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Largely varying patterns and trends of primary cancer-directed resection for gastric carcinoma with synchronous distant metastasis in Europe and the US: a population-based study calling for further standardization of care

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Abstract

Aims: The role of resection remains debated in cases of metastatic gastric carcinoma (mGC). Some mGCs are technically resectable. At the population level, the real-world application of resection for mGC remains largely unclear in most Western countries. This large, population-based international investigation aimed to reveal the resection patterns and trends for mGC and the treatment-associated factors in Europe and the US.

Methods: Data on cases with microscopically-confirmed primary invasive stomach carcinoma with distant metastasis were obtained from the nationwide cancer registries of the Netherlands, Belgium, Norway, Sweden, Estonia, and Slovenia and the US Surveillance, Epidemiology, and End Results-18 database. We calculated age-standardized rates of primary cancer-directed resection and assessed resection trends using linear regression. We investigated associations of treatment with patient and cancer factors using multivariable-adjusted log-binomial regression.

Results: Among 133,321 patients with gastric cancer, overall, 40,215 cases with mGC diagnosed between 2003–2017 were investigated. Age-standardized resection rates significantly declined over time in the US, Belgium, Sweden, and Norway (by 5–14%). Resection rates greatly differed from 5% to 16% in 2013–2014. Cases with older ages, cardia tumors, or tumors involving adjacent structures were significantly less often operated across most countries. Sex was not significantly associated with resection. Across countries the association patterns and strengths differed largely. With multivariable adjustment, resection rates decreased significantly in all countries except Slovenia and Estonia (prevalence ratio per year = 0.90–0.98), and the decreasing trends were consistently observed in various stratifications by age and location.

Conclusion: In Europe and the US, resection patterns and trends largely varied across countries for mGCs, which were mostly less often resected in the early 21st century. Various resection-associated factors were shown, with greatly varying association patterns and strengths. Our report could aid to identify discrepancies in clinical practice and highlight the great need for further clarifying the role of resection in mGCs to enhance standardization of care.

Keywords: great variations, large international population-based investigation, metastatic gastric carcinoma, patterns and trends, treatment

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Introduction

With over 1,000,000 new cases and about 800,000 associated mortalities estimated in 2018, gastric carcinoma (GC) is the fifth most often diagnosed malignancy and the third leading cause of malignancy-associated mortality globally.[1] Because of its insidious nature, a significant proportion of patients with GC have distant metastasis at initial diagnosis.[2] GC with distant metastasis is typically not amenable to curative surgical resection and is usually managed with chemotherapy with/without radiotherapy.[2–4] The prognosis of patients with metastatic GC (mGC) is very poor, with median survival ranging from about 4 months when managed with best supportive care only, to around 1 year when treated with palliative combination chemotherapy.[5–8]

The role of resection is still obscure among cases with mGC.[9] Some mGCs are technically resectable; palliative interventions used to relieve major symptoms may contribute to prolongation of life. Some studies[10–15] suggest that selected patients with mGC and with good performance status may benefit from resection by experienced hands in expert centers, while relevant prospective and/or randomized evidence remains lacking.

With obscure effectiveness, some surgeons operate on patients with mGC, possibly because of identification of metastatic disease only during or after operation or for palliative purposes. However, the real-world patterns and trends of such management at the population level remain greatly unclear in most Western countries.

In our large, population-based international investigation, the use of primary cancer-directed resection for mGC in Europe and the United States (US) in the early 21st century was revealed, and the treatment-associated factors were explored.

Methods

Data

Selection of eligible European nationwide population-based cancer registries after extensive retrieval and contact and reasons for exclusion have been detailed previously.[16] We included patient-level data of cases with GC from the nationwide cancer registries of the Netherlands, Belgium, Norway, Sweden, Estonia, and Slovenia, and the Surveillance, Epidemiology, and End Results (SEER)-18 Program of the US for analysis (Supplemental Table S1). The characteristics of the participating European registries have been previously detailed;[16,17]generally the quality of the data was high. Being an authoritative source for the US cancer statistics, the SEER database collects information from population-based cancer registries in the US.[18]

Tumor morphology and topography were in line with the International Classification of Diseases for Oncology, third edition (ICD-O-3). Cases with invasive primary carcinomas of the stomach (ICD-O-3 code, C16) confirmed microscopically during 2003 through 2017 were eligible. We included both cardia and non-cardia cancers. A detailed analysis of resection rates for non-metastatic GC has been reported elsewhere.[16] Here, we only analyzed cases with distant metastasis. Patients with non-stomach malignancies invading the stomach, or neoplasms originating from the germ-cell, neuroendocrine, or mesenchymal tissues were ineligible (Supplemental Table S2). We also excluded individuals diagnosed on the basis of autopsy or death certificate only.

Information on patient (age, sex, and diagnosis year), tumor (histology, differentiation, location, and stage), management (gastrectomy, chemotherapy, and radiation therapy), and follow-up (survival status and time) which was (re)coded according to a uniform standardized data-collection sheet was retrieved. Chemotherapy and/or radiotherapy were recorded with low sensitivity in the US and Estonia registry data. Neoadjuvant and adjuvant treatment could be hardly differentiated in the Norway and Estonia registry data, and adjuvant therapy was not recorded in the dataset from Sweden. Certain metastatic sites (bone, brain, liver, and lung) were only recorded in the registries from the US and the Netherlands.

We investigated primary cancer-directed resection and defined it as surgical excision of the primary cancer regardless of the type, radicality, and extent of gastrectomy and regional lymph node excision, of the concurrence of distant metastasectomy, and of the technique, approach, method, and procedure of surgery. We derived local cancer invasion and lymph node involvement from the tumor-node-metastasis (TNM) staging by the

Union for International Cancer Control/American Joint Committee on Cancer; we re-categorized them into subgroups that were consistent across the studied periods during which the sixth or seventh edition of staging had been in effect.

Ethics statement

The Ethics Committee affiliated to the Medical Faculty Heidelberg approved our observational, registry-based, and population-based investigation (S-064/2016). The secondary data presented are all anonymous without any risk of identification, with no individual case data shown.

Analyses

We analyzed data and presented results separately for each registry without pooling. We stratified age into four categories (<60, 60–69, 70–79, and ⩾80 year-old). We computed age-standardized resection rates with the use of the distribution of age of the cases from the US, with the greatest number of analyzed cases, as the standard. We used linear regression to evaluate the time trends of the standardized rates and graphically illustrated the rates over 2-calendar-year time. We showed graphically the patient age- and cancer location-stratified rates in 2010 and later.

The associations of treatment with patient and cancer features adjusting for diagnosis year, age group, sex, cancer histology, location, and adjacent structure invasion were investigated by computing the multivariable log-binomial regression models. We calculated the log-binomial maximal likelihood prevalence ratios (PRs).[19] We further performed analyses stratified by patient age, tumor histology, and location. We used the SAS software (version 9.4; Cary, NC, the US) for data analyses. A two-sided *p*-value of <0.05 indicated statistical significance.

Results

Features of overall cases with mGC

From a total of 133,321 registered patients with GC, we investigated 40,215 cases with metastatic cancer (Supplemental Table S1 and Table 1). The majority of the patients were males (59–68% across countries). The mean age was 65–70 years, with 41–55% of the patients aged ⩾70 years. Most often, the malignancies originated from the cardia (37–60%; 14% in Estonia) and were poorly-differentiated or undifferentiated (66–77%). 12–39% of the mGCs also invaded adjacent structures. Only a small proportion of the malignancies did not involve lymph nodes (5–24%; 44% in the US). It should be noted 9% (Sweden) to 21% (Belgium) of the patients with mGC underwent gastrectomy. In countries where data on non-surgical management were recorded with good sensitivity, chemotherapy was given to between 25% (Slovenia) and 62% (Belgium) of cases, and radiation therapy was less frequently used (7–10%).

Based on the information available on distant metastasis sites in the US and the Netherlands, the liver was the most frequent metastasis site (43% and 41%), followed by lung (15% and 10%) and bone (13% and 7%).

Characteristics of patients with resected mGC

Compared with overall patients with mGC, those with resected cancer were on average 1–3 years younger. Resected tumors were much less often located at the cardia (6–54%) and invaded adjacent structures less frequently (11–26%). Partial/subtotal gastrectomy was the most frequent primary cancer-directed resection (59–71%). On average, 9–19 lymph nodes were retrieved. In registries with data on non-operational treatment of high quality, neoadjuvant chemotherapy was used for from 8% (Slovenia) to 29% of cases (Belgium); however, neoadjuvant radiation therapy was scarcely used (1–5%). Adjuvant chemotherapy was applied from 26% (Norway) to 48% of cases (Belgium); however, adjuvant radiation therapy was much less often used (5–11%).

Trends of resection

We observed significantly decreasing trends of resection across all registries except those from the Netherlands ($P_{trend} = 0.132$), Estonia ($P_{trend} = 0.329$), and Slovenia ($P_{trend} = 0.139$; Figure 1). We identified the most dramatic decline in Norway (from 2003–2004 to 2013–2014: from 19% to 5%; $P_{trend} < 0.001$), and the least pronounced decline in Sweden (from 2005–2006 to 2013–2014: from 14% to 9%; $P_{trend} = 0.004$). We saw moderate declines in the US (from 2003–2004 to 2013–2014: 19% to 10%; $P_{trend} < 0.001$) and Belgium (from 2003–2004 to 2013–2014: 24% to 16%; $P_{trend} = 0.001$).

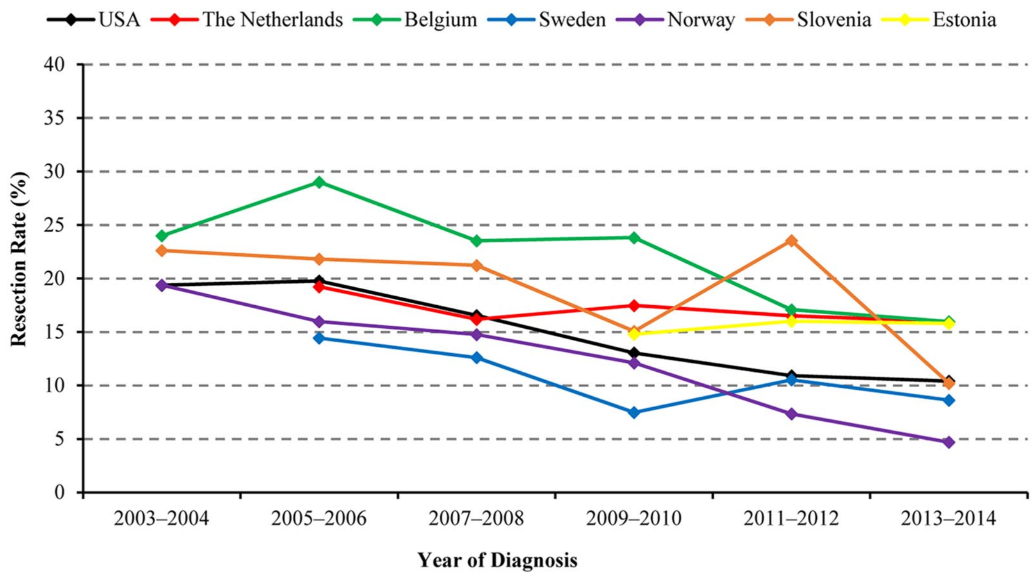

Figure 1. Age-standardized rates of resection for gastric carcinoma with synchronous distant metastasis.

Recent rates of resection by patient age and cancer location

We restricted cases to those who were diagnosed in 2010 and later, a more recent time period during which information was available from the registries of all the countries, to analyze rates of resection by patient age and cancer location (Figure 2). In most countries, rates of resection decreased with older ages, and were dramatically lower among cases aged 80 years or older [4% (Norway) to 17% (Belgium)] compared to in the others [<60 years: from 8% (Norway) to 25% (Slovenia); 60–69 years: from 8% (Norway and Sweden) to 18% (Slovenia); 70–79 years: from 7% (Norway) to 20% (Slovenia)], with great international variations observed. Rates of resection were mostly lower in tumors of the cardia [3% (Norway) to 17% (Belgium)] compared to those of the fundus/body [from 7% (Sweden) to 34% (Slovenia)] or of the antrum/pylorus [from 13% (Norway) to 30% (Belgium)].

Variables associated with resection

The log-binomial regression modeling with multivariable adjustment was used to further explore the treatment-associated factors in each country (Table 2). The findings further supported the decreasing rates of resection across most countries [PR = 0.90 (Norway) to 0.98 per year (the Netherlands), except Slovenia and Estonia].

We did not observe any significant associations of resection with patient sex. Older patients mostly underwent less often resection [*versus* <60 years, $PR_{70\text{–}79\,\text{years}} = 0.66$ (Slovenia) to 0.91 (the US); $PR_{\geqslant 80\,\text{years}} = 0.33$ (Slovenia) to 0.78 (the US and the Netherlands)]. Compared to cardia tumors, gastric fundus/body [PR = 1.40 (the Netherlands) to 2.56 (Slovenia)] and pylorus/antrum tumors [PR = 1.57 (Belgium) to 3.72 (Norway)] were more often resected across most countries. Resection was more frequently performed for signet ring cell cancers (SRCs) in the US (PR = 1.09) and Belgium (PR = 1.35). Patients with invasion of adjacent structure mostly underwent less often resection [PR = 0.34 (Sweden) to 0.65 (the US)].

Stratified analyses of the temporal resection trends

We further analyzed the association between resection and diagnosis year stratified by patient age, tumor histology, and location (Table 3). While the patterns and strengths of association across the various strata were mostly similar to the overall findings, we observed stronger decreasing trends for cardia tumors compared with non-cardia tumors in the US.

Discussion

To the best of our knowledge, our report is a population-based international investigation of the

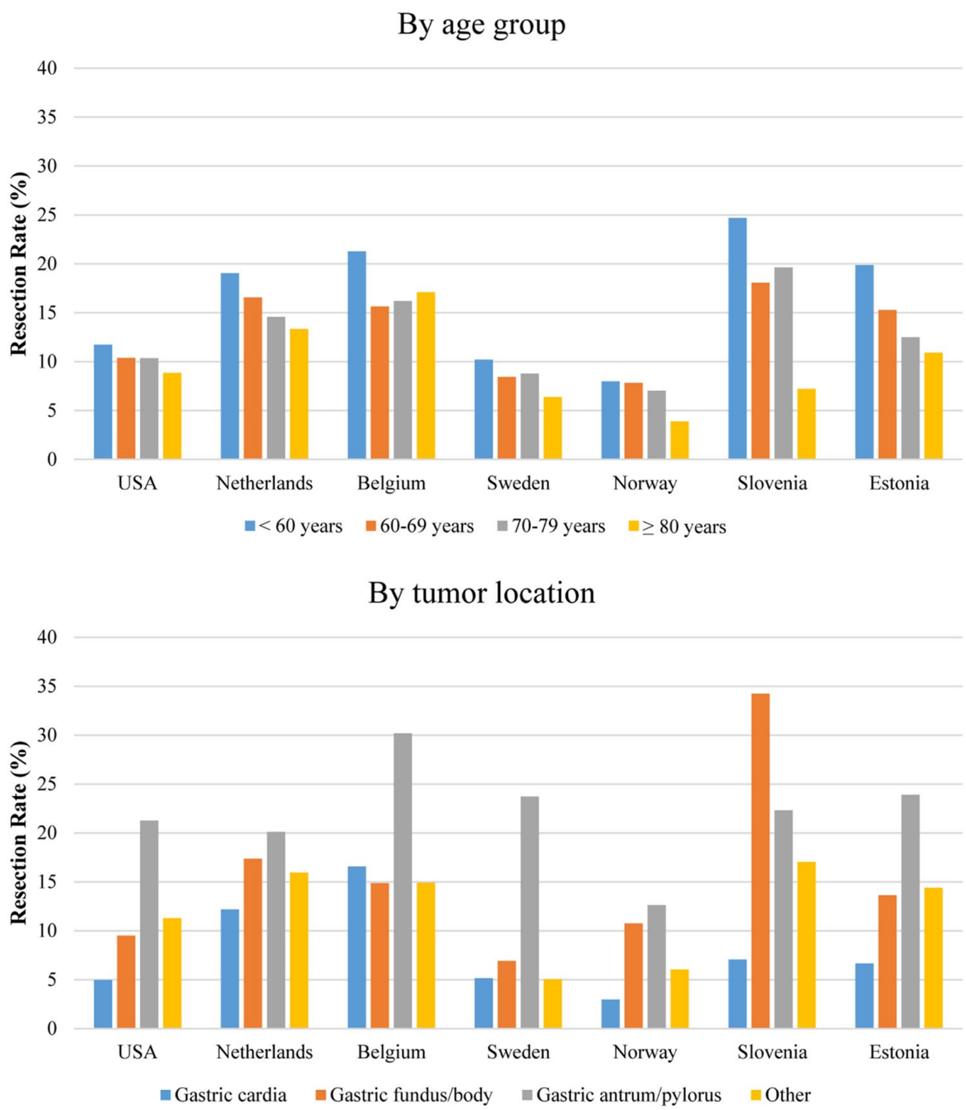

Figure 2. Rates of resection for gastric carcinoma with synchronous distant metastasis stratified by patient age and tumor location, 2010 or later.

largest scale on the patient and cancer features, resection patterns and trends, and factors associated with resection for mGCs in Europe and the US. Great variations across countries were revealed. Rates of resection mostly decreased for mGCs. We consistently observed decreasing trends across various stratifications. We further identified various patient and cancer factors associated with management.

In general, upfront excision of the primary malignancy is not routinely recommended for cases with mGC,[2,20] while resection could be considered for colorectal cancer with limited manageable metastasis, with possible survival benefits.[21,22] Although advances in surgery and perioperative care have contributed to fewer mortalities and morbidities, the role of resection is still debated among cases with technically resectable mGC.[9,23] Reports on trends of resection for mGCs in European countries have been rare. Some patients with mGC underwent primary cancer-directed gastrectomy, albeit with declining trends seen across most countries in our study. The decreasing trends remained after controlling for multiple patient and cancer features, and were mostly consistent across various stratifications by age, histology, and location. We further showed that the decreasing degree varied largely across countries, and that resection rates decreased on average by as much as 10% per year in Norway compared with 2% per year in the Netherlands. The

Table 1. Demographic and clinical features of total and resected patients with gastric carcinoma with distant metastasis.[a]

Variable	Category	The US		The Netherlands		Belgium		Sweden		Norway		Slovenia		Estonia	
		Total	Resected	Total	Resected	Total	Resected	Total	Resected	Total	Resected	Total	Resected	Total	Resected
n		23280	3232 (14)	7112	1201 (17)	2805	598 (21)	2783	254 (9)	1779	222 (12)	1655	323 (20)	801	119 (15)
Sex	Male	14864 (64)	1914 (59)	4637 (65)	750 (62)	1894 (68)	385 (64)	1711 (61)	144 (57)	1083 (61)	121 (55)	1057 (64)	200 (62)	471 (59)	68 (57)
Age at diagnosis	Year; as continuous	65 ± 14	64 ± 14	68 ± 12	67 ± 12	69 ± 13	67 ± 13	70 ± 12	68 ± 11	69 ± 13	68 ± 14	67 ± 12	64 ± 12	68 ± 13	65 ± 14
Age group	<60 years	8071 (35)	1211 (37)	1574 (22)	283 (24)	648 (23)	176 (29)	483 (17)	54 (21)	398 (22)	58 (26)	424 (26)	110 (34)	199 (25)	37 (31)
	60–69 years	5763 (25)	795 (25)	1948 (27)	338 (28)	690 (25)	138 (23)	752 (27)	74 (29)	415 (23)	47 (21)	424 (26)	91 (28)	213 (27)	33 (28)
	70–79 years	5585 (24)	764 (24)	2345 (33)	399 (33)	879 (31)	179 (30)	902 (32)	85 (33)	517 (29)	65 (29)	561 (34)	100 (31)	260 (32)	35 (29)
	⩾80 years	3861 (17)	462 (14)	1245 (18)	181 (15)	588 (21)	105 (18)	646 (23)	41 (16)	449 (25)	52 (23)	246 (15)	22 (7)	129 (16)	14 (12)
Tumor location[b]	Gastric cardia	7145 (50)	518 (27)	2143 (47)	266 (34)	889 (60)	175 (54)	856 (44)	52 (25)	465 (46)	30 (22)	240 (37)	29 (19)	70 (14)	5 (6)
	Gastric fundus/body	3165 (22)	395 (21)	1116 (24)	194 (25)	289 (19)	52 (16)	629 (32)	57 (28)	257 (25)	37 (27)	171 (26)	54 (36)	296 (61)	41 (53)
	Gastric antrum/pylorus	3950 (28)	981 (52)	1352 (29)	329 (42)	315 (21)	99 (30)	458 (24)	98 (47)	289 (29)	70 (51)	236 (36)	66 (44)	123 (25)	31 (40)
	Other	9020 (39)	1338 (41)	2501 (35)	412 (34)	1312 (47)	272 (46)	840 (30)	47 (19)	768 (43)	85 (38)	1008 (61)	174 (54)	312 (39)	42 (35)
Histology	Adenocarcinoma	16181 (70)	2160 (67)	5445 (77)	890 (74)	2226 (79)	443 (74)	NA	NA	1454 (82)	177 (80)	1393 (84)	289 (89)	425 (53)	69 (58)
	Signet ring cell carcinoma	5129 (22)	860 (27)	1221 (17)	248 (21)	414 (15)	120 (20)	NA	NA	174 (10)	28 (13)	101 (6)	19 (6)	249 (31)	36 (30)
	Other[c]	1970 (8)	212 (7)	446 (6)	63 (5)	165 (6)	35 (6)	NA	NA	151 (8)	17 (8)	161 (10)	15 (5)	127 (16)	14 (12)
Differentiation[d]	Well	374 (2)	46 (2)	65 (2)	14 (2)	173 (7)	24 (5)	–	5 (4)	30 (3)	2 (1)	48 (5)	11 (4)	27 (5)	4 (4)
	Intermediate	4021 (22)	552 (19)	847 (22)	167 (21)	635 (27)	123 (23)	–	21 (17)	248 (21)	43 (24)	214 (23)	55 (20)	154 (26)	26 (26)
	Poor/undifferentiated	13715 (76)	2383 (80)	3010 (77)	603 (77)	1532 (66)	390 (73)	–	95 (79)	904 (76)	132 (75)	681 (72)	209 (76)	411 (69)	70 (70)
Local invasion[e]	Lamina propria/submucosa	3875 (28)	182 (6)	111 (3)	19 (2)	90 (5)	14 (2)	48 (2)	10 (4)	–	4 (3)	20 (2)	5 (2)	3 (1)	1 (1)
	Muscularis propria/subserosa	3797 (28)	1073 (35)	1805 (53)	409 (49)	641 (36)	192 (33)	797 (38)	86 (35)	–	39 (34)	163 (20)	69 (23)	260 (47)	44 (42)
	Serosa	1773 (13)	1023 (33)	586 (17)	265 (32)	742 (42)	284 (49)	418 (20)	102 (42)	–	72 (63)	377 (45)	169 (57)	228 (41)	48 (46)
	Adjacent structures	4256 (31)	788 (26)	878 (26)	147 (18)	291 (17)	95 (16)	819 (39)	46 (19)	–		270 (33)	54 (18)	67 (12)	11 (11)
Positive lymph node[f]	0	7743 (44)	554 (18)	1002 (18)	160 (15)	268 (15)	62 (11)	504 (24)	49 (20)	–	16 (16)	–	19 (7)	18 (5)	5 (5)
	1–6	8308 (47)	1288 (42)	4150 (76)	700 (67)	1067 (58)	252 (44)	1127 (54)	107 (43)	–	50 (51)	–	75 (26)	233 (71)	44 (48)
	⩾7	1630 (9)	1237 (40)	287 (5)	187 (18)	519 (28)	262 (46)	470 (22)	95 (38)	–	33 (33)	–	193 (67)	77 (23)	42 (46)

(continued)

Table 1. (continued)

Variable	Category	The US		The Netherlands		Belgium		Sweden		Norway		Slovenia		Estonia	
		Total	Resected	Total	Resected	Total	Resected	Total	Resected	Total	Resected	Total	Resected	Total	Resected
Harvested node no.		\	13 ± 13	\	9 ± 17	\	NA	\	19 ± 17	\	NA	\	NA	\	NA
Resection type[g]	Partial/subtotal gastrectomy	\	1914 (59)	\	847 (71)	\	NA	\	91 (62)	\	NA	\	NA	\	NA
	Total/near-total gastrectomy	\	755 (23)	\	299 (25)	\	NA	\	47 (32)	\	NA	\	NA	\	NA
	Other	\	563 (17)	\	55 (5)	\	NA	\	9 (6)	\	NA	\	NA	\	NA
Neoadjuvant CHT[h]	Yes	\	NA	\	225 (19)	\	172 (29)	\	62 (24)	\	NA	\	27 (8)	\	NA
Neoadjuvant RT[h]	Yes	\	148 (5)	\	17 (1)	\	32 (5)	\	6 (2)	\	NA	\	7 (2)	\	NA
Total/adjuvant CHT[h]	Yes	12501 (54)	1724 (53)	2732 (38)	338 (28)	1745 (62)	284 (48)	NA	NA	522 (29)	58 (26)	408 (25)	120 (37)	254 (32)	36 (30)
Total/adjuvant RT[h]	Yes	3714 (16)	380 (12)	519 (7)	62 (5)	279 (10)	54 (9)	NA	NA	140 (8)	10 (5)	114 (7)	34 (11)	19 (2)	5 (4)
Variable	**Category**	**The US**		**The Netherlands**		**Belgium**		**Sweden**		**Norway**		**Slovenia**		**Estonia**	
		Total	**Resected**	**Total**	**Resected**	**Total**	**Resected**	**Total**	**Resected**	**Total**	**Resected**	**Total**	**Resected**	**Total**	**Resected**
Bone metastasis[i]	Yes	1557 (14)	54 (4)	457 (7)	46 (4)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Brain metastasis[j]	Yes	241 (2)	15 (1)	34 (1)	3 (<1)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Liver metastasis[k]	Yes	5150 (44)	365 (29)	2810 (41)	355 (31)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lung metastasis[l]	Yes	1787 (16)	78 (6)	672 (10)	70 (6)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

[a]Categorical data are shown as count [percentage (%)], and numeric data as mean ± standard deviation. Records are complete otherwise specified below.
[b]The percentages of gastric cardia, fundus/body, and antrum/pylorus cancers are the proportions compared to the total tumor cases of the three locations; 'other' includes lesser curvature, greater curvature, and overlapping lesion of stomach and stomach (NOS), and its proportion is relative to the whole cases.
[c]Cystic/mucinous/serous (excluding signet ring cell), squamous cell, ductal/lobular, complex, unspecified, and epithelial (NOS) neoplasms.
[d]Unknown differentiation: **total patients:** the US, 5170 (22%); the Netherlands, 3190 (45%); Belgium, 465 (17%); Sweden, 2614 (94%); Norway, 597 (34%); Slovenia, 712 (43%); Estonia, 209 (26%); **resected patients:** the US, 251 (8%); the Netherlands, 417 (35%); Belgium, 61 (10%); Sweden, 133 (52%); Norway, 45 (20%); Slovenia, 48 (15%); Estonia, 19 (16%).
[e]Unknown tumor local invasion: **total patients:** the US, 9579 (41%); the Netherlands, 3732 (53%); Belgium, 1041 (37%); Sweden, 701 (25%); Norway, 1162 (65%); Slovenia, 825 (50%); Estonia, 243 (30%); **resected patients:** the US, 166 (5%); the Netherlands, 361 (30%); Belgium, 13 (2%); Sweden, 903 (4%); Norway, 107 (48%); Slovenia, 26 (8%); Estonia, 15 (13%). Invasion of serosa and adjacent structures could not be differentiated from each other in Norway or Slovenia.
[f]Unknown positive lymph node: **total patients:** the US, 5599 (24%); the Netherlands, 1673 (24%); Belgium, 951 (34%); Sweden, 682 (25%); Norway, 1263 (71%); Slovenia, 1037 (63%); Estonia, 473 (59%); **resected patients:** the US, 153 (5%); the Netherlands, 154 (13%); Belgium, 22 (4%); Sweden, 3 (1%); Norway, 123 (55%); Slovenia, 36 (11%); Estonia, 28 (24%).
[g]Gastrectomy (NOS) or local resection. Available in Sweden since 2010.
[h]Non-surgical therapies in the US and Estonia had low sensitivity, and the counterpart category of "Yes" was "No/unknown". In Norway and Estonia, neoadjuvant and adjuvant therapies could not be distinguished from each other. Total CHT/RT is for total patients, and (neo)adjuvant CHT/RT for resected patients.
[i]Unknown bone metastasis: **total patients:** the US, 651 (5%); the Netherlands, 251 (4%); **resected patients:** the US, 63 (5%); the Netherlands, 53 (4%). Information in the US was only available since 2010 ($n = 12091$).
[j]Unknown brain metastasis: **total patients:** the US, 701 (6%); the Netherlands, 251 (4%); **resected patients:** the US, 60 (5%); the Netherlands, 53 (4%). Information in the US was only available since 2010 ($n = 12091$).
[k]Unknown liver metastasis: **total patients:** the US, 512 (4%); the Netherlands, 251 (4%); **resected patients:** the US, 44 (3%); the Netherlands, 53 (4%). Information in the US was only available since 2010 ($n = 12091$).
[l]Unknown lung metastasis: **total patients:** the US, 736 (6%); the Netherlands, 251 (4%); **resected patients:** the US, 52 (4%); the Netherlands, 53 (4%). Information in the US was only available since 2010 ($n = 12091$).
\, resection-specific variables not applicable for total patients; –, not shown due to >60% missing values; CHT, chemotherapy; NA, not available; NOS, not otherwise specified; RT, radiotherapy.

temporal trends in Slovenia and Estonia were insignificant and could possibly be explained by the paucity of the cases. Greatly discrepant rates of resection in 2013–2014 (5–16%) resulted from the largely varying temporal trends.

Observational studies[10–15] showed that palliative excision of primary tumor might enhance survival and quality of life within a selected subgroup of cases with mGC especially in expert centers. A meta-analysis[10] of about 20 randomized studies showed that cyto-reductive operation for mGC with peritoneal carcinomatosis was associated with enhanced survival outcomes up to 3 years, although not at 5 years. It should be noted, that, for patients with limited metastatic disease, no evidence supporting survival benefits associated with reduction gastrectomy, which aims at improving survival by reducing cancer volume, was observed in the randomized REGATTA study established in Asian patients.[24,25] However, in the German phase II AIO-FLOT3 trial,[26] cases with limited distant metastasis who received neoadjuvant chemotherapy and proceeded to resection had favorable survival outcomes. Another important study[27] evaluated cytoreductive surgery for selected patients with mGC treated with systemic chemotherapy by analyzing about 30,000 chemotherapy-treated patients from the National Cancer Database (NCDB) and applying the nearest-neighbor 1:1 propensity score-matching method; after matching, patients undergoing cytoreductive surgery comprising gastrectomy and metastasectomy had longer overall survival than those receiving no surgery [median: 16 *versus* 9 months; hazard ratio for surgery *versus* no surgery: 0.56, 95% confidence interval (CI) = 0.49–0.63]. The findings suggest that in addition to systemic chemotherapy, cytoreductive surgery may be associated with an overall survival benefit for a selected group of patients with mGC, which warrants further prospective investigation. Before further evidence is obtained, gastrectomy should only be regarded to be experimental for cases with mGC or for palliation purposes among tumors with stomach outlet obstruction.

Recent advancement in chemotherapy has contributed to great regression of tumor in some patients with initially inoperable mGC and might render them resectable after a good response.[3,4] While the pre-surgical management may improve resectability through down-staging cancer, it may as well allow abundant time for further development of more advanced tumors or even distant metastases.

The decreasing rates of resection may suggest the increasingly stricter criteria of selecting candidates for resection, which potentially leads to more favorable outcomes for patients undergoing gastrectomy. Recent advancement in diagnostics has made the identification of cases with metastatic cancer more efficient and therefore they less frequently received aggressive management.[28,29] Improvements in imaging, increase in use of diagnostic laparoscopy and of peritoneal washings may account for some of the trends, and more patients who were previously thought to have locoregional disease are now considered to have metastatic disease and may not be considered for surgical treatment.

Compared with cases with non-metastatic cancer,[16] those with mGC were younger and more often had cardia and poorly-differentiated or undifferentiated cancers, which more frequently involved adjacent structures and/or lymph nodes. The associations of resection with patient and cancer factors in mGCs were similar to those in non-metastatic diseases.[16] Older ages (especially ⩾70 years) and cardia cancers (especially when compared with antrum/pylorus cancers) were found to be significantly associated with less frequent resection. Before starting management for older individuals who are more often frailer and who have more frequent comorbidities and anticipated post-treatment morbidities or mortalities, generally it would be helpful to perform geriatric evaluation taking the overall conditions and expected lifespan into account. Distal cancers may be more frequently associated with obstructive symptoms which could not be easily managed by less aggressive measures like feeding tube, rendering them more frequent candidates for resection. Furthermore, proximal cancers could be more surgically challenging especially concerning anastomosis after resection.[30] Tumors with adjacent structures invasion were mostly less frequently resected, possibly because of the difficulty of surgery. Patients with SRCs, a quickly increasing patient group with inferior survival outcomes, have been revealed as inherently less sensitive to chemotherapy.[31–33] Metastatic SRCs were more frequently operated in certain countries, and the disparities across countries might be influenced by variations in SRC classification. The discrepant strengths and patterns of the correlations of treatment with patient and cancer features across countries underline the greatly differing clinical practice and the necessity for further clarification of the definitive role of resection in mGCs.

This difference in clinical practice could be explained in part by a lack of a uniform definition for cases with limited (oligo)metastatic cancer who are potentially suitable candidates for surgery. This lack of consensus is addressed by the OligoMetastatic Esophagogastric Cancer (OMEC) project, a multidisciplinary project endorsed by ESMO, IGCA, EORTC, ESTRO, ESSO, and ESDE which will establish a European multidisciplinary consensus statement for esophagogastric cancer with limited (oligo)metastasis (www.OMECproject.eu).

Our observational study has some limitations. National registry-based studies are particularly prone to unavoidable selection bias due to the retrospective nature. Among patients with mGCs, those with better performance status might be more likely to receive gastric resection. In our observational, population-based study of multiple nationwide European cancer registries and the US SEER-18 database, information on the Eastern Cooperative Oncology Group (ECOG) performance status or number of comorbidities for mGC was not available or had large proportions of missing values which prohibited a meaningful analysis in most registries, and was hence not included in the multivariable analyses; however, performance status and comorbidities might be important confounders that might impact the multivariable findings. The potential subtle differences in patients' demographics between countries might in part account for the varying resection trends. Being aware of this, we first showed the resection rates standardized by age, and further the multivariable-adjusted associations of year of diagnosis with resection. The relatively small proportion of cardia cancers in Estonia might be a factor impacting the overall trend of resection. Accordingly, we further looked into the multivariable-adjusted trends as revealed by the associations of year of diagnosis with resection, overall (Table 2) and in subgroups stratified by factors including tumor location (Table 3), and after adjustment for multiple variables including tumor location, resection trends remained similar both overall and in stratified analyses. Various studies on resection of the primary tumor and isolated metastases in mGC including the GYMSSA trial[34,35] evaluating gastrectomy plus metastasectomy followed by chemotherapy in oligometastatic GC highlight the importance to distinguish patients with different metastatic burdens especially between those with multiple non-resectable metastases and those with potentially resectable oligometastatic GC. In our population-based study only data on metastasis to bone, brain, liver, or lung were available in the US (since 2010) and the Netherlands (Table 1), and more specific information on metastatic burden (single resectable distant metastasis, oligometastatic disease, or multiple metastases) or number of metastases could not be derived from the current available information also considering that there might be distant metastases to other sites the information on which was not available. We focused on the application of resection; information on the use of modern systemic (including targeted) therapies, expensive palliative endoscopic treatment (stents), and diagnostic/staging laparoscopy, which is interesting to further investigate, was not available or had low sensitivity making this information not suitable for such pattern and trend association analyses across countries.

Registration quality may vary. Some variables (e.g., differentiation) were not incorporated into models considering the relatively large proportions of unknown data. Data were not pooled, given the possible heterogeneity; they were separately analyzed, shown, and interpreted for each individual registry. In some countries certain variables were not registered. Information on metastatic site was only available in the registries of the US (since 2010) and the Netherlands. Nevertheless, regardless of metastatic site, GCs with distant metastasis were recognized as unresectable disease across guidelines.[9,29,36] Notably, in Estonia, the proportion of cardia tumor was relatively low (14%), and SRC was commonly reported (31%). While this might indicate the varying disease patterns in different parts of Europe, possible discrepancies in registry and clinical practices may as well have some roles, highlighting the significance of further standardization. The study periods were not completely the same. Nonetheless, the time period 2003/2004–2013/2014 were mostly covered, and diagnosis year was included in all the multivariable-adjusted modelling. In addition, our study was limited to Europe and the US, and the findings might not be generalizable to the other countries, particularly those in East Asia in which the GC incidence rate is higher.

Table 2. Association of demographic and clinical features with resection for gastric carcinoma with distant metastasis using multivariable-adjusted log-binomial regression.

Variable	Category	The US	The Netherlands	Belgium	Sweden	Norway	Slovenia	Estonia
		PR (95% CI)[a]	PR (95% CI)[a]	PR (95% CI)[a]	PR (95% CI)[a]	PR (95% CI)[a]	PR (95% CI)[a]	PR (95% CI)[a]
Year of diagnosis	Per 1 year	**0.93** (0.92–0.94)	**0.98** (0.96–1.00)	**0.94** (0.92–0.97)	**0.96** (0.92–1.00)	**0.90** (0.86–0.93)	0.98 (0.95–1.01)	1.03 (0.94–1.13)
Sex	Female *versus* male	1.06 (0.99–1.13)	1.05 (0.94–1.17)	1.10 (0.95–1.28)	1.14 (0.90–1.44)	1.17 (0.92–1.49)	1.15 (0.94–1.40)	1.13 (0.81–1.58)
Age group	60–69 years	0.97 (0.90–1.06)	0.97 (0.84–1.12)	**0.77** (0.63–0.93)	0.87 (0.63–1.20)	0.76 (0.53–1.07)	0.93 (0.65–1.05)	0.80 (0.52–1.23)
<60 years as reference	70–79 years	**0.91** (0.84–0.99)	0.92 (0.80–1.06)	**0.78** (0.65–0.94)	0.76 (0.56–1.04)	**0.70** (0.50–0.96)	**0.66** (0.52–0.83)	0.74 (0.48–1.13)
	⩾80 years	**0.78** (0.70–0.86)	**0.78** (0.66–0.92)	**0.68** (0.54–0.84)	**0.49** (0.33–0.72)	**0.62** (0.44–0.87)	**0.33** (0.21–0.50)	**0.53** (0.30–0.95)
Tumor location	Gastric fundus/body	**1.65** (1.46–1.87)	**1.40** (1.18–1.66)	0.94 (0.71–1.25)	**1.50** (1.04–2.17)	**2.15** (1.36–3.39)	**2.56** (1.71–3.84)	2.02 (0.83–4.94)
Gastric cardia as reference	Gastric antrum/pylorus	**3.25** (2.94–3.59)	**1.95** (1.68–2.27)	**1.57** (1.27–1.94)	**3.57** (2.59–4.93)	**3.72** (2.47–5.60)	**2.46** (1.65–3.65)	**3.63** (1.48–8.94)
	Other[b]	**1.95** (1.76–2.15)	**1.31** (1.13–1.51)	1.00 (0.84–1.20)	0.93 (0.63–1.37)	**1.68** (1.12–2.51)	**1.45** (1.01–2.10)	1.95 (0.80–4.79)
Tumor histology	SRC *versus* non-SRC	**1.09** (1.02–1.18)	1.13 (1.00–1.29)	**1.35** (1.14–1.61)	–	0.98 (0.68–1.39)	0.78 (0.52–1.18)	0.89 (0.61–1.29)
Adjacent structure invasion	Yes *versus* no	**0.65** (0.61–0.70)	**0.49** (0.42–0.57)	0.86 (0.72–1.04)	**0.34** (0.23–0.49)	\	**0.42** (0.32–0.54)	0.80 (0.45–1.42)

[a]Prevalence ratios and 95% confidence intervals for resection *versus* non-resection were calculated using multivariable-adjusted log-binomial regression models adjusting for year of diagnosis, sex, age group, tumor location, and histology. For the association with adjacent structure invasion, this factor was additionally added into the main model. Previous cancer was available and also adjusted for in the US, the Netherlands, and Belgium. All models converged. PRs shown in bold are statistically significant.
[b]Lesser curvature, greater curvature, and overlapping lesion of stomach, and stomach (not otherwise specified).
–, not available; \, not estimable; CI, confidence interval; PR, prevalence ratio; SRC, signet ring cell carcinoma.

Table 3. Association of year of diagnosis (as continuous) with resection for gastric carcinoma with distant metastasis using multivariable-adjusted log-binomial regression.

Variable	The US	The Netherlands	Belgium	Sweden	Norway	Slovenia	Estonia
<70 years							
Resected/total no.	2006/13834	621/3522	314/1338	128/1235	105/813	201/848	70/412
PR per 1 year (95% CI)[a]	**0.93** (0.92–0.94)	0.99 (0.96–1.02)	**0.92** (0.89–0.96)	**0.93** (0.88–0.98)	**0.88** (0.84–0.93)	0.97 (0.93–1.00)	1.05 (0.93–1.18)
⩾70 years							
Resected/total no.	1226/9446	580/3590	284/1467	126/1548	117/966	122/807	49/389
PR per 1 year (95% CI)[a]	**0.93** (0.91–0.94)	**0.97** (0.94–0.99)	0.97 (0.93–1.00)	0.99 (0.93–1.04)	**0.91** (0.86–0.96)	0.99 (0.94–1.04)	1.03 (0.89–1.18)
Cardia							
Resected/total no.	518/7145	266/2143	175/889	52/856	30/465	29/240	5/70
PR per 1 year (95% CI)[a]	**0.90** (0.88–0.92)	0.99 (0.95–1.03)	**0.94** (0.90–0.99)	**0.89** (0.81–0.97)	/	/	/
Non-cardia							
Resected/total no.	1376/7115	523/2468	151/604	155/1087	107/546	120/407	72/419
PR per 1 year (95% CI)[a]	**0.94** (0.93–0.96)	**0.96** (0.94–0.99)	0.97 (0.93–1.02)	1.00 (0.95–1.05)	**0.90** (0.85–0.95)	0.98 (0.94–1.03)	1.05 (0.93–1.18)
Signet ring cell carcinoma							
Resected/total no.	860/5129	248/1221	120/414	–	28/174	19/101	36/249
PR per 1 year (95% CI)[a]	**0.92** (0.90–0.93)	1.00 (0.96–1.04)	**0.92** (0.87–0.96)	–	/	/	/

[a]Prevalence ratios and 95% confidence intervals for association of year of diagnosis (as continuous) with resection *versus* non-resection were calculated using multivariable-adjusted log-binomial regression models adjusting for sex, age group, tumor location, and histology. Previous cancer was available and also adjusted for in the US, the Netherlands, and Belgium. All models converged. Results were not shown for countries with <40 resected and/or <80 total cases. PRs shown in bold are statistically significant.
–, not available; /, not shown due to small case number (<40 resected and/or <80 total cases); CI, confidence interval; PR, prevalence ratio.

Of note, the greatest number of mGCs ever studied, consistently coded variables across multiple population-based nationwide cancer registries, strict quality control, careful selection of cases, and valid standardized statistics enable our work to present informative and important findings concerning care for mGC. Our report may aid to identify discrepancies in clinical practices and offer new pivotal references for making effective strategies for management of GC at the population level, which has possible pivotal relevance for guiding appropriate resource allocation and healthcare policymaking in Europe and the US.

Conclusions

In Europe and the US patterns and trends of resection largely varied across countries for mGCs, which mostly underwent less often primary cancer-directed resection in the early 21st century. Various variables were identified to be associated with resection, with greatly varying patterns and strengths of associations across countries. Our findings highlight the great need for further clarifying the role of resection in mGCs to enhance standardization of care.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Medical Faculty Heidelberg. Consent was waived considering the anonymous, observational, population-based, and registry-based nature. No individual patient data were reported.

Consent for publication

Not applicable.

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Availability of data and materials

The data that support the findings of this study are available from each participating registry, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

Supplemental material

Supplemental material for this article is available online.

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