Resected**	**Total**	**Resected**	**Total**	**Resected**	**Total**	**Resected**	**Total**	**Resected**	**Total**	**Resected**
Total [cases (%)]	37,526	24,975 (66.6)	11,309	7267 (64.3)	6429	5072 (78.9)	4482	2500 (55.8)	3402	2532 (74.4)	3250	2054 (63.2)
Accumulated follow-up (person-years)	90,330	77,430	29,996	26,701	21,387	19,195	10,766	8341	12,221	11,564	7657	6671
Diagnosed in 2010/later [cases (%)]	19,271 (51.4)	12,057 (48.3)	6482 (57.3)	3976 (54.7)	2803 (43.6)	2122 (41.8)	2741 (61.2)	1385 (55.4)	1582 (46.5)	1126 (44.5)	1479 (45.5)	805 (39.2)
Male sex [cases (%)]	23,850 (63.6)	15,916 (63.7)	7269 (64.3)	4779 (65.8)	4248 (66.1)	3403 (67.1)	2819 (62.9)	1586 (63.4)	2163 (63.6)	1635 (64.6)	2030 (62.5)	1321 (64.3)
Age at diagnosis (year; mean ± SD)	69 ± 13	67 ± 13	71 ± 12	68 ± 12	70 ± 13	69 ± 12	72 ± 12	69 ± 11	69 ± 12	67 ± 12	72 ± 12	70 ± 12
Age group [cases (%)]												
< 60 years	8596 (22.9)	6579 (26.3)	1913 (16.9)	1586 (21.8)	1263 (19.6)	1103 (21.7)	714 (15.9)	506 (20.2)	749 (22.0)	662 (26.1)	518 (15.9)	378 (18.4)
60-69 years	8791 (23.4)	6533 (26.2)	2615 (23.1)	2051 (28.2)	1382 (21.5)	1186 (23.4)	1043 (23.3)	720 (28.8)	768 (22.6)	634 (25.0)	722 (22.2)	528 (25.7)
70-79 years	10,445 (27.8)	7255 (29.0)	3678 (32.5)	2504 (34.5)	2109 (32.8)	1725 (34.0)	1394 (31.1)	831 (33.2)	1164 (34.2)	891 (35.2)	968 (29.8)	664 (32.3)
≥ 80 years	9694 (25.8)	4608 (18.5)	3103 (27.4)	1126 (15.5)	1675 (26.1)	1058 (20.9)	1331 (29.7)	443 (17.7)	721 (21.2)	345 (13.6)	1042 (32.1)	484 (23.6)
Tumor location [cases (%)][#]												
Gastric cardia	12,471 (47.1)	7304 (41.7)	3008 (35.9)	1739 (31.3)	1991 (54.9)	1499 (53.4)	1386 (38.5)	737 (34.9)	546 (26.8)	373 (22.6)	849 (38.6)	477 (32.3)
Gastric fundus/body	4448 (16.8)	2989 (17.1)	1875 (22.4)	1281 (23.1)	482 (13.3)	367 (13.1)	1017 (28.3)	611 (29.0)	546 (26.8)	486 (29.5)	486 (22.1)	322 (21.8)
Gastric antrum/pylorus	9574 (36.1)	7206 (41.2)	3495 (41.7)	2535 (45.6)	1151 (31.8)	939 (33.5)	1194 (33.2)	761 (36.1)	949 (46.5)	790 (47.9)	865 (39.3)	678 (45.9)
Others	11,033 (29.4)	7476 (29.9)	2931 (25.9)	1712 (23.6)	2805 (43.6)	2267 (44.7)	885 (19.7)	391 (15.6)	1361 (40.0)	883 (34.9)	1050 (32.3)	577 (28.1)
Differentiation [cases (%)][¶]												
Well	1905 (5.8)	1480 (6.4)	302 (4.1)	232 (4.3)	636 (11.6)	476 (10.8)	-	-	273 (10.5)	228 (10.7)	101 (4.1)	68 (4.1)
Moderate	9634 (29.4)	6714 (29.0)	2121 (28.5)	1602 (29.7)	1714 (31.2)	1359 (30.8)	-	-	717 (27.5)	601 (28.1)	692 (28.2)	491 (29.6)
Poor/undifferentiated	21,276 (64.8)	14,924 (64.6)	5014 (67.4)	3551 (65.9)	3143 (57.2)	2582 (58.5)	-	-	1619 (62.1)	1306 (61.2)	1658 (67.6)	1098 (66.3)
Unknown	4711 (12.6)	1857 (7.4)	3872 (34.2)	1882 (25.9)	936 (14.6)	655 (12.9)	3507 (78.2)	1552 (62.1)	793 (23.3)	397 (15.7)	799 (24.6)	397 (19.3)
T stage [cases (%)][§]												
T1 (invasion of lamina propria/submucosa)	11,503 (33.6)	7049 (28.5)	1563 (16.7)	1431 (19.9)	1425 (23.2)	1113 (22.2)	545 (14.8)	432 (18.4)	536 (19.8)	497 (21.1)	250 (14.6)	195 (15.3)
T2/3 (invasion of muscularis propria/subserosa)	14,709 (42.9)	11,736 (47.5)	5111 (54.6)	3968 (55.3)	2863 (46.5)	2434 (48.5)	1949 (53.0)	1199 (51.2)	1330 (49.2)	1226 (52.1)	666 (38.9)	538 (42.2)
T4a (invasion of serosa)	5055 (14.8)	4368 (17.7)	1686 (18.0)	1425 (19.8)	1598 (26.0)	1319 (26.3)	803 (21.8)	569 (24.3)	670 (24.8)	556 (23.6)	582 (34.0)	417 (32.7)
T4b (invasion of adjacent structures)	2993 (8.7)	1560 (6.3)	995 (10.6)	356 (5.0)	267 (4.3)	157 (3.1)	382 (10.4)	144 (6.1)	166 (6.1)	73 (3.1)	213 (12.4)	125 (9.8)
Unknown	3266 (8.7)	262 (1.0)	1954 (17.3)	87 (1.2)	276 (4.3)	49 (1.0)	803 (17.9)	156 (6.2)	700 (20.6)	180 (7.1)	1539 (47.4)	779 (37.9)

(Continues)

TABLE 1 (Continued)

Variable	The US, 2004-2015		Netherlands, 2005-2016		Belgium, 2004-2013		Sweden, 2006-2016		Slovenia, 2003-2015		Norway, 2003-2014	
	Total	Resected	Total	Resected	Total	Resected	Total	Resected	Total	Resected	Total	Resected
N stage [cases (%)][†]												
N0 (0 positive lymph node)	19,860 (54.2)	11,576 (46.5)	5101 (50.2)	3301 (45.7)	2774 (45.6)	2218 (44.6)	2272 (55.2)	1275 (51.3)	1351 (47.2)	1040 (43.7)	1787 (72.7)	989 (66.4)
N1/2 (1-6 positive lymph nodes)	12,255 (33.5)	9004 (36.1)	3737 (36.8)	2662 (36.8)	2362 (38.8)	1896 (38.2)	1383 (33.6)	848 (34.1)	984 (34.4)	874 (36.7)	544 (22.1)	407 (27.3)
N3a/3b (≥ 7 positive lymph nodes)	4504 (12.3)	4332 (17.4)	1328 (13.1)	1268 (17.5)	945 (15.5)	855 (17.2)	464 (11.3)	361 (14.5)	526 (18.4)	467 (19.6)	126 (5.1)	94 (6.3)
Unknown	907 (2.4)	63 (0.3)	1143 (10.1)	36 (0.5)	348 (5.4)	103 (2.0)	363 (8.1)	16 (0.6)	541 (15.9)	151 (6.4)	793 (24.4)	564 (27.5)
Harvested nodes (no.; mean ± SD)	\	15 ± 13	\	17 ± 16	\	NA	\	18 ± 14	\	NA	\	NA
Resection type												
Partial/subtotal gastrectomy	\	16,707 (66.9)	\	3690 (50.8)	\	NA	\	860 (62.1)	\	NA	\	NA
Total/near-total gastrectomy	\	5064 (20.3)	\	1877 (25.8)	\	NA	\	475 (34.3)	\	NA	\	NA
Others[**]	\	3204 (12.8)	\	1700 (23.4)	\	NA	\	50 (3.6)	\	NA	\	NA
Resection margin [cases (%)][##]												
Positive	\	NA	\	1005 (14.6)	\	NA	\	338 (15.3)	\	98 (8.0)	\	NA
Unknown	\	NA	\	393 (5.4)	\	NA	\	286 (11.4)	\	34 (2.7)	\	NA
Received neoadjuvant CHT [cases (%)][¶¶]	\	NA	\	2982 (41.0)	\	1144 (22.6)	\	840 (33.6)	\	207 (8.2)	\	NA
Received neoadjuvant RT [cases (%)][¶¶]	\	2473 (9.9)	\	399 (5.5)	\	195 (3.8)	\	188 (7.5)	\	104 (4.1)	\	NA
Received total/adjuvant CHT [cases (%)][¶¶]	16,717 (44.5)	11,643 (46.6)	4116 (36.4)	1716 (23.6)	2521 (39.2)	1641 (32.4)	NA	NA	1006 (29.6)	709 (28.0)	612 (18.8)	451 (22.0)
Received total/adjuvant RT [cases (%)][¶¶]	11,921 (31.8)	5753 (23.0)	1430 (12.6)	382 (5.3)	1024 (15.9)	644 (12.7)	NA	NA	824 (24.2)	633 (25.0)	186 (5.7)	87 (4.2)

*Records are complete otherwise specified below.

[#]The percentages of gastric cardia, fundus/body, and antrum/pylorus cancers are the proportions relative to the total tumor cases of the 3 locations; "others" include lesser curvature, greater curvature, and overlapping lesion of stomach and stomach not otherwise specified, and its proportion is relative to the total number of cases.

[¶]For the well, moderately, and poorly/undifferentiated categories, the percentages were calculated among cases with known differentiation.

[§]Based on the 8th AJCC TNM classification; for the T1 (invasion of lamina propria/submucosa), T2/3 (invasion of muscularis propria/subserosa), T4a (invasion of serosa), and T4b (invasion of adjacent structures) categories, the percentages were calculated among cases with known tumor T stage.

[†]Based on the 8th AJCC TNM classification; for the categories of N0 (0 positive lymph nodes), N1/2 (1-6 positive lymph nodes), and N3a/3b (≥ 7 positive lymph nodes), the percentages were calculated among cases with known N stage.

**The other resection type included gastrectomy (not otherwise specified) and local resection. Information on resection type was available in Sweden since 2010.

[##]For the category of positive resection margin, the percentages were calculated within cases with known resection margin. In Slovenia margin status was not available before 2009.

[¶¶]Non-surgical therapies in the US had low sensitivity, and the counterpart category of "Yes" was "No/unknown". In Norway, neoadjuvant and adjuvant therapies could not be distinguished from each other. Total CHT/RT is for total patients, and (neo)adjuvant CHT/RT for the resection cohort.

Abbreviations: CHT, chemotherapy; RT, radiotherapy; \, resection-specific variables not applicable for total patients; -, not shown due to > 60% missing values; NA, not available; SD, standard deviation.

(Belgium) to 67.6% (Norway)], with invasion to muscularis propria/subserosa [38.9% (Norway) to 54.6% (the Netherlands)], and without lymph node involvement [45.6% (Belgium) to 72.7% (Norway)]. In Europe, 18.8% (Norway) to 39.2% (Belgium) of patients received chemotherapy, and 5.7% (Norway) to 24.2% (Slovenia) received radiotherapy, 55.8% (Sweden) to 78.9% (Belgium) underwent resection.

In the resection cohort, smaller proportions were diagnosed in 2010 or later [39.2% (Norway) to 55.4% (Sweden)]. Male proportions were mostly greater [63.4% (Sweden) to 67.1% (Belgium)]. Patients undergoing resection were younger (mean ages, 67-70 years), with those ≥70 years making up smaller proportions [47.5% (the US) to 55.9% (Norway)]. Smaller proportions of resected cancers were located at the gastric cardia [22.6% (Slovenia) to 53.4% (Belgium)], and greater proportions at the antrum/pylorus [33.5% (Belgium) to 47.9% (Slovenia)]. In countries with available information, the mean number of harvested lymph nodes was 15 (the US) to 18 (Sweden), and partial/subtotal gastrectomy was the most common resection type [50.8% (the Netherlands) to 66.9% (the US)]. In Europe, 8.2% (Slovenia) to 41.0% (the Netherlands) of patients received neoadjuvant chemotherapy, and 3.8% (Belgium) to 7.5% (Sweden) received neoadjuvant radiotherapy; adjuvant chemotherapy was applied for 22.0% (Norway) to 32.4% (Belgium) of patients, and adjuvant radiotherapy for 4.2% (Norway) to 25.0% (Slovenia) of patients.

3.2 | Multivariable-adjusted OS trends

In the final cohort (Figure 1), the median OS time was 18 (the Netherlands and Norway) to 28 months (Belgium). Multivariable-adjusted Cox models were further used to disclose the OS trends in different countries (Table 2; Figure 2). Before adjusting for resection, improved OS was only observed in the US ($HR_{\text{per year}} = 0.99$; $HR_{\geq \textit{ vs. } <2010} = 0.96$). Temporal OS changes were insignificant in the Netherlands, Belgium, Slovenia, and Norway, and deteriorated OS was observed in Sweden ($HR_{\text{per year}} = 1.03$; $HR_{\geq \textit{ vs. } <2010} = 1.17$). After adjusting for resection, the decreasing trend became stronger in the US ($HR_{\text{per year}} = 0.98$; $HR_{\geq \textit{ vs. } <2010} = 0.88$), and the temporal trend became insignificant in Sweden. In Slovenia ($HR_{\text{per year}} = 0.99$; $HR_{\geq \textit{ vs. } <2010} = 0.92$) and Norway ($HR_{\text{per year}} = 0.97$; $HR_{\geq \textit{ vs. } <2010} = 0.86$), improved OS over calendar years was observed.

Sensitivity analyses for the final cohort by adding chemotherapy (adjuvant and/or neoadjuvant) as either a static or time-dependent covariate in the multivariable models or by limiting cases to those with tumor stage greater than T1N0 where endoscopic resection was rarely performed did not change the patterns of associations between OS and year of diagnosis in most of the countries, despite some changes in significances (Table 3). For example, the association with year of diagnosis as a dichotomized variable (≥ vs. < 2010) became insignificant in the US before adjusting for resection, while the point estimate of HR remained similar. When stratifying cancers by location, the patterns of associations between year of diagnosis and OS were similar for cardia and non-cardia non-metastatic GaCs in the US, Belgium, Sweden, Slovenia, and Norway. A significant increasing trend in mortality hazard was observed for cardia cancer in the Netherlands before adjusting for resection, but this trend disappeared after adjustment (Table 3; Supplementary Figures S1-S2).

In the resection cohort (Supplementary Figure S3), the median OS time ranged from 36 (Norway) to 45 months (the US). After multivariable adjustment, the adjusted 1-month OS rates showed slightly increasing or stable trends across countries (Supplementary Figure S4). Among the resection cohort who survived more than 1 month, OS was improved over calendar years in the US (adjusted $HR_{\text{per year}} = 0.98$; $HR_{\geq \textit{ vs. } <2010} = 0.95$), the Netherlands ($HR_{\text{per year}} = 0.99$; $HR_{\geq \textit{ vs. } <2010} = 0.95$), and Norway ($HR_{\text{per year}} = 0.97$; $HR_{\geq \textit{ vs. } <2010} = 0.77$), while the temporal changes in Belgium, Sweden, and Slovenia were insignificant (Table 2; Figure 3).

Patterns of the associations of OS with year of diagnosis in both the final cohort and the resection cohort remained mostly similar after multiple imputations (Table 2). Adjustment for additional prognostic factors available in certain countries did not alter the association patterns.

3.3 | OS-associated factors

Factors associated with OS in the final cohort are shown in Supplementary Table S5. Before adjusting for resection, male patients had shorter OS in the US (HR = 0.94), Belgium (HR = 0.85), and Slovenia (HR = 0.87). Older ages were associated with greater hazards for mortality [e.g., $HR_{70\text{-}79 \textit{ vs. } <60 \text{ years}} = 1.55$ (Norway) to 2.22 (Slovenia); $HR_{\geq 80 \textit{ vs. } <60 \text{ years}} = 2.55$ (the Netherlands) to 3.71 (Slovenia)]. Compared to gastric cardia cancers, both gastric fundus/body [HR = 0.65 (Slovenia) to 0.83 (Belgium)] and antrum/pylorus cancers [HR = 0.60 (Norway) to 0.81 (Sweden)] were associated with longer OS. Patients with well-differentiated [HR = 0.62 (the US); HR = 0.85 (Belgium)] and moderately-differentiated cancers [HR = 0.78 (the US); HR = 0.81 (Belgium)] had longer OS than those with poorly-differentiated/undifferentiated ones. More advanced T stage [e.g., $HR_{\text{T4a (invasion of serosa) } \textit{vs.} \text{ T1 (invasion of lamina propria/submucosa)}} = 1.45$ (the US) to 2.72 (Sweden); $HR_{\text{T4b (invasion of adjacent structures) } \textit{vs.}}$

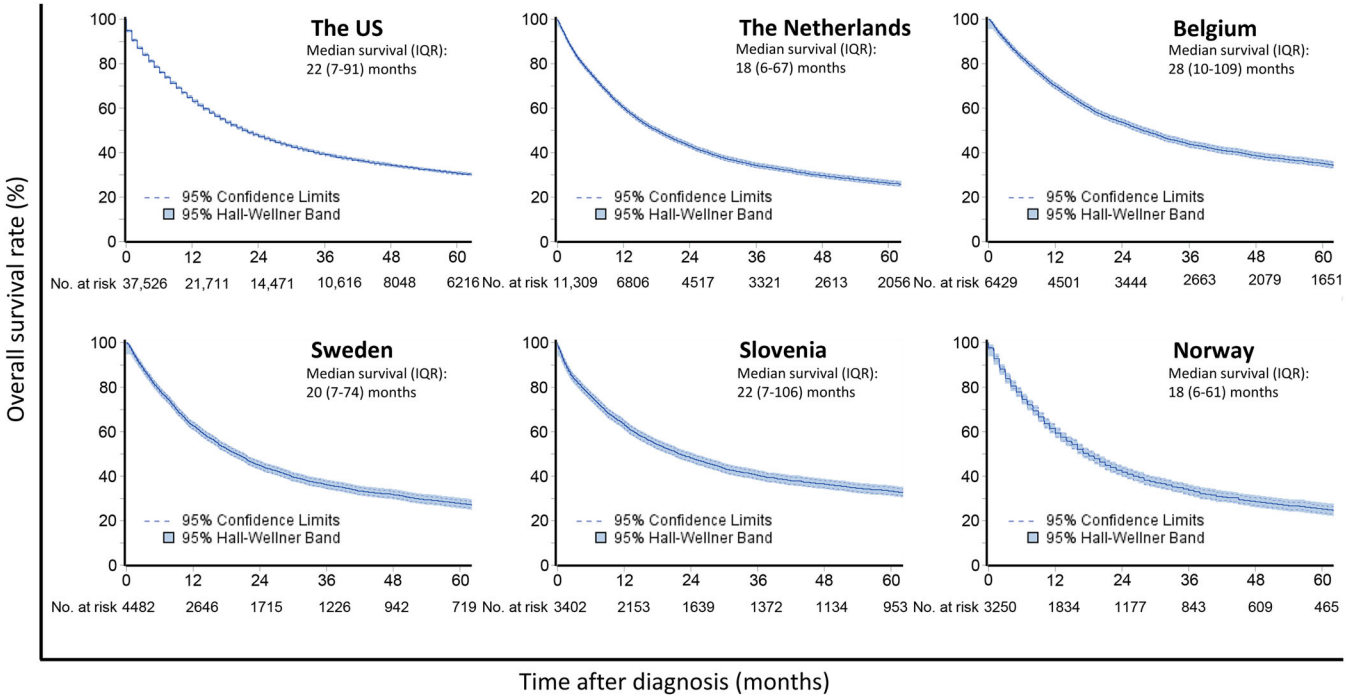

FIGURE 1 Unadjusted overall survival (OS) curves plotted by using the Kaplan-Meier method for patients with non-metastatic gastric adenocarcinoma in the final cohort. Median OS time is shown as point estimate (95% confidence interval). Abbreviations: IQR, interquartile range; CI, confidence interval.

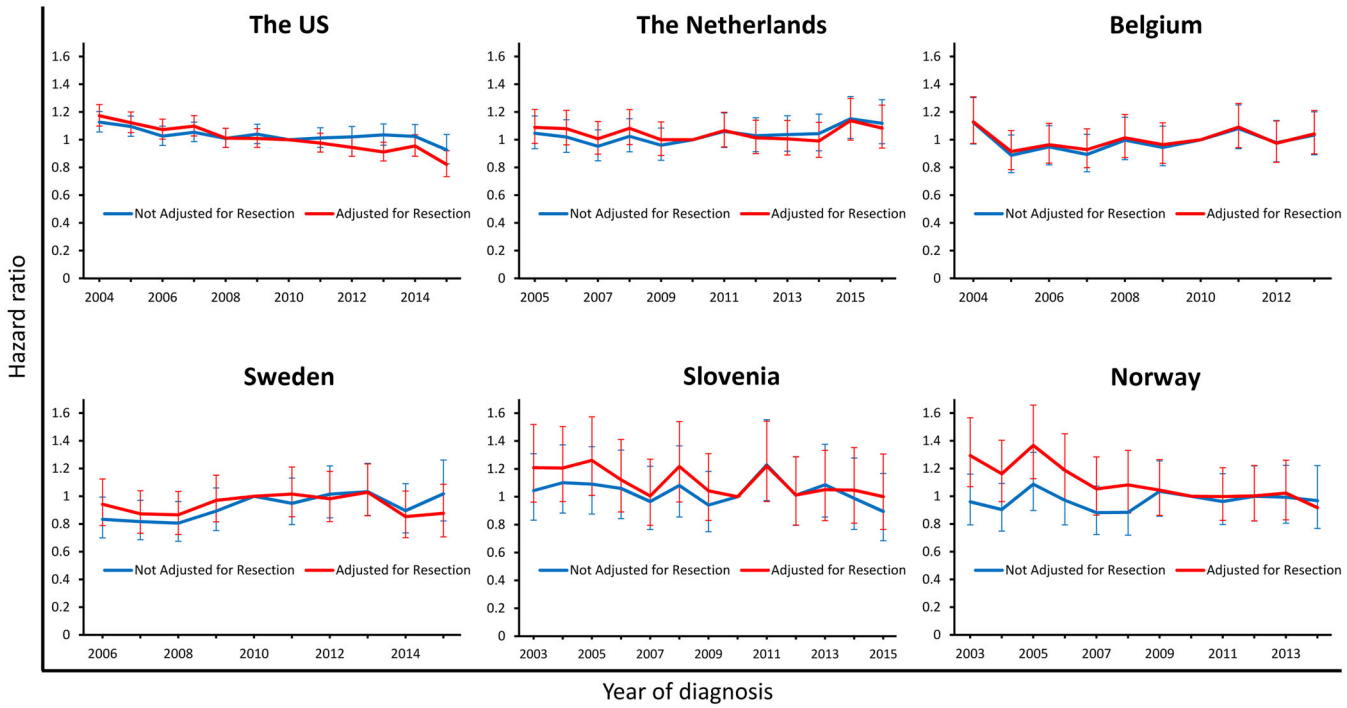

FIGURE 2 Temporal trends of adjusted hazard ratios for patients with non-metastatic gastric adenocarcinoma in the final cohort, without and with adjustment for resection. Associations of overall survival with year of diagnosis (as categorical; 2010 as reference) were evaluated using multivariable Cox proportional hazards regression models with adjustment for age, sex, tumor location, differentiation, T stage, N stage, and resection.

TABLE 2 Association of year of diagnosis with overall survival in patients with non-metastatic gastric adenocarcinoma in the final cohort and the resection cohort using multivariable-adjusted Cox regression before and after multiple imputations*

Cohort variable	The US	The Netherlands	Belgium	Sweden	Slovenia	Norway
Before multiple imputation						
The final cohort, not adjusted for resection						
Per 1 year	**0.99 (0.99-1.00)**	1.01 (1.00-1.02)	1.01 (0.99-1.02)	**1.03 (1.01-1.04)**	0.99 (0.98-1.01)	1.00 (0.99-1.02)
≥ *vs.* <2010	**0.96 (0.93-0.99)**	1.05 (1.00-1.11)	1.06 (0.99-1.15)	**1.17 (1.08-1.28)**	1.00 (0.91-1.10)	1.03 (0.94-1.12)
The final cohort, adjusted for resection						
Per 1 year	**0.98 (0.97-0.98)**	1.00 (0.99-1.01)	1.00 (0.99-1.02)	1.00 (0.99-1.02)	**0.99 (0.97-1.00)**	**0.97 (0.96-0.98)**
≥ *vs.* <2010	**0.88 (0.86-0.91)**	0.98 (0.93-1.04)	1.05 (0.97-1.13)	1.06 (0.97-1.16)	0.92 (0.83-1.02)	**0.86 (0.79-0.94)**
The resection cohort, conditioned to 1-month overall survival						
Per 1 year	**0.98 (0.97-0.99)**	**0.99 (0.98-1.00)**	1.00 (0.98-1.01)	1.00 (0.98-1.02)	1.00 (0.98-1.02)	**0.97 (0.95-0.99)**
≥ *vs.* <2010	**0.95 (0.91-0.99)**	0.95 (0.89-1.01)	1.02 (0.94-1.11)	1.06 (0.94-1.19)	1.11 (0.97-1.27)	**0.77 (0.67-0.89)**
After multiple imputation#						
The final cohort, not adjusted for resection						
Per 1 year	1.00 (0.99-1.00)	1.01 (1.00-1.01)	1.01 (1.00-1.02)	**1.02 (1.01-1.04)**	1.01 (0.99-1.01)	1.01 (0.99-1.01)
≥ *vs.* <2010	0.99 (0.96-1.01)	1.04 (1.00-1.09)	**1.08 (1.02-1.15)**	**1.15 (1.06-1.25)**	1.03 (0.95-1.12)	1.02 (0.94-1.12)
The final cohort, adjusted for resection						
Per 1 year	**0.98 (0.98-0.99)**	1.01 (1.00-1.01)	1.00 (0.99-1.01)	1.01 (1.00-1.03)	1.01 (0.99-1.01)	**0.98 (0.96-0.99)**
≥ *vs.* <2010	**0.91 (0.89-0.94)**	1.04 (0.99-1.09)	1.05 (0.98-1.11)	1.08 (1.00-1.18)	1.01 (0.92-1.10)	**0.89 (0.82-0.97)**
The resection cohort, conditioned to 1-month overall survival						
Per 1 year	**0.98 (0.97-0.98)**	**0.98 (0.97-0.99)**	0.99 (0.98-1.00)	1.00 (0.98-1.02)	1.00 (0.99-1.02)	**0.96 (0.94-0.98)**
≥ *vs.* <2010	**0.88 (0.85-0.91)**	**0.93 (0.87-0.99)**	1.01 (0.94-1.09)	1.04 (0.93-1.17)	1.10 (0.98-1.23)	**0.77 (0.67-0.88)**

*Results are shown as hazard ratios (95% confidence intervals) for associations of year of diagnosis with overall survival (OS) which were calculated using multivariable Cox regression models adjusting for sex, age group, tumor location, differentiation, T stage, N stage, and resection. The association of the year of diagnosis ≥ versus <2010 with OS was computed by replacing the continuous year of diagnosis with the categorical one in the multivariable models. The data on previous cancer were available in the US, the Netherlands, and Belgium and were adjusted. Analyses for patients in the resection cohort were conditioned to 1-month OS to minimize the effect of the potential heterogeneity in surgery quality and perioperative care. Hazard ratios shown in bold are statistically significant.

#Multiple imputations were performed using the *MICE* package in R and applying the following variables: year of diagnosis, sex, age, tumor location, morphology, differentiation, T, N, and M stages, resection, chemotherapy, radiotherapy, OS time and status, and previous cancer (in countries with available information).

$_{\text{T1 (invasion of lamina propria/submucosa)}}$ = 2.46 (the US) to 5.57 (the Netherlands)] and more advanced N stage [$HR_{\text{N1/2 (1-6 positive lymph nodes) } vs. \text{ N0 (0 positive lymph node)}}$ = 1.19 (the US) to 1.53 (the Netherlands); $HR_{\text{N3a/3b (≥7 positive lymph nodes) } vs. \text{ N0 (0 positive lymph node)}}$ = 1.67 (the US) to 2.84 (Slovenia)] were associated with shorter OS.

After adjusting for resection, the associations with age became weaker, especially for patients ≥80 years [$HR_{\geq 80 \ vs. \ <60 \text{ years}}$ = 1.94 (the Netherlands) to 3.24 (Belgium)], and the associations for gastric fundus/body and antrum/pylorus cancers became insignificant or markedly weakened. Stage T4b (invasion of adjacent structures) was less strongly associated with shorter OS than stage T1 (invasion of lamina propria/submucosa) [HR = 2.08 (the US) to 3.36 (Belgium)], while stage N3a/3b (≥7 positive lymph nodes) was more strongly associated with OS than stage N0 (0 positive lymph node) [e.g., HR = 2.20 (the US) to 3.34 (Slovenia)].

Factors associated with OS in the resection cohort are shown in Supplementary Table S6, and the association patterns were mostly similar to those for the final cohort, with association mostly being between the strengths calculated before and after adjustment for resection in the final cohort.

Associations of OS with additional factors were further investigated in registries with available information (Supplementary Table S7). Management in academic hospitals was associated with better OS in the Netherlands (HR = 0.86), Belgium (HR = 0.87), and Sweden (HR = 0.89). Resection in small-volume hospitals was associated with increased mortality hazards (e.g., $HR_{<10 \ vs. \ \geq 20 \text{ resections/year}}$ = 1.19 in both the Netherlands and Sweden). Smaller tumor size was associated with better OS in the US (e.g., $HR_{<2 \ vs. \ \geq 4 \text{ cm}}$ = 0.76). Patients with higher ECOG-PS [e.g., $HR_{\geq 3 \text{ versus } 0\text{-}1}$ = 1.72 (Belgium); HR = 3.44 (Sweden)] and ASA scores [e.g., $HR_{\geq 4 \text{ versus } 1\text{-}2}$ = 1.54 (Sweden)] had worse OS. Certain comorbidities including cardiovascular disease [HR = 1.14 (Belgium)], vascular disease [HR = 1.21 (the Netherlands)], diabetes [HR = 1.13 (Belgium)], and pulmonary disease [HR = 1.17 (the Netherlands); HR = 1.34 (Belgium)] were associated with worse

TABLE 3 Sensitivity and subgroup analyses of association of year of diagnosis as continuous or categorical variable with overall survival in patients with non-metastatic gastric adenocarcinoma in the final cohort without and with adjustment for resection*

Condition	The US		The Netherlands		Belgium		Sweden		Slovenia		Norway	
	Resection-unadjusted	*Resection-adjusted*	*Resection-unadjusted*	*Resection-adjusted*	*Resection-unadjusted*	*Resection-adjusted*	*Resection-unadjusted*	*Resection-adjusted*	*Resection-unadjusted*	*Resection-adjusted*	*Resection-unadjusted*	*Resection-adjusted*
The final cohort/baseline												
Year of diagnosis as continuous; per 1 year	**0.99** (0.99-1.00)	**0.98** (0.97-0.98)	1.01 (1.00-1.02)	1.00 (0.99-1.01)	1.01 (0.99-1.02)	1.00 (0.99-1.02)	**1.03** (1.01-1.04)	1.00 (0.99-1.02)	0.99 (0.98-1.01)	**0.99** (0.97-1.00)	1.00 (0.99-1.02)	**0.97** (0.96-0.98)
Year of diagnosis as categorical; ≥ *vs.* <2010	**0.96** (0.93-0.99)	**0.88** (0.86-0.91)	1.05 (1.00-1.11)	0.98 (0.93-1.04)	1.06 (0.99-1.15)	1.05 (0.97-1.13)	**1.17** (1.08-1.28)	1.06 (0.97-1.16)	1.00 (0.91-1.10)	0.92 (0.83-1.02)	1.03 (0.94-1.12)	**0.86** (0.79-0.94)
Adding chemotherapy as static variable												
Year of diagnosis as continuous; per 1 year	-	-	**1.02** (1.01-1.03)	**1.01** (1.00-1.02)	1.01 (0.99-1.02)	1.01 (0.99-1.02)	-	-	1.00 (0.99-1.01)	0.99 (0.98-1.00)	1.01 (0.99-1.02)	**0.97** (0.96-0.99)
Year of diagnosis as categorical; ≥ *vs.* <2010	-	-	**1.14** (1.08-1.20)	1.06 (1.00-1.12)	1.07 (0.99-1.15)	1.06 (0.98-1.14)	-	-	1.04 (0.94-1.15)	0.95 (0.86-1.05)	1.04 (0.95-1.14)	**0.86** (0.79-0.94)
Adding chemotherapy as time-dependent variable												
Year of diagnosis as continuous; per 1 year	-	-	**1.02** (1.01-1.03)	1.00 (0.99-1.01)	1.00 (0.99-1.01)	1.00 (0.99-1.01)	-	-	0.99 (0.98-1.00)	**0.98** (0.97-1.00)	-	-
Year of diagnosis as categorical; ≥ *vs.* <2010	-	-	**1.14** (1.07-1.21)	1.00 (0.94-1.07)	1.05 (0.98-1.14)	1.04 (0.96-1.12)	-	-	0.98 (0.88-1.09)	0.90 (0.81-1.00)	-	-
Patients with tumor stage >T1N0												
Year of diagnosis as continuous; per 1 year	**0.99** (0.99-1.00)	**0.98** (0.97-0.98)	**1.01** (1.00-1.02)	1.00 (0.99-1.01)	1.01 (1.00-1.02)	1.01 (0.99-1.02)	**1.03** (1.01-1.04)	1.00 (0.99-1.02)	0.99 (0.97-1.00)	**0.98** (0.96-0.99)	/	/
Year of diagnosis as categorical; ≥ *vs.* <2010	0.98 (0.94-1.01)	**0.90** (0.87-0.94)	**1.07** (1.01-1.13)	1.00 (0.94-1.05)	**1.11** (1.02-1.20)	**1.09** (1.01-1.18)	**1.18** (1.07-1.29)	1.06 (0.97-1.17)	0.94 (0.84-1.06)	**0.89** (0.79-0.99)	/	/
Patients with T stage >T1 (tumor invading >submucosa)												
Year of diagnosis as continuous; per 1 year	**0.99** (0.99-1.00)	**0.98** (0.97-0.99)	**1.01** (1.01-1.02)	1.00 (0.99-1.01)	1.01 (1.00-1.02)	1.01 (0.99-1.02)	**1.03** (1.01-1.04)	1.00 (0.99-1.02)	0.98 (0.97-1.00)	**0.97** (0.96-0.99)	/	/
Year of diagnosis as categorical; ≥ *vs.* <2010	0.98 (0.95-1.02)	**0.91** (0.88-0.94)	**1.08** (1.02-1.14)	1.00 (0.95-1.06)	**1.11** (1.02-1.20)	**1.09** (1.01-1.18)	**1.17** (1.07-1.29)	1.06 (0.96-1.17)	0.93 (0.82-1.04)	**0.88** (0.78-0.99)	/	/
Patients with cardia cancer												
Year of diagnosis as continuous; per 1 year	**0.99** (0.98-1.00)	**0.97** (0.96-0.98)	**1.02** (1.00-1.03)	**1.00 (0.98-1.02)**	0.99 (0.97-1.02)	0.99 (0.97-1.01)	**1.04** (1.01-1.07)	1.02 (0.99-1.05)	0.99 (0.96-1.02)	0.98 (0.95-1.01)	0.99 (0.97-1.02)	**0.96** (0.94-0.99)
Year of diagnosis as categorical; ≥ *vs.* <2010	**0.94** (0.89-0.99)	**0.86** (0.81-0.91)	**1.12** (1.01-1.25)	0.99 (0.89-1.10)	0.95 (0.83-1.09)	0.92 (0.81-1.06)	**1.31** (1.10-1.55)	1.16 (0.97-1.38)	1.08 (0.86-1.37)	0.95 (0.75-1.21)	0.96 (0.81-1.13)	**0.82** (0.70-0.97)
Patients with non-cardia cancer												
Year of diagnosis as continuous; per 1 year	**0.99** (0.98-1.00)	**0.98** (0.97-0.98)	1.00 (0.99-1.01)	0.99 (0.98-1.01)	1.01 (0.98-1.03)	1.00 (0.97-1.02)	1.02 (1.00-1.04)	0.99 (0.97-1.02)	1.00 (0.98-1.02)	0.99 (0.97-1.01)	0.99 (0.97-1.01)	**0.97** (0.95-0.99)
Year of diagnosis as categorical; ≥ *vs.* <2010	**0.95** (0.90-1.00)	**0.88** (0.84-0.93)	0.99 (0.92-1.07)	0.95 (0.88-1.03)	1.07 (0.93-1.23)	1.00 (0.86-1.15)	1.13 (1.00-1.27)	1.04 (0.92-1.18)	1.02 (0.88-1.19)	0.94 (0.81-1.10)	0.98 (0.84-1.13)	**0.86** (0.74-1.00)

*Hazard ratios and 95% confidence intervals for associations of year of diagnosis with overall survival were calculated using multivariable Cox regression models additionally adjusting for sex, age group, tumor location, differentiation, T stage, N stage, and resection. The data on previous cancer were available in the US, the Netherlands, and Belgium and were adjusted in multivariable analyses. Statistically significant hazard ratios are shown in bold.
-, not shown due to unavailable chemotherapy and/or treatment interval data; /, not shown for Norway due to too high proportions of missing values for both T stage (47.4%) and N stage (24.4%).

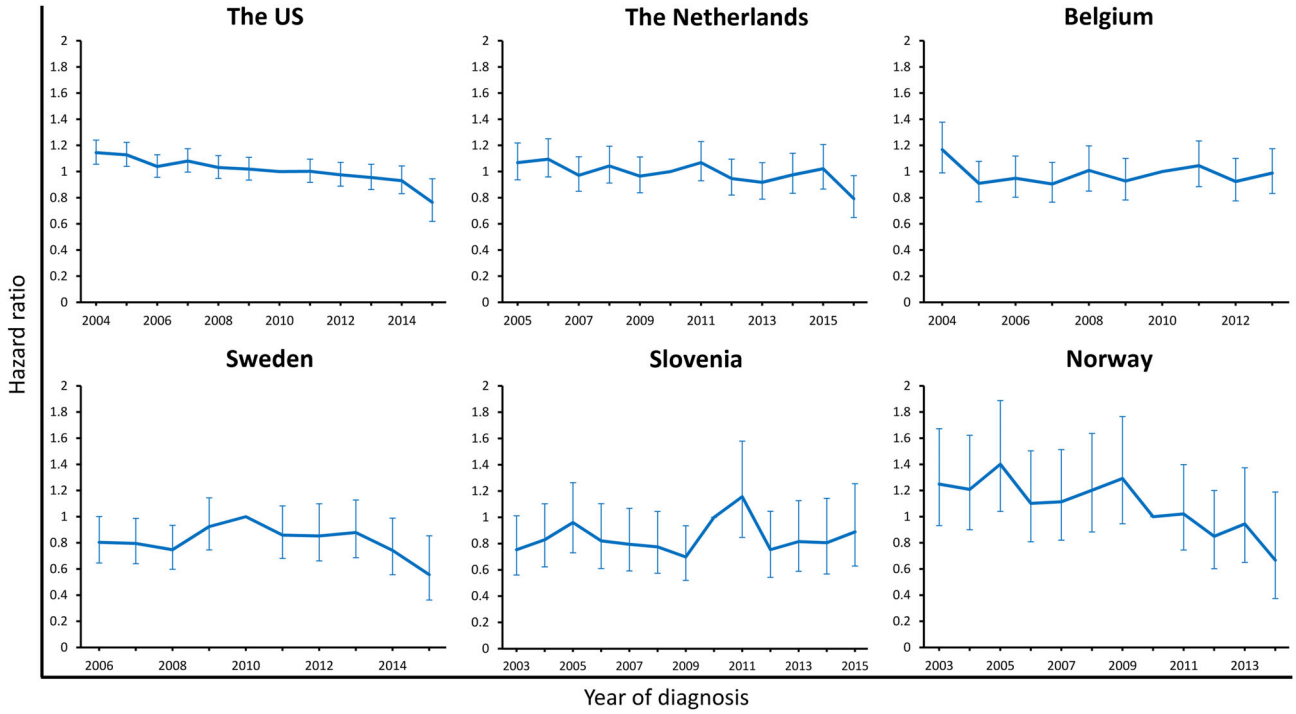

FIGURE 3 Temporal trends of adjusted hazard ratios for patients with non-metastatic gastric adenocarcinoma in the resection cohort, conditioned to 1 month. Associations of overall survival with year of diagnosis (as categorical; 2010 as reference) were evaluated using multivariable Cox proportional hazards regression models with adjustment for age, sex, tumor location, differentiation, T stage, and N stage.

OS, and ≥2 comorbidities were associated with increased mortality compared to 0 comorbidity in the Netherlands (HR = 1.18).

4 | DISCUSSION

Our international population-based investigation comprehensively described the temporal OS trends for all patients with non-metastatic GaCs and patients who underwent resection in Europe and the US, adjusting for multiple prognostic factors. For the final cohort, while the mortality hazard decreased in the US, no improvement in OS over years was observed in the investigated European countries, and OS was even decreased in Sweden. Adjustment for resection markedly affected the results and disclosed improving OS trends in most countries. Furthermore, the OS of the resection cohort was improved over time in the US, the Netherlands, and Norway. Together with our previous findings of the decreasing and non-optimal resection rates for non-metastatic GaC [2], these results suggest that progress in OS of patients with non-metastatic GaC may have been hampered by the decreasing and non-optimal resection rates in the US, Sweden, Slovenia, and Norway.

We have previously found that patients with non-metastatic GCs underwent less resections in the US and Europe [2]. The following reasons may explain the declining rates of resection. First, the criteria of selecting candidates for resection became increasingly stricter, as reflected by the ascending rates of clear-margin (R0) resection within all resections and the increasing proportions of resections with ≥15 lymph nodes examined for non-metastatic GCs [2]. Second, the use of perioperative therapy became more frequent. While the pre-resection management may improve resectability via down-staging cancer, it may also allow substantial time for further development of advanced malignancies or even metastatic diseases, possibly barring resection application. Increased access to and more frequent use of chemotherapy and/or radiotherapy and neoadjuvant chemotherapy-related toxicity may as well impede some patients from undergoing further resection [2]. Other factors influencing patient selection might also partly account for the declining trends of resection. The reasons for the declining trends of resection are not totally clear and require further investigations.

Previous studies on survival trends for GC patients mostly reported unadjusted findings, which may depend on multiple factors. While unadjusted OS data provide an essential overview, when investigating reasons for OS trends, adjustments are important. In the US, age-standardized 5-year net survival increased from 26% in 2001-2003 to 29% in 2004-2009 [8]; for GC patients who underwent resection, survival was also significantly

improved during 1988-2013 [7]. These are consistent with our findings of gradually decreasing mortality hazards for the final cohort and the resection cohort during 2004-2015. We further found consistently increasing OS for both cardia and non-cardia non-metastatic GaCs during 2004-2015 in the US. Earlier studies reported no significant changes in mortality risk for both overall and surgically-managed non-cardia cancers between 1983 and 2002 [14, 15]. Notably, we further found stronger increasing OS trends in the US after additionally adjusting for resection but not chemotherapy (adjuvant and/or neoadjuvant).

In the Netherlands, while there was no significant improvement in long-term survival during 1989-2009 [16], 30-day postoperative mortality was reduced and OS was improved for patients with non-cardia GC after centralization of GC surgery in 2012, since when hospitals which undertake GC surgery should perform a minimum of 10 gastrectomies yearly (this has increased to 20 since 2013) [17]. Notably, we did not observe any improvement in adjusted OS in the investigated European countries before adjusting for resection, and the mortality hazard was even increased over time in Sweden. Interestingly, after adjusting for resection, the worsening OS trend disappeared in Sweden, and significantly improved OS was detected in Slovenia and Norway.

In the present study, we found that the adjusted mortality hazards were increased for both cardia and non-cardia cancers when not adjusting for resection, without improvement in OS for the resection cohort. The adjustment for resection eliminated the increasing hazards for both tumor locations.

A major difference between the present study and most previous ones is that we accounted for multiple OS-associated factors and provided summarized information on key patient characteristics for each country. Comparing the results of analyses with various levels of adjustment can help to disclose the impact of specific variables on OS trends. Guidelines [5, 6, 18–21] recommend resection for medically-fit patients with resectable non-metastatic GaC (endoscopic resection for a small specific subgroup of patients with tumor invasion within lamina propria and without lymph node metastasis), and additional non-surgical therapy for most of these patients with disease stage >T1N0. In our analyses, improving OS trends over time became apparent only after adjustment for resection in most countries for the final cohort, those with disease stage >T1N0, and those with tumor invasion beyond submucosa. These results point to the potentially non-optimal pattern of decreasing resection rates with resection as a major obstacle hindering progress in non-metastatic GaC survival.

While perioperative chemotherapy is preferred in Europe following the MAGIC [22] and FLOT trials [23], adjuvant treatment is the only standard of care in the US following the INT-0116 trial [24]. While the differences in perioperative care may at least partly explain the discrepancies in OS trends between Europe and the US, the adjustment for chemotherapy (adjuvant and/or neoadjuvant) did not alter the association patterns across countries.

Adjustment for resection also impacted the patterns of associations between OS and certain variables. The negative associations with age became weaker, especially for patients ≥80 years. Older age was associated with less frequent resection, possibly due to more comorbidities and greater frailty scores [25]. However, some elderly patients may benefit from resection, and it is vital to well balance the benefits and harms for them and to precisely select those who would most likely benefit. Cardia cancers are generally considered to be associated with poorer prognosis and are less often resected due to operating challenges compared to non-cardia cancers [26]. However, resection remains the essential management approach for them. Indeed, non-cardia (gastric fundus/body and antrum/pylorus) GCs were associated with better survival compared to cardia cancers both in the final cohort, especially before adjustment for resection, and in the resection cohort. Interestingly, the associations of tumor location with OS became insignificant or markedly weakened after adjustment for resection, and the associations between tumor location and survival appeared slightly weaker for the resection cohort than for the final cohort. These patterns may suggest that the overall associations between tumor location and survival might be partly explained by differences in resectability. Again, our findings call for exploring possibilities of enhanced treatment application for cases with certain patient and tumor characteristics.

For the association analyses in the resection cohort, patients were conditioned to those surviving > 1 month to minimize the influence of possible heterogeneities in surgical quality and perioperative factors; the resection cohort might include some patients with postoperative complications, the information on which was not available. Thus, before showing the temporal trends in OS of patients surviving > 1 month, we first showed the changes in perioperative mortality per year in the resection cohort by depicting the temporal trends in multivariable-adjusted 1-month OS rate.

We found that before adjusting for resection, adjusted OS improved slightly in the US, did not significantly improve in the Netherlands, Belgium, Slovenia, or Norway, and worsened in Sweden. After adjusting for resection, the increasing OS trend became stronger in the US, and the worsening temporal trend became insignificant in Sweden. In Slovenia and Norway, improved OS over time emerged after resection adjustment. Improved OS in patients in the resection cohort was observed in the US, the Netherlands, and Norway. Adjustment for chemotherapy

(adjuvant and/or neoadjuvant) did not alter the observed associations. These findings suggest that progress in OS of the final cohort seems to have been impeded to a large extent by decreasing rates of resection. To improve the OS, more high-quality resection may be needed, which could be achieved by centralization of resection in specialized centers. Notably, various factors including patient preference, performance, nutrition, and psychosocial statuses, and organ function should all be carefully and comprehensively taken into account for treatment decisions. More advanced chemotherapeutic agents with better efficacy and lower toxicity may also contribute to better OS, which should be explored in future studies. Precise and individualized management of patients and better adherence to guidelines and standards may also result in enhanced OS. Other reasons for the possibly non-optimal OS trend should be addressed in future investigations.

The present study was limited by its observational nature. Some important variables were not recorded in registries from all or certain countries (e.g., tumor size). Endoscopic resection was not clearly recorded in most countries; however, our results were most probably not biased by this factor since sensitivity analyses by limiting cases to those with characteristics clearly ineligible/inadequate for endoscopic resection to minimize the impact of endoscopic management showed similar results. While information on surgical approach and lymphadenectomy degree was unavailable in most countries, randomized evidence has supported the equality or noninferiority in survival between open and laparoscopic gastrectomy [27–29] and between D1 and D2 lymphadenectomy [4]. Some variables had relatively high proportions of missing values and were thus not included in the main multivariable models (e.g., differentiation). Multiple imputations were thus further conducted and revealed mostly similar results. Taking the potential heterogeneity into consideration, data were not pooled, but were analyzed, shown, and interpreted separately for each country. Accordingly, data might not be directly and quantitatively comparable across counties, and the variations across countries could be partly reflected by the different temporal survival trends within each country. It is of note that the proportion of cardia cancers in the final cohort was relatively small in Slovenia (26.8%) compared to the other countries (35.9%-54.9%), possibly indicating the varying GC epidemiology or difficulty of correct registration in different parts of Europe. Accordingly, we further performed subgroup analyses stratified by tumor location. The study time periods were not exactly identical across countries. Nevertheless, they mostly covered the time period 2003-2016, and we adjusted for year of diagnosis in all multivariable models. There could be possibility of stage migration due to better diagnostics. If more staging laparoscopies and/or PET scans are performed, patients diagnosed with non-metastatic GaC previously might now be diagnosed with M1 disease. This possibility, which should contribute to improved OS in non-metastatic GaC patients, may further strengthen the messages of the present study. There might be other reasons for the observed temporal trends in survival, which could not be fully addressed in this observational study, and future investigations are encouraged to further reveal the degree of impact of decreasing resection rates on the seemingly non-optimal survival trends compared to other factors.

The present study had several implications. We reported the adjusted OS trends for both all patients with non-metastatic GaCs and patients who underwent resection across the US and Europe, and highlighted the impact of individual treatment variables on OS trends by comparing results before and after the adjustment for them in multivariable models. While the present study suggests that there may be room for improvement in clinical practice, the association results do not allow for causality inference, and the question of whether more resections are warranted needs to be addressed by further investigations. Nevertheless, the decreasing resection rates and the impact of the adjustment for resection on temporal OS trends should prompt careful reconsideration of the appropriate use of resection as the fundamental treatment modality for most non-metastatic GaCs in real-world settings. Our report disclosed important trends in non-metastatic GaC management and outcomes that warrant clinicians' and policymakers' attention. Inspired by research on volume-outcome relationships and in order to improve the adequacy of resection (D2) and short-term (e.g., complications) and long-term outcomes, GC surgery has shown increasing trends towards centralization and has been increasingly performed in specialized high-volume centers with required minimal number of gastrectomies per year in some countries, which may contribute to increased resection rates [17, 30–33]. It is highly desired to investigate whether more resections will contribute to improved survival in the years to come.

Adjustment for chemotherapy (adjuvant and/or neoadjuvant) did not significantly alter the observed survival associations in the present study. In the study period, the most commonly used chemotherapeutic agents for non-metastatic GaC majorly included fluorouracil-based and platinum-based drugs based on guidelines in use for the period [5, 6, 18–21]. Notably, non-surgical therapy was advancing with emerging novel therapeutic regimens superior to the previous ones, which would hopefully overcome or reverse the adverse survival trends in the years to come, and which might contribute to the gradual improvement of survival outcomes. It may take some time for the novel promising evidence to be incorporated into clinical practice to a large extent, and future studies on the impact of the increasing popularization of the

advancement of non-surgical therapy on survival trends are warranted.

5 | CONCLUSIONS

Multivariable-adjusted OS for patients with non-metastatic GaC mostly did not improve and even worsened in selected European countries, while it was slightly increased in the US in the early 21st century. Adjustment for resection but not chemotherapy did essentially overcome or even reverse the adverse OS trends in most countries. These findings suggest that progress in OS for patients with non-metastatic GaC may have been impeded to a large extent by decreasing rates of resection, the only potentially curative treatment for most resectable non-metastatic GaCs.

DECLARATIONS

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COMPETING INTERESTS

None declared.

CONSENT FOR PUBLICATION

Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee of the Medical Faculty Heidelberg.

AUTHOR CONTRIBUTIONS

Conception or design of the present study: Huang L, Jansen L, Schrotz-King P, Brenner H.

Acquisition, analysis, or interpretation of data: Huang L, Jansen L, Verhoeven R, Ruurda J, Van Eycken L, De Schutter H, Johansson J, Lindblad M, Johannesen T, Zadnik V, Zagar T, Lagrade S, van de Velde C, Schrotz-King P, Brenner H.

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Statistical analysis: Huang L.

Administrative, technical, or material support: van de Velde C, Schrotz-King P, Brenner H.

Supervision: Jansen L, Brenner H.

Huang L and Brenner H had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors have given final approval of the manuscript for submission and publication.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from each registry but restrictions apply to the availability of these data, which were used under license for the present study, and so are not publicly available. Data are, however, available upon reasonable request and with permission of each contributing registry.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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