

## Improvements in esophageal and gastric cancer care in Sweden—population-based results 2007–2016 from a national quality register

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**SUMMARY.** The Swedish National Register for Esophageal and Gastric cancer was launched in 2006 and contains data with adequate national coverage and of high internal validity on patients diagnosed with these tumors. The aim of this study was to describe the evolution of esophageal and gastric cancer care as reflected in a population-based clinical registry. The study population was 12,242 patients (6,926 with esophageal and gastroesophageal junction (GEJ) cancers and 5,316 with gastric cancers) diagnosed between 2007 and 2016. Treatment strategies, short- and long-term mortality, gender aspects, and centralization were investigated. Neoadjuvant oncological treatment became increasingly prevalent during the study period. Resection rates for both esophageal/GEJ and gastric cancers decreased from 29.4% to 26.0% ( $P = 0.022$ ) and from 38.8% to 33.3% ( $P = 0.002$ ), respectively. A marked reduction in the number of hospitals performing esophageal and gastric cancer surgery was noted. In gastric cancer patients, an improvement in 30-day mortality from 4.2% to 1.6% ( $P = 0.005$ ) was evident. Overall 5-year survival after esophageal resection was 38.9%, being higher among women compared to men (47.5 vs. 36.6%;  $P < 0.001$ ), whereas no gender difference was seen in gastric cancer. During the recent decade, the analyses based on the Swedish National Register for Esophageal and Gastric cancer database demonstrated significant improvements in several important quality indicators of care for patients with esophagogastric cancers. The Swedish National Register for Esophageal and Gastric cancer offers an instrument not only for the control and endorsement of quality of care but also a unique tool for population-based clinical research.

**KEY WORDS:** esophageal neoplasm, registry, stomach neoplasm.

### INTRODUCTION

The traditional view is that the highest level of evidence in clinical medicine is obtained from well-designed and adequately powered randomized controlled trials (RCTs). However, there are obvious limitations in the generalizability of outcomes of such trials, mandating complementary and confirmatory information preferably from real-world data in well-defined population-based studies as exemplified by prospective data retrieved from national registers.<sup>1</sup>

Assuming adequate coverage and high validity of data in registers, these can reflect general clinical practice and generate real-world evidence when certain methods or strategies are implemented widely. Data can also be used for benchmarking within or between countries.<sup>2,3</sup>

Sweden has a long tradition of fostering and endorsing national quality registers for a variety of diseases.<sup>4</sup> Today, broad ranges of high-quality national registers are operational and administered by the Swedish Board of Health and Welfare. Many of

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these have been well described and validated.<sup>5,6</sup> With the personal identification number,<sup>7</sup> unique to every Swedish citizen, researchers can combine and cross-link data from a wide range of different registers.

In 2006, The Swedish National Register for Esophageal and Gastric Cancer (NREV) was created with the primary purpose of describing and registering important aspects of the care of patients with esophageal and gastric cancer but also to support research and development of evidence-based treatments of these diseases. The NREV database has recently been validated documenting a high grade of completeness, accuracy, and concordance.<sup>8</sup> It is noteworthy that the period during which NREV has been operational coincides with the introduction and implementation of several new therapeutic concepts in the care of patients with esophageal and gastric cancer, such as the introduction of perioperative oncological treatment regimens as supported by several RCTs,<sup>9,10</sup> minimally invasive surgery, and centralization of esophageal and gastric resections.<sup>11–13</sup>

Hence, the aim of this study was to describe the development of esophageal and gastric cancer management, during the recent decade from 2007 to 2016, to elucidate the population-based consequences of corresponding changes in clinical practice.

## PATIENTS AND METHODS

### Background

NREV was initiated on 1 January, 2006 and receives annual financial support from the Swedish Government. The Steering Committee of NREV consists of surgeons, oncologists, pathologist, nurses, a patient representative, and statisticians representing university, regional, and county hospitals. The Steering Committee of NREV is responsible for establishing the national guidelines<sup>14</sup> for the care of patients with esophageal and gastric cancer, which are updated biennially. NREV also serves to facilitate research. The annual NREV report is available to the public and other interest groups.

### Data acquisition

NREV data, used in this study, were acquired in three surveys in which the individual hospital responsible for the diagnosis and treatment of the patients reported data directly to the register. The surveys were further processed and validated by trained staff at six regional cancer centers before data were finally filed into the register. Data were validated against the National Cancer Register annually, which has close to 100% coverage, and reminders were sent to hospitals if data were missing.

The details and validity of data in the different surveys are presented in detail elsewhere.<sup>8</sup> In brief,

the first survey consisted of the clinical work-up and treatment recommendations of all patients presenting with a new diagnosis of esophageal or gastric cancer (C15.0-C15.9 and C16.0-C16.9 according to ICD-10, C16.0A-C16.0C being coded as esophageal cancer according to TNM-7).<sup>15</sup> The second survey was used for all patients planned for resection and includes details about the surgical procedure. Since 2010, the register has incorporated data on endoscopic mucosal resections and submucosal dissections. The third survey was completed at the postoperative follow-up, but no earlier than 30 days after surgery. An additional oncological treatment survey was initiated in 2017 but is not yet fully operational. Since 2009, two standardized quality of life forms were sent to those patients alive 1 year after diagnosis. The routines for coding and the forms for registration are specified elsewhere<sup>14</sup> and are consistent with and updated according to national and international guidelines. Since 2012, the register has contained detailed data on postoperative complications using the Clavien-Dindo scoring system. During 2016 and 2017, a rebuild of the database was performed to facilitate data input and to conform the registration of complications with the recommendations from the Esophagectomy Complications Consensus Group.<sup>16</sup>

## STATISTICAL ANALYSIS

Patients, tumor, and treatment characteristics are presented in frequency tables. Comparisons between proportions were performed by  $\chi^2$  test. To compare results over time either the  $\chi^2$  test for trends or diagrams with median/mean values were used. Survival after resectional surgery was illustrated using Kaplan-Meier curves. Statistical analyses were performed using the SPSS<sup>®</sup> version 23 (SPSS Inc., Chicago, IL). Data extraction was performed from NREV April 27, 2018.

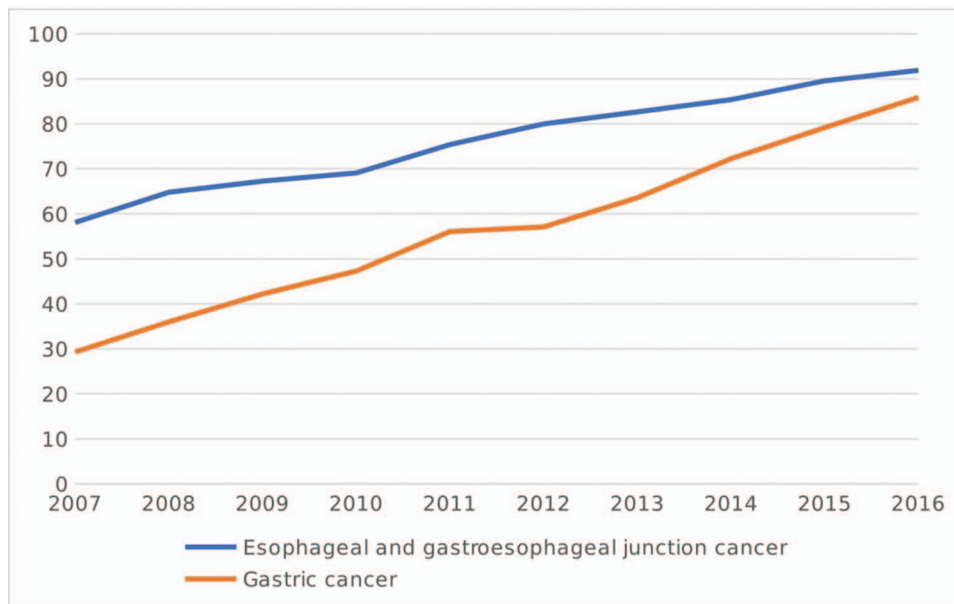
## ETHICS

The study was approved by the Regional Ethics Committee in Stockholm (Dnr 2013/1091-31/2 and 2016/1486-32).

## RESULTS

### Process

Since the launch of NREV, the average annual coverage grade for Survey 1 was 95.3%. The corresponding figures were 93.0% and 89.2% for Surveys 2 and 3, respectively. In 2007, 58.1% of the patients with esophageal/gastroesophageal junction (GEJ) cancer were presented at a Multi-Disciplinary Conference (MDC), compared to 91.9% in 2016 (Fig. 1). A similar



**Fig. 1** Percentage of patients with esophageal/gastroesophageal junction or gastric cancer presented to a Multi-Disciplinary Conference (MDC) before start of treatment.

increase was seen for patients with gastric cancer, albeit starting from a lower level (from 29.3% to 85.9%). The median duration from referral to a specialized upper gastrointestinal center to presentation at the MDC was stable over time between 20 and 25 days until 2015 when a sharp decrease in duration was seen for both patients with esophageal/GEJ and gastric cancer (Fig. 2). Over the years, a continuous trend toward fewer hospitals performing resectional surgery for both esophageal/GEJ and gastric cancer was seen, and (Fig. 3) in 2016, only four hospitals performed 20 or more esophageal resections and five hospitals more than 20 gastrectomies, all of which were university hospitals.

### Esophageal/GEJ cancer

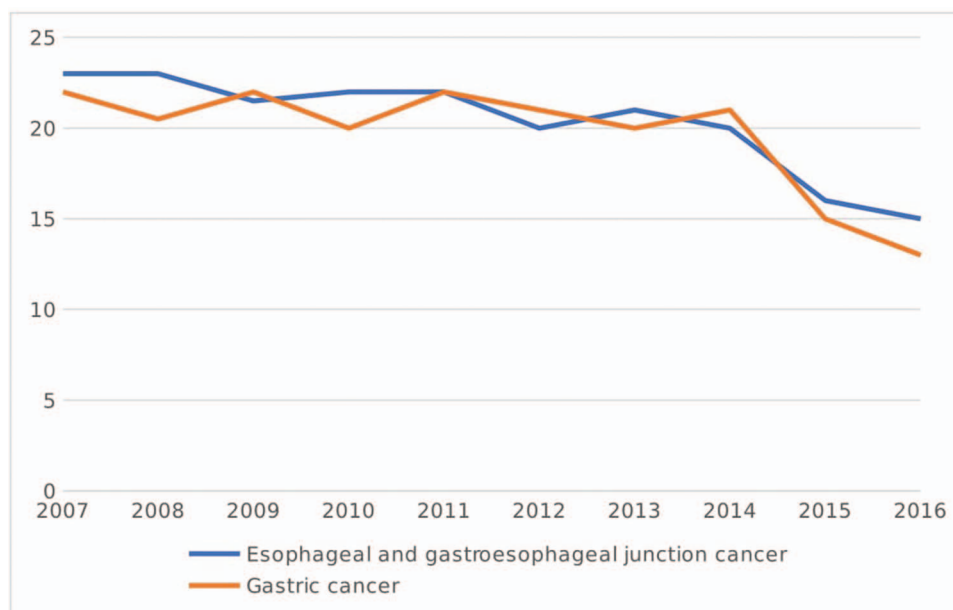
A total of 6,926 patients (5,124 males and 1,802 females) with esophageal/GEJ cancers were reported to the register between 2007 and 2016 (Table 1). Adenocarcinoma was the predominant subtype of esophageal tumor representing about two-thirds of all cases diagnosed and three-quarters of all resected patients. The lower third of the esophagus and the GEJ were the predominant tumor sites (73.2% of all patients diagnosed with esophageal/GEJ cancer and 84.5% in the resected group). Treatment with curative intent was recommended by the MDC in 41% (range 38–44%) of all patients with esophageal/GEJ cancers. Some 1,798 (26.0%) patients underwent resection for their tumor (endoscopic resections excluded). During the study period, resection rates for esophageal/GEJ cancer decreased from 29.4% to 26.0% ( $P=0.022$ ) (Fig. 4). Pronounced differences in resection rates were noted between the Swedish geographical regions

(ranging from 18.4% to 36.2% in 2016). Of all patients presenting with the diagnoses, a larger proportion of males eventually underwent resection (male:female ratio for all patients being 74.0:26.0% vs. resected patients 78.9:21.1%;  $P < 0.001$ ). Overall 5-year survival for all patients diagnosed with esophageal/GEJ cancer was 15.7% with no gender difference (females 16.3 vs. males 15.5%;  $P=0.26$ ). The overall 5-year survival after resectional surgery for esophageal/GEJ cancer was 38.5%, but we found it to be significantly higher in females compared to males (47.1% vs. 36.2%;  $P < 0.001$ ) (Fig. 5).

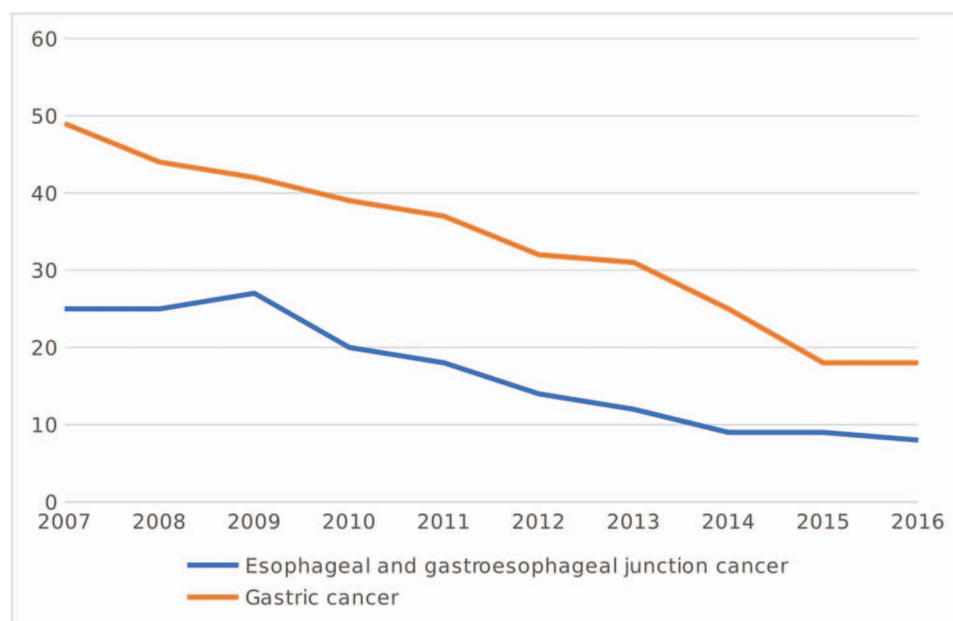
A significant increase in the use of preoperative oncological therapy was seen, from 42.6% of patients during the early years of the study period 2007–2010 compared to 76.4% in the latter years 2014–2016 ( $P < 0.001$ ). Combined chemoradiotherapy was the preferred treatment in 2014–2016 (53.6% of neoadjuvant regimens) (Table 2). The R0 resection rate was significantly higher at the end of the study period (91.3% vs. 86.7%;  $P=0.025$ ), and the 30- and 90-day postoperative mortalities were in the range of 1.9–2.2% and 5.6–6.0%, respectively, during the study period (Table 2). The anastomotic leakage rates ranged from 7.1% to 13.1%, except for a peak at 18% in 2015. (Fig. 6). An increase in the proportion of resections yielding  $\geq 15$  lymph nodes was also observed (58.2% vs. 75.3%) from 2007–2016 ( $P < 0.001$ ).

### Gastric cancer

A total of 5,316 patients (2,959 males and 2,357 females) with gastric cancer were enrolled in the register between 2007 and 2016 (Table 1). Treatment



**Fig. 2** Median time (days) from referral to treatment recommendation at the MDC among patients with esophageal/gastroesophageal junction or gastric cancer.



**Fig. 3** Number of hospitals performing esophageal or gastric cancer surgery in Sweden.

with curative intent was recommended by the MDC in 42% (range 40–45%) of all patients with gastric cancers of whom 1,896 (35.7%) patients underwent resection (endoscopic resections excluded). Resection rates for gastric cancer fell from 38.8% to 33.3% ( $P=0.002$ ) (Fig. 4) during the study period, again demonstrating large regional differences (from 20.7% to 41.5% in 2016). No significant gender difference in the proportion of patients having resectional surgery compared to all patients was noted (male:female ratio for all patients being 55.7:44.3% vs. resected patients 56.9:43.1%;  $P=0.368$ ). The overall 5-year

survival for all patients diagnosed with gastric cancer was 17.2%, with no significant gender difference (women 18.2% vs. men 16.4%;  $P=0.20$ ). The 5-year survival after resection was 35.9% (women 37.3% vs. men 34.8%;  $P=0.18$ ) (Supplement Fig. 1). Some 20.4% of patients received neoadjuvant treatment during 2007–2010 compared to 42.4% in 2014–2016 ( $P<0.001$ ), where chemotherapy alone was the most commonly administered treatment (39.9% in 2014–2016) (Table 3). The R0 rate centered around 80% during the whole study period. The 30-day mortality rate improved significantly from

**Table 1** Baseline and tumor characteristics in 12,242 esophageal/gastroesophageal junction and gastric cancer patients (%) from Survey I of NREV

	Esophageal/gastroesophageal junction cancer		Gastric cancer	
	Total	Resected	Total	Resected
<i>Age</i>				
>70 years	3,543 (51.2)	1,252 (69.6)	2,042 (38.4)	892 (47.0)
≤70 years	3,383 (48.8)	546 (30.4)	3,274 (61.6)	1,004 (53.0)
<i>ASA score</i>				
I–II	4,266 (61.6)	1,506 (83.8)	3,194 (60.1)	1,417 (74.7)
≥III	2,445 (35.3)	271 (15.1)	1,937 (36.4)	436 (23.0)
Unknown	215 (3.1)	21 (1.2)	185 (3.5)	43 (2.3)
<i>Sex</i>				
Male	5,124 (74.0)	1,418 (78.9)	2,959 (55.7)	1,078 (56.9)
Female	1,802 (26.0)	380 (21.1)	2,357 (44.3)	818 (43.1)
<i>Diagnosis</i>				
Adenocarcinoma	4,515 (65.2)	1,357 (75.5)	4,574 (86.0)	1,652 (87.1)
Squamous cell carcinoma	1,778 (25.7)	315 (17.5)	13 (0.2)	2 (0.1)
Other/unknown	633 (9.2)	126 (7.0)	729 (13.7)	242 (12.8)
<i>Location</i>				
Cervical	103 (1.5)	7 (0.4)		
Upper 1/3	317 (4.6)	31 (1.7)		
Middle 1/3	779 (11.2)	160 (8.9)		
Lower 1/3	2,713 (39.2)	748 (41.6)		
Overlapping	112 (1.6)	9 (0.5)		
Not specified	545 (7.9)	72 (4.0)		
Cardia I–III	2,357 (34.0)	771 (42.9)		
Fundus			343 (6.5)	100 (5.3)
Corpus			1,345 (25.3)	525 (27.7)
Antrum			1,307 (24.6)	643 (33.9)
Pylorus			422 (7.9)	192 (10.1)
Lesser curvature			282 (5.3)	114 (6.0)
Greater curvature			139 (2.6)	47 (2.5)
Overlapping			364 (6.8)	32 (1.7)
Not specified			1114 (21.0)	243 (12.8)
<i>cT</i>				
T0	14 (0.2)	3 (0.2)	19 (0.4)	4 (0.2)
T1	303 (4.4)	114 (6.3)	315 (5.9)	183 (9.7)
T2	957 (13.8)	480 (26.7)	751 (14.1)	501 (26.4)
T3	2,952 (42.6)	888 (49.4)	1,603 (30.2)	634 (33.4)
T4	1,054 (15.2)	73 (4.1)	1,017 (19.1)	146 (7.7)
Tis: carcinoma in situ	296 (4.3)	48 (2.7)	150 (2.8)	33 (1.7)
TX	1,329 (19.2)	192 (10.7)	1,420 (26.7)	386 (20.4)
Unknown	21 (0.3)	0 (0)	41 (0.8)	9 (0.5)
<i>cN</i>				
N0	2,585 (37.3)	981 (54.6)	2,381 (44.8)	1,266 (66.8)
N1	2,222 (32.1)	618 (34.4)	1,014 (19.1)	308 (16.2)
N2	669 (9.7)	108 (6.0)	406 (7.6)	99 (5.2)
N3	464 (6.7)	21 (1.2)	269 (5.1)	40 (2.1)
NX	952 (13.7)	67 (3.7)	1,192 (22.4)	171 (9.0)
Unknown	34 (0.5)	3 (0.2)	54 (1.0)	12 (0.6)

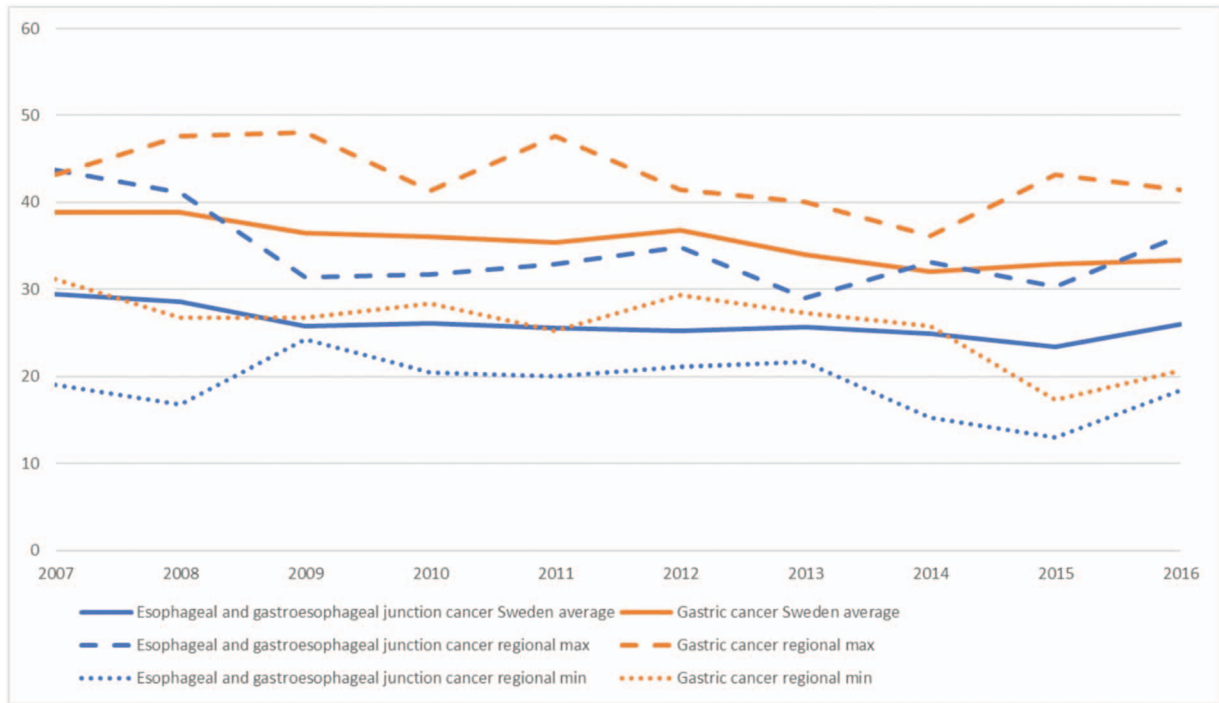
4.2% to 1.6% ( $P=0.005$ ), but the decrease in 90-day mortality from 8.5% to 5.5% did not reach statistical significance ( $P=0.061$ ) (Table 3). An increase in the proportion of  $\geq 15$  lymph nodes resected was observed from 35.7% in 2006 to 74.0% in 2016 ( $P < 0.001$ ).

## DISCUSSION

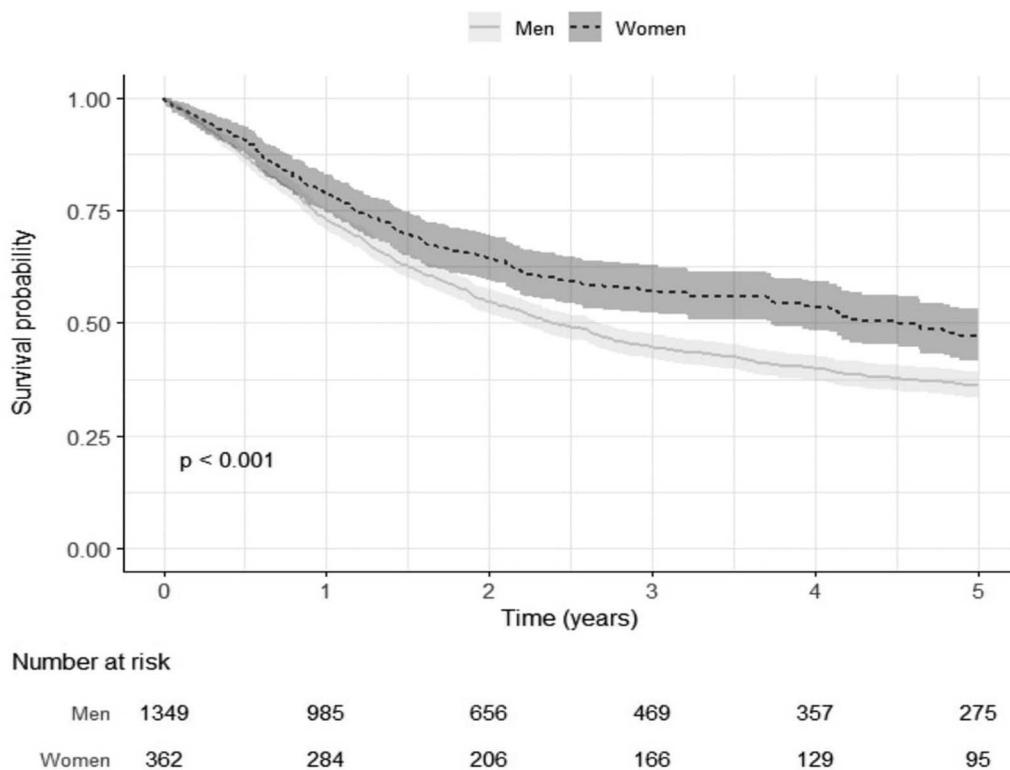
NREV has reached a position with adequate nationwide coverage and high accuracy and validity of data.<sup>8</sup> In this population-based register, we can now present data on improvements in patient logistics, centralization of care, and a decrease in short-term mortality for gastric cancer patients.

The history of the NREV seems quite typical for the launch and development of national registers, as exemplified by e.g. the Swedish National Prostate Cancer Register.<sup>17</sup> Even so, NREV does not reach the same degree of completeness as comparable national registers in Denmark and The Netherlands.<sup>18,19</sup> The most likely reason is that, in contrast to the latter two registers, registration in NREV is still optional and not compulsory.

The outcomes of RCTs,<sup>9,10</sup> advocating the value of neoadjuvant treatment, have had significant impact on the management of esophagogastric cancer patients in Sweden. We observed a steadily growing proportion of Swedish patients receiving preoperative oncological treatment, albeit to a lesser



**Fig. 4** Resection rates (%) for esophageal/gastroesophageal junction and gastric cancer, respectively, with regional maximum and minimum values.



**Fig. 5** Esophageal and gastroesophageal junction cancer. Estimated 5-year survival with 95% confidence intervals after surgical resection.

extent than in other countries.<sup>3</sup> Both 30- and 90-day mortality rates for resections of esophageal/GEJ cancer remain unchanged, whereas a decline in the corresponding figures for gastric cancer was seen. This could, in part, be explained by the process

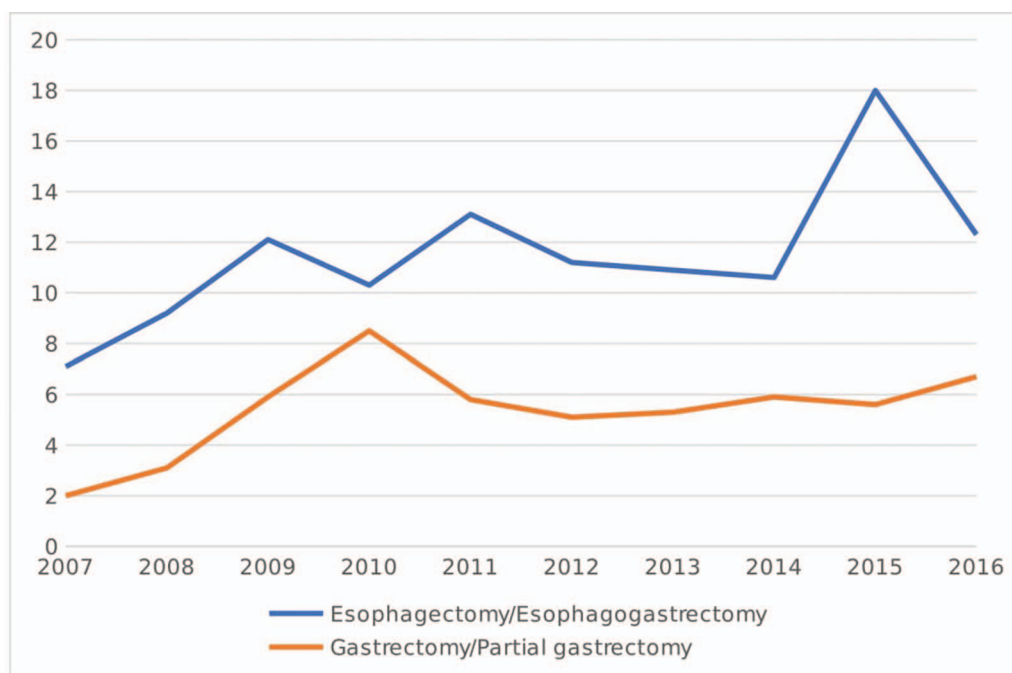
of centralization of these complex procedures in Sweden during this period, most notably accentuated for by gastric cancer. Though, it was not until 2016, a formal recommendation from the Swedish Board of Health and Welfare stated that only six

**Table 2** Treatment characteristics and outcomes for 1,711 patients (%) after surgical resection for esophageal and gastroesophageal junction cancer from Survey 2 of NREV

	2007–2010	2011–2013	2014–2016	P value*
<i>Preoperative treatment</i>	274/643 (42.6)	306/501 (61.1)	433/567 (76.4)	<0.001
Chemo–/radiotherapy	154 (24.0)	152 (30.3)	304 (53.6)	
Chemotherapy	116 (18.0)	153 (30.5)	127 (22.4)	
Radiotherapy	4 (0.6)	1 (0.2)	2 (0.4)	
None	367 (57.1)	192 (38.3)	122 (21.5)	
Unknown	2 (0.3)	3 (0.6)	12 (2.1)	
<i>Type of surgery</i>				N/A
Esophagogastrectomy	71 (11.0)	67 (13.4)	42 (7.4)	
Esophagectomy	450 (70.0)	354 (70.7)	446 (78.7)	
Gastrectomy	57 (8.9)	49 (9.8)	60 (10.6)	
Partial gastrectomy	42 (6.5)	15 (3.0)	15 (2.6)	
Others/missing	23 (3.6)	16 (3.2)	4 (0.7)	
R0 †	517/596 (86.7)	351/407 (86.2)	451/494 (91.3)	0.025
<i>Mortality</i>				
30 days	12/643 (1.9)	11/501 (2.2)	11/567 (1.9)	0.916
90 days	38/643 (5.9)	30/501 (6.0)	32/567 (5.6)	0.848

\*Chi-square test for trend.

†R0: no viable tumor cells at resection margins. Calculated only on patients with full information on proximal, distal, and circumferential resection margins. N/A, not applicable.



**Fig. 6** Anastomotic leakage (%) after surgical resection for esophageal and gastric cancer.

hospitals were to perform surgery for esophageal and gastric cancer. The steady rise in the proportion of patients being presented to an MDC, which have been shown to be of pivotal importance for the optimization of therapeutic outcomes,<sup>20</sup> is also attributed to this centralization process. Another possible effect of centralization is the rise in the proportion of patients with more than 15 lymph nodes identified in their specimen after surgery.<sup>18</sup> In line with the Danish experience,<sup>18</sup> compulsory adherence to the recommendation on centralization might lead to even more uniform treatment and possibly better outcomes for these patients. Inspired by the Danish

example,<sup>21</sup> the Swedish Government launched the campaign Cancer Patient Pathways in 2015. The intention was to shorten the time from suspicion of cancer to diagnosis and start of treatment. Effects of this campaign may well be reflected in this study (Fig. 2).

One of the many objectives of nationwide registers, such as the NREV, is to secure quality of care and minimize the risk of regional imbalances within the country. Assuming high validity of the data entered into the register, comprehensive comparisons can be conducted between regions within a country or between countries.<sup>2,3</sup> Resection rates for

**Table 3** Treatment characteristics and outcomes for 1,851 patients (%) after surgical resection for gastric cancer from Survey 2 of NREV

	2007–2010	2011–2013	2014–2016	<i>P</i> value*
<i>Preoperative treatment</i>	173/850 (20.4)	191/567 (33.7)	184/434 (42.4)	<0.001
Chemo–/radiotherapy	3 (0.4)	6 (1.1)	10 (2.3)	
Chemotherapy	169 (19.9)	184 (32.5)	173 (39.9)	
Radiotherapy	1 (0.1)	1 (0.2)	1 (0.2)	
None	668 (78.6)	375 (66.1)	245 (56.5)	
Unknown	9 (1.1)	1 (0.2)	5 (1.2)	
<i>Type of surgery</i>				N/A
Esophagogastrectomy	5 (0.6)	6 (1.1)	4 (0.9)	
Esophagectomy	2 (0.2)	0 (0)	1 (0.2)	
Gastrectomy	318 (37.4)	226 (39.9)	180 (41.5)	
Partial gastrectomy	467 (54.9)	322 (56.8)	248 (57.1)	
Others/missing	58 (6.8)	13 (2.3)	1 (0.2)	
R0†	616/786 (78.4)	405/503 (80.5)	313/387 (80.9)	0.27
<i>Mortality</i>				
30 day	36/850 (4.2)	13/567 (2.3)	7/434 (1.6)	0.005
90 day	72/850 (8.5)	42/567 (7.4)	24/434 (5.5)	0.061

\*Chi-square test for trend.

†R0: no viable tumor cells at resection margins. Calculated only on patients with full information on proximal, distal, and circumferential resection margins. N/A, not applicable.

both esophageal and gastric cancer have decreased in Sweden during the years 2007–2016 (Fig. 4). Increased use of neoadjuvant chemoradiotherapy in patients with resectable esophageal and GEJ tumors may partly explain the higher R0 rates in the latter part of the study period (Table 2), while no obvious impact on resection rates was evident (Fig. 4). Declining resection rates may though be partly explained by improved diagnostics in terms of increased use of positron emission tomography and diagnostic laparoscopy in the diagnostic processes of esophageal and gastric cancers, respectively. Still, regional differences in resection rates mandate further investigation to ensure that all patients with esophagogastric cancer, regardless of geographical location, are assessed and managed with equal professional standard and quality of care. A weekly national online MDC for all Swedish surgical centers was started in 2017 with the aim of offering not only a forum for discussion of more complex cases but also as an initiative to harmonize the care of all patients on a nationwide basis.

The implementation of new surgical techniques such as the minimally invasive approach for esophageal and gastric cancers must always be monitored with great scrutiny. Minimally invasive surgery for esophagogastric cancer surgery was widely introduced in Sweden in 2012. The technique has been used increasingly, and in 2016, 65% of the esophageal and 20% of the gastric resections were performed using a minimally invasive technique. In 2015, an increase in anastomotic leakages following esophageal resections was noted. In line with the findings of others,<sup>18,22</sup> this may well be attributed to learning curve problems following the introduction of the minimally invasive approach for esophageal resections.

NREV, just like its Danish counterpart DECV, contains information on all patients diagnosed with

esophageal and gastric cancer in their respective countries<sup>18</sup> contrasting to the Dutch database DUCA, which only contains information on patients undergoing surgery.<sup>19</sup> NREV thereby also harbors the option to be used to investigate the reasons why a patient is not selected for resectional surgery. Within the framework of the register, a variety of factors have hitherto been explored, to define factors allegedly affecting the extent to which resection with curative intent is offered and the prognosis after surgery.<sup>23–25</sup> The observed difference in the male:female ratio in patients who were selected for resectional surgery for esophageal and GEJ cancer, compared to all patients with this diagnosis, is noteworthy. Furthermore, Swedish women have significantly better long-term survival than men after resectional surgery for esophageal/GEJ cancer. This issue is the subject for ongoing research projects and hopefully will the continued expansion of the database lead to and foster analyses and results of the underlying causes. Since approximately one-third of patients diagnosed with these tumors undergo curative resection, most patients are only eligible for palliation. Evidently, focused clinical trials within this latter group are warranted.

In conclusion, during the recent decade, the analyses based on the nationwide NREV database demonstrated significant improvements in several important quality indicators of care for patients with esophagogastric cancer. NREV offers an instrument not only for the control and endorsement of quality of care but also a unique tool for population-based clinical research.

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