


# International comparison of treatment strategy and survival in metastatic gastric cancer

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**Background:** In the randomized Asian REGATTA trial, no survival benefit was shown for additional gastrectomy over chemotherapy alone in patients with advanced gastric cancer with a single incurable factor, thereby discouraging surgery for these patients. The purpose of this study was to evaluate treatment strategies for patients with metastatic gastric cancer in daily practice in five European countries, along with relative survival in each country.

**Methods:** Nationwide population-based data from Belgium, Denmark, the Netherlands, Norway and Sweden were combined. Patients with primary metastatic gastric cancer diagnosed between 2006 and 2014 were included. The proportion of gastric resections performed and the administration of chemotherapy (irrespective of surgery) within each country were determined. Relative survival according to country was calculated.

**Results:** Overall, 15 057 patients with gastric cancer were included. The proportion of gastric resections varied from 8.1 per cent in the Netherlands and Denmark to 18.3 per cent in Belgium. Administration of chemotherapy was 39.2 per cent in the Netherlands, compared with 63.2 per cent in Belgium. The 6-month relative survival rate was between 39.0 (95 per cent c.i. 37.8 to 40.2) per cent in the Netherlands and 54.1 (52.1 to 56.9) per cent in Belgium.

**Conclusion:** There is variation in the use of gastrectomy and chemotherapy in patients with metastatic gastric cancer, and subsequent differences in survival.

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## Introduction

Gastric cancer is the fifth most common malignancy in the world, responsible for an estimated 723 000 deaths in 2012<sup>1</sup>. In the Western world, approximately half of patients present with metastatic disease (stage IV) at time of diagnosis<sup>2</sup>. The prognosis for this group of patients is dismal, with a median survival of only 10 months<sup>3</sup>.

The value of a palliative resection in patients with metastatic gastric cancer remains controversial. According to current European clinical practice guidelines, patients with stage IV disease should be considered for palliative chemotherapy, as it improves survival, reduces disease-related symptoms and improves quality of life (QoL) compared with best supportive care alone<sup>3,4</sup>. Resection of the primary tumour is generally not recommended<sup>4</sup>.

**Table 1** Overview of registry according to country

	Belgium	Denmark	Netherlands	Norway	Sweden
Registry	Belgian Cancer Registry	Danish Clinical Registry of Carcinomas of the Oesophagus, the Gastro-oesophageal Junction and the Stomach (DECV)	Netherlands Comprehensive Cancer Organization	Cancer Registry of Norway	Swedish National Register for Oesophageal and Gastric Cancer
Organization	Population-based cancer registry	National Quality Registry	Population-based cancer registry	Population-based cancer registry	National Quality Registry
Data collection	Per centre, data managers, pathology laboratories and use of medical claims data	Per centre, data managers	Per centre, data managers	Per centre, data managers	Per centre, data managers

Accuracy and completeness (more than 95 per cent of patients with cancer in the population are registered) of the data were confirmed by the individual registries.

A palliative resection is indicated in some patients with bleeding, obstruction or perforation<sup>5</sup>. The extent to which these patients benefit from a palliative resection remains unclear<sup>6–8</sup>. Observational studies have considerable selection bias as only a proportion of patients undergo surgery, reflecting those who are physically more fit with better performance status.

Recently, a multicentre trial from the Far East, the REGATTA trial<sup>9</sup>, investigated whether additional gastrectomy led to survival benefit compared with chemotherapy alone in patients with incurable advanced gastric cancer. In this trial, 175 patients with a incurable factor, limited to either liver, peritoneum or para-aortic lymph nodes, were included from 2008 to 2013. Overall survival at 2 years in an interim analysis was 31.7 (95 per cent c.i. 21.7 to 42.2) per cent for chemotherapy alone compared with 25.1 (16.2 to 34.9) per cent for gastrectomy plus chemotherapy, leading to closure of this study due to futility. The authors stated that gastrectomy could no longer be justified for patients with incurable advanced gastric cancer<sup>9</sup>.

The German prospective phase II AIO-FLOT3 trial<sup>10</sup> recently investigated outcomes in patients with limited metastatic disease of the stomach and gastro-oesophageal junction. Results of this trial showed that patients who received neoadjuvant chemotherapy followed by surgery had a favourable survival.

The purpose of the present study was to analyse treatment strategies and their relation to survival in patients with metastatic gastric cancer, using national data from five participating European countries, the EURECCA (EUropean REgistration of Cancer Care) Upper GI Group.

## Methods

Patients diagnosed with primary metastatic (cardia and non-cardia) gastric cancer between 2006 and 2014 were

included. Gastric cancer was defined as C16 of the ICD-10<sup>11</sup>. Localization of the tumour was divided into proximal (C160 and C161), middle (C162, C165, C166), distal (C163, C164) and unknown (C168 and C169) sites. Data were collected from the Belgian Cancer Registry, the Danish Clinical Registry of Carcinomas of the Oesophagus, the Gastro-oesophageal Junction and the Stomach, the Netherlands Comprehensive Cancer Organization, the Cancer Registry of Norway, and the Swedish National Register for Oesophageal and Gastric Cancer (*Table 1*). Accuracy and completeness (registration of more than 95 per cent of patients with cancer in the population) of the data were confirmed by the individual registries<sup>12–18</sup>.

Follow-up was from date of diagnosis to either death, end of the study period, or loss to follow-up, whichever came first. Data sets from the respective countries were merged. Patients with pM1 disease status were included. When data on pM category were missing, patients with cM1 according to the sixth (2006–2009) or seventh (2010–2014) TNM classification of malignant tumours<sup>19,20</sup> were included.

The proportion of patients undergoing a gastric resection (yes/no) and the proportion who received chemotherapy (yes/no) were analysed. Gastric resection was defined as surgical resection of the primary tumour. Construction of a gastroenterostomy without resection and endoscopic stenting techniques were not included. Use of chemotherapy was defined as the administration of chemotherapeutic agents, irrespective of surgery. Where data on gastric resections or use of chemotherapy were missing, they were considered as being not used.

## Statistical analysis

Proportions of patients undergoing gastric resection and/or chemotherapy were compared between the

**Table 2** Patient and tumour characteristics for primary metastatic gastric cancer, according to country

	Belgium (n = 2742)	Denmark (n = 1994)	Netherlands (n = 6547)	Norway (n = 1288)	Sweden (n = 2486)
No. of inhabitants in 2014 ( $\times 10^6$ )	11	6	17	5	10
Age (years)					
< 60	622 (22.7)	501 (25.1)	1434 (21.9)	297 (23.1)	436 (17.5)
60–69	680 (24.8)	669 (33.6)	1781 (27.2)	315 (24.5)	653 (26.3)
70–79	831 (30.3)	597 (29.9)	2134 (32.6)	357 (27.7)	801 (32.2)
$\geq 80$	609 (22.2)	227 (11.4)	1198 (18.3)	319 (24.8)	596 (24.0)
Sex					
M	1820 (66.4)	1424 (71.4)	4250 (64.9)	775 (60.2)	1540 (61.9)
F	922 (33.6)	570 (28.6)	2297 (35.1)	513 (39.8)	946 (38.1)
Localization					
Proximal	1024 (37.3)	1280 (64.2)	2104 (32.1)	357 (27.7)	122 (4.9)
Middle	302 (11.0)	714 (35.8)*	1162 (17.7)	207 (16.1)	574 (23.1)
Distal	336 (12.3)	*	1227 (18.7)	400 (15.8)	400 (16.1)
Unknown	1080 (39.4)	*	2054 (31.4)	521 (40.5)	1390 (55.9)
Grade					
Good	171 (6.2)	3 (0.2)	58 (0.9)	24 (1.9)	4 (0.2)
Medium	614 (22.4)	25 (1.3)	762 (11.6)	183 (14.2)	22 (0.9)
Poor	1394 (50.8)	51 (2.6)	2638 (40.3)	653 (50.7)	66 (2.7)
No differentiation	85 (3.1)	6 (0.3)	33 (0.5)	4 (0.3)	9 (0.4)
Unknown	478 (17.4)	1909 (95.7)	3056 (46.7)	424 (32.9)	2385 (95.9)
Year of diagnosis					
2006–2008	772 (28.2)	505 (25.3)	2072 (31.6)	471 (36.6)	765 (30.8)
2009–2011	938 (34.2)	629 (31.5)	2290 (35.0)	435 (33.8)	855 (34.4)
2012–2014	1032 (37.6)	860 (43.1)	2185 (33.4)	382 (29.7)	866 (34.8)

Values in parentheses are percentages. \*Subdivision of location of gastric cancer was not available in the Danish data set.

participating countries. Relative survival, expressed as relative excess risk (RER) and adjusted RER (adjusted for age, sex and year of diagnosis), was estimated using the Ederer II method<sup>21</sup>. The country with the highest proportion of gastric resections and use of chemotherapy was used as the reference category.

STATA<sup>®</sup>/SE version 12.0 (StataCorp, College Station, Texas, USA) and SPSS<sup>®</sup> version 21.0 (IBM, Armonk, New York, USA) were used for all analyses.  $P < 0.050$  was considered statistically significant.

## Results

A total of 15 057 patients with metastatic gastric cancer were included. Patient characteristics according to country are shown in *Table 2*.

In Denmark, 64.2 per cent of the tumours were located proximally, compared with 37.3, 32.1, 27.7 and 4.9 per cent in Belgium, the Netherlands, Norway and Sweden respectively. Overall median follow-up was 140 (i.q.r. 51–319) days, and per country was 202 (72–421) days in Belgium, 174 (62–364) days in Denmark, 120 (46–277) days in the Netherlands, 140 (51–319) days in Norway and 112 (45–299) days in Sweden. Some 0.4 per cent of follow-up data was missing.

## Treatment strategy

In Belgium, approximately one in five patients (18.3 per cent) underwent a gastric resection, compared with 12.5, 9.2, 8.1 and 8.1 per cent in Norway, Sweden, the Netherlands and Denmark respectively. Information on the use of chemotherapy was available only in the Belgian and Dutch data sets. In Belgium, chemotherapy was administered in 63.2 per cent of the patients, compared with 39.2 per cent in the Netherlands.

A minority (4.1 per cent) of patients in the Netherlands had both a gastric resection and received chemotherapy, compared with 11.2 per cent in Belgium. In Belgium, 6.9 per cent of patients had a gastric resection only and 46.2 per cent received chemotherapy only, compared with 4.0 and 31.5 per cent respectively in the Netherlands.

## Relative survival

The 6-month relative survival rate was 54.1 (95 per cent c.i. 52.1 to 56.9) per cent in Belgium and 49.6 (47.3 to 51.9) per cent in Denmark, compared with 42.6 (39.8 to 45.4) per cent in Norway, 39.6 (37.6 to 41.5) per cent in Sweden and 39.0 (37.8 to 40.2) per cent in the Netherlands. Compared with Belgium (reference), survival was shorter

in the Netherlands (adjusted RER 1.44, 95 per cent c.i. 1.38 to 1.51;  $P < 0.001$ ), Norway (adjusted RER 1.39, 1.29 to 1.48;  $P < 0.001$ ), Sweden (adjusted RER 1.33, 1.26 to 1.41;  $P < 0.001$ ) and Denmark (adjusted RER 1.16, 1.09 to 1.24;  $P < 0.001$ ).

## Discussion

Variations in treatment strategy and survival of patients with metastatic gastric cancer were evaluated in a large population-based cohort from five European countries. There were substantial differences in the sites of the primary tumour within the stomach across the five countries, differences in the proportions of gastric resection, and in the use of chemotherapy for the two countries with data on this treatment.

According to European guidelines, patients with metastatic gastric cancer should be considered for palliative chemotherapy and be offered appropriate targeted agents, as this strategy prolongs overall survival compared with best supportive care<sup>4</sup>. Not all national guidelines follow these recommendations. For instance, according to the Dutch guidelines<sup>22</sup>, a partial palliative gastric resection should be considered for patients younger than 70 years and with only a single parameter of incurability. These differences might have contributed to the variation found in the proportions of gastric resection between countries in the present study (range from 8.1 per cent in Denmark and the Netherlands to 18.3 per cent in Belgium). A notable finding was that in the Netherlands, the country with the highest incidence of patients with gastric cancer (Table 1) and therefore the largest denominator in proportion, the percentage of gastric resections was the lowest. These findings suggest that there may actually be large differences in the incidence of metastatic gastric cancer between countries or that there are significant differences in the quality of registry data or use of imaging modalities to determine the likely extent of disease.

There has been a steady increase in the use of chemotherapy for metastatic gastric cancer in the Netherlands. This was reported<sup>23</sup> to have risen from 5 per cent in 1990 to 36 per cent in 2011. The present findings showed that chemotherapy use in the Netherlands was 39.2 per cent between 2006 and 2014. This is still low compared with Belgium, where 63.2 per cent of patients received chemotherapy in the same time interval. This higher use of chemotherapy in Belgium has been described previously in patients with colonic cancer<sup>24</sup>.

Compared with the other countries, an aggressive treatment strategy was employed in Belgium involving a high proportion of gastric resections and a high proportion

of patients receiving chemotherapy. At all measured time points in the present study, the highest relative survival for all participating countries was seen in Belgium, possibly indicating that an aggressive treatment strategy might be associated with better relative survival. This assumption might be substantiated if data on the use of chemotherapy in all five countries were available.

QoL was not measured in the REGATTA trial, or by these national registries. QoL is just as important as survival for many of these patients. Patients may choose a better QoL over prolonged survival, avoiding risks after surgery and toxicity from chemotherapy. A validated QoL questionnaire for patients with gastric cancer (EORTC QLQ-OG25) should be employed in future studies<sup>25–27</sup>.

The present findings give an insight into the proportion of gastric resections and use of chemotherapy in daily practice. Some differences between registries are noteworthy. The distribution of tumour locations (proximal *versus* others) was quite different in Denmark than in the other countries, raising concerns over definitions. The lack of and limited data on the use of chemotherapy in the national registries of Denmark, Norway and Sweden were a further limitation and highlighted non-uniformity of registered data in these European registries. In addition, the study results are likely to be biased by residual confounding. Additional data including localization and volume of metastatic disease, co-morbidity, performance status, emergency surgery, type and number of the courses of chemotherapy could all have influenced the results. The increasing use of targeted agents may vary across countries and, as a result, systemic treatment could be quite different<sup>28</sup>.

The present study, using population-based data from five European countries, suggests that an aggressive treatment strategy with a gastric resection might be considered an option for patients with metastatic gastric cancer in the Western world, in contrast with the findings of the REGATTA trial<sup>9</sup>. There are important differences between patients in these registries and those in the REGATTA trial, where patients were excluded if they presented with acute symptoms such as bleeding or obstruction, the trial cohort was limited to 175 patients, and only those with a single incurable factor were included. Conversely, a larger cohort study using data from the Dutch Gastric Cancer Trial<sup>6</sup> reported that a palliative resection was beneficial for patients younger than 70 years if metastases were restricted to one site.

Despite the likelihood that patients in the present study would have a greater burden of advanced disease than those in the REGATTA trial, the more aggressive

treatment strategy, including resection as practised in Belgium, seemed to be associated with better relative survival. As a result, inclusion of gastric resection in the options for patients presenting with metastatic disease should still be considered in the West. New chemotherapy regimens in combination with surgery have been shown to be beneficial in oligometastatic disease<sup>10</sup>.

## Disclosure

The authors declare no conflict of interest.

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