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Trends in incidence, treatment and survival of gastric adenocarcinoma between 1990 and 2007: A population-based study in the Netherlands

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ABSTRACT

Background: Survival of gastric cancer in the Western world remains poor. We conducted a retrospective population-based study to evaluate trends in incidence, treatment and outcome of gastric adenocarcinoma.

Methods: All patients diagnosed with gastric adenocarcinoma during 1990–2007 in the Dutch Eindhoven Cancer Registry area were included ($n = 4797$). Trend analyses were conducted for incidence, mortality, tumour and patient characteristics, treatment and crude overall survival, according to tumour location (cardia versus non-cardia). Temporal changes in the odds of undergoing surgery and the risk of death were analysed by means of multivariable regression methods.

Results: Age-standardised incidence decreased among males (24–12 per 100,000 inhabitants) and females (10–6); mortality rates decreased at a similar pace. The proportion of cardia tumours remained stable. Stage distribution worsened over time among patients with cardia (stages I and II: 32% in 1990–1993 and 22% in 2006–2007, $p = 0.005$) and non-cardia (stage IV: 33% in 1990–1993 and 40% in 2006–2007, $p = 0.0003$) cancer. Chemotherapy rates increased in all settings. Five-year survival worsened over time for patients with non-cardia tumours. Age and stage had significant influence on survival after stratification for tumour localisation. After adjustments for relevant factors (i.e. stage), the risk of death decreased since the late 90s for patients with a cardia tumour (hazard ratio 0.8, $p = 0.01$).

Conclusion: The absence of improvement in survival rates indicates the need for earlier detection and prospective studies to evaluate new therapy regimens with standardised surgery and pathology.

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1. Introduction

Of all cancers, mortality of gastric cancer ranks fourth in Europe for males and females.[1] Although mortality and incidence declined since the second half of the previous century, survival rates remained dismal in Europe with a relative 5-year survival of 25%.[2,3] There has been a shift towards a higher relative incidence of the diffuse type histology and gastric cardia tumour location, which both tend to have lower survival rates.[4,5] A large difference in incidence and survival is found between the East and the West. In Japan gastric cancer is endemic, and screening is implemented since 1983 (Health Service Law for the Elderly, 1983, Japan). In the West, screening is not cost-effective and due to lack of pathognomic signs, it is usually detected at a late (incurable) stage. In Japan, a (modified) D2 resection is performed for gastric cancer. Several studies in the West found no difference in survival between D1 and D2 resection, but there was a higher postoperative morbidity and mortality after D2 resection.[6,7] The SWOG-9008/INT 0116 study found perioperative chemoradiotherapy to be superior compared to surgery alone. The study was criticised since chemoradiotherapy mostly corrected for incomplete surgery (D0 resection).[8] In Britain, the Magic trial found better survival rates for patients who received chemotherapy compared to surgery alone; although 80% proceeded to surgery, only 42% finished the complete regimen. The benefit of higher survival rates seems mostly attributable to neoadjuvant chemotherapy.[9] In the Netherlands, at this moment there is no consensus about curative treatment, although guidelines are under construction. Mostly, a gastrectomy with regional lymphadenectomy is performed, increasingly combined with perioperative chemotherapy in recent years.

This population-based study aims to assess changes in incidence, mortality and survival from gastric cancer, thereby considering recent developments in patient and tumour characteristics and treatment modality.

2. Methods

2.1. Data collection

The Eindhoven Cancer Registry collects data on all patients with newly diagnosed cancer in a large part of the southern Netherlands. The registry area presently comprises 2.3 million inhabitants. This population-based registry is notified by 6 pathology departments, 10 community hospitals and 2 radiotherapy institutions.

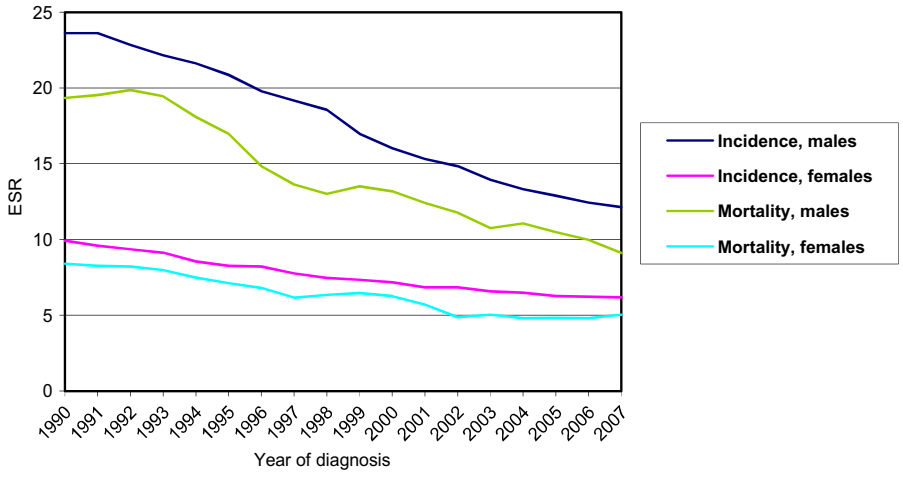


Fig. 1 – Incidence of gastric adenocarcinoma per 100,000 person-years in the south of the Netherlands, according to gender (European Standardised Rate (ESR), 5-year moving averages).

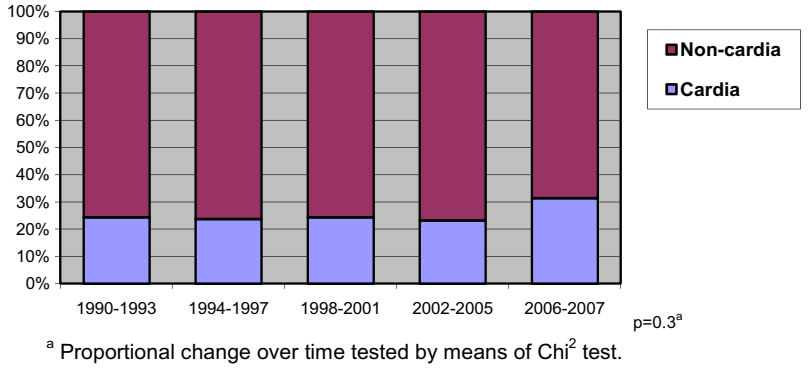


Fig. 2 – Proportional subsite distribution of newly diagnosed gastric adenocarcinoma according to period of diagnosis.

Between 1990 and 2007, 4797 cases of primary gastric adenocarcinoma (C16; morphology codes included according to ICD-O classification: 8010, 8020, 8021, 8140-8389 (except 8240 and 8246), 8480, 8481 and 8490; other morphologies were excluded or did not occur during the study period) were diagnosed in the Eindhoven Cancer Registry area. Information on diagnosis, staging and treatment is routinely extracted from the medical records by specially trained administrators

Table 1 – General patient characteristics of patients diagnosed with gastric adenocarcinoma in the south of the Netherlands, according to localisation and period of diagnosis (percentages in parentheses).

	1990–1993	1994–1997	1998–2001	2002–2005	2006–2007	*p*-Value[b]
Cardia						
Age (years)						
<55	45 (15)	57 (21)	44 (18)	46 (20)	26 (19)	
55–64	94 (32)	62 (23)	53 (22)	58 (25)	32 (23)	
65–74	84 (29)	91 (34)	78 (33)	73 (32)	38 (27)	
75+	69 (24)	59 (22)	65 (27)	54 (23)	43 (31)	
						0.2
Gender						
Males	227 (78)	209 (78)	175 (73)	178 (77)	108 (78)	
Females	65 (22)	60 (22)	65 (27)	53 (23)	31 (22)	
						0.7
Comorbidity[a]						
No comorbidity		110 (41)	83 (35)	76 (33)	39 (28)	
One comorbid condition		71 (26)	66 (28)	61 (26)	40 (29)	
Two or more comorbid conditions		50 (18)	65 (27)	73 (31)	50 (36)	
Unknown		38 (14)	26 (11)	21 (9)	10 (7)	
						<0.0001
Socio-economic status						
High	78 (27)	67 (25)	62 (26)	67 (29)	34 (24)	
Intermediate	106 (36)	109 (41)	95 (40)	100 (43)	57 (41)	
Low	78 (27)	72 (27)	68 (28)	50 (22)	35 (25)	
Institutionalised	19 (7)	11 (4)	12 (5)	13 (6)	9 (6)	
Unknown	11 (4)	10 (4)	3 (1)	1 (0)	4 (3)	
						0.3[c]
Non-cardia						
Age (years)						
<55	84 (9)	86 (10)	87 (12)	75 (10)	31 (9)	
55–64	163 (18)	161 (19)	138 (18)	131 (17)	62 (18)	
65–74	293 (33)	285 (33)	238 (32)	254 (33)	115 (32)	
75+	362 (40)	332 (38)	282 (38)	302 (40)	145 (41)	
						0.9
Gender						
Males	551 (61)	531 (61)	449 (60)	465 (61)	201 (57)	
Females	351 (39)	333 (39)	296 (40)	297 (39)	152 (43)	
						0.7
Comorbidity[a]						
No comorbidity		296 (34)	201 (27)	184 (24)	69 (20)	
One comorbid condition		268 (31)	224 (30)	198 (26)	104 (29)	
Two or more comorbid conditions		201 (23)	2416 (32)	299 (39)	152 (43)	
Unknown		99 (12)	74 (11)	81 (11)	28 (8)	
						<0.0001
Socio-economic status						
High	181 (20)	167 (19)	183 (25)	196 (26)	89 (25)	
Intermediate	297 (33)	294 (34)	267 (36)	255 (33)	134 (38)	
Low	318 (33)	291 (34)	236 (32)	240 (32)	104 (29)	
Institutionalised	78 (9)	85 (10)	50 (7)	52 (7)	14 (4)	
Unknown	28 (3)	27 (3)	9 (1)	19 (2)	12 (3)	
						0.03[c]

[a] Comorbidity registered since 1993.

[b] Proportional change over time tested by means of Chi^2 test for age, comorbidity and socio-economic status, and by means of two-sided Cochran-Armitage trend test for gender.

[c] Chi^2 test excluding institutionalised patients and patients with unknown SES.

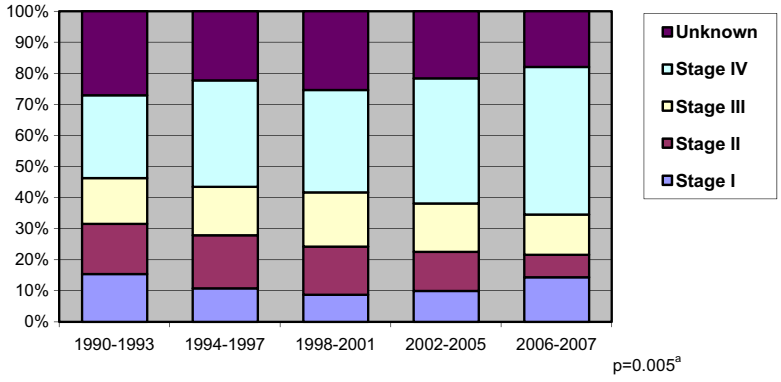
of the cancer registry. Registration takes place 6–18 months after diagnosis. By means of an independent case ascertainment method, the completeness of the registration is estimated to exceed 95%.[10] Vital status of all patients diagnosed until 1st January 2007 was assessed on 1st January 2008 through merging with the Municipal Administrative Databases, where all deceased and emigrated persons in the Netherlands are registered. Socio-economic status (SES) of the patient was defined at neighbourhood level (based on postal code of residence area, 17 households on average) combining mean household income and mean value of the house/apartment. The latter was derived from individual fiscal data made available at an aggregated level. Postal codes were assigned to one of three SES categories: low, intermediate and high.[11] For patients residing in nursing homes, a separate SES category was assigned. Since 1993, prognostically relevant concomitant conditions are recorded from the medical records according to a slightly adapted version of the Charlson Index.[12,13]

2.2. *Analyses*

Incidence and mortality rates are shown as the 5-year moving average of the number of new patients per deaths per 100,000 inhabitants per year (1990–2007). The trends are age standardised, using the European Standardised Rate (ESR). Trends in subsite distribution are shown as the proportional distribution of tumours arising in the cardia (comprising gastro-oesophageal junction, C16.0) or non-cardia (fundus, corpus, lesser curvature, greater curvature, antrum and pylorus or overlapping, C16.1-9) in the respective period (1990–1993, 1994–1997, 1998–2001, 2002–2005, 2006–2007). Tumours were registered according to the ICD-O (International Classification of Diseases for Oncology) edition of the respective period.[14] Disease-specific mortality of gastric adenocarcinoma (as stated on death certificate) was made available at an aggregated level by Statistics Netherlands (CBS). Although the use of death certificates might not guarantee 100% accuracy, it is not likely that the validity has changed during the study period.

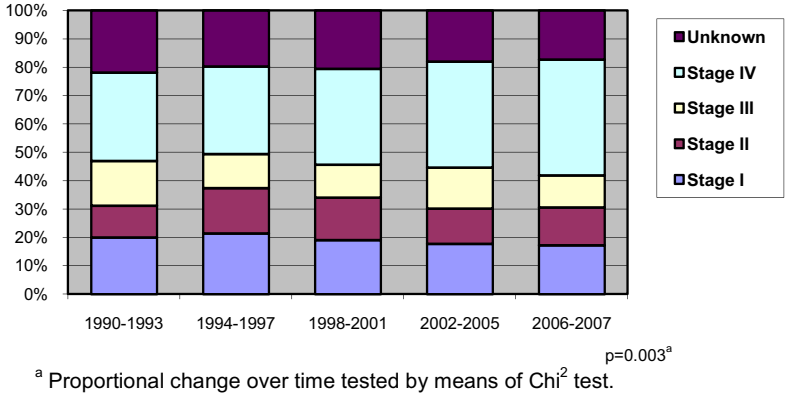
Differences in patient and tumour characteristics between periods of diagnosis (1990–1993, 1994–1997, 1998–2001, 2002–2005, 2006–2007) were analysed using a two-sided Cochran-Armitage trend test or a Chi^2 test, stratified by cardia and non-cardia tumour localisation. Data on comorbidity are shown since the period 1994–1997.

Trends in proportional stage distribution stratified by cardia versus non-cardia tumour localisation are shown as the proportional distribution of the Tumour Node Metastasis (TNM) stage in the respective period. Stage was designated post-operatively, if unknown, then pre-operative stage was



[a] Proportional change over time tested by means of Chi^2 test.

Fig. 3a – Proportional stage distribution of newly diagnosed patients with *cardia* gastric adenocarcinoma in the south of the Netherlands, according to period of diagnosis.



[a] Proportional change over time tested by means of Chi^2 test.

Fig. 3b – Proportional stage distribution of newly diagnosed patients with *non-cardia* gastric adenocarcinoma in the south of the Netherlands, according to period of diagnosis.

used. Chi^2 tests were used to test for changes in stage distribution.

Primary treatment of patients with gastric cancer is shown by stage and by period, stratified by cardia versus non-cardia tumour localisation. Changes in management of these patients were tested using a Chi^2 test. The chance of undergoing surgery for patients with stages I–III gastric cancer was tested by means of a multivariable logistic regression, for cardia and non-cardia tumour localisation. Data from patients diagnosed from 1994 and onwards were included, to be able to adjust for the confounding effect of comorbidity.

Since cause-of-death was not available at individual patient level, survival was calculated using all-cause mortality. Differences in 5-year crude overall survival were tested using the log-rank test. Follow-up was complete for patients diagnosed until 1st January 2007, and period of diagnosis was divided into four periods (1990–1993, 1994–1997, 1998–2001, 2002–2006). A multivariable proportional hazards regression analysis – stratified by cardia versus non-cardia tumour location – was used to discriminate independent risk factors for death. Data from 1995 and onwards were used to be able to adjust for comorbidity.

All tests were two-sided. p-Values <0.05 were considered statistically significant. All analyses were performed using SAS/STAT® statistical software (SAS system 9.1.3, SAS Institute, Cary, NC).

Table 2 – Primary treatment of patients with gastric adenocarcinoma in the south of the Netherlands, according to period of diagnosis and stage of disease, stratified by tumour localisation.[a,b]

	1990–1993	1994–1997	1998–2001	2002–2005	2006–2007	p-Value [c]
Cardia						
Stage I	*N* = 45	*N* = 29	*N* = 21	*N* = 23	*N* = 20	
Surgery[d]	84%	79%	90%	87%	85%	0.7
(Neo)adjuvant chemotherapy[e]	0%	0%	0%	5%	12%	0.01
Stage II	*N* = 47	*N* = 46	*N* = 37	*N* = 29	*N* = 10	
Surgery[d]	94%	96%	97%	97%	80%	0.6
(Neo)adjuvant chemotherapy[e]	0%	0%	6%	4%	13%	0.03
Radiotherapy	19%	4%	5%	3%	10%	0.05
Stage III	*N* = 43	*N* = 42	*N* = 42	*N* = 36	*N* = 18	
Surgery[d]	74%	55%	81%	61%	67%	0.7
(Neo)adjuvant chemotherapy[e]	3%	0%	3%	9%	17%	0.05
Chemotherapy alone	0%	0%	0%	0%	5%	0.06
Radiotherapy	16%	19%	14%	22%	6%	0.6
Stage IV	*N* = 78	*N* = 92	*N* = 79	*N* = 93	*N* = 66	
Surgery[d,f]	14%	8%	5%	8%	5%	0.06
(Neo)adjuvant chemotherapy[e]	0%	0%	0%	14%	33%	0.04
Chemotherapy alone	22%	22%	27%	28%	36%	0.05
Radiotherapy	24%	19%	20%	26%	21%	0.9
Non-cardia						
Stage I	*N* = 180	*N* = 185	*N* = 142	*N* = 135	*N* = 61	
Surgery[d]	96%	98%	94%	92%	95%	0.1
(Neo)adjuvant chemotherapy[e]	0%	0%	0%	0%	12%	<0.0001
Stage II	*N* = 101	*N* = 138	*N* = 112	*N* = 95	*N* = 47	
Surgery [d]	97%	97%	92%	95%	91%	0.08
(Neo)adjuvant chemotherapy [e]	0%	0%	3%	2%	21%	<0.0001
Stage III	*N* = 142	*N* = 104	*N* = 86	*N* = 110	*N* = 40	
Surgery[d]	76%	76%	78%	69%	75%	0.4
(Neo)adjuvant chemotherapy[e]	2%	0%	0%	4%	20%	<0.0001
Chemotherapy alone	2%	1%	1%	9%	10%	0.003
Radiotherapy	3%	1%	2%	3%	0%	0.7
Stage IV	*N* = 281	*N* = 267	*N* = 252	*N* = 285	*N* = 144	
Surgery[d,f]	33%	30%	25%	19%	19%	<0.0001
(Neo)adjuvant chemotherapy[e]	3%	3%	5%	4%	36%	<0.0001
Chemotherapy alone	8%	10%	13%	17%	18%	0.004
Radiotherapy	3%	2%	4%	5%	6%	0.008

[a] Percentages in parentheses.
[b] Post-operative stage of disease; if unknown, then clinical stage of disease.
[c] Proportional change over time tested by means of two-sided Cochran-Armitage trend test.
[d] With or without (neo)adjuvant therapy.
[e] Percentage of patients who underwent resection.
[f] Resection of primary tumour.

3. Results

The age-standardised incidence of gastric cancer among males decreased from 24 patients per 100,000 inhabitants in the beginning of the 1990's to 12 in 2007 (Fig. 1). For females, the incidence decreased from 10 to 6 patients per 100,000 inhabitants. Age-standardised mortality rates followed the same pattern as incidence rates, however with a slight increase for females during the most recent years.

The proportional subsite distribution did not change significantly towards a higher proportion of patients with a cardia tumour location, except for an increasing trend in the most recent period (Fig. 2). This distribution was age dependent, with younger patients having a higher proportion of cardia tumours ($p < 0.0001$) (results not shown).

Patient characteristics are shown in Table 1 for patients diagnosed since 1990, for cardia and non-cardia tumours separately. Since 1994–1997 the age distribution shifted towards a higher proportion of patients diagnosed at the age of 75 or older for cardia carcinoma, also comprising an increase of patients presenting with comorbidity for both cardia and non-cardia tumours. Among patients with non-cardia tumours, there seemed to be a trend towards an increasing proportion with a high socio-economic status.

The proportional stage distribution worsened over time among patients with a cardia (proportion stages I and II: 32% in 1990–1993 versus 22% in 2006–2007, $p = 0.005$) tumour (Fig. 3a). Among patients with a non-cardia tumour location, there was a rising proportion of patients presenting with stage IV (31% in 1990–1993 versus 40% in 2006–2007, $p = 0.003$) (Fig. 3b). The stage distribution was more favourable among patients with non-cardia gastric cancer compared to patients with cardia gastric cancer ($p < 0.0001$). Disease stage was more often unknown among elderly patients; however, among those patients without missing disease stage information, elderly had a more favourable stage distribution than younger patients (results not shown).

Resection rates remained at a high level among patients with non-cardia gastric cancer, while they decreased among stages I, II and IV patients with cardia cancer (Table 2). Resection rates were lower among patients with a tumour located in the cardia. The proportion of patients receiving (neo)adjuvant chemotherapy increased in all stages, especially in the most recent period. Among stage IV patients, the use of chemotherapy without resection increased with time.

Among patients with stages I–III cardia or non-cardia gastric adenocarcinoma, the odds of receiving surgery was smaller among older patients and among stage III patients compared to stage I patients (Table 3). Among patients with stages I–III gastric non-cardia adenocarcinoma the odds of undergoing surgery showed a decreasing trend over time.

Five-year survival for patients with gastric cardia adenocarcinoma remained more or less stable (≈10%), while 5-year survival rates decreased for patients with non-cardia adenocarcinoma (from 22% in 1990–1993 to 14% in 2002–2006, $p = 0.004$) (Figs. 4a and 4b). Five-year survival of patients with stages I–III disease who underwent surgery remained stable over time for non-cardia adenocarcinoma, and showed some fluctuations for cardia adenocarcinoma (Figs. 5a and 5b).

After adjustment for a number of relevant tumour and patient characteristics the risk of dying was equal for patients with a non-cardia and cardia tumour location. Stratified for tumour localisation, older age and a more advanced disease stage were significant prognostic factors (Table 4). Among non-cardia patients, also male gender, the presence of two or more comorbid conditions, and being institutionalised negatively influenced the risk of death. The risk of dying decreased over time among patients with cardia cancer, and remained stable among patients with non-cardia gastric cancer.

4. Discussion

The epidemiology of gastric cancer has changed drastically in the Southern part of the Netherlands between 1990 and 2007. Incidence has decreased, while overall 5-year survival worsened. The proportional incidence of cardia carcinoma remained stable until the most recent years. Prognostic factors found were age and stage after stratification for tumour localisation.

Table 3 – Odds ratio (OR) of undergoing surgery for patients with stages I–III gastric *cardia* and *non-cardia* adenocarcinoma diagnosed between 1995 and 2007 in the south of the Netherlands; logistic regression analyses adjusted for all listed variables.

	Cardia		Non-cardia	
	OR	*p*-Value	OR	*p*-Value
Age (years)				
<55	0.9	0.9	0.8	0.6
55–64[a]	1.0		1.0	
65–74	0.5	0.2	0.7	0.3
75+	0.1	<0.0001	0.5	0.03
Gender				
Males[a]	1.0		1.0	
Females	1.1	0.8	0.8	0.2
Comorbidity[a]				
No comorbidity[a]	1.0		1.0	
One comorbid condition	0.7	0.6	0.8	0.3
Two or more comorbid conditions	0.7	0.6	0.7	0.2
Unknown				
Socio-economic status				
High [a]	1.0		1.0	
Intermediate	0.9	0.8	0.9	0.8
Low	0.9	0.9	1.0	0.9
Institutionalised	0.3	0.4	1.0	0.9
Stage				
I[a]	1.0		1.0	
II	3.7	0.04	0.9	0.8
III	0.2	<0.0001	0.2	<0.0001
Period of diagnosis				
1994–1997[a]	1.0		1.0	
1998–2001	3.0	0.02	0.7	0.2
2002–2005	1.4	0.5	0.5	0.03
2006–2007	1.7	0.3	0.6	0.2

[a] Reference group.

Since the second half of the previous century there has been a dramatically decline worldwide in the incidence and mortality rates of gastric carcinoma.[15] Our and previous studies in the Netherlands confirmed these trends.[4] This is probably due to changes in dietary patterns, better cooling techniques (e.g. refrigerator) and reduction of *Helicobacter pylori* infection. Fruit and vegetables are believed to be protective to gastric cancer, and excess intake of salt increases the risk of gastric cancer.

Reports have noted a (proportional) increase in incidence of gastric cancer located to the cardia, which is counterbalanced by a decrease in incidence of distal gastric carcinoma.[16,17] Distal cancer is associated with (precancerous lesions due to) *H. pylori* infection. The fall in incidence in distal cancer is associated with the treatment of *H. pylori*.[18,19] The rise in cardia carcinoma still cannot be explained, although obesity seems to be of influence.[20] In the Netherlands and some countries, however, previous studies showed no increase in the incidence of cardia cancer.[21,22] Our results confirm this, although in the most recent period a small proportional rise was seen in cardia carcinoma. Some suggest that misclassification of distal oesophageal cancer as gastric cardia cancer explains the non-increasing incidence of cardia carcinoma. In 1978, the ICD-9 recommended that all cancers arising at the gastro-oesophageal junction should be coded as cardiacarcinoma. Throughout the years, there was more awareness of the difference between distal oesophageal cancer and cardia cancer, which led to different classification. This might not have played a role in our region, as one would expect a decline in incidence of cardiacarcinoma due to different classification.[23] It is suggested that cardia cancer has a more aggressive behaviour and different epidemiologic and biologic characteristics, which worsen prognosis. Prognosis is particularly poor, with a 5-year survival of 10% compared to 14% (most recent period) for the other parts of the stomach in our region. This difference in survival is confirmed by other studies, although prognosis in the East is still far better with a 5-year survival of 62%.[4,24]

Gastric carcinoma can be divided into two distinct histological patterns, a diffuse and an intestinal type according to the Laurèn classification.[25] In the last decades, a rise in the incidence of diffuse type of carcinoma is seen

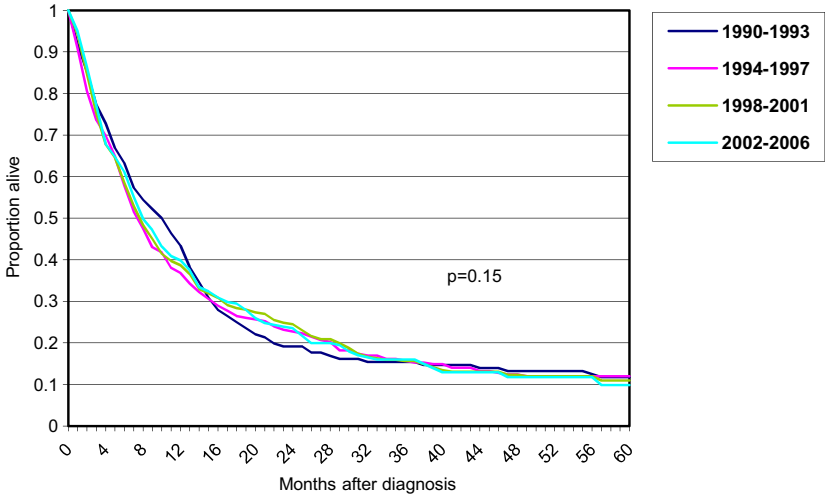


Fig. 4a – Five-year crude overall survival of patients with gastric *cardia* adenocarcinoma, according to period of diagnosis.

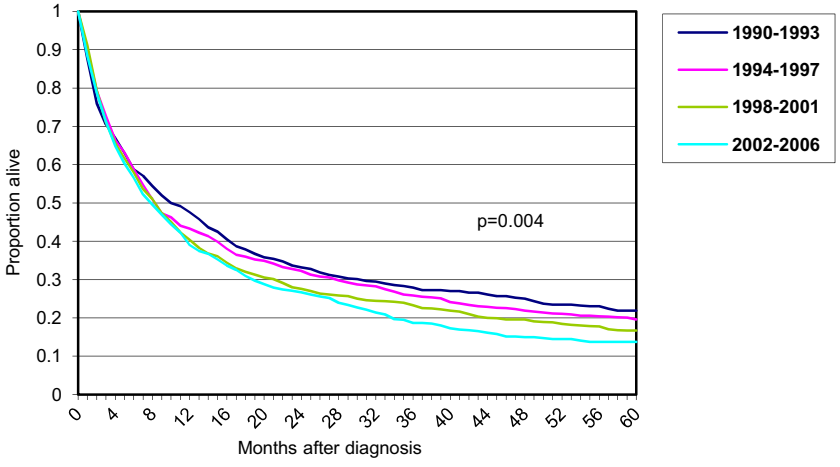


Fig. 4b – Five-year crude overall survival of patients with gastric *non-cardia* adenocarcinoma, according to period of diagnosis.

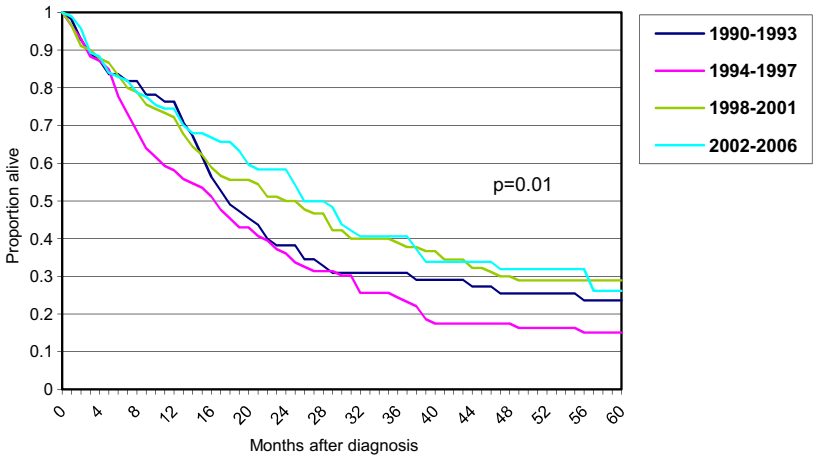


Fig. 5a – Five-year crude overall survival of patients with stages I–III gastric *cardia* adenocarcinoma who underwent surgery, according to period of diagnosis.

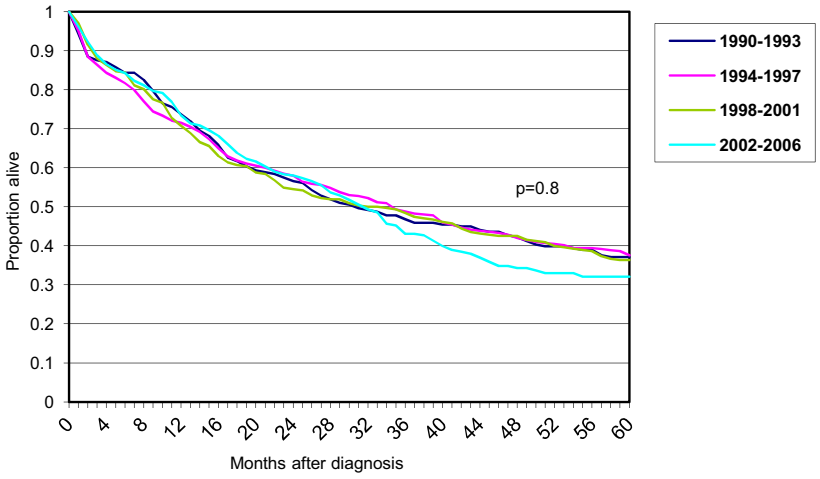


Fig. 5b – Five-year crude overall survival of patients with stages I–III gastric *non-cardia* adenocarcinoma who underwent surgery, according to period of diagnosis.

worldwide.[26] The relation to survival and histology is still not clear. Some report no relationship between survival and histology, while others describe an association with worse prognosis for the diffuse type, with a 5-year survival of 20–67% versus 36–76% for the intestinal type.[16,27] No discrimination could be made between these different types of adenocarcinoma for the majority of patients registered in the Eindhoven Cancer Registry. As different histological types can be associated with different survival, it is important to distinguish between the different types of carcinoma.

A large proportion of patients with gastric cancer has already reached stage IV at time of diagnosis (47% for cardia and 41% for non-cardia in 2006–2007), especially compared to countries where gastric cancer is endemic, e.g. Japan. This is due to late presentation of symptoms and the lack of pathognomonic signs together with the absence of a screening programme. The increased proportion of patients presenting with distant metastases might partially be explained by better pre-operative staging due to improved imaging modalities.

Treatment changed over the period from 1990 to 2007. Many studies have been conducted to elucidate the effectiveness of other treatment modalities. In the USA adjuvant radiotherapy is given according to the SWOG-trial,[28] and in the East an extended lymphadenectomy is performed. In our country, standard care for curable disease, until recently, consisted of gastric resection without (neo)adjuvant therapy,[29] although in more recent years more patients are treated with chemotherapy as reflected in our results.

In our country a limited lymphadectomy is performed, for two large European studies did not prove better survival of a D2 resection versus a D1 resection. Only ~1% of all operated patients underwent a D2 resection (results not shown).

Gastric cancer remains a disease with poor survival. In Europe mortality rates decreased, although it is still 4th on the list of cancer related deaths.[1] Overall 5-year survival remained about 10% for cardia carcinoma and decreased to 14% for non-cardia carcinoma from 1990 to 2004, in comparison to 5-year survival of 10–40% in other Western countries and of 68% in Eastern countries.[30–32] These differences in

Table 4 – Risk of dying (hazard ratio) for patients with gastric adenocarcinoma, diagnosed between 1995 and 2006 in the south of the Netherlands.[a]

	HR	p-Value
Localisation		
Cardia	1.0	
Non-cardia [b]	1.0	0.4

	Cardia		Non-cardia	
	HR	p-value	HR	p-value
Age (years)				
<55	1.0	0.7	0.9	0.5
55–64[b]	1.0		1.0	
65–74	1.0	0.9	1.2	0.002
75+	1.4	0.01	1.5	<0.0001
Gender				
Males[a]	1.0		1.0	
Females	0.9	0.1	0.9	0.03
Comorbidity				
No comorbidity[b]	1.0		1.0	
One comorbid condition	1.0	0.9	1.0	0.9
Two or more comorbid conditions	1.2	0.1	1.2	0.02
Socio-economic status				
High[b]	1.0		1.0	
Intermediate	1.0	0.9	1.0	0.7
Low	1.1	0.6	1.0	0.9
Institutionalised	1.3	0.3	1.3	0.03
Stage				
I[b]	1.0		1.0	
II	1.9	0.0006	2.1	<0.0001
III	2.7	<0.0001	3.3	<0.0001
IV	5.4	<0.0001	5.1	<0.0001
Unknown	2.8	<0.0001	2.9	<0.0001
Type of resection				
Total gastrectomy	1.5	0.2	1.1	0.3
Subtotal gastrectomy[b]	1.0		1.0	
Oesophageal-cardiac	1.4	0.3	n.a.	
Multi-organ resection	1.7	0.2	1.1	0.8
Other/unspecified	2.1	0.006	2.0	<0.0001
Period of diagnosis				
1994–1997[b]	1.0		1.0	
1998–2001	0.9	0.2	1.1	0.2
2002–2006	0.8	0.01	1.0	0.7

n.a. = not applicable.
[a] Adjusted for all listed variables (tumour site only included in model for non-cardia).
[b] Reference group.

survival worldwide can be caused by (1) different disease hypothesis, due to racial and environmental differences, (2) stage migration, i.e. the extended lymphadenectomy performed in Japan can lead to better staging performance and upstaging, (3) treatment, i.e. due to different treatment better results may be obtained.[33] Verdecchia and colleagues[33] showed that nearly 60% of the variability in survival of gastric cancer between European countries could be explained by differences in age, sex, period of diagnosis, subsite of the stomach, histological subtype and stage at diagnosis.

Although 5-year crude survival analysis did not show any improvement over time, the hazard ratio slightly decreased for cardia carcinoma in the period from 1995 to 2006 after adjustment for a number of relevant patient and tumour characteristics. Survival was better for patients with a non-cardia carcinoma versus cardia carcinoma. The prognostic significance of older age and more advanced stage in our multivariable analysis is comparable to results of other studies.[16,27,31,34] Other prognostic factors associated with worse survival reported in literature are male gender, positive resection margins, positive lymph nodes or rate of positive lymph nodes.[16,27,31,34]

5. Conclusion

Age-adjusted incidence of gastric cancer decreased in the South of the Netherlands. In contrast to other reports, the proportional incidence of cardia carcinoma did not change over the past decades, besides a small increase in most recent years. Stage distribution and prognosis remained poor. Five-year survival rates remained ~10% for cardia carcinoma since 1990, but decreased for non-cardia adenocarcinoma (22–14%). It is of substantial importance to improve early detection, and to conduct prospective studies investigating the feasibility and survival benefit of (neo)adjuvant chemo(radio)therapy with standardised surgery and pathology.

Conflict of interest statement

None declared.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2010.02.013.

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