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PART III

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CHAPTER 13

Changes in treatment patterns and their influence on short-term mortality and long-term survival in patients with stage I-III gastric cancer in the Netherlands

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ABSTRACT

BACKGROUND

Studies investigating perioperative chemotherapy and/or radiotherapy changed the treatment of curable gastric cancer in the Netherlands. These changes were evaluated including their influence on survival.

PATIENTS AND METHODS

Data on patients diagnosed with gastric cancer from 1989-2009 were obtained from the Netherlands Cancer Registry. Changes over time in surgery and administration of perioperative chemotherapy, 30-day mortality, 5-year survival, and adjusted relative excess risk (RER) of dying were analyzed with multivariable regression for cardia and non-cardia gastric cancer.

RESULTS

Most patients with stage I and II disease underwent surgery. Since 2005 more patients are treated with preoperative and/or postoperative chemotherapy. Postoperative mortality ranged from 1% to 7% and 0.4% to 12.2% in cardia and non-cardia cancer (<55 - >75 year). Five-year survival for cardia cancer and non-cardia cancer stage I-III and X (unknown stage) was 33% and 50% (2005-2008). The RER of dying was associated with period of diagnosis, age, gender, region, stage, (neo)adjuvant chemotherapy in case of cardia cancer, and type of gastric resection in case of non-cardia cancer.

CONCLUSIONS

Administration of (neo)adjuvant chemotherapy has increased without improvement in long term survival, but it is still too early to expect an improvement in survival as a result of chemotherapy use.

INTRODUCTION

Despite attempts to improve quality of care, survival rates for gastric cancer in the Netherlands remain dismal. For all stages cardia cancer, 5-year overall survival rates of 10% are reported, while for non-cardia cancer 5-year survival is 14%.¹ Other European studies report 5-year overall survival rates of 15-32%.² Postoperative mortality rates vary from 5.2 to 12.1% in different countries in Europe.^{3,4}

Over the past decades, many trials have been conducted to improve survival of patients with gastric cancer. In the Dutch D1-D2 trial, no benefit was found for a D2 resection after 5 years of follow-up, which was the result of a high postoperative mortality in the D2 group. However, after 15 years, cancer-specific mortality and the number of recurrences was lower in the D2 group.⁵ In other trials the role of preoperative and postoperative therapy in gastric cancer treatment was investigated. In the MAGIC trial, a benefit was proven for patients receiving perioperative chemotherapy consisting of epirubicin, cisplatin and 5-FU (ECF), although it is suggested that the survival benefit was mainly achieved by neoadjuvant chemotherapy.⁶ In the United States Intergroup 0116 study that was conducted in the nineties, a survival benefit for patients receiving postoperative chemoradiotherapy was found. However, 54% of the patients received a D0 lymphadenectomy. It is therefore suggested that postoperative chemoradiotherapy mainly improves survival in patients with inadequate lymph node dissection.⁷ A retrospective study conducted in the Netherlands showed a decreased local recurrence rate and higher overall survival for patients who underwent a D1 resection followed by postoperative chemoradiotherapy, compared to D1 surgery alone. No difference was found for D2 surgery alone versus D2 surgery with postoperative chemoradiotherapy.^{8,9} In 2009, these studies led to the formation of the first official guideline for treatment of gastric cancer in the Netherlands. For stage II and III gastric cancer, it is recommended to offer neoadjuvant chemotherapy based on an ECF schedule. If a patient did not receive neoadjuvant chemotherapy and the resection margins were tumor-positive (R1), adjuvant chemoradiotherapy is recommended.¹⁰

The aims of the current study were to describe changes in the treatment of gastric cancer in the Netherlands, separately for cardia and non-cardia gastric cancer, and to analyze the possible effect of these changes in treatment patterns on postoperative mortality and long-term survival.

PATIENTS AND METHODS

DATA COLLECTION

Data were obtained from the nationwide Netherlands Cancer Registry (NCR). This registry serves the total Dutch population of 16.6 million inhabitants. The NCR is based on notification of all newly diagnosed malignancies in the Netherlands by the national automated pathological archive (PALGA). Additional sources are the national

registry of hospital discharge, hematology departments and radiotherapy institutions. Completeness is estimated to be at least 95%.¹¹ The information on vital status was initially obtained from municipal registries and from 1994 onwards from the nationwide population registries network, consisting of 8 regions during the study period. These registries provide complete coverage of all deceased Dutch citizens.

Patients diagnosed between January 1st 1989 and December 31st 2008 with a tumor of the stomach according to the International Classification of Diseases (ICD) were included in the current study. To evaluate trends over time, the study period was divided in five intervals of four years. Tumors were staged according to the International Union Against Cancer (UICC) TNM classification that was used in the year of diagnosis. Clinical stage group was used in case of missing pathological TNM stage group. If stage was not known, it was defined as X. Follow-up for vital status was complete until December 31st, 2010.

STATISTICAL ANALYSES

All analyses were performed separately for cardia and non-cardia cancer. Differences in patient and tumor characteristics were analyzed with the Chi square test. Trends in treatment, including the use of preoperative and postoperative chemotherapy, and resection, were analyzed as proportional distributions.

The chance to undergo surgery and receive chemotherapy for patients with stage I-III and X (unknown stage) gastric cancer was analyzed with multivariable logistic regression. For chemotherapy, the analyses were restricted to patients diagnosed after 2004 because only a very small proportion of patients received chemotherapy before 2005. For patients diagnosed between 2005 and 2008, the chance of dying within 30 days after resection was calculated with multivariable logistic regression. Before 2005, date of resection was not registered by the NCR, and 30-day mortality could not be calculated.

Traditional cohort-based relative survival analysis was calculated; the number of days was calculated from the date of diagnosis until death of any cause (event) or alive at last follow-up (censored). Then, relative survival was calculated correcting for age- and gender-specific background mortality, as a proxy of disease-specific survival. Only patients who underwent surgery were included.

The independent relative excess risk (RER) of dying for relevant patient and tumor characteristics was calculated by means of multivariable relative survival analysis with Poisson regression.

RESULTS

Between 1989 and 2008, 10,294 patients were diagnosed with cardia cancer, and 30,017 patients were diagnosed with non-cardia cancer in the Netherlands. Patient and tumor characteristics are shown in Table 1. The age and gender distribution differed between cardia and non-cardia cancer: median age was 69.3 years for cardia cancer, and 72.9 years for non-cardia cancer. Patients with cardia cancer were more often males compared

Table 1. Patient characteristics, all diagnosed patients (1989-2008)

	Cardia cancer		Non-cardia cancer		P
	N	%	N	%	
Total	10294	100	30017	100	
Sex					
male	7942	77	17888	60	<0.001
female	2352	23	12129	40	
Age					
<55	1557	15	3260	11	< 0.001
55-64	2263	22	4894	16	
65-74	3298	32	9086	30	
≥75	3176	31	12795	43	
TNM stage group					
I	1188	12	5603	19	< 0.001
II	1408	14	3913	13	
III	1805	18	5014	17	
IV	3815	37	10701	36	
X	2078	20	4786	16	
Tumor location					
middle			8470	28	
pylorus			10596	35	
unknown/overlapping			10951	37	
Tumor grade					
well/moderate	3191	31	7277	24	< 0.001
poor/undifferentiated	4636	45	15305	51	
unknown	2467	24	7435	25	
Period of diagnosis					
1989-1992	2001	19	7260	24	< 0.001
1993-1996	2134	21	6490	22	
1997-2000	2192	21	5804	19	
2001-2004	1991	19	5435	18	
2005-2008	1976	19	5028	17	
Region					
I	1819	18	4931	16	< 0.001
II	466	5	1971	7	
III	799	8	1973	7	
IV	2211	21	6932	23	
V	856	8	2294	8	
VI	1718	17	4888	16	
VII	1116	11	2779	9	
VIII	1309	13	4249	14	

to patients with non-cardia cancer.

Trends in treatment over time are depicted in Figure 1, separately for stage I, II, and III. Resection rates remained stable for stage I and II disease, but decreased for stage III cardia cancer with 20% ($P < 0.001$). The proportion of patients treated with chemotherapy increased significantly in every stage group ($P < 0.001$).

In Table 2, resection percentages and the adjusted chance to undergo a resection for patients with stage I-III and X gastric cancer diagnosed between 1989 and 2008 are shown. Elderly patients less often underwent a resection (<55 years old versus ≥75 years old: odds ratio (OR) 0.2 and 0.3 for respectively cardia and non-cardia cancer). Resection rates for stage I and II were similar, both for cardia and non-cardia gastric cancer, while

Table 2. Multivariate logistic regression on the chance to undergo a resection, stage I-III and X, all diagnosed patients (1989-2008)

	Cardia cancer			Non-cardia cancer		
	Resection rate (%)	OR	P	Resection rate (%)	OR	P
Sex						
male (ref)	58	1.0		69	1.0	
female	44	0.9	0.075	65	1.0	0.498
Age						
<55 (ref)	79	1.0		85	1.0	
55-64	75	0.8	0.133	82	0.7	0.003
65-74	64	0.6	< 0.001	77	0.5	< 0.001
≥75	26	0.2	< 0.001	52	0.3	< 0.001
TNM stage group						
I (ref)	82	1.0		92	1.0	
II	84	0.9	0.483	94	1.1	0.177
III	71	0.3	< 0.001	75	0.2	< 0.001
X	5	0.02	< 0.001	7	0.01	< 0.001
Tumor location						
middle (ref)				71	1	
pylorus				77	1.2	0.002
unknown/overlapping				51	0.5	< 0.001
Tumor grade						
well/moderate (ref)	62	1.0		75	1.0	
poor/undifferentiated	62	0.8	0.032	72	0.9	0.1
unknown	27	0.2	< 0.001	47	0.3	< 0.001
Period of diagnosis						
1989-1992 (ref)	58	1.0		71	1.0	
1993-1996	57	1.0	0.956	68	0.7	< 0.001
1997-2000	52	0.8	0.097	66	0.7	< 0.001
2001-2004	51	0.7	0.002	65	0.7	< 0.001
2005-2008	57	1.0	0.891	62	0.6	< 0.001
Region						
I (ref)	57	1.0		67	1.0	
II	59	0.8	0.294	74	1.1	0.379
III	62	0.9	0.595	69	1.0	0.774
IV	49	0.5	< 0.001	66	0.7	< 0.001
V	50	0.5	< 0.001	68	0.7	0.009
VI	57	1.0	0.890	66	0.7	0.007
VII	56	1.0	0.881	63	0.7	< 0.001
VIII	55	0.6	0.002	67	0.9	0.111

ref: reference category, OR: odds ratio

resection rates for stage III cardia and non-cardia gastric cancer were significantly lower (OR cardia: 0.3, OR non-cardia: 0.2, $P < 0.001$). For non-cardia gastric cancer, the chance of undergoing surgery decreased over time (2005-2008 OR 0.6, $P < 0.001$). Resection rates significantly differed between regions, from 49% to 62% for cardia cancer and from 63 to 74% for non-cardia cancer.

In Table 3, the proportion of patients treated with chemotherapy and the adjusted chance to receive chemotherapy is shown for patients with stage I-III and X, resected for cardia and non-cardia cancer between 2005 and 2008. A younger age, diagnosis in a more recent time interval, and, for patients with non-cardia cancer, a more advanced stage were associated with a higher chance for receiving chemotherapy. Again, large regional

Table 3. Multivariate logistic regression on the chance to receive preoperative and/or postoperative chemotherapy, stage I-III and X, only resected patients (2005-2008)

	Cardia cancer			Non-cardia cancer		
	Chemotherapy use (%)	OR	P	Chemotherapy use (%)	OR	P
Total	29			21		
Sex						
male (ref)	30	1.0		20	1.0	
female	28	0.8	0.398	22	0.7	0.885
Age						
<55 (ref)	44	1.0		52	1.0	
55-64	33	0.5	0.037	35	0.4	< 0.001
65-74	29	0.4	< 0.001	21	0.3	< 0.001
≥75	10	0.1	< 0.001	4	0.0	< 0.001
TNM stage group						
I (ref)	31	1.0		17	1.0	
II	35	1.2	0.550	23	1.7	0.002
III	22	0.8	0.343	21	1.8	0.003
X	78	3.2	0.105	75	15.6	< 0.001
Tumor location						
middle (ref)				20	1.0	
pylorus				20	1.0	0.936
unknown/overlapping				23	1.1	0.567
Tumor grade						
well/moderate (ref)	22	1.0		11	1.0	
poor/undifferentiated	23	1.1	0.739	20	1.5	0.069
unknown	60	3.5	< 0.001	36	3.3	< 0.001
Year of diagnosis						
2005 (ref)	10	1.0		5	1.0	
2006	21	2.8	0.004	12	3.2	< 0.001
2007	36	6.7	< 0.001	26	9.1	< 0.001
2008	54	14.0	< 0.001	40	20.1	< 0.001
Region						
I (ref)	23	1.0		25	1.0	
II	37	1.9	0.222	23	1.2	0.627
III	22	0.9	0.849	25	1.0	0.946
IV	22	0.7	0.220	16	0.4	< 0.001
V	20	0.7	0.461	19	0.7	0.338
VI	39	2.6	0.007	17	0.5	0.010
VII	58	4.5	0.001	25	1.1	0.761
VIII	23	0.6	< 0.001	22	0.7	0.153

ref: reference category, OR: odds ratio

variations could be noted, ranging from 20% to 58% for cardia cancer and from 16% to 25% for non-cardia cancer.

In Table 4, 30-day mortality is shown in percentages and as the adjusted risk after resection for gastric cardia and non-cardia cancer between 2005 and 2008. For cardia and non-cardia cancer combined, 30-day mortality after resection was 6.7%. The risk of dying postoperatively strongly increased with age, from 1% for patients younger than 55 years to 8% among patients aged 65-74 years after resection for cardia cancer ($P = 0.043$), and from 0.4% to 12% for patients aged 75 years or older after resection for non-cardia cancer ($P = 0.002$) (Figure 2). Thirty-day mortality rates were lower for females compared to males after resection for non-cardia cancer. Statistically, there were no

Figure 1. Patterns of care for patients with (a) stage I, (b) stage II, (c) stage III cardia and non-cardia gastric cancer in the Netherlands, 1989-2008

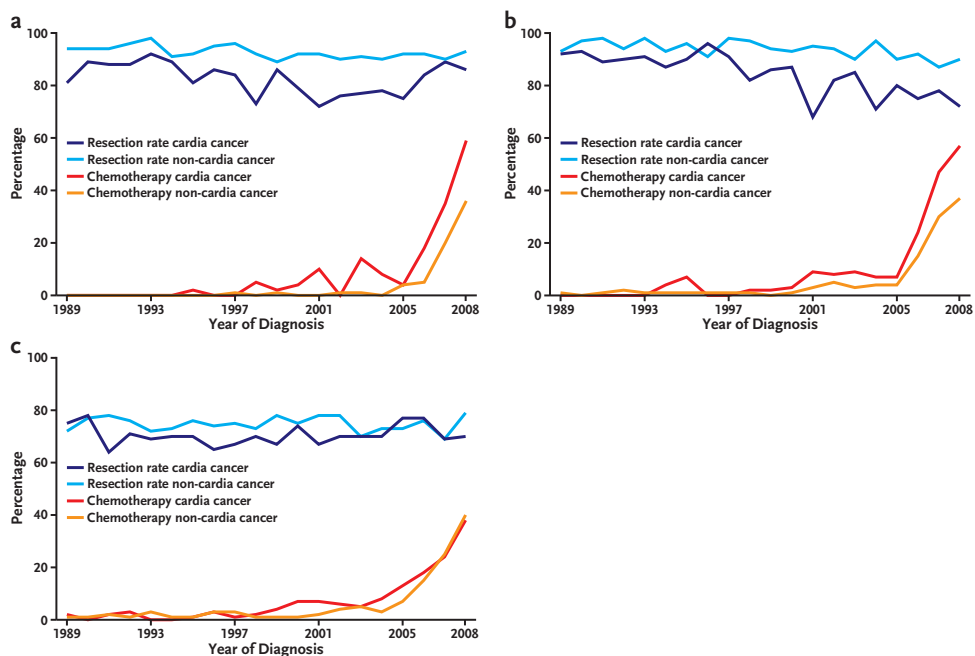
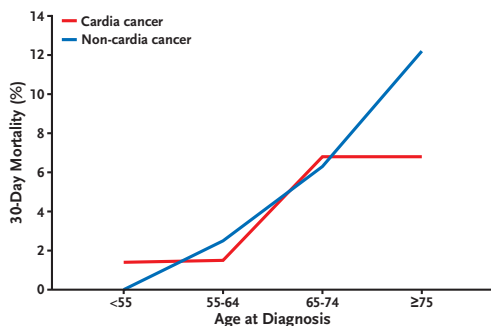


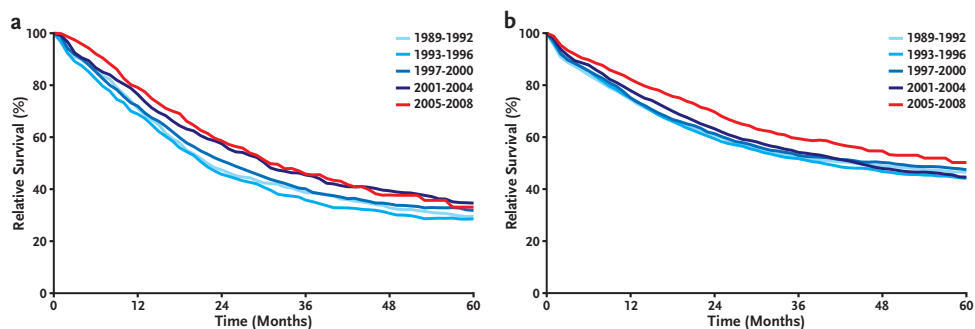
Figure 2. Thirty-day mortality after resection for gastric cancer in the Netherlands, 2005-2008



regional differences.

Five-year relative survival rates of patients who underwent a resection for stage I-III and X remained about 33% for patients with cardia cancer, and improved somewhat from 47 to 50% (not significant) for patients with non-cardia cancer (Figure 3). After adjustment for available patient and tumor characteristics, the risk of dying (RER) after being diagnosed with gastric cancer was lower in the period 2005-2008 compared to the period 1989-1992, both for cardia and non-cardia cancer. The risk of dying was higher for older patients and for males, and again regional variation was considerable (Table 5).

Figure 3. Five-year relative survival after resection for stage I-III and X (a) cardia cancer, (b) non-cardia cancer in the Netherlands, 1989-2008



DISCUSSION

Over the study period, resection rates for both cardia and non-cardia cancer remained relatively stable. The administration of preoperative and postoperative chemotherapy significantly increased from 2005 to 2008. Survival rates remained stable for both types of gastric cancer.

Resection rates were clearly lower for stage III compared to stage I and II gastric cancer. In cardia cancer, resection rates were lower compared to non-cardia cancer. Main factors adversely affecting resection rates were older age, higher tumor stage, a more recent period of diagnosis, interregional variation and unknown tumor differentiation grade. In non-cardia cancer the location of the tumor was a factor of influence as well.

Before the introduction of the national guideline for treatment of gastric cancer in 2009 the administration of preoperative and postoperative chemotherapy was not recommended. In 2006, the MAGIC trial was published which led to a change in treatment in the Netherlands as well as in the UK and the USA.¹²⁻¹⁴ In the latest period, after 2005, there was a significant increase in the number of patients treated with chemotherapy, both for cardia and non-cardia cancer. Even in stage I cardia and non-cardia cancer there was a remarkable increase in chemotherapy administration (59% and 36% respectively). As chemotherapy is administered based on clinical stage while the analyses for the current study were based on pathological stage, it is possible that due to downstaging after neoadjuvant chemotherapy, patients with a pathological stage I had a clinical stage II. Furthermore, it is quite difficult to assess the clinical stage. Non-invasive imaging modalities such as computed tomography (CT) and positron emission tomography (PET) do not have a high sensitivity for T-stage and lymph node metastases. Endoscopic ultrasonography (EUS) could determine T-stage although this is not implemented in the routine work-up of gastric cancer in the Netherlands.^{10,15-17} Therefore, preoperative chemotherapy might have been administered more liberally.

The majority of mortality rates reported in literature are derived from clinical trials. This can be subject to a selection or publication bias. The current epidemiological study

Table 4. Multivariate logistic regression on 30-day mortality (2005-2008)

	Cardia cancer			Non-cardia cancer		
	30-day mortality (%)	OR	P	30-day mortality (%)	OR	P
Total	4			7		
Sex						
male (ref)	5	1.0		8	1.0	
female	3	0.7	0.478	6	0.7	0.060
Age						
<55 (ref)	1	1.0		0.4	1.0	
55-64	2	2.1	0.536	3	6.0	0.083
65-74	8	8.9	0.043	7	11.0	0.020
≥75	7	6.4	0.099	12	23.0	0.002
TNM stage group						
I (ref)	6	1.0		6	1.0	
II	4	0.6	0.324	5	0.9	0.769
III	3	0.4	0.093	9	1.6	0.047
X						
Tumor location						
middle (ref)				8	1.0	
pylorus				5	0.6	0.031
unknown/overlapping				11	1.5	0.126
Tumor grade						
well/moderate (ref)	5	1.0		8	1.0	
poor/undifferentiated	4	0.5	0.167	7	1.0	0.987
unknown	5	1.7	0.370	7	0.8	0.568
Neoadjuvant treatment						
none (ref)	5	1.0		8	1.0	
chemotherapy	2	0.2	0.087	3	0.7	0.344
radiotherapy	4	0.9	0.873			
chemoradiation	5	1.0	0.939			
Year of diagnosis						
2005 (ref)	6	1.0		8	1.0	
2006	5	0.5	0.199	9	1.1	0.740
2007	5	0.4	0.155	7	0.9	0.786
2008	3	0.5	0.279	5	0.9	0.637
Region						
I (ref)	5	1.0		9	1.0	
II	15	3.3	0.152	5	0.5	0.203
III	7	3.2	0.124	6	0.5	0.150
IV	2	0.6	0.560	7	0.6	0.081
V	4	1.6	0.461	9	1.1	0.878
VI	3	0.9	0.612	6	0.5	0.051
VII	4	0.6	0.943	11	1.5	0.273
VIII	5	0.5	0.645	7	0.9	0.790

ref: reference category, OR: odds ratio

provides non-biased postoperative mortality rates in the Netherlands. Thirty-day mortality in the latest period (2005-2008) was 6.7% for cardia and non-cardia cancer combined. Although this leaves room for improvement, this is lower compared to the postoperative mortality rate in the nineties.^{3,4,18} Apart from surgical skills, postoperative mortality depends on selection of patients, anesthetic perioperative care and postoperative care at the ICU and the ward. It is imperative to improve treatment to prevent postoperative

Table 5. Relative excess risk (RER) of death, all diagnosed patients (1989-2008)

	Cardia cancer		Non-cardia cancer	
	RER	95% CI	RER	95% CI
Sex				
male (ref)	1.0		1.0	
female	0.8	0.68-0.87	0.9	0.85-0.96
Age				
<55 (ref)	1.0		1.0	
55-64	1.1	0.99-1.30	1.1	0.99-1.23
65-74	1.2	1.10-1.42	1.3	1.19-1.44
≥75	1.5	1.24-1.73	1.6	1.45-1.75
TNM stage group				
I (ref)	1.0		1.0	
II	2.4	2.10-2.81	3.1	2.83-3.36
III	3.6	3.09-4.11	5.3	4.91-5.73
X	2.7	2.03-3.57	3.3	2.78-4.00
Tumor location				
middle (ref)			1.0	
pylorus			1.1	0.99-1.14
unknown			1.3	1.23-1.43
Tumor grade				
well/moderate (ref)	1.0		1.0	
poor/undifferentiated	1.3	1.20-1.46	1.2	1.17-1.33
unknown	1.0	0.86-1.23	1.2	1.06-1.29
Type of resection				
subtotal gastrectomy (ref)	1.0		1.0	
total gastrectomy	1.0	0.73-1.30	1.1	1.04-1.26
esophagocardiac resection	1.0	0.88-1.34		
other	1.1	0.83-1.42	1.0	0.93-1.14
Chemotherapy				
no (ref)	1.0		1.0	
yes	0.8	0.65-1.00	0.9	0.79-1.11
Period of diagnosis				
1989-1993 (ref)	1.0		1.0	
1993-1996	1.1	0.92-1.23	1.1	0.98-1.17
1997-2000	0.9	0.81-1.08	1.0	0.95-1.14
2001-2004	0.8	0.66-0.92	1.0	0.90-1.10
2005-2008	0.8	0.67-0.99	0.8	0.69-0.91
Region				
I (ref)	1.0		1.0	
II	1.4	1.08-1.76	0.9	0.76-1.01
III	1.1	0.90-1.46	0.9	0.72-1.01
IV	1.2	1.05-1.42	1.1	0.96-1.16
V	1.4	1.11-1.66	1.1	0.97-1.25
VI	1.0	0.86-1.27	0.9	0.76-0.96
VII	1.2	0.98-1.38	1.0	0.90-1.13
VIII	1.4	1.14-1.61	1.0	0.93-1.16

ref: reference category, RER: relative excess risk, 95% CI: 95% confidence interval

deaths and to increase survival rates. Therefore, mortality rates could be improved by centralizing gastric cancer care to dedicated high volume hospitals. Although a recent study did not demonstrate a difference in survival rates between low- and high-volume hospitals for gastric cancer,¹⁹ as of 2012, centralization has been implemented with a minimum of 10 gastrectomies per hospital per year, and as of 2013 this minimal volume standard will be increased to 20 gastrectomies per hospital per year. Furthermore,

multidisciplinary consultation should be implemented prior to and after surgery and knowledge of the national guidelines is imperative. With these new quality standards for gastric cancer treatment, endorsed by the Dutch Association for Surgical Oncology, adherence to the guidelines implemented in 2009 can be accomplished.

For both cardia and non-cardia there was no significant improvement in 5-year survival. In Europe, 5-year survival rates for resected gastric cancer are 23.8-35.8% compared to a survival rate of 33% in cardia and 50% in non-cardia cancer in the Netherlands.²⁰ One of the most important factors influencing survival is lymph node (N) stage.^{21,22} A minimum of 15 lymph nodes is recommended for gastric cancer (UICC/AJCC).²³ Studies performed in the Netherlands show that this criterion is still not met.^{22,24} A modified type of lymph node dissection with less morbidity and mortality rates compared to a D2 dissection, but with more lymph nodes retrieved than a D1 dissection could be a solution. First results of a study investigating the role of a D1-extra dissection (dissection of lymph node station 3-9, and depending on location 1, 2, 10, and 12a according to the Japanese classification)²⁵ are promising; a mean lymph node yield of 30.8 (range 13-58) is achieved with acceptable morbidity and low postoperative mortality (unpublished results). The use of chemotherapy has only exponentially grown since 2007. This rise has not resulted in an increased survival rate yet. However, it is probably too early to see any differences in survival curves.

This study has some limitations. In these analyses all patients receiving surgery with stage I, II and III were included. However, in the NCR it is not registered whether the intent of a resection was curative or palliative, which might lead to an underestimation of survival rates, especially in stage III. Cause of death is not registered; this might lead to a bias in the RER and survival rates especially in the older patient. On the other hand, our results are consistent with results found in literature.^{3,4}

Despite a strong increase in the use of preoperative and postoperative chemotherapy for gastric cancer in the Netherlands, still many patients are treated with surgery alone. Mortality rates have declined in the last decade, but there is still room for improvement. Both for cardia and non-cardia gastric cancer, long-term survival rates have not significantly improved over the past 20 years. More studies are needed to investigate the effect of a (modified) extended lymphadenectomy, the use of chemotherapy and/or radiotherapy and the effect of centralization on mortality and survival for patients with resectable gastric cancer.

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