PART III

Surgical quality assurance

CHAPTER 12

Gastric cancer: decreasing incidence but stable survival in the Netherlands

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ABSTRACT

BACKGROUND

Gastric cardia and non-cardia cancer exhibit differences in biological and epidemiological features. Aims of this study were to analyze trends in incidence, stage distribution, and survival over a 20-year period in the Netherlands, separately for both types of gastric cancer.

PATIENTS AND METHODS

Data on all patients with a diagnosis of gastric cancer in the period 1989-2008 were obtained from the nationwide Netherlands Cancer Registry. Time trends in incidence (analyzed as European Standard Rate per 100,000 (ESR)) and relative survival were separately analyzed for cardia and non-cardia gastric cancer.

RESULTS

A total of 13,384 patients were included. Incidence rates per 100,000 for cardia cancer declined from 5.7 to 4.3 for males and remained stable for females (1.2). For non-cardia cancer, the incidence in males declined from 25 to 14 and in females from 10.4 to 6.9. Proportional incidence in stage IV cardia and non-cardia cancer increased in 2004-2008 (cardia 32% to 42%, non-cardia 33% to 45%). Five-year survival rates for stage I-III and X (unknown) remained stable (cardia cancer: 20%, non-cardia gastric cancer: 31%). Five-year survival for stage IV disease was 1.9% and 1.0% for cardia and non-cardia gastric cancer.

CONCLUSIONS

The incidence of gastric cancer in the Netherlands strongly decreased over the past decades, in particular for non-cardia gastric cancer. Survival remained dismal. Improvement of survival remains a challenge for the multidisciplinary team involved in gastric cancer treatment.

INTRODUCTION

Gastric cancer can be subdivided in two distinct forms according to location: cardia cancer and non-cardia cancer. These two entities are reported to have a different epidemiological and biological behavior. The declining incidence in gastric cancer throughout the world is mostly attributed to a fall in incidence of non-cardia cancer.[1-3] *Helicobacter pylori* infection is reported to be a risk factor for non-cardia cancer. It causes the formation of precancerous lesions.[4,5] Eradication of *Helicobacter pylori* in the Western world is associated with a fall in incidence of non-cardia gastric cancer. Gastric cardia cancer on the other hand is associated with obesity and gastroesophageal reflux disease.[6-8] The literature on incidence rates of cardia cancer is somewhat conflicting, with decreasing, stable and increasing incidence rates reported.[1,6,9-14]

Survival of gastric cancer remains dismal in the Western world, with reported 5-year survival rates of 10-20%,[15,16] in contrast to Asian survival rates.[17,18] This has been attributed to more aggressive surgery, differences in staging, and an intrinsic biological difference between Asian and Western gastric cancer patients.[19,20] In both the Western and Asian world survival of cardia gastric cancer is lower compared to non-cardia cancer.[10,18]

In this study, the results of the first nation-wide population-based study on incidence and survival rates for gastric cancer in the Netherlands are presented. Trends in incidence, stage distribution, and survival rates for cardia and non-cardia gastric cancer were evaluated over a period of 20 years.

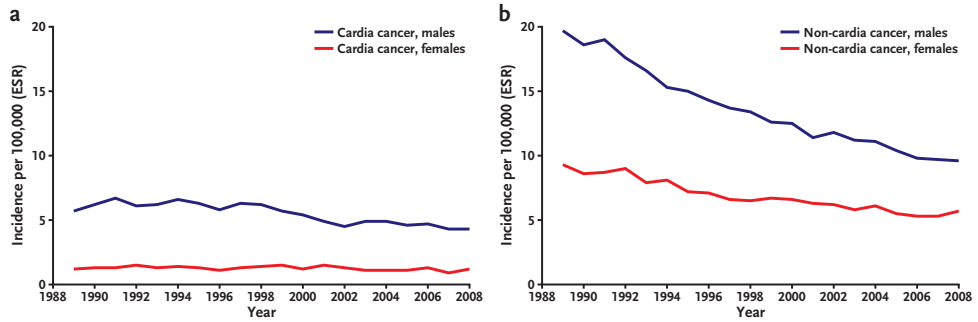
METHODS

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 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%.[21] The information on vital status was initially obtained from municipal registries and from 1994 onwards from the nationwide population registries network. These registries provide complete coverage of all deceased Dutch citizens.

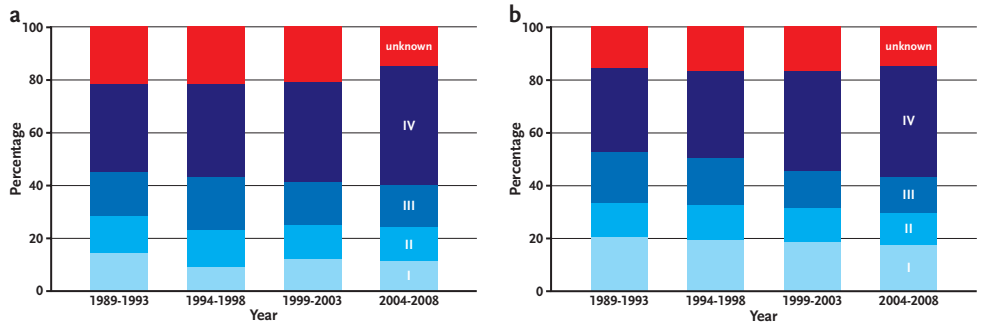
Patients diagnosed from 1989 to 2008 with a tumor of the stomach, classified as ICD-9 151 and ICD-10 C16 according to the International Classification of Diseases (ICD), were included. Tumors were staged according to the International Union Against Cancer TNM classification that was used at the date of diagnosis. Between the 4th and 5th edition TNM classification, nodal staging was changed. Starting with the 5th edition, nodal status was based on the absolute number of positive lymph nodes, rather than the location of the lymph node metastases. There were no differences between the 5th and 6th edition TNM classification. Clinical stage was used in case of missing pathological stage.[22-24] To evaluate trends over time, the study period was divided in four intervals of five years.

Figure 1. Incidence rates of (a) cardia cancer and (b) non-cardia cancer in the Netherlands, 1989-2008



ESR: European Standardized Rate per 100.000 inhabitants

Figure 2. Stage distribution per period for (a) cardia cancer, (b) non-cardia cancer



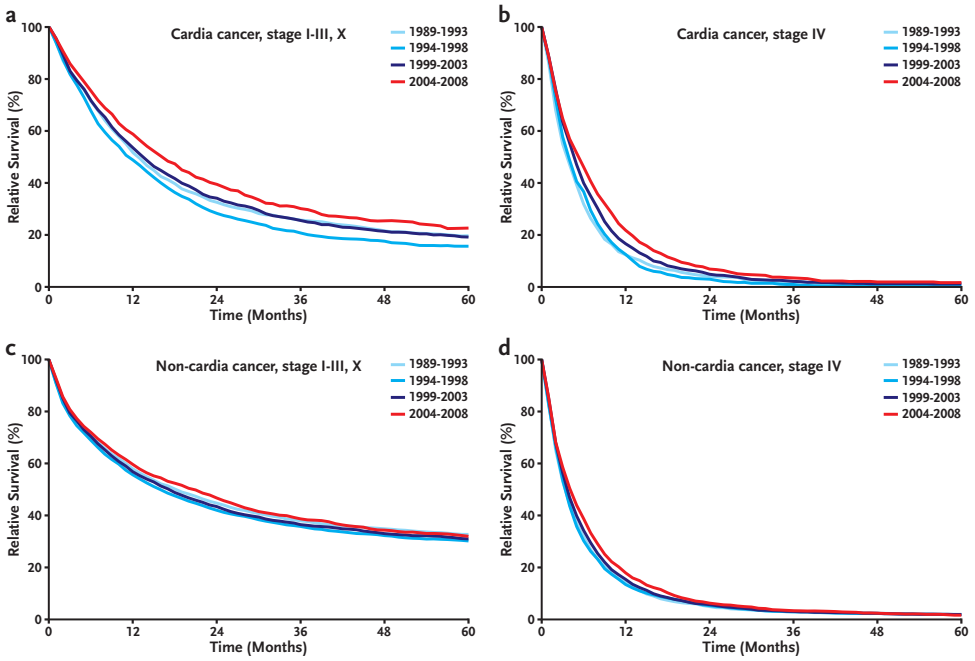
STATISTICAL ANALYSES

Annual incidence rates were calculated per 100,000 person-years, using the annual mid-year population size as obtained from Statistics Netherlands. Rates were age-standardized to European Standardized Rates (ESR). Changes were evaluated by calculating the estimated annual percentage change (EAPC) and the corresponding 95% confidence interval. To calculate this, a regression line was fitted to the natural logarithm of the rates, using the calendar year as regressor variable (i.e. $y = ax + b$ where $y = \ln(\text{rate})$ and x = calendar year, then $EAPC = 100 * (e^a - 1)$).

TNM stage group was calculated by using pathological T, N and M stage. If pathological confirmation was lacking, clinical T, N and/or M stage was used. Analyses were stratified for stage (stage I-III/X vs. stage IV). Differences in stage distribution between periods of diagnosis were tested by means of a Chi square test.

Follow-up for vital status was complete until December 31st, 2009. Traditional cohort-based relative survival analysis was performed; the number of days was calculated from the date of diagnosis until death of any cause (event) or alive at last follow-up (censored).

Figure 3. Relative survival for cardia and non-cardia cancer in the Netherlands, 1989-2008



Then, relative survival was calculated correcting for age- and gender-specific background mortality, as a proxy of disease-specific survival.

SAS software (SAS system 9.2, SAS Institute, Cary, NC) was used to perform the statistical analyses. For all analyses, a *P*-value < 0.05 was considered significant.

RESULTS

PATIENT CHARACTERISTICS AND INCIDENCE

A total of 13,384 patients diagnosed with gastric cancer were included (Table 1). The number of new cases of cardia cancer in males decreased from 2115 in 1989-1993 (annual average 423) to 2059 in 2004/2008 (annual average 412). The number of females with cardia cancer remained stable at about 133 patients per year. The number of new cases with non-cardia cancer decreased in males from 1257 to 927 per year (average of 5-year period), and from 863 to 655 in females. Median age for both cardia and non-cardia gastric cancer did not change over the years.

Age-standardised incidence rates (per 100,000 person-years) by gender are shown in Figure 1. The ESR in males decreased from 25/100,000 in 1989 to 14/100,000 in 2008, and decreased in females from 10.4/100,000 to 6.9/100,000. The estimated annual percentage change in incidence was -2.2 (95% CI -2.8 to -1.6) for males with cardia cancer, -0.94 (95% CI -1.9 to -0.02) for females, -3.8 (95%CI -4.1 to -3.6) for males with non-cardia cancer, and -2.9 (95% CI -3.2 to -2.5) for females.

TUMOR STAGE

The proportion of patients with stage IV at diagnosis (pathological or clinical) increased for both cardia (from 32% in 1989-1993 to 45% in 2004-2008, $P < 0.001$) and non-cardia cancer (from 31% in 1989-1993 to 43% in 2004-2008, $P < 0.001$), with a corresponding decrease in the percentage of patients with an unknown stage (Figures 2a and 2b).

SURVIVAL

Five-year relative survival estimates for stage I-III and stage X gastric cancer remained low between 1989 and 2008 (Figures 3a and 3c). For cardia cancer stage I-III and X, 5-year survival remained about 20%, and for non-cardia cancer stage I-III and X, 5-year survival remained about 31%. For stage IV cardia cancer, 5-year survival was 1.0%, for non-cardia cancer, this was 1.9% (Figures 3b and 3d). Changes in survival estimates between analyzed periods of diagnosis were not statistically significant.

DISCUSSION

In the Netherlands, survival of gastric cancer remains dismal and has not improved. The incidence of gastric cancer has markedly declined during the last century, a trend that has continued in the last decade. This decrease has also been reported in other parts of the world.[25] It has mainly been attributed to a fall in incidence of non-cardia cancer, which is confirmed in the present study. The incidence of cardia cancer increased in the early 90's, but since then it has been declining. The decline in incidence of non-cardia cancer was however steeper compared to cardia cancer. This results in a somewhat higher proportional incidence of cardia cancer nowadays in both genders. Some studies report an increase in cardia cancer,[2,13,26,27] although others report a stable or declining incidence.[1,9,14,28] What should be taken into account is that in several studies the exact tumor location was unspecified, thereby biasing the results. Although the classification in the register's topography rules have not changed, changes in diagnostic procedures and definitions could have caused a shift from cardia cancer to distal esophageal cancer. Previous studies conducted in the Netherlands showed a rise in the incidence of distal esophageal cancer.[14,28] Although reclassification might partly explain the increase in esophageal adenocarcinoma, it is likely that the greater part of the increase in esophageal adenocarcinoma is a true rise in disease burden. Several factors are thought to affect the incidence of gastric cancer. *Helicobacter pylori* infection leads to superficial gastritis, which might progress to atrophic gastritis and loss of acid secretion. Eventually dysplasia and gastric cancer develop, especially in the distal stomach.[4,12,29] As *Helicobacter pylori* seems to play a role in early carcinogenesis, eradication probably will not prevent the development of gastric cancer in patients with gastritis due to *Helicobacter pylori*. Due to changes in lifestyle and dietary pattern (improved sanitation) the prevalence of *Helicobacter pylori* infection has declined.[30,31] Increased consumption of fruit and vegetables and lower salt consumption have also reduced the incidence of gastric cancer.[32]

Table 1. Sex and age distribution for cardia and non-cardia cancer in the Netherlands, 1989-2008 (N = 13,384)

	1989-1993		1994-1998		1999-2003		2004-2008	
	N	%	N	%	N	%	N	%
Cardia cancer								
Sex								
male	2115	*76*	2330	*78*	2080	*75*	2059	*76*
female	668	*24*	675	*22*	701	*25*	665	*24*
Age								
<55	382	*14*	476	*16*	421	*15*	413	*15*
55-64	636	*23*	590	*20*	620	*22*	600	*22*
65-74	905	*33*	1006	*33*	866	*31*	802	*29*
≥75	860	*31*	933	*31*	874	*31*	909	*33*
median age	68.8		69.7		69.2		69.5	
Non-cardia cancer								
Sex								
male	6287	*59*	5338	*59*	4870	*58*	4634	*59*
female	4314	*41*	3790	*41*	3492	*42*	3277	*41*
Age								
<55	1204	*11*	1042	*11*	1037	*12*	929	*12*
55-64	1715	*16*	1462	*16*	1370	*16*	1344	*17*
65-74	3224	*30*	2757	*30*	2477	*30*	2273	*29*
≥75	4458	*42*	3867	*42*	3481	*42*	3365	*43*
median age	72.7		72.9		72.8		73.1	

Cardia cancer differs from non-cardia cancer, biologically and epidemiologically. Two distinct etiologies have been described for cardia cancer. The first etiology is associated with an *Helicobacter pylori* infection. It causes atrophic gastritis and eventually develops to gastric cancer of the diffuse and intestinal tumor type (according to the Lauren classification)[33], suggesting a similar pathway as for non-cardia cancer.[12,34] The second etiology is associated with obesity and gastro-esophageal reflux disease which are independent risk factors for cardia cancer. However, the relative risk for cardia cancer is not as high as the risk for adenocarcinoma of the esophagus.[6-8,12,34] In the current study, a difference in age distribution was found between cardia and non-cardia cancer. Non-cardia cancer is diagnosed more often in people of an older age (73.1 versus 69.5 years). Cardia cancer prevalence is more equally divided between the age groups. The male-female ratio is 3:1 for cardia cancer and 1.5:1 for non-cardia cancer. This is confirmed in other studies.[9,11]

For both types of gastric cancer, a rise in proportional incidence of stage IV cancer at the time of diagnosis was observed in the present study. In the period 2004-2008, at the time of diagnosis more than 40% of patients had developed stage IV gastric cancer in both cardia and non-cardia cancer. Due to late presentation of symptoms and lack of pathognomonic signs gastric cancer is more likely to be detected in a late stage. The rise in stage IV cancer in our study might be due to stage migration; because of improved imaging modalities distant metastases are seen at an earlier stage so more patients are classified in a more advanced stage group compared with earlier years when imaging

techniques were less effective. In countries where gastric cancer is endemic, such as Japan, screening programs have been developed, and gastric cancer is detected in a much earlier stage.[35] In the Netherlands, this would not be cost-effective due to the lower incidence rates. Differences in race, age and sex distribution, histological distribution, staging (leading to stage migration), and treatment all may be of influence on the survival discrepancy between East and West.

During the study period, the prognosis of gastric cancer in the Netherlands remained dismal. Survival for patients with both cardia and non-cardia cancer did not improve over time. The prognosis for non-cardia cancer was better compared to cardia cancer, with five-year survival rates of 31% versus 20% for stage I-III and X. Stage IV cardia and non-cardia cancer both have a poor 5-year survival rate of 1-2%. The worse survival of cardia cancer can largely be explained by different histopathological characteristics. Cardia cancer is mostly detected in a more advanced stage, with a deeper penetration of the stomach wall and more tumor positive lymph nodes. Furthermore, it is more often poorly differentiated and has a greater diameter.[18,36] In a study analyzing all types of gastric cancer, the presence of cardia cancer was an independent risk factor for lower survival, indicating this might be a more aggressive form of gastric cancer.[18] As it is not cost-effective to perform a screening program for early detection of gastric cancer, it is imperative to improve treatment to increase survival. Centralization could be a solution and has been initiated in the Netherlands as of 2012. Improvement of the surgical and pathological technique as well as improvement of perioperative care are essential to improve survival.

Over the past 20 years, the age-adjusted incidence rate of gastric cancer in the Netherlands has declined for both males and females. Survival remained dismal, with 5-year survival rates of 20% for stage I-III and X cardia cancer and 31% for non-cardia cancer. Improving gastric cancer care on a nationwide level remains a challenge for the multidisciplinary team treating gastric cancer patients.

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