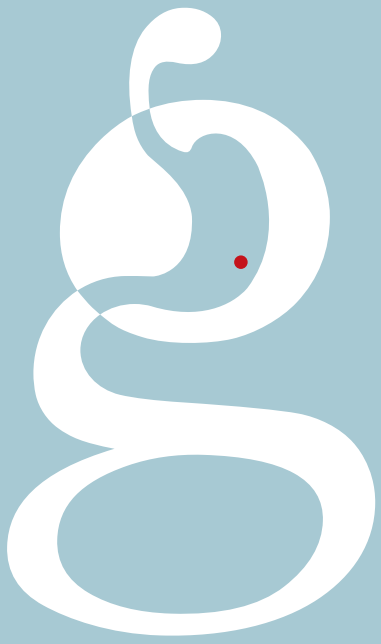

gastric cancer

trends and treatment strategies in the Netherlands:

challenges ahead

Anneriet Elisabeth Dassen

Gastric Cancer Trends and Treatment Strategies in the Netherlands: Challenges Ahead

Anneriet Dassen

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Gastric Cancer Trends and Treatment Strategies in the Netherlands: Challenges Ahead

Trends en behandelingsstrategieën bij maagkanker in Nederland: nog vele uitdagingen te gaan

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Chapter 1
Introduction

GASTRIC CANCER TRENDS AND TREATMENT STRATEGIES IN THE NETHERLANDS: CHALLENGES AHEAD

INTRODUCTION

In this thesis trends and treatment of gastric cancer in the Netherlands are discussed. Gastric cancer is a challenging disease, because outcome with respect to postoperative mortality and long-term survival remains dismal; improvement of diagnostics and treatment is therefore of utmost importance. The fact that gastric cancer is becoming a rarer disease may hamper improvement, since a lower incidence might decrease experience with and attention for this disease. Although improved, postoperative mortality is still high in the Netherlands in comparison to countries in the Far East and specialized centers [1-4]. Five-year survival rates are comparably lower (21% versus 69%) [1;5]. Improvement of the aforementioned mortality and survival rates has yet to be realized. Several treatment modalities have been subject of clinical studies.

As surgery is still the only treatment available for cure from gastric cancer, in the 20th century two surgical phase III trials have been conducted in Europe to determine the survival benefit of an extended lymphadenectomy, the so-called D2 lymphadenectomy. Because in both studies postoperative mortality was high after a D2 resection (10-13%) [6;7], nowadays, therefore, in the Netherlands a limited lymphadenectomy is most often performed. The role of perioperative chemotherapy and/or chemoradiotherapy has been investigated as well, and led to changes in treatment strategies in the Western world [8;9]. In the Netherlands, patients usually undergo perioperative chemotherapy, mainly consisting of epirubicin, a platinum based chemotherapeuticum and 5 Fluorouracil (5-FU) or analogue [10].

In the first two parts of this thesis, an evaluation of gastric cancer with respect to incidence, mortality, survival, staging and treatment is described. In the latter part, quality of care is evaluated and the results of the DoCCS study, a multicenter phase II feasibility study of neoadjuvant *do*cetaxel, *c*isplatin and *c*apecitabine and protocolized *s*urgery in resectable gastric cancer are described.

TRENDS IN INCIDENCE AND SURVIVAL

Since the beginning of the past century, incidence in gastric cancer has decreased dramatically, due to better hygiene, alteration of food conservation resulting in a lower prevalence of *Helicobacter Pylori* infection and a different dietary pattern. *H. Pylori* is associated with the intestinal type of gastric cancer, mainly in distal gastric cancer [11]. With the

decrease of distal gastric cancer, proximal gastric cancer incidence increased relatively in the latter part of the 20th century. Gastric cardia and non-cardia cancer are likely to be different diseases, as epidemiological as well as histological features differ between the two types. In Chapter 2, incidence and survival rates have been investigated for cardia and non-cardia cancer separately. This study is based on the nationwide cancer registry in the Netherlands. Chapter 3 handles the epidemiologic changes of gastric cancer in the Southern part of the Netherlands where registration has been implemented a long time ago. Changes in treatment strategies, with respect to perioperative therapy and type of surgery are described as well.

STAGING IN GASTRIC CANCER

For adequate treatment strategies, it is important to have valuable information about Tumour, Nodal and distant Metastasis stage (according to the Union Internationale Contre le Cancer/ American Joint Committee on Cancer, UICC/AJCC) [12]. Patients with well-differentiated non-ulcerating tumours infiltrating mucosa or the superficial submucosa, and less than 3 cm in circumference can be treated with endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). Gastric resection together with a lymphadenectomy has high morbidity and mortality rates, and in case of distant metastases it is undesirable to expose a patient to this type of surgery and its subsequent risks without any benefits and chance for curation. Staging in gastric cancer is difficult, currently being accomplished by the use of endoscopy, followed by a CT scan of the abdomen and thorax. Endoscopic ultrasonography can be performed to determine T-stage, in case of a probable T1 stage, but is unreliable for determining N-stage [10;13]. CT-scan is used to determine T, N and M stage, but accuracy is moderate. Accuracy for other imaging modalities, like MRI and abdominal ultrasonography is moderate as well [14]. In Chapter 4, the results of a review investigating sensitivity and specificity for FDG-PET to stage gastric cancer are described.

In breast cancer, sentinel lymph node biopsy to determine axillary lymph node metastasis is highly accurate and therefore common practice. Sentinel lymph node biopsy is used in melanoma as well [10;15]. The sentinel lymph node is regarded as the first lymph node a tumour will drain to and is therefore the detector of lymph node metastasis. This concept has been explored in gastric cancer, to determine the N-stage in patients with T1 disease. As mentioned above, T1 disease can be treated with EMR or ESD. In Chapter 5, the results of a systematic review regarding the role of sentinel lymph node biopsy in early gastric cancer (EGC), defined as T1Nany, is described.

Next to preoperative staging, postoperative staging is problematic as well. In the 6th TNM [16] classification, N1 stage was defined as 1-6 positive lymph nodes found, N2 stage

as 7-15 and N3 stage as more than 15 positive nodes. To be diagnosed as N3 stage, and subsequently stage IV disease, at least 16 lymph nodes should be harvested during surgery and investigated by the pathologist. Even though in the 7th TNM [12] classification N-stage has changed, with N3a stage defined as 7-15 metastatic lymph nodes and N3b more than 15 metastatic lymph nodes, in the overall TNM classification no discrimination is made between N3a and N3b stage. The lymph node yield has consequences for long-term survival on patient group basis due to stage migration effect and on individual patient basis due to therapeutic effect. In the West, the lymph node yield is (mostly) lower than the recommended 15 [17]. This has probably a dual cause, i.e. due to inadequate lymphadenectomy and due to inadequate pathological examination. This subject is addressed to in Chapter 6.

Not only in the Netherlands but in most countries in the 'West' harvesting of lymph nodes remains challenging for surgeons and pathologists. New staging systems have been proposed, the lymph node ratio (LNR) is one of them. LNR is defined as the amount of positive lymph nodes divided by the amount of retrieved lymph nodes. This new staging modality could be a better predictor of long-term survival, even if less than the recommended number of lymph nodes has been found during pathological examination. Although shortly discussed in chapter 6, this subject is further outlined in Chapter 7.

TREATMENT AND QUALITY OF CARE IN GASTRIC CANCER

With a higher lymph node yield, higher survival rates are described in specialized centers with high volume surgery. Short-and long-term survival are besides patient- and tumour characteristics not only dependent on the surgeon, but also on the surgical and anesthesia team. Furthermore, care of the intensive care unit and surgical ward are of utmost importance. It is believed that exposure to a higher volume of this type of surgery can ameliorate the whole process in a hospital with a subsequent positive influence on mortality and survival. In several countries, centralization of low volume surgery has been realized. In the Netherlands, since 2012, surgery for gastric cancer has been restricted to hospitals operating at least 10 patients with gastric cancer per year, and as of 2013, this amount has been raised to 20 resections per year. In Chapter 8, the effect of the surgical volume per hospital on mortality and survival rates for gastric and oesophageal cancer is evaluated, with all pitfalls accounted for.

Halfway through the past decade the results of the MAGIC trial [9] were published. In this phase III trial, patients were treated with perioperative chemotherapy, consisting of epirubicine, cisplatin and 5-FU. Although this was a demanding treatment schedule, a survival benefit was seen in the group of patients treated with chemotherapy. This led

to changes in national and international guidelines for the treatment of curable gastric cancer. To define the changes in treatment modalities and to establish its influence on long-term survival we conducted a population based investigation, these results are presented in Chapter 9.

DoCCS-study

The MAGIC trial chemotherapy schedule was challenging for patients with respect to toxicity. From the 250 patients assigned to receive chemotherapy, 42% completed the whole regimen [9]. Even so, there was a survival benefit which could be related to the pre-operative chemotherapy. Gastric cancer surgery has high morbidity and mortality rates, and it can be difficult for patients with a partial stomach or no stomach left to undergo postoperative chemotherapy. Other chemotherapy schedules have been investigated and a docetaxel based schedule gave promising results [18;19]. This led to the design of the DoCCS-study, a phase II study, in which patients are treated with four cycles of neo-adjuvant docetaxel, cisplatin and capecitabine. As mentioned above, improvement of surgery, especially with respect to the lymphadenectomy, is challenging. Although results from specialized centers and high volume countries favour a D2 lymphadenectomy [2], randomized controlled trials in the West have shown worse survival rates. The high postoperative mortality rates after a D2 lymphadenectomy were mainly attributed to the concomitant distal pancreatectomy and/or splenectomy [6;7]. To improve the retrieved lymph node count and to prevent high postoperative mortality rates we designed an adjusted lymphadenectomy. Lymph node stations (Japanese classification) are resected according to preferential spreading depending on tumour location, without the need of a distal pancreatectomy and/or splenectomy. The results of the feasibility of the treatment with neoadjuvant chemotherapy and the D1*extra* lymphadenectomy are described in subsequently Chapter 10 and 11.

During the DoCCS study a rare and often fatal complication occurred in two patients. Both suffered from small bowel necrosis very likely caused by enteral feeding, leading to immediate surgery with additional small bowel resection. Despite all efforts, one patient died due to this complication. In Chapter 12 these cases are described and the relation with the above described treatment strategy is discussed.

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Part I

Trends in incidence and survival

Chapter 2

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 across the world. 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.

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 47.295 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 to 7. 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.

Conclusion

The incidence of gastric cancer in the Netherlands markedly decreased over the past decades, in particular of non-cardia 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, *i.e.* gastric cardia cancer and gastric non-cardia cancer. These two entities are reported to show different epidemiological and biological behavior. The declining incidence in gastric cancer [1] throughout the world is mostly attributed to a fall in incidence of non-cardia cancer [2;3]. The literature on incidence rates of cardia cancer is somewhat conflicting, with decreasing, stable and increasing incidence rates reported [4-8]. This in contrast to adenocarcinoma of the distal oesophagus which has increased markedly [9-11].

Survival of gastric cancer remains dismal in the Western world, with reported 5-year survival rates of 10-30% [12], in contrast to Asian survival rates (69%) [13]. The latter has been attributed to the availability of screening programs, more aggressive surgery, differences in staging, and an intrinsic biological difference between Asian and Western gastric cancer patients [14;15]. In both Western and Asian countries survival of cardia gastric cancer is lower compared to non-cardia cancer [16;17].

In this paper, the results of this nation-wide population-based study on incidence and survival rates for gastric cancer in the Netherlands are presented. Trends in incidence, mortality, 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, haematology departments and radiotherapy institutions. Completeness is estimated to be at least 95% [18]. The information on vital status was initially obtained from municipal registries and from 1994 onwards from the nationwide population registries network. Both these registries provide complete coverage of all deceased Dutch citizens. Disease specific mortality rates were obtained from Statistics Netherlands (CBS).

Patients diagnosed from 1989 to 2008 with a tumour of the stomach, classified as ICD-9 151 and ICD-10 C16 according to the International Classification of Diseases (ICD), were included. Tumours 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, the classification was changed for nodal staging. Starting with the 5th edition, nodal (N) 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 group was used in case of missing pathological TNM stage group [19-21]. Stage X was assigned to patients with unknown stage. To evaluate trends over time, the study period was divided in four intervals of five years.

Statistical analyses

Annual incidence and mortality rates were calculated per 100,000 person-years, using the annual mid-year population size as obtained from Statistics Netherlands. Rates were age-standardised to European Standardised 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(rate) and x = calendar year, then EAPC = 100 * (ea – 1)).

TNM stage 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 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.

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 47.295 patients diagnosed with gastric cancer were included (Table 1). The incidence of cardia cancer decreased in males, and remained stable in females. The incidence of non-cardia cancer decreased in both males and females. The median age for both cardia and non-cardia cancer remained stable (Table 1).

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 10/100.000 to 7/100.000. The estimated annual percentage change in incidence was -3.4 (95% CI -3.6 to -3.2) for males, -2.6 (95% CI -2.9 to -2.2) for females, -2.2 (95% CI -2.8 to -1.6) for males with cardia cancer, -0.94 (95% CI -1.9 to -0.02)

Table 1. Age and gender distribution of all patients with gastric cancer.

Cardia								
	1989-1993		1994-1998		1999-2003		2004-2008	
Age (yrs)	N	%	N	%	N	%	N	%
<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
Gender								
Male	2115	76	2330	78	2080	75	2059	76
Female	668	24	675	22	701	25	665	24
Non-cardia								
Age (yrs)	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
<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
Gender								
Male	6287	59	5338	59	4870	58	4634	59
Female	4314	41	3790	41	3492	42	3277	41

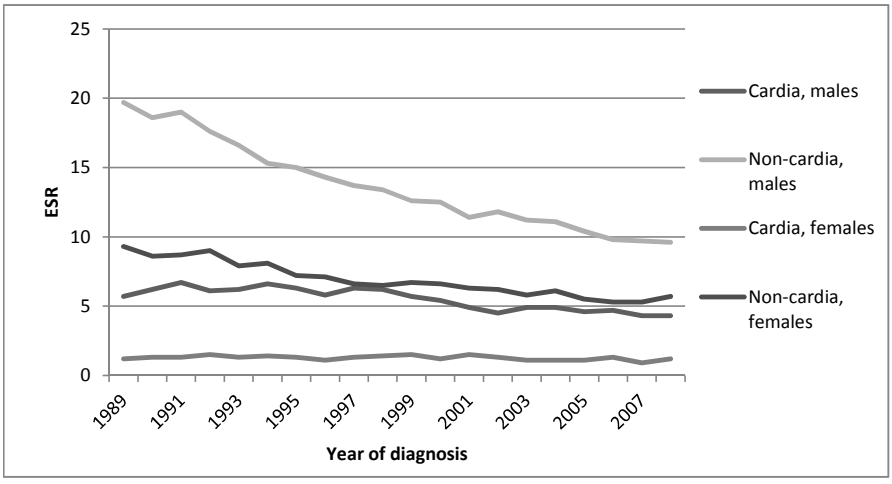

Figure 1. Trends in incidence according to location and gender, the Netherlands 1989-2008.
ESR=European Standardized Rate per 100.000 inhabitants

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. Age-standardised mortality rates declined for both men (from 20.8 to 9.2) and women (from 8.2 to 4.3).

Tumour 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*> 0.0001) and non-cardia cancer (from 31% in 1989-1993 to 43% in 2004-2008, *P*> 0.0001), with a corresponding decrease in the percentage of patients with an unknown stage (Figures 2a and 2b).

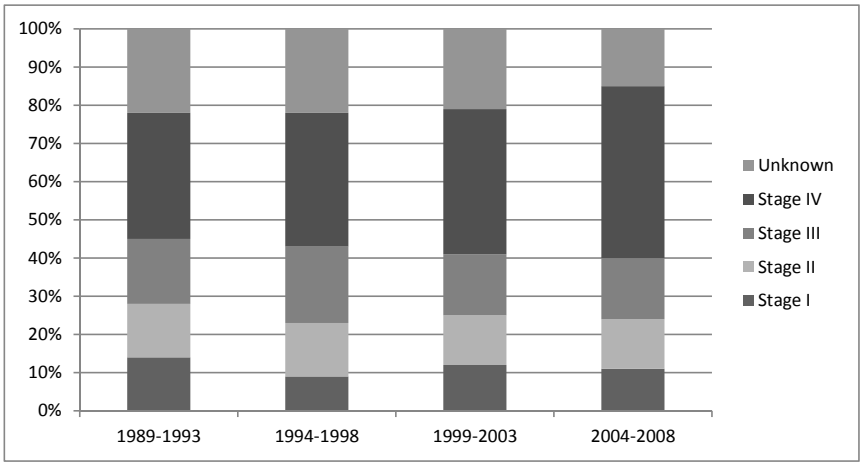

Figure 2a. Stage distribution according to period, cardia

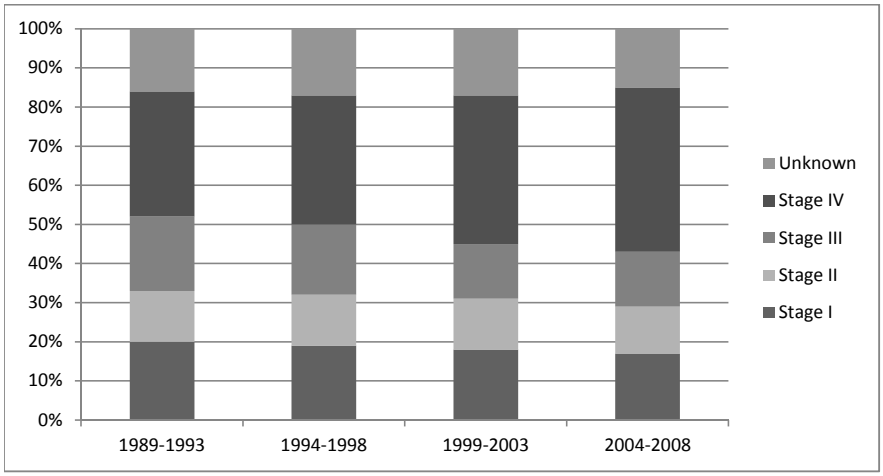

Figure 2b. Stage distribution according to period, non-cardia

Survival

Five-year relative survival estimates for stage I-III and stage X gastric cancer remained low between 1989 and 2008 (figure 3a, b, c and 3d). 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%. Changes in survival estimates between analyzed periods of diagnosis were not statistically significant.

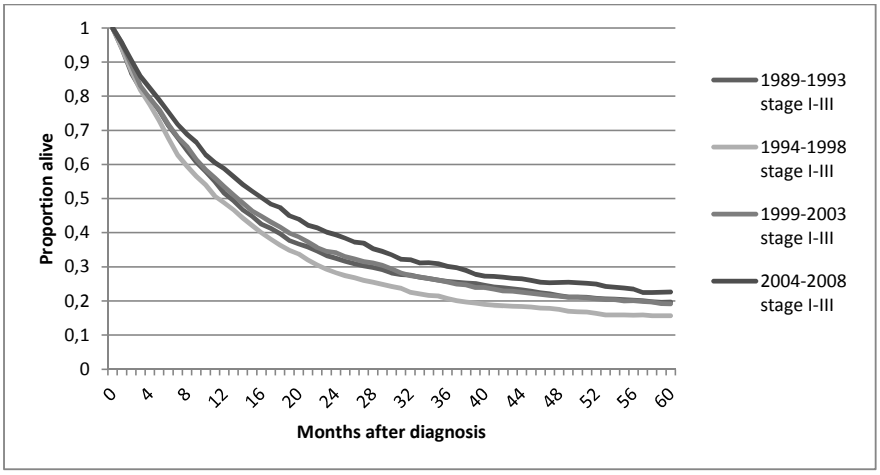

Figure 3a. Relative survival stage I-III cardia cancer according to period

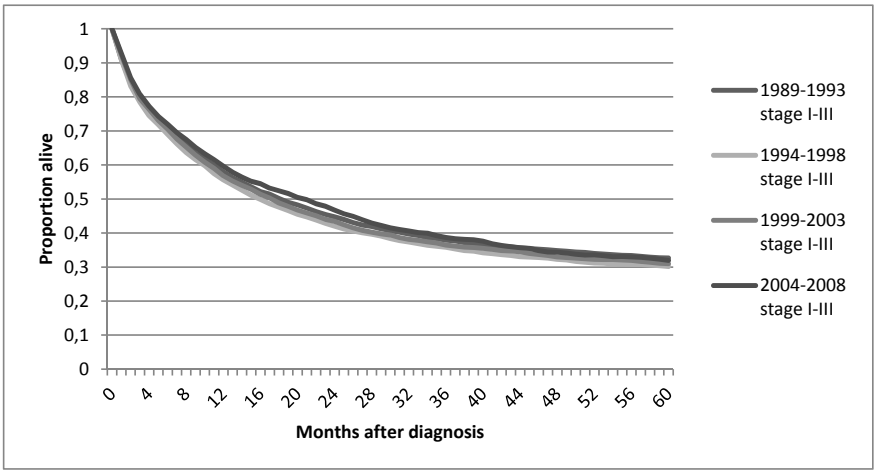

Figure 3b. Relative survival stage I-III non-cardia cancer according to period.

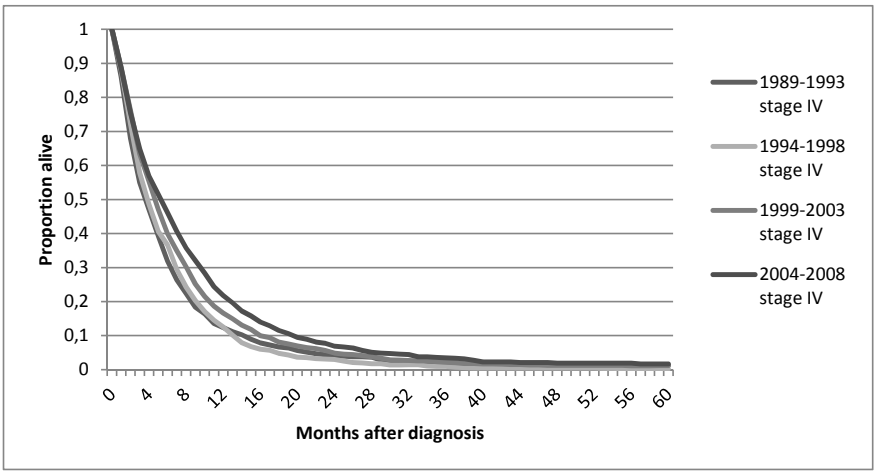

Figure 3c. Relative survival stage IV cardia cancer according to period

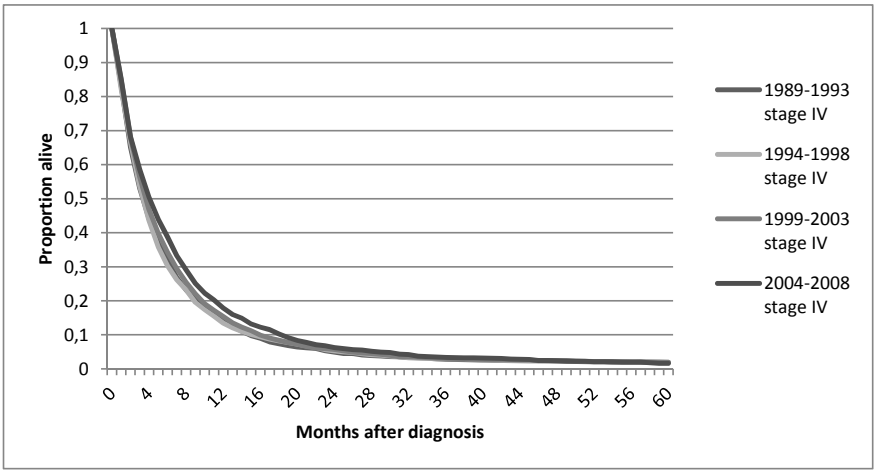

Figure 3d. Relative survival stage IV non-cardia cancer according to period

DISCUSSION

In the Netherlands, survival of gastric cancer remains dismal and has not improved during the past two decades. as a result of differential epidemiological and clinical changes. The incidence of gastric cancer has markedly declined during the last century [22], mainly due to a fall in incidence of non-cardia cancer, which is confirmed in the present study. The incidence of cardia cancer increased in this study 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 [23;24], although others report a stable or declining incidence [25;26]. However, in several if not most studies the exact tumour location was often unspecified, thereby potentially biasing the results. In the current study, the distinction between cardia and non-cardia cancer was based on the International Classification of Disease classification system, which does not incorporate the nowadays frequently used Siewert classification. Although the classification in the registry's topography rules have not changed, changes in diagnostic procedures and definitions could have caused a shift from cardia cancer to distal oesophageal cancer. Previous studies conducted in the Netherlands showed a marked rise in incidence of distal oesophageal cancer [27;28]. Although reclassification might partly explain the increase in oesophageal adenocarcinoma, it is likely that the greater part of the increase in oesophageal adenocarcinoma is a true rise in disease burden. Finally, in the 7th TNM classification, a tumour arising in the proximal 5 cm of the stomach and crossing the gastro-oesophageal junction is classified as oesophageal carcinoma. This further could influence the change in the incidence of oesophageal and cardia cancer in the future.

Several factors are thought to affect the incidence of gastric cancer. *Helicobacter pylori* infection leads to chronic gastritis, which may progress to atrophic gastritis, intestinal metaplasia and loss of acid secretion. Eventually dysplasia and gastric cancer develop, especially in the distal stomach [29-31]. Eradication of *Helicobacter pylori* in patients with early gastric cancer substantially decreased the risk of development of metachronous gastric cancer, which suggests that eradication therapy has played a role in the decline in gastric cancer incidence [32]. Due to changes in lifestyle (i.e. improved hygiene and sanitation) and dietary pattern the prevalence of *Helicobacter pylori* infection has declined. Also, increased consumption of fruit and vegetables and lower salt consumption have reduced the risk of gastric cancer [33]. Cardia cancer differs from non-cardia cancer, biologically and epidemiologically. Two distinct etiologies have been described for cardia cancer. The first is associated with an *Helicobacter pylori* infection, suggesting a similar pathway as for non-cardia cancer [34;35]. The second etiology is associated with a high BMI and gastro-oesophageal reflux disease which are independent risk factors for cardia cancer. A decreasing prevalence of *Helicobacter pylori* in combination with increasing prevalence of obesity in the Netherlands may explain the stabilization of cardia cancer incidence in our study during recent years.

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. 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 such as computed tomography 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 sensitive. In the studied period, 3 editions of the TNM classification were used in staging gastric cancer. In each consecutive classification stage IV disease was applied to a 'lower' T and N stage, which could have led to a higher proportion of patients with stage IV disease in this study. In countries where gastric cancer is endemic, such as Japan, screening programs have been developed[36], and gastric cancer is detected in a much earlier stage. In the Netherlands, this would not be cost-effective due to the much lower incidence rates. Besides differences in race, age, sex distribution and histological distribution, differences in staging (leading to stage migration) and treatment may be of influence on the survival discrepancy between East and West.

Over the study period, the prognosis of gastric cancer in the Netherlands remained dismal both for cardia and for non-cardia cancer. The prognosis for cardia cancer was worse compared to non-cardia cancer, which 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 tumour positive lymph nodes. Furthermore, it is more often poorly differentiated and has a larger diameter [37;38]. 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 [39]. As it is not cost-effective to perform a screening program for early detection of gastric cancer in a low incidence population, it is imperative to improve treatment to increase survival. Centralization may be part of a solution. Although a recent Dutch study showed no benefit of gastric cancer surgery in high volume versus low volume hospitals, due to a low percentage of high volume surgery, it has shown its benefit in oesophageal cancer and cancer of the proximal gastric cardia[40;41]. Centralization for gastric cancer has been implemented since 2012. Improvement of the surgical and pathological technique as well as improvement of perioperative care is essential to improve survival.

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Chapter 3

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=4 797). Trend analyses were conducted for incidence, mortality, tumour and patient characteristics, treatment, and crude overall survival, according to tumour location (cardia vs. non-cardia). Temporal changes in the odds of undergoing surgery and the risk of death were analyzed by means of multivariable regression methods.

Results

Age-standardised incidence decreased among males (24 to 12 per 100 000 inhabitants) and females (10 to 6); mortality rates decreased at a similar pace. The proportion of cardia tumours remained stable. Stage distribution worsened over time among patients with cardia (stage I and II: 32% in 1990-93 and 22% in 2006-07, p=0.005) and non-cardia (stage IV: 33% in 1990-93 and 40% in 2006-07, 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 localization. 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 standardized surgery and pathology.

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 criticized since chemoradiotherapy mostly corrected for incomplete surgery (Do 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.

METHODS

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.

Between 1990 and 2007, 4 797 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 of the cancer registry. Registration takes place 6 to 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 of January 2007 was assessed on 1st of 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 neighborhood 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 3 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].

Analysis

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 standardized, using the European Standardized Rate (ESR). Trends in subsite distribution are shown as the proportional distribution of tumours arising in the cardia (comprising gastro-esophageal 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 localization. Data on co-morbidity are shown since the period 1994-1997.

Trends in proportional stage distribution stratified by cardia vs. non-cardia tumour localization are shown as the proportional distribution of the Tumour Node Metastasis (TNM) stage in the respective period. Stage was designated postoperatively, if unknown, then preoperative stage was 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 vs. non-cardia tumour localization. Changes in management of these

patients were tested using a Chi^2 test. The chance of undergoing surgery for patients with stage I-III gastric cancer was tested by means of a multivariable logistic regression, for cardia and non-cardia tumour localization. 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 of 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 vs. 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 co-morbidity.

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).

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 (figure 1). For females, the incidence decreased from 10 to 6 patients per 100 000 inhabitants. Age-

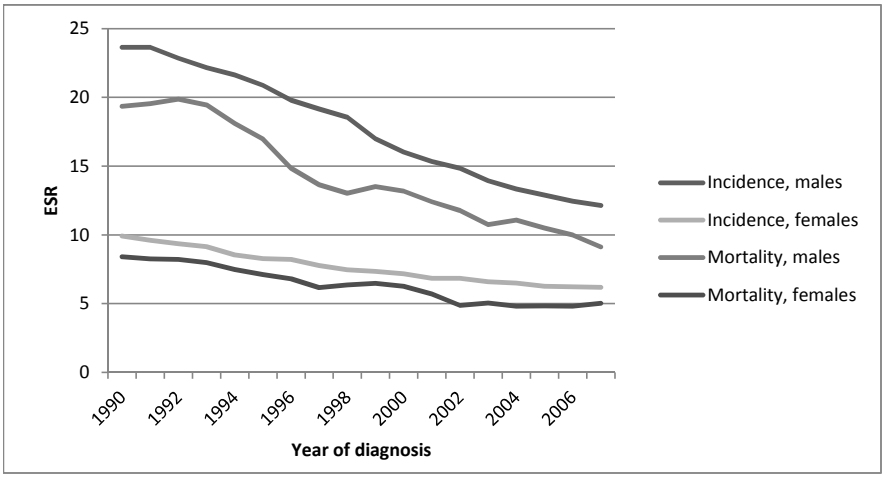

Figure 1. Incidence of gastric adenocarcinoma per 100.000 person-years in the south of the Netherlands, according to gender (European Standardised Rate (ESR), 5-year moving averages).

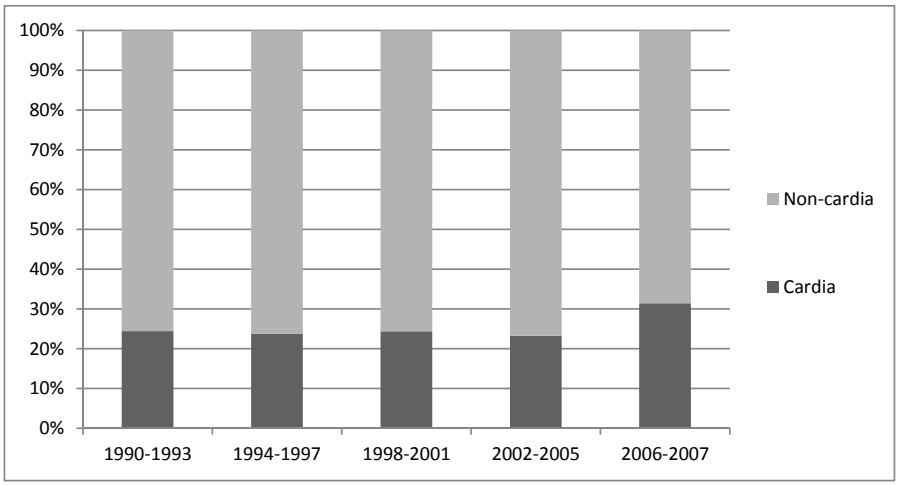

Figure 2. Proportional subsite distribution of newly diagnosed gastric adenocarcinoma according to period of diagnosis.
Proportional change over time tested by means of Chi2 test, p=0.3.

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

	1990-1993	1994-1997	1998-2001	2002-2005	2006-2007	p-value[b]
Age (yrs)						
<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 (37)	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]

[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.

Table 1b. General patient characteristics of patients diagnosed with gastric adenocarcinoma in the south of the Netherlands, according to *non-cardia* and period of diagnosis (percentages in parentheses).

	1990-1993	1994-1997	1998-2001	2002-2005	2006-2007	p-value[b]
Age (yrs)						
<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.

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 (figure 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 1a and b for patients diagnosed since 1990, for cardia and non-cardia tumours separately. Since 1994-97 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.

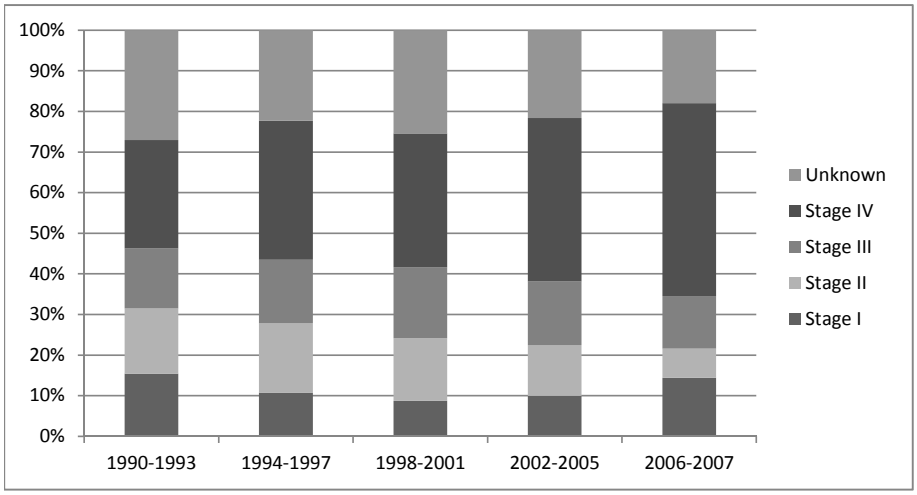

Figure 3a. Proportional stage distribution of newly diagnosed patients with *cardia* gastric adenocarcinoma in the south of the Netherlands, according to period of diagnosis. Proportional change over time tested by means of Chi^2 test, p=0.005.

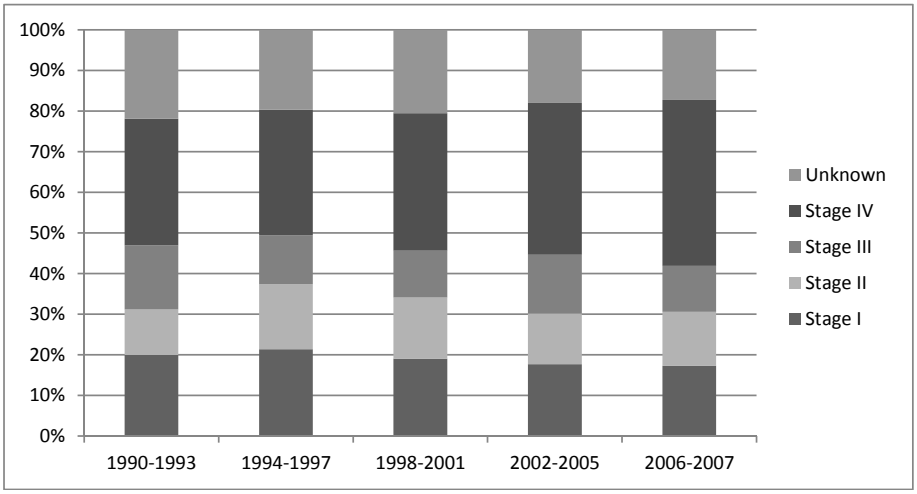

Figure 3b. Proportional stage distribution of newly diagnosed patients with *non-cardia* gastric adenocarcinoma in the south of the Netherlands, according to period of diagnosis. Proportional change over time tested by means of Chi^2 test,p=0.003.

The proportional stage distribution worsened over time among patients with a cardia (proportion stage I and II: 32% in 1990-93 vs. 22% in 2006-07, p=0.005) tumour (figure 3a). Among patients with a non-cardia tumour location, there was a rising proportion of patients presenting with stage IV (31% in 1990-1993 vs. 40% in 2006-2007, p=0.003) (figure 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

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

		1990-1993	1994-1997	1998-2001	2002-2005	2006-2007	p-value[c]
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

[a] Percentages in parentheses
[b] Postoperative 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

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 stage I, stage II, and stage IV patients with cardia cancer (table 2a and b). Resection rates were lower among patients with a tumour located in the cardia. The proportion of patients receiving (neo)adjuvant chemotherapy increased

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

		1990-1993	1994-1997	1998-2001	2002-2005	2006-2007	p-value [c]
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] Postoperative 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

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 stage 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 stage 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

Table 3. Odds ratio (OR) of undergoing surgery for patients with stage I-III gastric *cardia* and *non-cardia* adenocarcinoma diagnosed between 1995 and 2006 in the south of the Netherlands; logistic regression analyses adjusted for all listed variables.

	Cardia		Non-cardia	
	OR	p-value	OR	p-value
Age (yrs)				
<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

adenocarcinoma (from 22% in 1990-93 to 14% in 2002-06, p=0.004) (figure 4a and b). Five-year survival of patients with stage I-III disease who underwent surgery remained stable over time for non-cardia adenocarcinoma, and showed some fluctuations for cardia adenocarcinoma (figure 5a and b).

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.

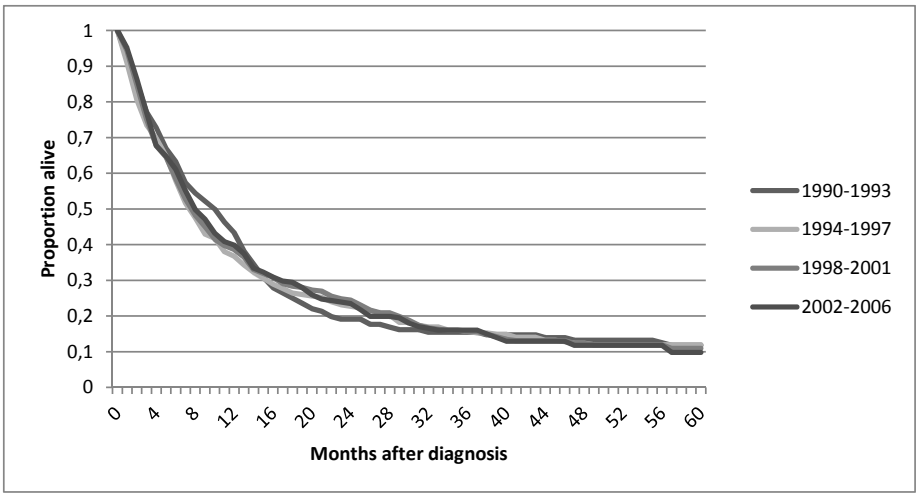

Figure 4a. Five-year crude overall survival of patients with gastric *cardia* adenocarcinoma, according to period of diagnosis. p=0.15.

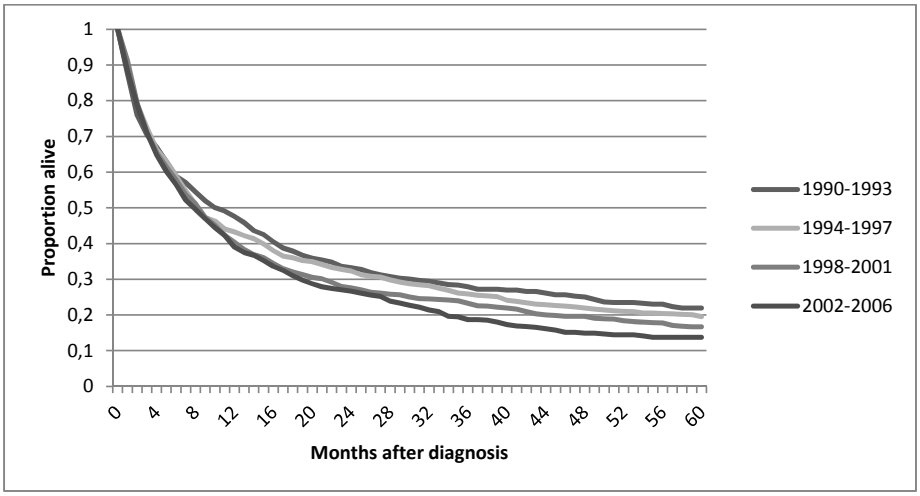

Figure 4b. Five-year crude overall survival of patients with gastric *non-cardia* adenocarcinoma, according to period of diagnosis. p= 0.004.

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 2 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.

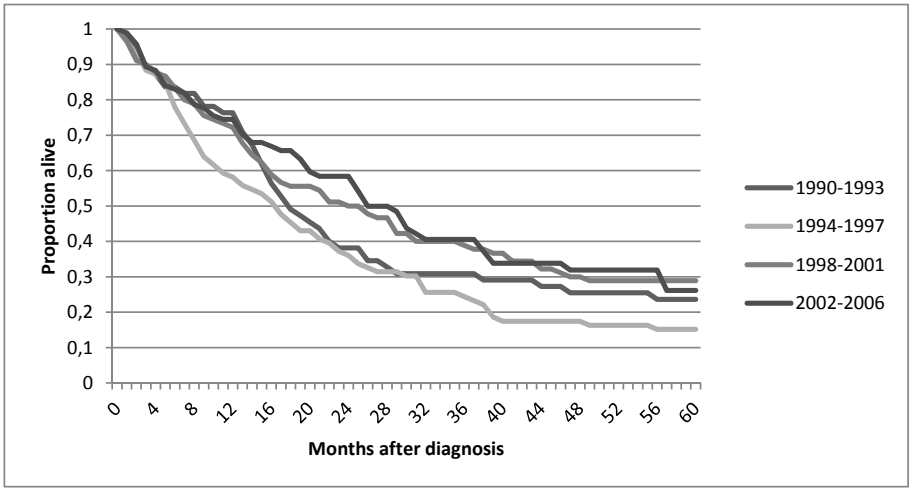

Figure 5a. Five-year crude overall survival of patients with stage I-III gastric *cardia* adenocarcinoma who underwent surgery, according to period of diagnosis. p=0.01.

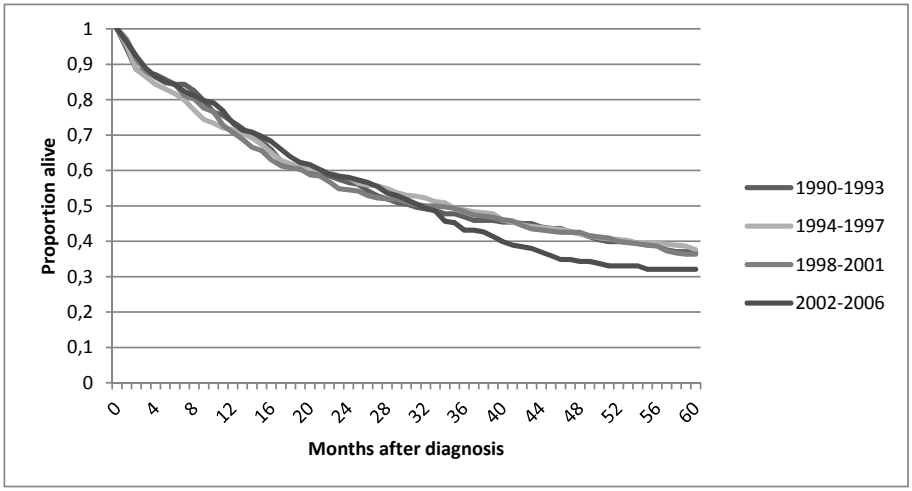

Figure 5b. Five-year crude overall survival of patients with stage I-III gastric *non-cardia* adenocarcinoma who underwent surgery, according to period of diagnosis. p=0.8.

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		
Cardia	1.0			
Non-cardia [b]	1.0	0.4		
	Cardia		Non-cardia	
	HR	p-value	HR	p-value
Age (yrs)				
<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

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

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 localization.

Since the second half of the previous century there has been a dramatically decline worldwide in the incidence and mortality rates of gastric carcinoma . Our and previous studies in the Netherlands confirmed these trends [15]. 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 esophageal 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-esophageal junction should be coded as cardiacarcinoma. Throughout the years, there was more awareness of the difference between distal esophageal 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 differrence 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 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 program. 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 [8], 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 [28], 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 vs. 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 [29-31]. These differences in 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 [32]. Verdecchia and colleagues [32] 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 noncardia carcinoma vs. 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;30;33]. 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;30;33].

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 to 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 standardized surgery and pathology.

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Part II

Staging in gastric cancer

Chapter 4

FDG-PET has no definite role in preoperative imaging in gastric cancer

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ABSTRACT

Background

Gastric cancer is fourth on the incidence list of cancers worldwide with a high disease-related mortality rate. Curation can only be achieved by a radical resection including an adequate lymphadenectomy. However, prognosis remains poor and cancer recurrence rates are high, also due to lymph node metastases. To improve outcome, (neo)adjuvant treatment strategies with chemo- and/or radiotherapy regimes are employed.

Aims

Accurate staging of gastric cancer at primary diagnosis is essential for adequate treatment. In this non-systematic review the role 18-F-Fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) in preoperative staging is investigated. Furthermore, the results of neoadjuvant chemotherapy-induced tumour response monitoring by FDG-PET are discussed.

Results and conclusion

It is concluded that currently FDG-PET has no role in the primary detection of gastric cancer due to its low sensitivity. FDG-PET shows, however, slightly better results in the evaluation of lymph node metastases in gastric cancer compared to CT and could have therefore a role in the preoperative staging. Improvement in accuracy could be achieved by using PET/CT or other PET tracers than FDG, but these modalities need further investigation. FDG-PET, however, adequately detects therapy responders at an early stage following neoadjuvant chemotherapy.

INTRODUCTION

Nowadays, the standard imaging tools for gastric cancer are computed tomography (CT), endoscopic ultrasonography (EUS) and sometimes diagnostic laparoscopy. These imaging modalities have a moderate degree of sensitivity and specificity in detecting lymph node metastases [1-5]. Preoperative staging is currently performed using CT of thorax, abdomen and pelvis [6]. CT is an anatomy-based diagnostic technique with a limited sensitivity for lymph node metastases due to non-enlarged tumour harbouring lymph nodes, and limited specificity due to enlarged inflammatory nodes. Moreover, approximately 23% of patients clinically and radiologically free of distant metastases appear to have distant abdominal metastases upon surgery [7]. Consequently, studies investigating better non-invasive staging modalities are necessary.

18-F-Fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) could be a solution for these problems. It is a non-invasive imaging technique based on the altered glucose metabolism of cells. Presence of cancer is detected by the increased glucose metabolism in neoplastic cells. This imaging tool has been shown to be superior to CT with regard to accuracy in the evaluation of mediastinal lymph nodes in patients with lung cancer, and has a higher sensitivity in detecting lymph node metastasis in oesophageal cancer [8;9]. These results have stimulated investigators to conduct studies investigating the role of FDG-PET in gastric cancer staging. This review discusses the accuracy of FDG-PET in preoperative staging of gastric cancer, and its role in tumour response monitoring.

METHODS

Literature search

Relevant studies were identified through a search of the electronic databases PubMed/Medline and Cochrane library. The following search terms were used: 'gastric cancer', 'gastric carcinoma', oesophagogastric junction cancer', 'oesophagogastric junction carcinoma', 'FDGPET', 'positron emission tomography' and 'pet$' in line with advised guidelines [10]. Inclusion criteria for non-systematic review were: study objective to investigate the role of PET in staging gastric cancer, article in the English language and a total patient inclusion exceeding 10 patients. Furthermore, a hand search was performed by checking reference lists in selected articles. Studies investigating the role of PET in oesophageal and oesophagogastric junction cancer combined were excluded, unless a sub-analysis was made between these two entities.

The search on PubMed/Medline and the Cochrane library revealed respectively 146 studies. After reviewing the titles and abstracts, five prospective studies [4;11-14], and seven retrospective studies [5;15-20] were included, with a total of 607 patients. Of these, one specifically investigated the value of FDG-PET in peritoneal metastasis [20] and two others investigated the role of FDG-PET in monitoring tumour response after chemotherapy [12;14], which are separately discussed. Additionally, two studies discussing the role of PET in recurrent gastric cancer are presented [21-23].

RESULTS AND DISCUSSION

FDG-PET imaging

Imaging with FDG-PET is based on the altered glucose uptake of neoplastic cells (Fig. 1). FDG is a radiolabelled glucose analogue. It accumulates in cells after cellular uptake by

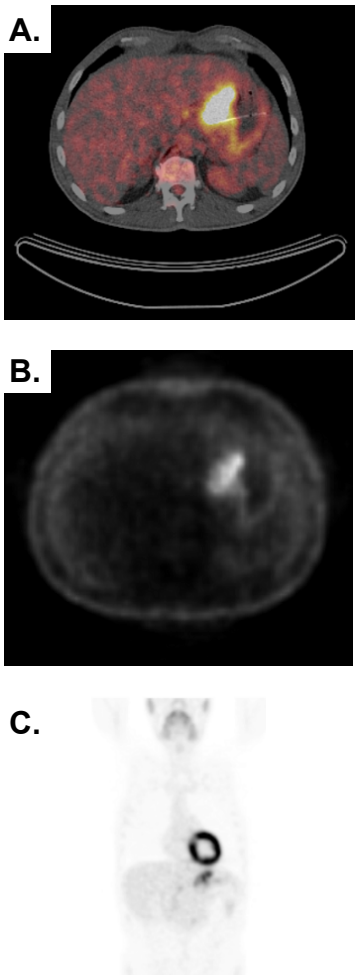

Figure 1. Representative FDG-PET image of a patient with primary gastric cancer without lymph node or distant metastases. A+B. Transversal slides of respectively CT-PET fusion and FDG-PET examinations highlighting pathological FDG-PET uptake in the gastric wall. No lymph node or distant metastases are observed. C. Frontal slide of total body FDG-PET examination with physiological FDG-PET uptake in the myocardium, and pathological uptake in the gastric wall. Again, no lymph node or distant metastases are observed.

mainly glucose transporters (GLUTs) located on the cell membrane and phosphorylation by hexokinases intracellular. GLUT-1 is the main cell surface protein facilitating the active uptake of FDG. Neoplastic cells overexpress GLUT-1 on their membranes resulting in higher uptake. The expression of GLUT-1 itself correlates with tumour aggressiveness and cancer-related mortality [24]. Apart from visual analysis, an often-used semi-quantitative method to assess the uptake of FDG in a tumour is the standard uptake value (SUV). This is the measurement of FDG-uptake in a tumour volume normalised on the basis of a distribution volume. SUVs are dependent on several parameters, such as time after FDG injection, tumour size, blood glucose levels, and spatial resolution of the reconstructed images [25;26]. Relative values, as are SUV changes, measured with accorded and compa-

rable protocols are reliable. Moreover, inter-observer correlations are consistently high (r^2 0.90-0.98)[12].

Primary tumour

Most studies included in this review studied the feasibility of primary tumour detection by FDG-PET in gastric cancer. The studies show that FDG-PET is not an accurate imaging technique for the primary diagnosis of a gastric primary tumour, combining high specificity with low sensitivity. About 20% of patients with gastric cancer are non-assessable by FDG-PET. Sensitivity rate for detecting the primary tumour varies between 58 and 94% amongst studies (median 81.5%) [5;11;15-19]. Specificity ranges from 78 to 100% (median 100%).

Detection of gastric carcinoma by FDG-PET is partly complicated by background signalling, partly due to high physiological uptake of FDG in the normal gastric wall as a result of its dense blood flow. Moreover, variable and sometimes intense, highly located uptake background activity is observed in the normal gastric wall, resembling false-positive pathological uptake [15;17]. Actively creating gastric distension by water ingestion could augment FDG-PET specificity [12;21].

Sensitivity of primary tumour identification by FDG-PET is influenced by several other determinants. The location of the tumour (i.e. proximal/middle/lower one third) is shown to influence the sensitivity of FDG-PET [12;15-17]. Even in the normal gastric wall different SUV uptakes are found between the upper and lower part of the stomach. Two studies found a higher detection rate by FDG-PET of a gastric carcinoma located in the proximal part of the stomach compared to a distal carcinoma [27].

A second determinant is tumour size or T-stage. The sensitivity of FDG-PET ranges from 26 to 63% in early gastric cancer (EGC; median 43.5%, SUV range 2.1-2.8) to 93-98% in locally advanced gastric cancer (AGC; median 94%; SUV range 4.3-7.9). FDG-PET as part of screening programs for the detection of gastric cancer in asymptomatic patients yields even worse results [13]. A sensitivity of 10% was found with additionally primarily false positive findings [13]. There are some explanations for this difference. Several studies report a correlation between tumour invasion as an independent factor and overexpression of GLUT-1 receptors. Possibly, the increased need for glucose due to the augmented cell metabolism and cell division in advanced cancer is the cause for GLUT-1 overexpression and higher FDG-uptake [28]. The relative volume effect can be a reason for the higher detection rate of AGC, as the discrimination between physiological and pathological gastric wall uptake enlarges. This makes FDG-PET an inaccurate method for screening and primary tumour detection [13].

Furthermore, a clear difference in sensitivity of FDG-PET is found between different histological carcinoma subtypes (Fig. 2). According to the Japanese Classification [29-31], gastric carcinoma can be divided in tubular (TC), moderately differentiated (MC),

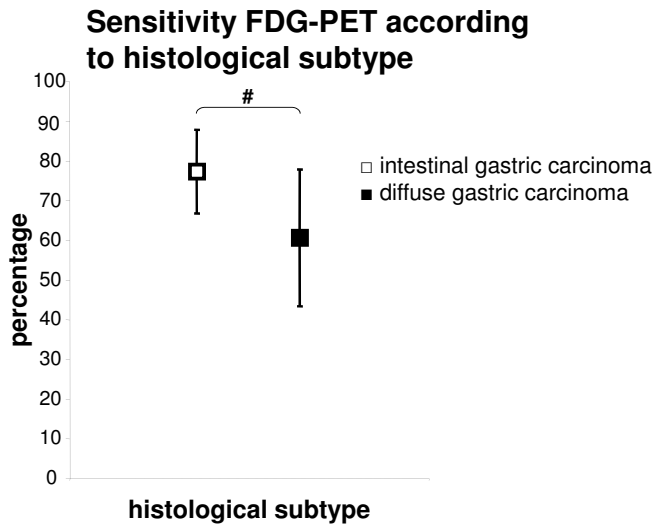

Figure 2. Sensitivity of FDG-PET according to histological subtype. The observed sensitivity for the intestinal subtype gastric carcinoma is significantly higher compared to diffuse gastric carcinoma (n=109 patients), respectively 77 versus 61%, as obtained by several studies. Open box: intestinal gastric carcinoma. Closed box: diffuse gastric carcinoma (n=122). # $P < 0.05$. Data according to references 14, 16-18

mucinous adenocarcinoma (MAC) and signet ring cell carcinoma (SRC). Particularly the non-intestinal (i.e. diffuse) subtype and carcinomas containing signet ring cells display a consistently low detectability by FDG-PET [12;15;16]. For TC and MC, SUV counts of 7.7-13.2 were found, which were significantly higher compared to those for MAC and SRC (4.1-7.7) [4;5;11;17;19]. This is due to a higher expression of GLUT-1 on the cell membrane of these neoplastic cells, as is proven for the cohesive gastric carcinoma type (i.e. TC, PC) [24;32]. Other factors influencing the low FDG uptake in MAC and SRC are the diffuse growth pattern of non-intestinal gastric cancer, the high content of metabolically inert mucus and the low tumour cell density [12;15;24]. For these entities, FDG-PET seems to have little or no value in the primary detection of gastric cancer.

Lymph node metastases

Five studies investigated the value of FDG-PET in detecting lymph node metastasis (Fig. 3) [4;5;11;16;17]. Sensitivity for metastasis to N1 lymph nodes was very low, ranging from 17.6 to 46.4% (median 27.5%) compared to CT (sensitivity of 58-89.3% median 68%). This could be explained by the relative low spatial resolution of FDG-PET (5-7 mm). The perigastric lymph nodes, therefore, cannot be distinguished from the primary tumour or the normal stomach wall. FDG-PET and CT both have a low sensitivity of respectively 33-46.2 and 44-63.1% in detecting metastases at N_2 andN_3 lymph nodes stations. Specificity,

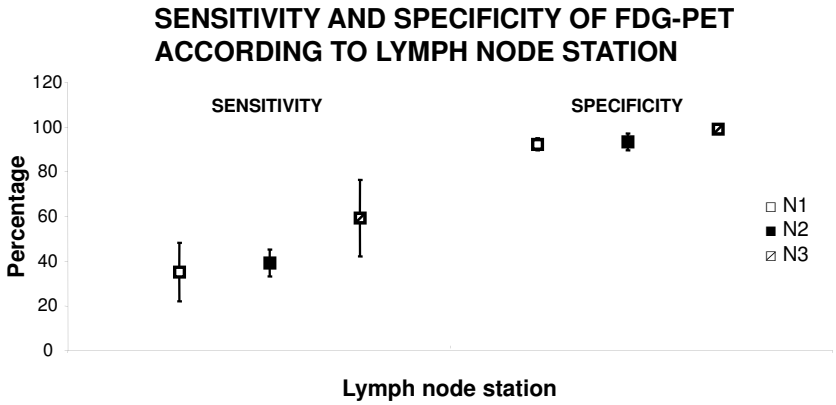

Figure 3 Sensitivity and specificity of FDG-PET according to lymph node station. Lymph node stations are defined according to the Japanese classification. Sensitivity percentages for lymph node metastases are very poor, especially in the N1 and N2 groups. On the contrary, specificity is obviously better, with the best detection results in the N3 lymph node groups. Open box: N1 lymph node station group. Closed box: N2 lymph node station group. Squared box: N3 lymph node station group. Data according to references 11;12;22;24;25

on the contrary, was higher in N1 and N2 lymph node stations with FDG-PET, ranging between 91 and 100% (median 96%), compared to CT. FDG-PET has a better positive predictive value for lymph node metastasis in comparison to CT, which may alter planning of therapy, as treatment strategy changes due to especially N3 lymph node metastasis from curative surgery to a palliative strategy. A combination of anatomy-based imaging by CT and metabolically-based imaging by FDG-PET using PET/CT might therefore augment the detection or denial of lymph node involvement.

Peritoneal carcinomatosis

Three studies investigated the role of FDG-PET in detecting peritoneal carcinomatosis [11;19;20]. PET has little value in detecting peritoneal carcinomatosis. It has a low sensitivity (range 9-50%; median 32.5%), however, there is a relatively high specificity (63-99%; median 88.5%). In two studies, patients with peritoneal carcinomatosis were described, with respectively sensitivity rates of 0 (4 patients) and 20% (5 patients) [4;18]. In the study of Kim et al. [4], pathological examination of peritoneal lesions showed extensive fibrosis around relatively few malignant cells, which could be an explanation for the low FDG-PET sensitivity. The small size of the peritoneal lesions (<5 mm) could be another reason

for the low detection rate. Currently used CT-scanning has a poor sensitivity as well, showing a specificity even worse than FDG-PET. Diagnostic laparoscopy still plays an undefined role in staging gastric cancer. It is highly sensitive for peritoneal metastases detection, however, it has little value in predicting regional lymph node metastasis [2;3]. The risks and morbidity of a staging laparoscopy do not weigh up to the benefits, as eventually only a small portion of patients will benefit from it [33]. With higher sensitivity of CT and higher specificity of PET, fusion of these imaging modalities may be more useful than either one of these alone. In case of suspicion of peritoneal carcinomatosis based on PET and/or CT, diagnostic laparoscopy could be performed to prevent unnecessary laparotomies.

Distant metastasis

Unexpectedly, not much is known about the role of FDG-PET in detecting distant metastasis. One series found a sensitivity and specificity of 85% and 74% for the detection of liver metastasis; 67% and 88% for lung metastasis; 24% and 76% for ascites; 4% and 100% for pleural carcinomatosis, and 30% and 82% for bone metastasis respectively [19]. As is the case for peritoneal carcinomatosis, the low number of tumour cells in ascites, pleural and bone metastasis can be an explanation for the low FDG-PET sensitivity.

Monitoring tumour response

The use of neoadjuvant (or induction) chemotherapy in the treatment of gastric cancer has evolved largely in recent years.34e36 Better surgicopathological results could be obtained with this treatment modality, especially a reduction in microscopically irradical resections, in residual tumour positive lymph nodes and tumour invasion in adjacent organs upon surgery. It is of vital importance to discriminate between responders and non-responders to chemotherapy, as in the latter chemotherapy could result in unnecessary risk for therapy-related morbidity with co-existing tumour growth. In 80% of all patients, gastric tumours are assessable by FDG-PET, and around 30-40% of the gastric carcinoma patients are responders with current chemotherapy regimens as defined by tumour regression [12;14]. Histopathological complete tumour regression is infrequently found [12;34-36]. Thoracoabdominal CT-scanning is commonly used to monitor tumour response. CT-observed tumour response depends on tumour size reduction, which is a relative late sign of response (RECIST-criteria) [37]. An earlier sign of response is the chemotherapy-induced reduction in tumour metabolic rate, which could be detected by FDG-PET. Two, relative small, studies (44 and 22 patients respectively) showed that the fractional change in glucose consumption can be assessed by FDG-PET immediately following the first cycle of chemotherapy [12;14]. Moreover, FDG-PET has been shown to be not only a predictor of neoadjuvant chemotherapy-induced clinical and histopathological response, but also, particularly, overall survival [12;14]. Patients with a metabolic response

had a 2 yr survival of 90%, in contrast to 40% in nonresponders [12]. In addition, 100% of the non-responders could be detected by FDG-PET, and subsequently withdrawn from neoadjuvant therapy proceeding to immediate surgery. FDG-PET evaluated treatment correctly in 80% of responders and non-responders combined [12;14]. Future goals are the delineation and validation of SUV decrement thresholds with adequate sensitivity and specificity to discriminate between beneficiaries and nonbeneficiaries of neoadjuvant chemotherapy. Currently, a cut-off level of 35% decrease in SUV is used with 75% sensitivity[12;14]. The role of FDG-PET in monitoring tumour response in gastric cancer has to be evaluated further, with possible clinical interesting results ahead of us.

Monitoring tumour recurrence

Tumour recurrence is directly associated with gastric cancer-related mortality, particularly early recurrence (<1 yr disease-free survival)[38]. Especially peritoneal recurrence is common [38]. No curative treatment modalities are left for these patients and the aim of care is palliation. An exception to this rule is late recurrence (>5 yr disease-free survival), which coincides with sporadic cancer mortality [38]. The extent of lymph node metastasis at primary diagnosis is the most important independent factor determining the timing of tumour recurrence [38]. Clinical surveillance is the most frequently used follow up modality, as current endoscopic and radiologic (ultrasonography, barium study and CT) are not sensitive enough for early recurrence detection and no reliable biochemical markers are known to correlate with recurrence [22;23]. Especially radiological examination is based on anatomical findings, thereby limited by postoperative, non-cancerous changes. The detection of active neoplastic metabolism theoretically increases the advantage of FDG-PET above CT. However, also FDG-PET lacks diagnostic accuracy in the early detection of recurrence with sensitivity and negative predictive values of respectively 70 and 60% [22]. The high physiological gastric remnant uptake and the low spatial resolution of current hardware unable FDG-PET to detect early recurrence [21;22]. Creating gastric distension by water ingestion increases the discriminative ability of FDG-PET and could reduce false-positivity [21]. On the other hand, the use of PET-CT fusion images could decrease the number of false-positive FDG-PET scans by locating PET hot spots on anatomical landmarks.

Future perspectives

Gastric tumour staging could possibly be improved by fusion of FDG-PET and CT imaging. The use of PET-CT fusion images will augment the detection accuracy, mainly by reducing the number of false-positive images by locating FDG-PET hot spots on anatomical landmarks, thereby increasing sensitivity and specificity. PET-CT fusion imaging is currently used in staging multiple forms of cancer. In non-small cell lung cancer, PET has a superior role over CT in diagnosing metastasis to mediastinal lymph nodes [9;39].

PET-CT fusion has a higher accuracy in assessing tumour stage compared to PET alone. Furthermore, PET-CT resulted in better lymph node staging by using the CT localisation [40;41]. PET-CT fusion images have proven to result in better detection of metastatic lymph nodes in oesophageal cancer. In a study comparing PET-CT with PET, sensitivity, specificity and accuracy for diagnosing lymph node metastasis were higher for PET-CT (93.9% vs. 81.7%, 92.1% vs. 87.3%, 92.4% vs. 86.2% respectively) [42]. With CT and PET combined in staging gastric cancer, imaging of morphologic and metabolic changes in the primary tumour and metastatic lymph nodes may give better preoperative staging, and studies are needed.

A new development is FLT-PET imaging. FLT (3- deoxy-3-18F-fluorothymidine) is a pyrimidine analogue, and has proven to be a stable PET tracer that accumulates in proliferating tissue and malignant tumours [43]. FLT is a substrate for thymidine kinase 1, which is an enzyme involved in the production of thymidine monophosphate. Hermann et al. [44] performed a pilot study assessing the feasibility of FLT-PET compared to FDG-PET in gastric cancer. They found a sensitivity of 100% of FLT-PET for primary tumour detection (60% of tumours were signet ring cell carcinoma), compared to a sensitivity of FDGPET of 69% (p-value < 0.001). Background activity was low. This suggests that FLT-PET is a potential superior imaging modality for staging gastric cancer, especially for histologic subtypes with low FDG-uptake. Further investigations are needed to evaluate the value of FLT-PET in gastric cancer.

CONCLUSION

In conclusion, FDG-PET has no role in primary tumour detection due to its low sensitivity, especially in early gastric cancer and the non-intestinal type. FDG-PET has, however, slightly better positive predictive value for the detection of lymph node metastasis in comparison to CT in N1 and N2 stations; furthermore, it has a reasonable sensitivity for liver and lung metastases. FDG-PET therefore improves current preoperative staging in advanced gastric cancer.

FDG-PET could have a significant role in monitoring tumour response during neoadjuvant chemotherapy. It adequately detects therapy responders at an early stage. Furthermore, FDG-PET is accurate in predicting the histopathological response and even long term prognosis. This makes FDG-PET a valuable adjunctive in neoadjuvant gastric cancer treatment.

The results of positron emission tomography in the evaluation and monitoring of gastric cancer may improve in the near future. The use of PET-CT fusion imaging hasimproved imaging in several cancer types. Its use in gastric cancer is currently under investigation. The use of new PET tracers, such as FLT, withholds promising perspectives

for the future. Therefore, continuous research of PET imaging in gastric cancer should be advocated.

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Chapter 5

Sentinel lymph node biopsy to direct treatment in early gastric cancer. A systematic review of the literature

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ABSTRACT

Gastric cancer is one of the main causes of cancer-related deaths around the world. The prevalence of early gastric cancer (EGC) among all gastric cancers of 45e51% in Japan, but only 7e28% in Western countries. The prevalence of EGC is growing partly because of better diagnostics and screening programs. Possible treatment options for EGC treatment are expanded by the introduction of endoscopic mucosal resection and endoscopic submucosal dissection Therefore, detailed knowledge about nodal metastatic risk is warranted. We performed a systematic review of the literature concerning studies investigating the role of sentinel lymph node biopsy in EGC and whether there is enough proof to introduce SLN as a part of treatment for EGC in the Netherlands. Several detection substances (dye or radiocolloid) and injection methods (submucosal or subserosal) are investigated. An overall sensitivity percentage of 85.4% was found. In comparison, high and clinically sufficient percentages were observed for specificity (98.2%), negative predictive value (90.7%) and accuracy (94%). Subgroup analyses showed that the combination of dye and radiocolloid detection substances is the best method for sentinel lymph node detection in early gastric cancer. However, the precise method of sentinel lymph node biopsy in EGC has to be determined further. Large, randomized series should be initiated in Europe to address this issue.

INTRODUCTION

Early gastric cancer (EGC) is defined as tumor invasion confined to the mucosa or submucosa, irrespective of nodal metastases, i.e. T1N0-2 (see Table 1). This definition reflects an appreciation that EGC represents a subset of gastric cancers that has a favorable prognosis compared to invasive gastric cancers that extend beyond the submucosa (T2-4). Gastric cancer is one of the most common causes of cancer mortality worldwide. The incidence of gastric cancer and the percentage of gastric cancer-related deaths are unevenly distributed throughout the world. The disease is most common in the Eastern World with the prevalence of EGC among all gastric cancers 45-51% in Japan, but only 7-28% in western countries [1]. Differences in treatment strategies for EGC between Japan and western countries are maintained [1]. Most screening programmes for gastric cancer have been developed in Asian countries [2]. In the Netherlands the primary curative therapy of all stages of gastric cancer consists of the complete resection of the tumor and prophylactic lymph node dissection. The extent of lymph node dissection is still much debated [3]. However, the need for a prophylactic lymph node dissection in EGC is probably negligible with respect to locoregional recurrence and overall survival, because of the very low risk of finding positive lymph nodes (see Table 1) [4;5]. It is estimated that 80e97% of the patients with EGC do not benefit from a lymphadenectomy, but are harmed by the coinciding morbidity. Non-invasive and endoscopic techniques as computed tomography (CT), magnetic resonance imaging (MRI) and endoscopic ultrasonography (EUS) are limited by their low sensitivity rates in predicting lymph node metastases in gastric cancer. For this problem sentinel lymph node biopsy could be helpful [6]. Investigators from the East and West are stimulated to conduct multiple

Table 1. T-status and Observed Metastatic Lymph Node Involvement According to Depth of Tumor Invasion

T-status	Depth of tumor invasion of gastric wall	Metastatic lymph node involvement	Reference
T_{is}	Intraepithelial tumor without invasion of lamina propria		Yi Y et al, Radiotherapy and Oncology 2010
T_{1a}	Tumor invasion of mucosa and/or muscularis mucosa	2 – 5%	
T_{1b}	Tumor invasion of submucosa	6 – 23%	
T_2	Tumor invasion of muscularis propria or subserosa	10 – 41%	
T_3	Tumor penetration of serosa	70%	
T_4	Tumor invasion of adjacent structures	84%	

Derived from International and Japanese Gastric Cancer Associations (*Gastric Cancer 1998;1:10-24)* and the International Union Against Cancer (UICC) TNM staging system (*6th ed, 2002*) T_{is} (carcinoma in situ). Early gastric cancer is defined as tumor invasion confined to the mucosa or submucosa, irrespective of nodal metastases, i.e. T_1N_0. The incidence of lymph node metastasis is low in early gastric cancer patients, with more than a 90% 5-year survival rate. The overall prognosis for patients with gastric cancer remains poor, with a 5-year survival rate of 5 to 15%. (Akoh, 1992; Itoh, 1989)

studies investigating the role of sentinel lymph node (SLN) biopsy in EGC in the past decade. The surgical treatment of early gastric cancer relates to the extent of lymphadenectomy. Therefore detailed knowledge about the nodal metastatic risk is warranted. In this systematic review we investigate whether there is enough proof to introduce SLN as a treatment for EGC in the Netherlands.

METHODS

Systematic search

Relevant studies were identified through a search of the electronic database PubMed. The following search terms were used: "gastric cancer", "gastric carcinoma", "early gastric cancer", "sentinel lymph node", "sentinel node". Inclusion criteria were: study objective to investigate the role of SLN biopsy in gastric cancer, article in the English language and inclusion of at least 10 patients in the study. Twenty-one studies fulfilled the inclusion criteria. Subsequently, reference lists of the selected studies were crosschecked. The selection and analysis of studies has been performed independently by three investigators (DJL, HWS, RLAL, AED). Studies available for analysis (ref 7e26) were subjected to a quality control using the QUADAS tool [7]. Quality was considered to be good for two studies, moderate for 12 studies and poor for four studies. The selection and analysis of the studies has been performed independently by three investigators (DJL, HWS, AED).

Statistics

The following definitions were used:

SLN detection rate = number of patients with detected SLNs / total number of patients investigated.

SLN positivity rate (SLN+) = number of patients with positive SLN / total number of patients with detected SLNs.

Sensitivity = number of patients with true positive SLN / (number of patients with true positive SLN + number of patients with false negative SLN).

Specificity = number of patients with true false SLN / (number of patients with true false SLN + number of patients with false positive SLN).

Positive predictive value (PPV) = number of patients with true positive SLN / (number of patients with true positive SLN + number of patients with false positive SLN).

Negative predictive value (NPV) = number of patients with true negative SLN / (number of patients with true negative SLN + number of patients with false negative SLN).

Accuracy (ACC) = (number of patients with true positive SLN + number of patients with true negative SLN) / total number of patients with detected SLNs.

The accuracy of the various procedures for detecting sentinel lymph nodes and subgroup analysis were tested with Meta-Disc software using negative likelihood ratios, and subgroup analyses were performed according to detection method [8]. *P < 0.05* was determined significant.

RESULTS

An overview of the results from the studies included in the analysis is presented in Table 2. A total of 1314 patients were included in the 21 reviewed studies, with a mean number of 63 patients per study (range 13-211; median 53). Tumor depth varied between T1 and T3 between the studies. All studies excluded patients with metastatic disease. Largely, the SLN detection methods used in these studies can be separated on the basis of detection substance employed into two groups, i.e. radiocolloid or dye. Four of the 21 studies investigated multiple modalities for SLN biopsy [9-13]. In 16 of the 21 studies a detection dye (indocyanine green, isosulfan blue or patent blue) was used [9-11;13-24], while a radiocolloid (99mTc tin colloid, 99mTc sulphur colloid or 99mTc colloidal rhenium sulphide) was used in nine [11-13;15;20;25-28]. Of these 21 studies one compared, but did not combine both methods [11]. In 3 other studies the combination of a dye and radiocolloid was used to maximize SLN detection [9;13;20]. The method of application (pre-/peroperative and submucosal/-serosal) is depending on the substance employed. All studies using a radiocolloid injected the detection substance peritumorally in the submucosal layer of the stomach via endoscopic route one day preoperatively. In nine out of 17 an endoscope was used in to inject the dye in the submucosal layer [9-11;13;16;17;20;21;23], while 8/17 injected the detection substance peritumorally in the subserosal layer during laparotomy [14;15;18;19;22-24]. In one study the detection effect of indocyanine green was enhanced by using infrared ray electronic endoscopy (IREE).18 Another study using dye detection investigated the difference between the submucosal and subserosal techniques, 23 three others used the submucosal dye application in combination with a radiocolloid [9;13;20].

The SLN detection rates varied from 66.7 to 100% (mean 94.7%; median 96.6) between the studies. The low SLN detection rate of 66.7% was observed in the study investigating the role of the size of radiocolloid particles related to detection success. A detection rate of 66.7% was found with a particle size of 500 nm, while with the other investigated particle sizes of 100 and 50 nm detection rates of 100% were observed. The three dye and radiocolloid combination studies showed detection rates of respectively 100%, 100% and 97%. With all detection methods combined, a mean of 3.5 SLNs per patient was observed (range 1.6-10.5; median 3). The highest number of SLNs per patient was found with the combination of indocyanine green and IREE; here, the detection rate was 98.8%. SLN positivity (SLN +) varied significantly between studies with a range of 5.2-

Table 2. Results Sentinel Lymph Node (SLN) Procedures in Gastric Cancer

Reference	**Method**	**TNM^**	**N**	**Detection succes-rate**	**SLN/pt (range)**
Hiratsuka M, et al. Surgery 2001	Indocyanine green; subserosal; laparotomy	T_{1-2}	74	98.6%	2.6 (1-9)
Kitagawa Y, et al. Br J Surg 2002	^{99m}Tc tin colloid; submucosal; endoscopically	T_{1-2}	145	95%	3.6 (1-8)
Hundley JC, et al. Am Surg 2002.	Isosulfan blue; subserosal, laparotomy	T_{1-3}	14	100%	2.8 (1-5)
Ichikura T, et al. World J Surg 2002	Indocyanine green; submucosal; endoscopically	T_{1-2}	62	100%	4.5# (1-12)
Hayashi H, et al. J Am Coll Surg 2003	^{99m}Tc tin colloid +	T_{1-2}	31	90%	3.7
	Patent blue; submucosal; endoscopically			90%	3.6
	(cb)			100%	
Miwa K, et al. Br J Surg 2003	Patent blue; submucosal; endoscopically	T_{1-3}	211	96.2%	6 (1-16)
Simsa J, et al. Acta Chir Belg 2003	Patent blue; subserosal; laparotomy	T_{1-3}	13	100%	
Ryu KW, et al. EJSO 2003	Isosulfan blue; subserosal; laparotomy	T_{1-2}	71	91.5%	2.5 (1-8)
Reference	Method	TNM^	N	Detection succes-rate	SLN/pt (range)
Tonouchi H, et al. Dig Surg 2003Ù	^{99m}Tc tin colloid +	T_1	17	82.4%	2.8 (1-9)
	Patent blue; submucosal; endoscopically		17	88.2%	2.5 (1-6)
	(cb)		17	100%	4.2 (2-9)
Uenosono U, et al. Canc Lett 2003	^{99m}Tc tin colloid;	T_{1-2}			
	500 nm		12	66.7%	1.8 (0-4)
	100 nm		13	100%	3.8 (1-6)
	50 nm		11	100%	3.0 (1-7)
	submucosal; endoscopically (overall)		36	88.9%	2.9 (0-7)
Kim M-C, et al. Ann Surg 2004	^{99m}Tc tin colloid; submucosal; endoscopically	T_{1-3}	46	93.5%	2 (1-8)
Isozaki H, et al. Gastric Cancer 2004	Isosulfan blue; submucosal; endoscopically	T_{1-3}	144	97.2%	3.3 (1-9)
Song X, et al. Am J Surg 2004	Isosulfan blue; subserosal; laparotomy	T_{1-3}	27	96.3%	2.7 (1-6)
Nimura H, et al. Br J Surg 2004	Indocyanine green; submucosal; endoscopically	T_{1-2}	84	98.8%	5.5
	+ IREE			98.8%	10.5

SLN+¶	Sens	Spec	PPV	NPV	Acc SLN status	Acc frozen biopsy	Skip metastasis† (detected)	SLN micrometastasis‡
12.3%	90%	100%	100%	98.4%	98.6%	-	-	-
7.8%	91.7%	100%	100%	98.4%	98.6%	-	0.8% (100%)	-
28.2%	70%	75%	90%	50%	70%	-	-	0%
24%	86.7%	100%	100%	95.7%	93.5%	-	1.6% (0%)	-
10.7%	85.7%	100%	100%	95.5%	96.4%	-	-	0%
21.4%	71.4%	100%	100%	91.3%	92.9%	-	-	0%
22.8%	100%	100%	100%	100%	100%			
5.2%	88.6%	100%	100%	97.8%	98.1%	98.6%	1.4% (100%	-
61.5%	100%	100%	100%	100%	100%	84.6%	-	0%
28.2%	61.1%	100%	100%	87%	89.2%	-	10.8% (0%)	-
SLN+¶	Sens	Spec	PPV	NPV	Acc SLN status	Acc frozen biopsy	Skip metastasis† (detected)	SLN micrometastasis‡
17.6%	100%	100%	100%	100%	100%	33.3%ÙÙ	11.8% (50%)	66%
37.5%	100%	100%	100%	100%	100%	100%	25%	-
7.7%	100%	100%	100%	100%	100%	100%	0%	-
18.2%	100%	100%	100%	100%	100%	100%	9.1%	-
18.8%	100%	100%	100%	100%	100%	100%	9.4%	-
25.6%	84.6%	100%	100%	93.8%	95.3%	97.7%	7% (100%)	0%
-	-	-	-	-	-	-	-	-
20%	100%	100%	100%	100%	100%	-	0	-
8.4%	63.6%	100%	100%	94.7%	95.2%	-	-	-
13.3%	100%	100%	100%	100%	100%	-	-	-

Table 2. *Continued*

Reference	**Method**	**TNM^**	**N**	**Detection succes-rate**	**SLN/pt (range)**
Zulfikaroglu B, et al. Surgery 2005	148 MBq ^{99m}Tc filtered sulfur colloid; submucosal; endoscopically	T_{1-3}	32	97%	2.4 (1-8)
Gretschel S, et al. EJSO 2005.	^{99m} Tc colloidal rhenium sulphide; +	T_{1-3}	15	93.3%	3 (1-5)
	Patent blue; submucosal; endoscopically		19	100%	3 (1-6)
	(cb)		34		
Lee JH, et al. EJSO 2005	Isosulfan blue; subserosal (laparotomy)	T_{1-2}	71	91.5%	2.5
	versus				
	submucosal (endoscopically)		50	94%	2.9
Park DJ, et al. EJSO 2006	Indocyanine green; subserosal;	T_{1-2}	100	94%	4.4
	laparotomy		50		
Mochiki E, et al. Am J Surg 2006	^{99m}Tc colloidal rhenium sulphide; submucosal; endoscopically	T_{1-3}	59	96.6%	3.8 (1-10)
Gretschel S, et al. Ann Surg Oncol 2007	^{99m}Tc colloidal rhenium sulphide; +	T_{1-3}	35	97%	3 (1-10)
	Patent blue; submucosal; endoscopically		35	97%	3 (1-6)
	(cb)		35	97%	3 (1-10)
Cozzaglio et al. EJSO 2010	Patent blue dye technique	T_{1-3}	29	96.5%	1.6 (1-3)

Abbreviations: Acc accuracy; cb combination; IREE infrared ray electronic endoscopy; NPV negative predictive value; PPV positive predictive value; Sens sensitivity; Spec specificity; SLN sentinel lymph node.
^ The actually observed T-status is mentioned; all studies excluded patients with metastatic disease. ¶ SLN positivity (+) for metastasis is calculated by the equation: patient with SLN positive for tumor/total patients with SLNs found.
† Skip metastases are defined as lymph node metastases in D2 or D3 compartments, without involvement of the perigastric D1 compartment. Percentage calculated by the equation: patient with skip metastasis/total patients studied.
‡ SLN micrometastasis detection rate is defined by the equation: SLN micrometastasis positive/total SLN metastasis positive.
# Based on the results of group patients injected with 4 ml 1.25% indocyanine green, excluding the group injected with 8ml 0.63% indocyanine green, as the former is the preferred method to identify SLNs according to the investigators.
ˆStudy investigating laparoscopic gastrectomy with lymphatic mapping.
ˆˆ In the SNs of 2 of 3 patients with positive lymph nodes micrometastasis were found in frozen-sections by immunohistochemistry staining, not in the frozen-section examination by hematoxylin & eosin staining (diagnostic accuracy frozen biopsy 1 out of 3, 33%).
*and**Results of respectively hematoxylin&eosin and immunohistochemistry staining on final pathological non-frozen examination.

SLN+¶	Sens	Spec	PPV	NPV	Acc SLN status	Acc frozen biopsy	Skip metastasis† (detected)	SLN micrometastasis‡
18%	100%	95.5%	90%	100%	96.7%	97%	10% (100%)	0%
57.1%	88.9%	100%	100%	83.3%	92.9%	-	11.1% (0%)	
73.4%	100%	100%	100%	100%	100%	-	7.1% (0%)	
								21.7%
16.9%	61.1%	100%	100%	87%	89.2%	-	-	-
10.6%	45.5%	100%	100%	85.7%	87.2%	-	-	-
11.7%*	78.6%*	100%*	100%*	96.4%*	96.8%*	-	-	4.3%
22.2%**	71.4%**	100%**	100%**	88.6%**	91.1%**	-	-	
35.1%	83.3%	100%	100%	89.2%	93%	-	-	-
64.7%	91.7%	100%	100%	83.3%	94.1%	-	-	
47.1%	66.7%	100%	100%	55.6%	76.5%	-	-	
64.7%	91.7%	100%	100%	83.3%	94.1%	-	-	
61%	75%	75%	88%	55%	75%	-	-	18%

Table 3. Summary of Results of Sentinel Lymph Node Biospy Procedures

	Sens	Spec	PPV	NPV	Acc
Mean	85.4%	98.2%	99%	90.6%	94%
Median	88.9%	100%	100%	95.7%	96.4%
Range	45.5– 100%	75 – 100%	88 – 100%	50 – 100%	70 – 100%

Abbreviations: Acc accuracy; NPV negative predictive value; PPV positive predictive value; Sens sensitivity; Spec specificity. All number are presented in percentages.

73.4% (mean 28.1%; median 21.4%). No association could be observed between tumour depth and SLN + as result of the given data.

Table 3 shows the overall results of all studies combined. The mean and median percentages for the sensitivity were 85.4% and 88.9% respectively with a wide range from 45.5% to 100%. Low sensitivity percentages of less than 90% were observed in 13/21 studies [9-13;16;17;19;23;24;27;28]. In two of the 13 studies better sensitivity percentage of 90-100% was obtained by using the combination method [15;24], while one showed a similar result with IREE [21]. In general, a low sensitivity percentage was found for all detection substances (i.e. dye or radiocolloid) and application methods (i.e. submucosal via endoscopic route or subserosal via laparotomy). A high sensitivity was found in studies using a subserosal dye technique or combination method. The mean and median negative predictive value (NPV) for all studies combined were 90.7 and 95.7%. The mean overall specificity (Spec) and positive predictive value (PPV) were 98.2 and 99% respectively. Positive SLNs proved to be false-positive very rarely [15]. Good results are seen for the accuracy (Acc) percentages (mean 94%; median 96.4%).

Subgroup analyses according to detection method (see Table 4) showed better discriminative power for the radiocolloid detection method then dye methods, irrespective

Table 4. Negative Likelihood Ratio for Sentinel Lymph Node Biopsy Procedures

	N	neg LHR	95% CI	
Total	31	0,230	0,178	0,297
Dye total	16	0,283	0,209	0,382
SM	9	0,264	0,162	0,430
SS	7	0,308	0,217	0,430
Radiocolloid	11	0,163	0,108	0,247
Dye and radiocolloid	3	0,101	0,037	0,342

Abbreviations: N number of studies; neg LHR negative likelihood ratio; CI confidence interval
The included number SLN biopsy procedures (*N*) is 31, because all individual arms of the studies are counted.

of the application method of the dye. However, a tendency towards the best discriminative power was seen for the combination of dye and radiocolloid.

DISCUSSION

In this systematic review of the current literature not enough proof was found to introduce SLNB in the treatment protocol for EGC in the Netherlands. The overall sensitivity of <90% is just too low to justify immediate introduction of the SLN biopsy procedure in EGC in analogy of the requested sensitivity percentage of >95% for SLN biopsy as in other solid organ malignancies. For a proper implementation of the SLN biopsy procedure in early gastric cancer several problems need to be solved. First, the amount of false-negative SLN biopsy results should be limited to increase the sensitivity of the procedure. A sensitivity of at least 90e95% should be guaranteed for safe introduction of the procedure in patient care. The lack of expertise is part of the explanation for the current low sensitivity. Several investigators report a significant increase in the sensitivity of SLN biopsy with growing experience with the procedure [10;24], but it is not known exactly how many patients are needed to complete the learning curve [24]. Although some investigators claim that they were able to optimize their technique with a learning curve of less than ten cases [10], it seems reasonable to assume that the plateau-phase in the learning curve is reached when detection and accuracy rates are around 95%. Secondly the literature about EGC and SLN procedures is mainly coming from the Asian countries. Because the incidence of gastric cancer is higher in these countries and because the tumour types seem to differ, it may be hazardous to extrapolate the results from these studies to patients in Western countries [29;30]. One of the differences is the frequency of the locations of the gastric tumors related to the differences in risk factors. The most important risk factor for gastric cancer is an infection by *Helicobacter pylori* bacteria. This infection is primarily related to distal gastric cancer [29], which is where most of the tumours of patients from the Eastern world are primarily located. This in contrast to the countries in the in the Western world where most of the gastric cancers are located in the cardia. This difference, among others, can be of importance for the ability of the SNL procedure to detect positive lymph nodes.

In the papers included in our review no clear distinction is made between early gastric cancer (T1) and locally advanced gastric cancer (T2-4). Therefore, not all results are comparable. However, we can postulate that the SLN biopsy procedure could be relevant for clinical practice in EGC to limit the extent of surgery. Lymph node metastases are present in 84% of all patients with gastric cancer (ref 30, Table 1). Based on current knowledge prophylactic lymphadenectomy could be omitted in patients with a T1 tumor and SLN biopsy negative for metastasis. In these patients, the finding of a posi-

tive SLN biopsy should be followed by a lymphadenectomy as part of standard therapy. Lymphadenectomy should also be applied as a standard procedure for patients with T_2, T_3 and T_4 tumours, because for patients with these stages of gastric cancer the risk of lymph node metastasis is well above 50% (Table 1) and using SLN biopsy will not be of any benefit for them.

Considering all the above, the combination of dye and radiocolloid for lymph node detection is the best on most counts. The precise role of sentinel lymph node biopsy in ECG remains to be determined. Large, randomized series should be initiated in Europe to address this issue. Advances in laparoscopic and endoscopic surgical procedures and a growing older patient population with comorbidities require such initiatives as less-extended procedures are performed. It is recommended to perform a minimum of ten procedures using the combination of dye and radiocolloid substances before clinically initiating SLN biopsy in EGC.

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Chapter 6

Lymph node examination among patients with gastric cancer: variation between departments of pathology and prognostic impact of lymph node ratio

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ABSTRACT

Introduction

At least 15 lymph nodes should be retrieved for proper TNM-staging in gastric cancer. We evaluated nodal harvest and examined its relation to stage distribution and survival at a population-based level, including the value of N-ratio (metastatic/evaluated) as a staging modality.

Methods

All patients resected for primary Mo gastric cancer diagnosed in 1999-2007 in the Dutch Eindhoven Cancer Registry area were included (N=880). Determinants of lymph node evaluation and their relationship with stage and survival were assessed in multivariable regression analyses. N-ratio categories were determined (N ratio 0, 0%; N ratio 1, 0.1%–19%; N ratio 2, 20%–29%; N ratio 3, ≥ 30%)

Results

The median number of lymph nodes examined was 7, dependent on N-stage (No: 7; N+: 8). It varied between departments of pathology from 5 to 9. This variation remained after adjustment for relevant patient- and tumour factors. Stage distribution differed between pathology departments (proportion No ranging from 14% to 21%, p=0.003). Among resected patients with NoMo disease and <7 nodes examined, 5-year survival was 56%, compared to 69% among patients with ≥7 nodes examined (p=0.012). Five-year survival for N-ratio 0 was 58%, N-ratio 1 50%, N-ratio 2 18% and N-ratio 3 11% (p<0.0001), while 5-year survival ranged from 58% for No, 17% for N1, and 11% for N2/3 (p<0.0001).

Conclusion

In this series of patients with a relatively low number of evaluated lymph nodes, a high prognostic accuracy of N-ratio was found. However, improvement in nodal assessment is mandatory.

INTRODUCTION

Gastric cancer is still one of the leading cancers in incidence and mortality throughout the world. Mortality of gastric cancer ranks fourth in Europe for males and fifth in 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 14-32% [2]. In the southern Netherlands, overall 5-year survival is 18% [3]. The only curative treatment is surgery with (partial) gastric resection and lymph node dissection. The type of lymph node dissection is still under discussion. Japan and some other countries perform an extended lymphadenectomy, the so-called D2- or D3-dissection. Several large studies have been conducted to evaluate the outcome of patients after a D2-dissection in the West [4;5]. As they found no survival benefit for this type of dissection, with higher post-operative morbidity a D2-dissection is therefore no general practice in our country. The long-term results after a median survival of 15 years did find lower regional recurrence and gastric cancer related deaths after a D2-dissection. It was suggested that a D2-dissection should be recommended, especially in view of the availability of a spleen-saving (and therefore safer) D2-dissection [6].

It is widely accepted that lymph node status and lymph node ratio, together with T and M stage, are the most important prognostic factors [7;8]. According to several studies and guidelines (UICC) a resection with at least 15 lymph nodes should be performed for proper staging and disease control. As in most countries where a D1-dissection is performed these numbers cannot be met, N-ratio (metastatic/evaluated) is proposed as a new N-staging modality.

In this perspective, we conducted a retrospective study in the southern part of the Netherlands to evaluate the amount of lymph nodes dissected and examined its relation to stage distribution and survival.

PATIENTS AND METHODS

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 grew from an area covering 850,000 to about 2.3 million inhabitants. This population-based registry was notified by 6 pathology departments, 10 community hospitals (20 at the beginning of the 1970's but many of them have merged) at 15 locations, and 2 radiotherapy institutions.

All patients resected for primary gastric cancer (ICD-O (International Classification of Diseases for Oncology) code C16 [7]) without evidence for distant metastasis, diagnosed between 1999 and 2007 in the Dutch Eindhoven Cancer Registry area were included

(N=880). Information on diagnosis, staging, and treatment is routinely extracted from the medical records by specially trained administrators of the cancer registry. Registration takes place 6 to 18 months after diagnosis. By means of an independent case ascertainment method, the completeness of the registration is estimated to exceed 95%.

Stage distribution is based on the Tumour Node Metastasis (TNM) system (International Union Against Cancer (UICC) classification 6th edition). Subsite distribution is divided as follows: cardia (comprising gastro-esophageal junction, C16.0), middle part (fundus, corpus, lesser curvature, and greater curvature (the two latter not classifiable to C16.0 - C16.4], C16.1, C16.2, C16.5, and C16.6), pyloric part (antrum and pylorus, C16.3 and C16.4), overlapping lesions (C16.8), and not otherwise specified (C16.9). Tumour characteristics registered furthermore include number of lymph nodes examined, number of positive lymph nodes, and grade of tumour differentiation. Prognostically relevant concomitant conditions are recorded from the medical records according to a slightly adapted version of the Charlson Index. This item was not registered before 1993; since 1995 these data are reliable and validated [9]. Socio-economic status (SES) of the patient was defined at neighborhood 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 3 SES categories: low (1st-3rd decile), intermediate (4th-7th decile), and high (8th-10th decile) [9]. For patients residing in nursing homes, a special SES category was assigned. Vital status of all patients diagnosed until 1st of January 2007 was assessed on 1st of January 2008 through merging with the Municipal Administrative Databases, where all deceased and emigrated persons in the Netherlands are registered. Population and mortality data were obtained from Statistics Netherlands (CBS) (CBS, 2007. Voorburg/Heerlen).

Analysis

Differences between the departments of pathology according to the number of lymph nodes evaluated and the postoperative nodal status were tested by means of a Kruskal Wallis test. The independent influence of institution or patient and tumour characteristics on the number of lymph nodes evaluated was analyzed by means of a logistic regression analysis. To examine the hypothesis that the number of lymph nodes examined is related to survival, 5-year crude overall survival differences between patients with the median number or less versus more than the median number of nodes examined were tested using a log-rank test, stratified for N status. Furthermore, the ratio between the number of metastatic and evaluated lymph nodes was determined. Cutoff values for N-ratio intervals were determined based on the prognosis of patients and the number of patients included within each category. Patients were categorized into 4 groups: N-ratio 0 (number of metastatic nodes / number of evaluated nodes * 100%=0%), N-ratio 1 (0.1-

19%), N-ratio 2 (20-29%), and N-ratio 3 (≥30%). Five-year survival was compared between these groups using a log-rank test. A multivariable proportional hazards regression analysis was used to discriminate independent risk factors for death. To compare the prognostic value of nodal status and N-ratio, the model was first built with inclusion of nodal status and lymph node count, and then repeated with N-ratio instead of the aforementioned variables.

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).

RESULTS

General characteristics and departments of pathology

Three out of the six departments of pathology served one hospital, while two departments covered 3 hospitals each. One hospital has been served by two departments of pathology during the study period for logistic reasons.

The general characteristics of all patients are shown in Table 1. The median age was 69 years. The majority of patients was male, and presented with comorbidity. A large proportion of patients had poorly differentiated tumours. Few patients received neoadjuvant treatment; the most commonly performed resection was a subtotal gastrectomy. Twelve percent of patients had 15 or more lymph nodes examined.

Table 1. General characteristics of all 880 patients who underwent resection for M0 gastric carcinoma, diagnosed between 1999 and 2007 in the southern Netherlands.

Age (years)		
Median (range)	69	(13-100)
	N	(%)
Gender		
Male	574	(65)
Female	306	(35)
Socio-economic status		
Low	234	(27)
Intermediate	320	(36)
High	282	(32)
Institutionalised	28	(3)
Unknown	16	(1)

Table 1. *Continued*

Comorbidity		
No comorbidity	265	(30)
One comorbid condition	248	(28)
Two or more comorbid conditions	313	(36)
Unknown	54	(7)
Tumour site		
Cardia	168	(19)
Middle part	222	(25)
Antrum and pylorus	323	(37)
Overlapping, unknown	167	(19)
Stage		
IA	108	(12)
IB	226	(26)
II	280	(32)
IIIA	180	(20)
IIIB	27	(3)
IV[a]	40	(5)
Unknown	19	(2)
Tumour grade		
Moderately/well differentiated	269	(30)
Poorly differentiated	520	(56)
Unknown	91	(14)
Preoperative treatment		
Chemo- and/or radiotherapy	29	(3)
None	861	(97)
Type of resection		
Total gastrectomy	192	(21)
Subtotal gastrectomy	509	(58)
Oesophageal-cardiac resection	118	(13)
Multi-organ resection	29	(3)
Unspecified type of resection	32	(4)
No. of lymph nodes evaluated		
0	66	(7)
1-2	60	(7)
3-5	120	(14)
6-8	170	(19)
9-11	111	(13)
11-14	75	(9)
≥15	105	(12)
Exact number unknown	173	(20)

[a] Excluding patients with distant metastases (M1)

Nodal evaluation

The median number of lymph nodes evaluated varied between 5 in department #6 to 9 in departments #1 and #4 (p<0.0001) (Table 2). In total, a median number of 7 nodes was evaluated between 1999 and 2007. There was also a large variation between the departments concerning the proportions of patients with no exact number of evaluated nodes stated in the pathology report. Often, terms were used such as 'a few' or 'a number of', indicating that lymph nodes were indeed evaluated.

Five out of six departments of pathology showed an increasing trend over time in the number of evaluated lymph nodes. In total, the median number of evaluated nodes increased from 6 in the period 1999-2001, to 8 in 2004-2007. Within the last period, the median number of nodes evaluated continued to rise to 13 in department #3 and to 14 in department #4 in 2007 (results not shown).

Among patients with N+ disease, there was a larger proportion of patients with an unknown exact number of nodes evaluated, but also a larger proportion of patients with 15 or more nodes evaluated (median 8 nodes compared to 7 among No patients). Postoperative N stage differed between the departments of pathology (*p*=0.003) (Table 2). In the departments with a higher median number of lymph nodes evaluated, a smaller proportion of patients was diagnosed with No disease. Compared to the other departments, in department #1 a higher proportion of patients was diagnosed with N3 disease, and a smaller proportion with unknown N stage.

Table 2. Median number of lymph nodes evaluated and proportion N0, according to department of pathology

Dep. of pathology	Median number of nodes evaluated	Range	Proportion of patients with unknown number of evaluated nodes		%N0
			Unknown whether any nodes have been evaluated	At least 1 node evaluated, but exact number not stated in medical file [a]	
1	9	0-31	0%	0%	15%
2	6	0-21	1%	28%	20%
3	7	0-35	1%	27%	20%
4	9	0-41	2%	12%	17%
5	7	0-36	1%	8%	20%
6	5	0-21	3%	45%	22%
total	7	0-41	1%	19%	19%

Difference of median numbers of lymph nodes evaluated across departments of pathology: chi^2 test p<0.0001

Differences in postoperative nodal status between departments of pathology: chi^2 test p=0.003

[a] Often stated in the pathology report as: 'a few', or 'a number of'.

Table 3. Odds of having 7 or more lymph nodes evaluated, calculated by means of a multivariable logistic regression analysis (model including all listed variables).

	Odds ratio	95% CL
Age (yrs)		
<70 [a]	1.0	
70+	0.8	0.6-1.1
Gender		
Males [a]	1.0	
Females	1.3	0.9-1.8
Comorbiditya		
No comorbidity [a]	1.0	
One comorbid condition	0.7	0.5-1.2
Two or more comorbid conditions	0.5	0.3-0.7
Unknown	1.3	0.6-2.9
T-stage		
T1	0.4	0.2-0.7
T2 [a]	1.0	
T3	0.9	0.6-1.5
T4	0.4	0.2-0.9
N-stage		
N0 [a]	1.0	
N+	2.3	1.6-3.2
Tumor site		
Cardia	1.6	0.8-3.3
Middle part	1.1	0.7-1.7
Pyloric part [a]	1.0	
Other/unknown	1.1	0.7-1.9
Tumour grade		
Moderately/well differentiated [a]	1.0	
Poorly differentiated	1.3	0.9-2.0
Unknown	0.8	0.4-1.5
Neoadjuvant treatment		
No [a]	1.0	
Yes	0.8	0.3-1.7
Type of resection		
Total gastrectomy	1.9	0.1-3.0
Subtotal gastrectomy [a]	1.0	
Oesophageal-cardiac resection	1.3	0.6-2.8
Multi-organ resection	5.0	1.4-14.5

Table 3. *Continued*

	Odds ratio	95% CL
Department of pathology		
1	1.0	0.6-1.9
2	0.3	0.2-0.5
3	0.9	0.5-1.5
4	1.5	0.9-2.3
5 [a]	1.0	
6	0.5	0.3-1.1
Period of diagnosis		
1999-2003 [a]	1.0	
2004-2007	1.4	1.0-1.9

[a] Reference category
CL=confidence limits

In Table 3, the results of a multivariable logistic regression analysis (adjusting for all variables listed) show that patients with two or more comorbid conditions, patients with a T1 or T4 tumour, and patients whose resection specimen was examined in department of pathology #2 had a significantly lower chance of having 7 or more nodes evaluated compared to the respective reference groups. Patients with N+ disease and patients undergoing a total gastrectomy or a multi-organ resection had a higher chance of having 7 or more nodes examined. Patients being diagnosed more recently also had a higher odds of having more nodes evaluated, but this reached borderline significance only (p=0.06).

Survival

Five-year survival was significantly higher among patients with No, Mo disease which had 7 or more nodes evaluated compared to patients with less than 7 nodes evaluated (Figure 1a). Among patients with N+, Mo disease, no prognostic effect of lymph node count could be noted (Figure 1b). Five-year survival clearly differed according to nodal status, ranging from 58% for patients with No disease, 17% for patients with N1 disease, and 11% for patients with N2/3 disease (Figure 1c). Classifying patients according to lymph node ratio yielded a comparable survival gap between patients with N-ratio of 0 and patients with an N-ratio of 2 or 3 (Figure 1d). Patients with an N-ratio of 1 however, only fared slightly less well than patients with an N-ratio of 0 (50% vs. 58%). After adjustment for relevant patient and tumour characteristics, the risk of death (hazard ratio (HR)) was strongly correlated with nodal stage and with lymph node count (Table 4). Exchanging these two variables for N-ratio yielded comparable effects, but note again the only borderline significant worse survival of patients with N-ratio 1 compared to

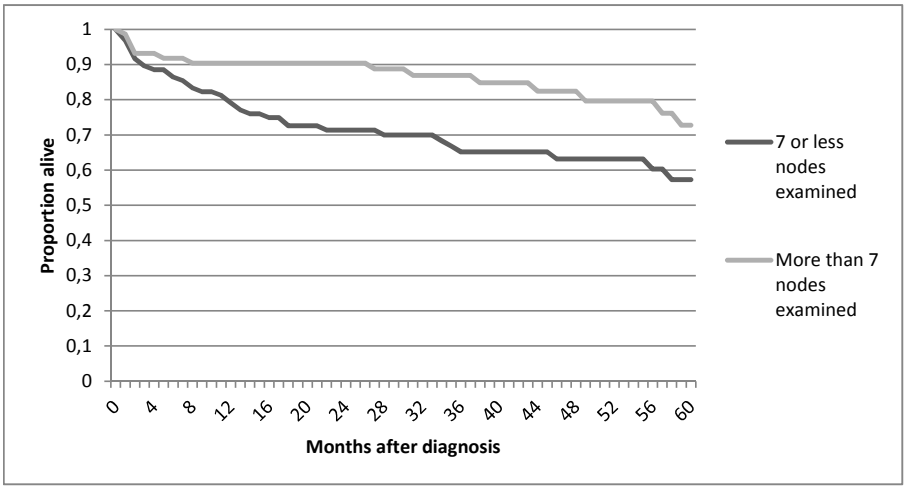

Figure 1a. Five-year crude survival of resected N0, M0 gastric cancer patients, according to number of nodes evaluated. Log-rank: p=0.009

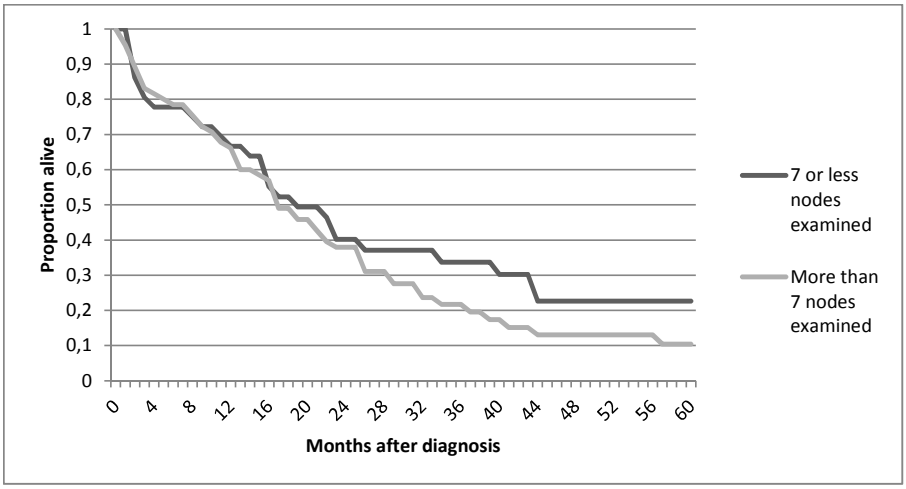

Figure 1b. Five-year crude survival of resected N+, M0 gastric cancer patients, according to number of nodes evaluated. Log-rank: p=0.379

N-ratio o. To a lesser degree, T-stage and having two or more comorbid conditions also were of prognostic importance.

Without inclusion of N-ratio or lymph node count and nodal status in the model, patients who had their resection specimen examined in department of pathology #2 exhibited a significant increased risk of death (HR 1.3, 95% confidence limits 1.01-1.7) (results not shown).

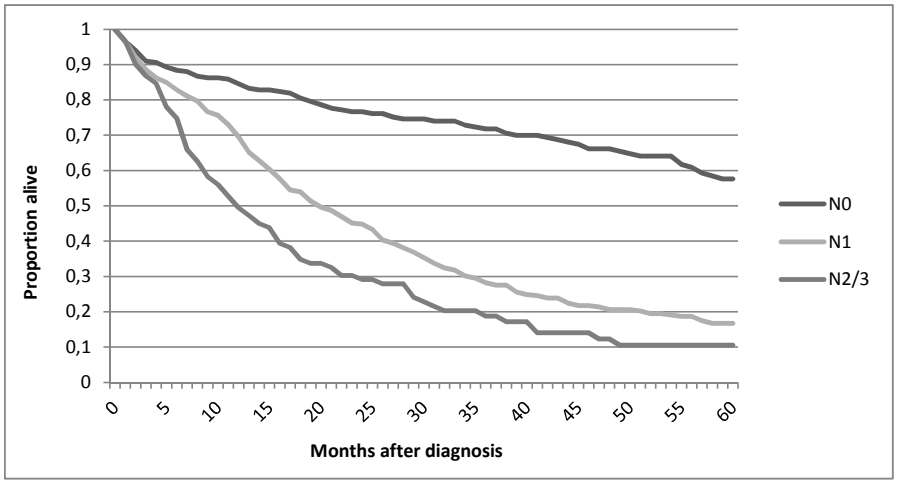

Figure 1c. Five-year crude survival of resected M0 gastric cancer patients, according to nodal status. Log-rank: p<0.0001

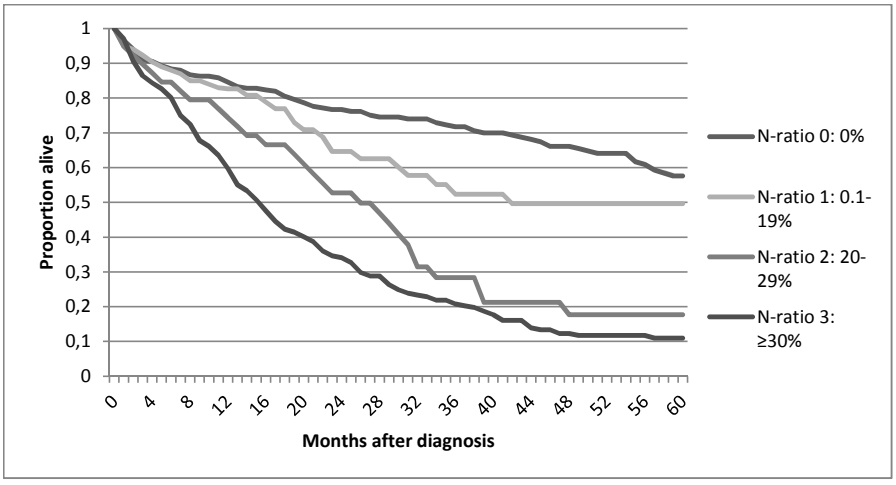

Figure 1d. Five-year crude survival of resected M0 gastric cancer patients, according to lymph node ratio (ratio between number of metastatic and evaluated lymph nodes). Log-rank: p<0.0001

Table 4. Multivariable proportional hazard regression analysis for patients who underwent resection for gastric cancer between 1999 and 2006 in the south of the Netherlands (model including all listed variables).

	Model including N-stage and number of evaluated lymph nodes separately		**Model including N-ratio**	
	Hazard ratio	95% CL	Hazard ratio	95% CL
Age (yrs)				
<70 [a]	1.0		1.0	
70+	1.1	0.9-1.3	1.1	0.9-1.4
Gender				
Males [a]	1.0		1.0	
Females	0.9	0.7-1.1	0.9	0.7-1.1
Comorbiditya				
No comorbidity [a]	1.0		1.0	
One comorbid condition	1.1	0.9-1.4	1.1	0.9-1.4
Two or more comorbid conditions	1.3	1.0-1.7	1.3	1.0-1.7
Unknown	0.9	0.6-1.5	0.9	0.5-1.4
T-stage				
T1	0.6	0.4-0.8	0.6	0.4-0.9
T2 [a]	1.0		1.0	
T3	1.1	0.9-1.5	1.2	0.9-1.5
T4	1.7	1.0-2.7	1.8	1.0-2.9
N-stage				
N0 [a]	1.0		*n.a.*	
N1	2.9	2.2-3.6		
N2/3	4.5	3.1-6.2		
Number of evaluated lymph nodes				
<7 [a]	1.0		*n.a.*	
≥7	0.7	0.6-0.9		
N-ratio				
Ratio 0 (0%) [a]	*n.a.*		1.0	
Ratio 1 (0.1-19%)			1.5	1.0-2.2
Ratio 2 (20-29%)			3.1	2.0-4.6
Ratio 3 (≥30%)			3.8	2.9-4.9
Tumor site				
Cardia	0.9	0.6-1.4	0.9	0.6-1.3
Middle part	0.9	0.7-1.2	0.9	0.7-1.2
Pyloric part [a]	1.0		1.0	
Other/unknown	1.4	1.0-1.9	1.3	1.0-1.8

Table 4. *Continued*

	Model including N-stage and number of evaluated lymph nodes separately		Model including N-ratio	
Tumour grade				
Moderately/well differentiated [a]	1.0		1.0	
Poorly differentiated	1.0	0.8-1.3	0.9	0.7-1.2
Unknown	1.0	0.7-1.6	0.9	0.7-1.5
Neoadjuvant treatment				
No [a]	1.0		1.0	
Yes	0.8	0.4-1.4	0.9	0.5-1.6
Type of resection				
Total gastrectomy	1.2	0.9-1.6	1.2	0.9-1.7
Subtotal gastrectomy [a]	1.0		1.0	
Oesophageal-cardiac resection	1.0	0.7-1.6	1.0	0.6-1.6
Multi-organ resection	1.4	0.7-2.6	1.4	0.7-2.6
Department of pathology				
1	0.8	0.6-1.1	0.8	0.6-1.1
2	1.1	0.8-1.5	1.1	0.8-1.4
3	0.9	0.6-1.2	0.9	0.6-1.2
4	1.0	0.7-1.3	1.0	0.7-1.3
5 [a]	1.0		1.0	
6	0.9	0.6-1.4	1.0	0.6-1.5
Period of diagnosis				
1999-2002 [a]	1.0		1.0	
2003-2006	1.0	0.8-1.3	1.0	0.8-1.3

[a] Reference category
n.a. = not applicable
CL=confidence limits

DISCUSSION

Nodal stage (N-stage) is one of the most important prognostic factors in gastric cancer. Proper N-staging is therefore needed to predict outcome in patients. According to UICC/AJCC guidelines in gastric cancer at least 15 lymph nodes should be investigated to correctly assess N-stage (6th and 7th edition). Additionally, several studies have shown the importance of N-ratio in staging gastric cancer [7;10]. In this retrospective study we investigated the amount of lymph nodes evaluated and N-ratio after surgery for gastric carcinoma, and its relationship to survival in the Southern part of the Netherlands.

Nodal evaluation

This region is served by 10 community hospitals, all draining on 6 departments of pathology; the median number of investigated lymph nodes between departments of pathology varied between 5 and 9 lymph nodes per patient, with a median number of 7 in the whole region. These results are confirmed by other studies, where the median number of lymph nodes examined also varied between different geographical regions [11;12]. The region is characterised by the absence of an academic hospital in our region. Recent Dutch studies showed that hospital characteristics also influenced nodal yield in colon cancer; especially academic centres showed a higher median lymph node yield [13;14]. Volume did not seem to have an effect. Also after adjustment in a multi-level analysis for these and other relevant factors, differences between departments of pathology remained, probably suggesting variation in diligence and effort put in these time-consuming examinations. Fat-clearing agents are not widely used in the Netherlands. Although a minimum number of at least 15 lymph nodes is considered mandatory for proper staging, more studies reported an insufficient number of investigated lymph nodes [11;12]. Factors associated with a higher amount of lymph nodes in these studies were younger age, female gender, Asian race, and more radical surgery [11;15]. Obesity has been suggested to be of influence as well [16]. In the present study, we did not find an effect of age or gender, but we did find an effect of more radical surgery. Obviously, in a total gastric resection more surrounding tissue is removed, resulting in more lymph nodes retrieved. Other factors associated with the amount of lymph nodes found were comorbidity, T- and N-stage, and department of pathology. Practice of surgeons and pathologists can influence the amount of lymph nodes found. In the Netherlands, mostly a D1 resection is performed. Several prospective studies have proven no benefit of a D2 resection over a D1 resection with high postoperative morbidity and mortality [4;5], although latest analyses showed lower gastric cancer related deaths and locoregional recurrence 15 years after a D2 dissection [6]. The number of lymph nodes evaluated in our region reflects the type of lymph node dissection performed. Only in 21 patients a D2 resection was reported in the study period. Although the amount of harvested lymph nodes can partly be accounted to the type of surgery, patient characteristics can be of influence as well. In a D2 resection on cadavers a range from 17 to 44 lymph nodes per patient was reported [17]. Considering the inter-individual variation in nodal count, this might lead to an inadequate lymph node dissection among certain patients. Furthermore, as patients grow older the amount of lymph nodes decreases. Differences in immunologic reaction can play a role as well. The immune reaction against neoplastic cell products alters the shape and morphology of lymph nodes. An advanced T-category might as well stimulate immune reaction, but the larger size of the tumour also might stimulate surgeon and pathologist for more aggressive lymph node harvesting. In addition, in advanced T-stage, the risk of lymph node metastases rises. Metastatic lymph nodes have a greater size, which makes harvesting

and examining them easier. The positive association between N-stage and the number of lymph nodes evaluated reflects this as well.

Besides treatment and patient- and tumour-related characteristics, inadequate lymph node harvesting might be related to the pathological examination. Different techniques of pathologic examination influences the total number of lymph nodes found. One retrospective study found more lymph node metastases when they retrospectively sectioned lymph nodes at three levels instead of one [18]. Using fat clearing technique instead of conventional techniques increased nodal yields [19]. In a previous report from the Eindhoven Cancer Registry, pathology practice was linked to the adequacy of nodal assessment in colon cancer [14]. However, the increasing median number of lymph nodes in 5 out of 6 departments of pathology in our study suggests a rise in awareness of the importance of an adequate nodal examination. There also is a role for the surgeon as well in improving quality of treatment by performing a more thorough lymph node dissection. In the end, it remains a joint responsibility of pathologist and surgeon, and communication and feedback are essential in increasing and maintaining quality of nodal assessment.

Survival

Five-year survival was significantly higher when 7 or more lymph nodes were investigated among NoMo patients. In most other studies, the threshold was set at 15 resected lymph nodes as in concordance with the UICC/AJJC guidelines, with hazard ratios of ~0.50 in favour of evaluation of more than 15 lymph nodes [12;15;20;21]. In our region, only 12% of patients had > 15 investigated lymph nodes, making evaluations at this cut-off point less reliable. Several hypotheses have been mentioned to explain the positive correlation between survival and the number of evaluated lymph nodes. One hypothesis is understaging. Understaging can be a result of a minimum amount of lymph nodes retrieved. Another hypothesis is reduction of tumour burden. With an extended lymphadenectomy, tumour burden is reduced. Even pNo patients with a lymph node count of more than 15 are found to have better survival [7]. This can be attributed partly to the removal of lymph nodes with micrometastasis, which are difficult to detect in normal pathological evaluation [20]. The fact that in our study the number of lymph nodes examined had a larger influence on survival among node-negative than among node-positive patients confirms this hypothesis. Where the effect of reduction of tumour burden becomes more important than understaging is not clear, although a prospective study of Siewert et al suggested a threshold around 15 to 20 lymph nodes [7]. This was confirmed by other, retrospective studies [12;21]. Unfortunately we were not able to adjust for radicality of resection , since this item was not routinely collected during the whole study period. Also, we could not discriminate between resections with curative versus palliative intent. However, since we included only patients who were metastasis-free

at time of diagnosis (Mo), we assume that the proportion of patients undergoing a tumour resection with strict palliative intent was very low, and has therefore probably not influenced our results.

To overcome the problem of inadequate nodal harvest in staging, the lymph node ratio (N-ratio) has been suggested This is defined as the amount of positive lymph nodes divided by the total amount of retrieved lymph nodes. It gives information about the N-stage and about the extent of lymph node dissection. In breast, colon and rectal cancer it has proven its superior prognostic information over N-stage according to the TNM classification [22-25]. In all studies evaluating N-ratio in gastric cancer, as we know of, it has proven to be an important independent prognostic factor in multivariate analysis, as confirmed by the results of our study [7;8;10;14;26-28]. We found a 5-year survival of 50% in N-ratio group 1, while these patients would have been assigned to at least the N1 group using the traditional TNM classification (6th edition), with an expected 5-year survival of maximum 17%, These results suggest a higher prognostic value of the N-ratio system in comparison to the traditional TNM classification, although more analyses should be performed to confirm this. One of the drawbacks of the N-ratio is that there are no standardized categories in literature; N-ratio groups can therefore be fit to the used dataset. Because of the low number of patients with a low N-ratio we used a higher cut-off point. This can bias our results and therefore give a higher prognostic value than the TNM-classification; some authors have questioned the clinical usefulness in case of low numbers of nodes [29]. In the new AJCC/UICC TNM classification (7th edition; N1 category: 1-2 positive nodes, N2 category: 3-6 positive nodes, N3a 7-15 positive nodes, N3b >15 positive nodes) N-category is adjusted to overcome the lower prognostic value of the 6th edition (N1 category 1-6 positive nodes, N2 category 7-15 positive nodes, N3 >15 positive nodes). The role of staging according to N-ratio is therefore still not clear and should be further investigated. It should be mentioned that improvement in staging should primarily be done by adequate lymph node harvesting and assessment.

CONCLUSION

Even though lymph node count improved over time, improvement in nodal assessment is still mandatory. Five-year survival in NoMo patients was positively correlated with lymph node count. Also in this series of patients with a relatively low number of evaluated lymph nodes, a high prognostic accuracy of N-ratio was found.

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Chapter 7

The Lymph Node Ratio as a prognostic factor for gastric cancer

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ABSTRACT

Introduction

To predict prognosis of gastric cancer, an adequate assessment of the stage of gastric cancer is important. The UICC/AJCC TNM-classification is the most commonly used classification system. For adequate N-staging at least 15 lymph nodes should be retrieved. In some countries, this amount of lymph nodes is not met, which can lead to understaging. Therefore, the lymph node ratio (LNR) is proposed as an alternative N-staging modality. The purpose of this study was to compare the different staging modalities.

Patients and methods

We included all patients who underwent surgery for gastric cancer, newly diagnosed between 2000-2009 and staged patient by UICC/AJCC TNM 5^{th}/6^{th} or 7^{th} and by lymph node ratio. We conducted crude survival analysis, univariate and multivariate analyses of according to the different staging systems.

Results

The 5-year overall survival rates ranged from 58% for No disease to 18% in case of more than 15 metastatic lymph nodes. The distribution of overall 5-year survival according to LNR was 58% for LNR0 and 10% for LNR3. Univariate analysis showed that all the UICC/AJCC TNM classification systems as well as the LNR were strong prognostic factors for overall survival. The LNR correlated less with the number of nodes examined.

Conclusion

LNR is as a good prognostic tool for overall survival, it is an independent prognostic factor with a more homogenous spread of hazard ratios and 5-year survival rates than UICC/AJCC systems. Furthermore, the LNR has a lower correlation with the number of nodes examined, making it less vulnerable for stage migration.

INTRODUCTION

Gastric cancer is the fourth most common type of cancer worldwide and ranks second with respect to cancer-related death in Europe [1]. In 2009, nearly 2000 people were newly diagnosed and almost 1500 patients died from gastric cancer [2]. Although incidence and mortality rates are decreasing, survival is worsening [3]. To predict prognosis the assessment of the stage of gastric cancer is important. The number of metastatic lymph nodes is considered to be the most reliable prognostic indicator for patients with radically resected gastric cancer [4]. In 1968 the Union Internationale Contra le Cancer (UICC) founded the UICC/AJCC Tumor Node Metastasis (TNM) classification system for malignant tumors. Several versions of this classification system have been used. The Japanese Gastric Cancer Association developed another classification for gastric cancer, however the UICC/AJCC is the superior and most commonly used classification system [5].

However, the difficulty of the UICC/AJCC TNM-classification is that for adequate N-staging at least 15 lymph nodes should be retrieved. Literature expresses that in some Western countries including the Netherlands, this amount of lymph nodes is not met by surgeons or pathologists, which can lead to understaging [6]. Apart from the UICC/AJCC system, another N-staging system was developed, which would not need the required 15 lymph nodes for adequate staging, i.e. the so-called metastatic lymph node ratio (LNR). The purpose of this study is to compare the different UICC/AJCC TNM $5^{th}/6^{th}/7^{th}$-staging systems comparing number of examined lymph nodes with the LNR and to determine which system has the best prognostic value for gastric cancer patients.

PATIENTS AND METHODS

Patients

Data from the Eindhoven Cancer Registry (ECR) were used, which is maintained and hosted by the Comprehensive Cancer Centre South. The ECR collects data on all patients diagnosed with cancer in the south of the Netherlands, an area with about 2.4 million inhabitants. The ECR is served by ten community hospitals, six pathology departments and two radiotherapy institutes. We included 973 surgical patients with Mo primary gastric cancer, newly diagnosed between 2000 and 2009.

Patient characteristics such as gender, date of birth, postal code, co morbidities and socio-economic status (SES) as well as tumor characteristics such as date of diagnosis, subsite (International Classification of Diseases for Oncology (ICD-O-3)), histology, stage, grade and treatment were obtained routinely from the medical records by specially trained administrators [7]. Follow-up of vital status of all patients was complete up to 1

January 2011. In addition to passive follow-up via the hospitals, information was actively obtained from civil municipal registries and the Central Bureau for Genealogy.

Tumor sub-localization was divided as follows: cardia, middle part fundus, corpus, lesser and greater curvature, pyloric part, overlapping lesions, and not otherwise specified. Furthermore, tumor characteristics included number of lymph nodes examined, number of positive nodes, and grade of tumor differentiation. Relevant co-morbidities were recorded from the medical records according to a slightly adapted version of the Charlson Index [8]. SES of the patients was defined at neighborhood level; postal codes were assigned to one of three SES categories: low (1st-3rd decile), intermediate (4th-7th decile), and high (8th-10th decile). For patients residing in nursing homes, a special SES category was assigned.

Registration took place 6 to 18 months after diagnosis. The quality of the data is high, due to thorough training of the registration clerks and a variety of computerized consistency checks at regional and national levels. Completeness is estimated to be at least 95% [9].

Staging

Patients were classified according to the UICC/AJCC TNM 5th/6th, 7th and to the LNR. LNR is defined as the number of positive lymph nodes divided by the total number of lymph nodes found in the specimen (Table 1).

The LNR cut-off points were based on the most common used cut-off points for the LNR used in literature. Second, we compared different cut-off points by means of the distribution of patients on the categories and we used survival as an independent variable and determined by log-rank test.

Table 1. The different classification systems

	UICC/AJCC TNM 5/6 N-classification	**UICC/AJCC TNM 7 N-classification**	**LNR**
Stage	(number of metastatic lymph nodes)	(number of metastatic lymph nodes)	(percentage of metastatic lymph nodes)
0	0	0	0
1	1-6	1-2	0.1-19
2	7-15	3-6	20-29
3	≥ 15	A: 7-15	≥ 30
		B: ≥ 15	

Statistical analysis

Survival was calculated according to the Kaplan-Meier method and compared by log-rank test. Survival time was calculated from the date of diagnosis to death or the 1st of January 2011 for those alive. Univariate and multivariate analyses of prognostic factors were performed using the Cox proportional hazard model. The LNR categories were stratified into UICC/AJCC TNM N categories and vice versa. This to assess whether LNR or TNM N-classification shows any survival benefit where the opposing staging system fails to predict this. The accepted level of significance was $p<0.05$. The data were analyzed using SAS statistical software (SAS system 9.2, SAS Institute, Cary, NC).

RESULTS

The median age of Mo gastric cancer patients was 69 years (27- 94 years). The majority of patients were male and 59% of the patients had one or more co-morbidities. Most tumors were found in the antrum and pylorus of the stomach and were poorly differentiated. Pre-operative treatment was given to a small proportion of patients and subtotal gastrectomy was the most common type of resection. In the majority of patients between 3 and 10 lymph nodes were examined (41%) (Table 2).

Figures 1 and 2 show the crude overall survival according to the UICC/AJCC TNM 5th/6th and 7th classification systems. The 5-year overall survival ranged from 58% for No disease

Table 2. Descriptives of the study population (n=973)

	N	%
Median age (range) (yrs)	69 (27-94)	
Gender		
Males	625	64
Females	348	36
Socio-economic status		
Low	286	29
Intermediate	352	36
High	280	29
Institutionalized	29	3
Unknown	26	3
Comorbidity		
None	320	33
1	293	30
≥2	283	29
Unknown	77	8

Table 2. *Continued*

	N	%
Tumour site		
Cardia	183	19
Middle part	236	24
Antrum and pylorus	364	37
Overlapping, unknown	190	20
Stage		
IA	123	13
IB	259	27
II	307	32
IIIA	213	22
IIIB	36	4
IV	35	4
Differentiation grade		
Moderate/well	275	28
Poor	563	58
Unknown	135	14
Preoperative treatment		
Chemo- and/or radiotherapy	133	14
None	840	86
Type of resection		
Total gastrectomy	223	59
Subtotal gastrectomy	571	23
Oesophageal-cardiac resection	126	13
Multi-organ resection	31	3
Unspecified type of resection	22	2
Number of lymph nodes evaluated		
0	58	6
1-2	69	7
3-6	198	20
7-10	203	21
11-14	151	16
≥ 15	145	15
Exact number unknown	145	15
Unknown	4	0

to 18% in case of more than 15 metastatic lymph nodes. In stage N1 according to the 5th/6th TNM classification overall 5-year survival was 19%. In the 7th TNM classification the 5th/6th TNM N1 stage is divided in N1 and N2, with a 5-year survival of 27% and 11% respectively. In this cohort of patients having Mo gastric cancer, stage N3b of the 7th

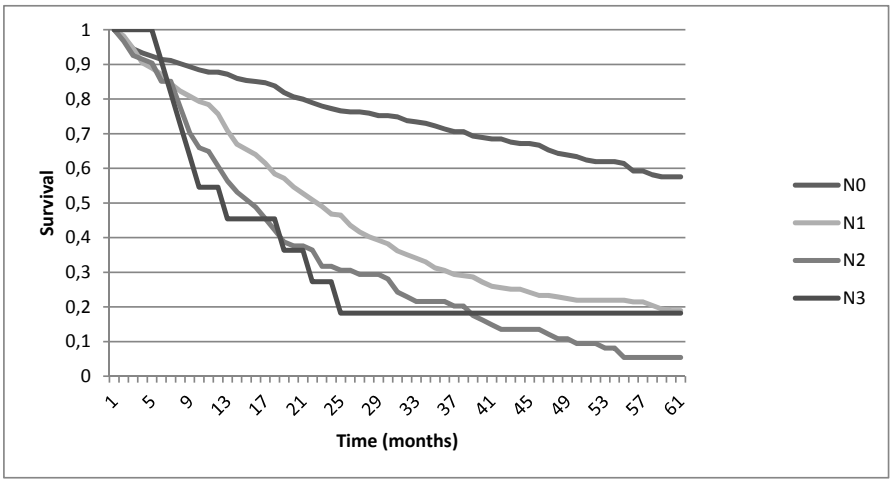

Figure 1. Overall crude survival of M0 gastric cancer patients diagnosed in the ECR region between 2000 and 2009 according to TNM6 N stage. Log rank p <0.001

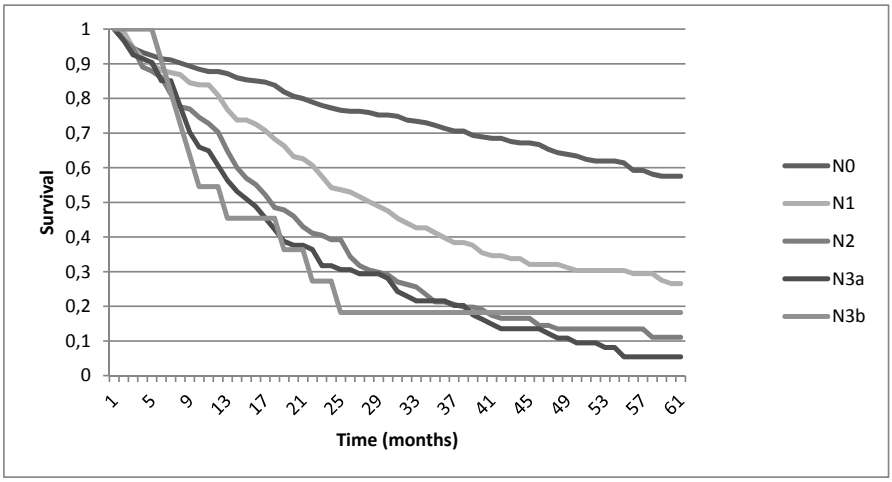

Figure 2. Overall crude survival of M0 gastric cancer patients diagnosed in the ECR region between 2000 and 2009 according to TNM7 N stage. Log Rank p <0.001

TNM-classification showed a better prognosis then the N3a stage in terms of overall survival. The distribution of overall crude 5-year survival according to LNR ranged from 58% for LNR0 to 10% for LNR3 (Figure 3). Univariate Cox survival showed that either the TNM $5^{th}/6^{th}$ and 7^{th} classification as well as the LNR were strong prognostic factors for overall survival. The univariate analyses showed similar results as multivariate analyses after adjustment for relevant patient and tumor characteristics listed in table 3.

In multivariate analysis, the $5^{th}/6^{th}$ TNM N stage, age, co- morbidities and 6^{th} TNM T-stage had an independent effect on survival in the first model. UICC/AJCC $5^{th}/6^{th}$ TNM

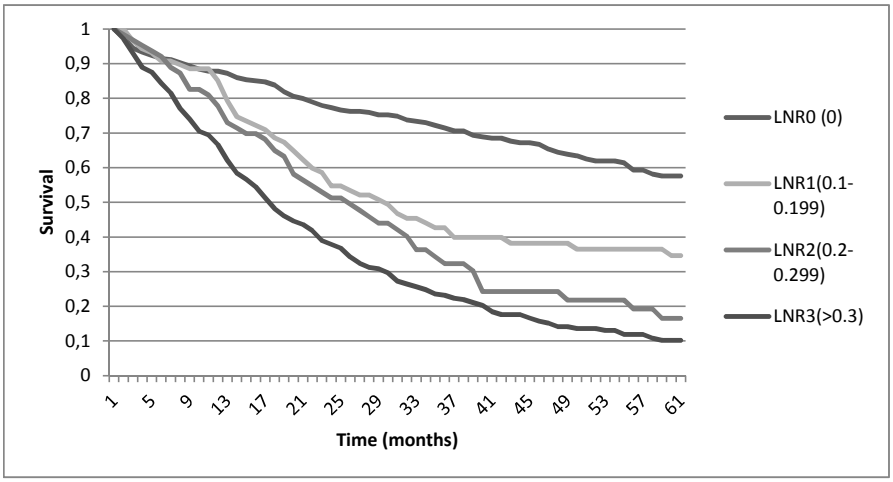

Figure 3. Overall crude survival of M0 gastric cancer patients diagnosed in the ECR region between 2000 and 2009 according to N ratio. Log Rank p <0.001

N2-stage had a higher hazard ratio than N3-stage, 3.48 (95% CI 2.64-4.59) versus 2.51 (95% CI 1.33-4.72). In our models concerning TNM 7th and LNR the aforementioned factors also had an independent effect on survival. In the second model UICC/AJCC 7th TNM N2 and N3a stage had a higher hazard ratio then stage N3b. In the last model the hazard ratios for the various LNR stages increased from 1,72 (95% CI 1.25-2.37) in LNR1 to 3.22 in LNR3 (95% CI 2.59-4.10) (Table 3). This table also shows that patient distribution among different classification systems is best in UICC/AJCC TNM 7th.

There was a significant correlation between number of lymph nodes examined and the UICC/AJCC TNM 7th (correlation coefficient =0.33; p<0.001) or TNM 5th/6th N-classification (correlation coefficient = 0.33; p<0.001). The LNR correlated less but was still significant (correlation coefficient= 0,11; p = 0.0019). There was no significant difference in survival after stratifying LNR stage 3 in different UICC/AJCC TNM N stages. For the other LNR groups, stratification for N stage was not possible due to small numbers and little variation within the LNR group. The LNR showed significant differences within N1 stage of the 5th/6th or 7th TNM in terms of survival. In the 7th TNM classification patients with a N1 stage and a LNR1 had a 5-year overall survival of 39%, while patients with a LNR stage 3 had a 5year overall survival of 15% (p =0.0404). For TNM 6th N1 patients similar survival differences were found (Table 4a and 4b).

Table 3. Overall multivariate survival analysis for M0 gastric cancer patients.

		Hazard Ratio (95% Confidence Interval)		
	N	**Model 1**	**Model 2**	**Model 3**
TNM 5/ 6 N stage				
N0	387	1.0		
N1	372	2.32 (1.92-2.80)*		
N2	99	3.48 (2.64-4.59)*		
N3	12	2.51 (1.33-4.72)*		
Exact number unknown	49	2.35 (1.64-3.34)*		
TNM 7 N stage				
N0	387		1.0	
N1	189		1.85 (1.48-2.32)*	
N2	183		3.07 (2.46-3.84)*	
N3a	99		3.56 (2.70-4.70)*	
N3b	12		2.54 (1.35-4.78)**	
Exact number unknown	49		2.39 (1.68-3.41)*	
N ratio				
0 (0)	382			1.0
1 (0.01-0.19)	87			1.72 (1.25-2.37)*
2 (0.20-0.29)	63			2.54 (1.81-3.55)*
3 (0.30-1.00)	288			3.22 (2.59-4.10)*
Missing	207			2.29 (1.81-2.91)*
Age (yrs)				
<70	491	1.0	1.0	1.0
70+	482	1.25 (1.06-1.47)*	1.29 (1.09-1.52)*	1.28 (1.08-1.51)**
Gender				
Males	625	1.0	1.0	1.0
Females	348	0.92 (0.78-1.09)	0.94 (0.80-1.12)	0.98 (0.83-1.17)
Comorbidity				
None	320	1.0	1.0	1.0
1	293	1.23 (1.00-1.50)**	1.21 (0.99-1.48)	1.18 (0.97-1.45)
2 or more	283	1.51 (1.23-1.86)*	1.54 (1.25-1.90)*	1.45 (1.18-1.78)**
unknown	54	1.17 (0.82-1.67)	1.20 (0.84-1.71)	1.09 (0.76-1.56)
TNM 6 T stage				
T1	152	0.52 (0.38-0.70)*	0.54 (0.40-0.73)*	0.47 (0.35-0.64)*
T2	528	1.0	1.0	1.0
T3	255	1.28 (1.07-1.52)**	1.28 (1.07-1.53)*	1.31 (1.09-1.56)**
T4	35	1.87 (1.28-2.74)**	1.97 (1.34-2.89)*	1.92 (1.31-2.81)**

Table 3. *Continued*

		Hazard Ratio (95% Confidence Interval)		
	N	**Model 1**	**Model 2**	**Model 3**
Number of lymph nodes examined				
<7	325	1.18 (0.98-1.42)	1.18 (0.98-1.42)	1.00 (0.84-1.20)
≥7	499	1.0	1.0	1.0
Tumour site				
Cardia	183	0.89 (0.65-1.22)	0.87 (0.64-1.19)	0.90 (0.66-1.23)
Middle part	236	0.82 (0.66-1.02)	0.83 (0.67-1.04)	0.84 (0.68-1.05)
Pyloric part	364	1.0	1.0	1.0
Other/unknown	190	1.10 (0.87-1.38)	1.08 (0.86-1.36)	1.03 (0.83-1.29)
Type of resection				
Total gastrectomy	191	1.18 (0.96-1.46)	1.19 (0.96-1.47)	1.31 (1.06-1.61)*
Subtotal gastrectomy	571	1.0	1.0	1.0
Oesophageal-cardia resection	126	1.28 (0.91-1.81)	1.30 (0.92-1.83)	1.41 (1.00-1.99)
Multi-organ resection	31	1.29 (0.83-2.00)	1.26 (0.81-1.96)	1.43 (0.92-2.22)
Neoadjuvant treatment				
No	840	1.0	1.0	1.0
Yes	133	0.99 (0.76-1.28)	1.00 (0.77-1.30)	1.07 (0.83-1.40)

Model 1: Multivariate analysis with TNM 5/6 N stage, model 2 : Multivariate analysis with TNM 7 N stage, model 3: Multivariate analysis with lymph node ratio.
*p ≤ 0.001; ** p<0.05

Table 4a. 5-yr overall survival for N stage 1 and N stage 2 (TNM 7) according to lymph node ratio

	TNM 7 N1 n=187		**TNM 7 N2 n=183**	
	N	5-yr overall survival	N	5-yr overall survival
Lymph node ratio				
1 (0.1-0.19)	78	39*	8[a]	
2 (0.20-0.29)	38	18	20	18
3 (0.30-1.00)	52	15	137	11
Missing	19	21	18[a]	

*p<0.05; [a] not available due to small numbers

Table 4b. 5-yr overall survival for N stage (TNM 6) according to lymph node ratio

	TNM 6 N1 n=370		TNM 6 N2 n=183	
	N	5-yr overall survival	N	5-yr overall survival
Lymph node ratio				
1 (0.1-0.19)	86	35*	8[a]	
2 (0.20-0.29)	58	18	20	17
3 (0.30-1.00)	189	12	137	11
Missing	37	11	18[a]	

*p<0.05; [a] not available due to small numbers

DISCUSSION

The results of this study show that the various versions of the TNM classification and the LNR are independent prognostic factors for overall survival. The LNR had the best homogenous spread of overall crude 5-year survival and hazard ratios, and correlated the least with the total amount of lymph nodes examined.

In 1997 the UICC/AJCC introduced the 5th edition of the UICC/AJCC TNM Classification of Malignant Tumors [10]. At this time N stage was defined as: N1 having metastases in 1-6 lymph nodes, N2 having metastases in 7-15 lymph nodes and N3 as having metastases in more than 16 lymph nodes. Subsequently in 2002, the UICC/AJCC came with the 6th edition of the UICC/AJCC TNM-staging system, which was only slightly different from the previous one and remained the same in terms of N stage. After the 7th edition was published in 2010 there was a reclassification for the T and the N stage, which resulted in a shift from stage IV to stage III disease [11]. In this edition N stage was defined as N1 having metastases in 1-2 lymph nodes, N2 in 3-6 lymph nodes, N3a in 7-15 lymph nodes, and N3b in more than 15 lymph nodes [12]. A minimum of 15 lymph nodes examined is necessary for adequate staging using the TNM classification system. In the Netherlands and various other countries this amount is often not met. Previous research done in the Comprehensive Cancer Centre South showed that this can partly be explained by differences between the various pathology departments [6], showing a difference in the median number of detected lymph nodes. The region of the Comprehensive Cancer Centre South is served by six departments of pathology and the number of lymph nodes assessed varied between 5 and 9 lymph nodes per patient, with a median number of 7 in the whole region. Also after adjustment in a multi-level analysis for relevant factors, differences between departments of pathology remained, probably suggesting variation in diligence and effort put in these time-consuming examinations. They did not find an effect of age, gender or operating volume. The latter would make centralization of surgery for gastric cancer less effective for harvesting more lymph nodes.

Centralization of gastric cancer surgery has been a frequently discussed topic in the Netherlands. Recent literature on the difference between low (1-5 gastrectomies) and high (over 20 gastectomies) volume hospitals confirmed the improved harvesting of lymph nodes in high volume hospitals [13]. On the other hand, this study fails to show if they meet the minimal amount of lymph nodes needed, making an alternative N staging modality still necessary. However, since 2012, gastrectomies in the Netherlands are centralized to a minimum of 10/year and as of 2013 to a minimum of 20/year.

Further known factors associated with a higher detected number of lymph nodes are younger age, comorbidity, female gender, Asian race, obesity and more radical surgery [6;14-16]. Obviously, in a total gastric resection more surrounding tissue is removed, resulting in more lymph nodes retrieved and assessed. In the Netherlands, mostly a D1 resection is performed. The type of lymph node dissection during surgery is still subject to discussion and there is no worldwide consensus about this. There are different types of lymphadenectomy. In a D1 resection perigastric lymph nodes are removed, while in a D2 resection additionally the lymph nodes around the left gastric artery, the common hepatic artery and splenic artery are removed, depending on location of the tumor [17]. Limited research has been done for LNR for gastric cancer treated with a limited lymphadenectomy, as usually conducted in the Western world including the Netherlands. Nevertheless adequate research has been done in extended lymphadenectomy and for various other types of carcinomas [18].

This study implicates that LNR is as a good prognostic tool for overall survival in a population with a limited lymphadenectomy and a minimal amount of lymph nodes harvested during surgery and/or examined during pathology. The results show that LNR is an independent prognostic factor with a more homogenous spread of hazard ratios and crude 5-year overall survival rates than UICC/AJCC TNM-classification system's 5th, 6th and 7th version. Furthermore, the LNR has a lower correlation with the number of lymph nodes examined, making it less vulnerable for stage migration: finding metastases that had previously been unidentified which results in upstaging of patients. The identification of metastases can be done by examining and/or harvesting more (metastatic) lymph nodes during surgery and pathology [19]. In a small population the LNR showed a survival benefit where the conventional staging system failed to predict any benefit (Table 4a and b). Patients with a UICC/AJCC TNM 5th/6th or 7th N1 stage and a LNR stage 3, have a prognosis that is closer to an UICC/AJCC TNM N2 stage disease.

Compared to the 5th/6th version of the UICC/AJCC TNM classification, the 7th version had a more homogenous spread in 5-year overall survival. Although the 7th TNM N3b stage had a better 5 year overall survival then N2 and N3a, the spread among all curves is more homogenous when comparing UICC/AJCC TNM 5th/6th with 7th. Nevertheless it failed to show a benefit in multivariate survival analysis, with 7th TNM N3b-stage having a better prognostic value than N2 and N3a-stage. This is probably due to the small amount

of patients with N3b stage. UICC/AJCC 7th TNM classification correlated as strong as the 5th and 6th version with the total number of lymph nodes examined, making it more vulnerable for stage migration. It seemed to be less influenced by confounding factors when comparing univariate with multivariate analysis.

When reviewing the literature for the prognostic impact of LNR compared to the 5th/6th UICC/AJCC TNM-classification, most studies demonstrate that LNR is a better prognostic tool than the 5th/6th UICC/AJCC TNM-classification. The LNR is proven to be the strongest independent prognostic factor in terms of overall survival and a prognostic factor for recurrence of disease [20;21]. It also minimizes stage migration by being an independent prognostic factor without being influenced by the amount of lymph nodes examined [18]. Whereas stage migration is suggested to be at least 10% and up to 25% in the conventional TNM classification systems, LNR halves the stage migration phenomenon [22;23]: in a study done by Persiani et. al.[24], stage migration was found in 19% of the cases classified by the 5th 6th UICC/AJCC TNM-system, and in only 11% of the cases when LNR was applied [24]. As stated by our results and in the literature the LNR gives a more homogenous stratification of the survival curves [25]. In addition, literature shows that LNR can make a prognostic difference between different UICC/AJCC TNM N stages: N1 patients having a LNR less than 9% have similar survival as patients with No gastric cancer, and patients with a LNR between 10% and 25% have a prognosis similar to a TNM 5th/6th N2-stage. On the contrary, UICC/AJCC TNM N stages cannot significantly distinguish in survival between different LNR groups [26]. The power of our research refrains us from drawing this conclusion, but our evidence suggests a prognostic benefit for LNR within different TNM stages in terms of survival. Several studies also endorse these benefits for a D1 lymph node dissection, but all studies have a higher average amount of lymph nodes harvested [23].

When comparing literature about the 5th/6th UICC/AJCC TNM-classification with its successor, conclusions vary. Some evidence suggests the 7th edition being the best classification for predicting overall survival: they found in that the 7th edition N stage is an independent factor for predicting overall survival instead of the 5th/6th edition N stage multivariate survival analysis. They also showed a statistically significant difference between survival in 7th N1 and N2 stages, but not in 5th/6th N2 and N3 stages. This research has been done in both extended as limited lymph node dissection [12;27], and could not be confirmed by our results. Others suggest the new TNM system to be a major reclassification, without improving the assessment of patient prognosis even showing inferior distribution in survival curves. In this study, the type of lymph node dissection is not mentioned [28]. Our results do also show a major redistribution but also a more homogenous spread of survival curves.

Little is published about the prognostic value of the 7th UICC/AJCC TNM classification compared to the LNR. However, it has been reported that in the 7th edition of the TNM

staging system the proportion of advanced TNM N stage increases when the number of examined lymph nodes increases, being prone to stage migration. This in contrast to the LNR which was constant regardless of the number of lymph nodes examined. It also showed better patterns of patient distribution between LN stages and a better distribution of survival curves. The research has been done in both limited as extended lympadenectomy. Literature showing small numbers of lymph nodes after surgery demonstrated the LNR to be of low clinical utility due to a small number of patients in the first LNR stage [29;30]. The latter was not being reproduced in our research, nor did the LNR show a better distribution of patients, but it did show a better distribution of survival curves.

From a critical point of view the weaker aspect of this study might be found in the cut off points of the LNR. These are chosen by the authors and could be chosen in favor of this study or LNR itself. Another point of criticism is that this research used overall survival instead of disease specific survival. Unfortunately the use of disease specific survival was not possible because the ECR does not register the cause of death.

CONCLUSION

In this population-based study on patients with Mo gastric cancer who usually underwent a limited lymph node dissection and who thus generally have a small number of lymph nodes examined, the lymph node ratio is a good and simple prognostic instrument. It has the best homogenous spread of overall crude 5-year survival and hazard ratios and it is less vulnerable for stage migration then the UICC/AJCC TNM classification and might be able to make a significant difference within different N stadia.

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Part III

Treatment and quality of care in gastric cancer

Chapter 8

Effect of hospital volume on postoperative mortality and survival after esophageal and gastric cancer surgery in the Netherlands between 1989 and 2009

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ABSTRACT

Background

High hospital volume is associated with better outcomes after esophagectomy and gastrectomy. In the Netherlands, a minimal volume standard of 10 esophagectomies per year was introduced in 2006. For gastrectomy, no minimal volume standard was set. Aims of this study were to describe changes in hospital volumes, mortality and survival, and to explore if high hospital volume is associated with better outcomes after esophagectomy and gastrectomy in the Netherlands.

Methods

From 1989-2009, 24,246 patients underwent esophagectomy (N=10,025) or gastrectomy (N=14,221) in the Netherlands. Annual hospital volumes were defined as very low (1-5), low (6-10), medium (11-20), and high (≥21). Volume-outcome analyses were performed using Cox regression, adjusting for year of diagnosis, case-mix, and the use of multimodality treatment.

Results

From 1989-2009, the percentage of patients treated in high-volume hospitals increased for esophagectomy (from 7% to 64%), but decreased for gastrectomy (from 8% to 5%). Six-month mortality (from 15% to 7%) and thee-year survival (from 41% to 52%) improved after esophagectomy, and to a lesser extent after gastrectomy (six-month mortality: 15%-10%, three-year survival: 55-58%). High hospital volume was associated with lower 6-month mortality (HR 0.48, $P < 0.001$) and longer 3-year survival (HR 0.77, $P < 0.001$) after esophagectomy, but not after gastrectomy.

Conclusions

Esophagectomy was effectively centralized in the Netherlands, improving mortality and survival. Gastrectomies were mainly performed in low volumes, and outcomes after gastrectomy improved to a lesser extent, indicating an urgent need for improvement in quality of surgery and perioperative care for gastric cancer in the Netherlands.

INTRODUCTION

Esophageal and gastric cancer are highly lethal malignancies [1]. Despite surgery, which is the cornerstone of curative treatment for these diseases, survival is low, and compared to other surgical procedures, postoperative mortality is high. In the Western world, 5-year survival rates are below 25% for esophageal cancer [2;3], and do not exceed 40% for gastric cancer [2;4].Reported postoperative mortality after esophagectomy varies from 2% for specialized centers [5] to 10% for certain nationwide registries [6]. After gastrectomy, postoperative mortality varies between 3% to well above 10% [7;8]. To reduce mortality and improve survival, it has been suggested that these high-risk operations should be performed in specialized centers with adequate annual volumes. Many studies have investigated volume-outcome relations after esophagectomy and gastrectomy, but the relative importance of volume after gastrectomy in particular is disputed [9;10].

In the Netherlands, a relation between high hospital volume and low postoperative mortality was demonstrated for esophagectomy in 2000 [11]. Despite extensive discussions within the Dutch Society of Surgery, this study did not lead to significant changes in referral patterns for esophagectomies on a national level. Therefore, as of 2006 a minimum volume of 10 esophagectomies per year was enforced by the Dutch Healthcare Inspectorate, and as of 2011 the Dutch Society of Surgery recommends a minimal volume of 20 esophagectomies per year. For gastrectomy, no minimum volume standard has been established in the Netherlands.

Aims of the present study were to describe changes in annual hospital volumes, postoperative mortality, survival, and lymph node yields for esophagectomy and gastrectomy in the Netherlands between 1989 and 2009, and to explore whether there is any association between annual hospital volume for esophagectomy and gastrectomy, and postoperative mortality, survival, and lymph node yield.

PATIENTS AND METHODS

The Netherlands Cancer Registry

Data were obtained from the Netherlands Cancer Registry (NCR), which covers all hospitals in the Netherlands, a country of 16.5 million inhabitants. Information on all newly diagnosed malignancies is routinely collected by trained registrars from the hospital records 6-18 months after diagnosis. Quality and completeness of the data is high [12].

Topography and morphology were coded according to the International Classification of Diseases for Oncology (ICD-O) [13]. ICD-O morphology codes were used to classify tumors as adenocarcinoma (8140-8145, 8190, 8201-8211, 8243, 8255-8401, 8453-8520, 8572, 8573, 8576), squamous cell carcinoma (SCC) (8032, 8033, 8051-8074, 8076-8123) and other

or unknown histology (8000-8022, 8041-8046, 8075, 8147, 8153, 8200, 8230-8242, 8244-8249, 8430, 8530, 8560, 8570, 8574, 8575). Tumors were staged according to the International Union Against Cancer (UICC) TNM classification in use in the year of diagnosis. 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. Follow-up was complete for all patients until December 31st, 2009. The study was approved by the NCR Review Board.

Patients

Between January 1989 and December 2009, 71,090 patients with esophageal or gastric cancer were diagnosed in the Netherlands (Figure 1). Patients who did not undergo surgical treatment (N = 43,646) and patients without information on the hospital were the diagnosis was established, or where surgery was performed (N = 8), were excluded, leaving 27,436 resections available to calculate annual hospital volumes. After establishing annual hospital volumes, patients with in-situ carcinoma (N = 288), and patients with distant metastases (N = 2902) were excluded, leaving 24,246 patients with non-metastatic invasive carcinoma available for volume-outcome analyses.

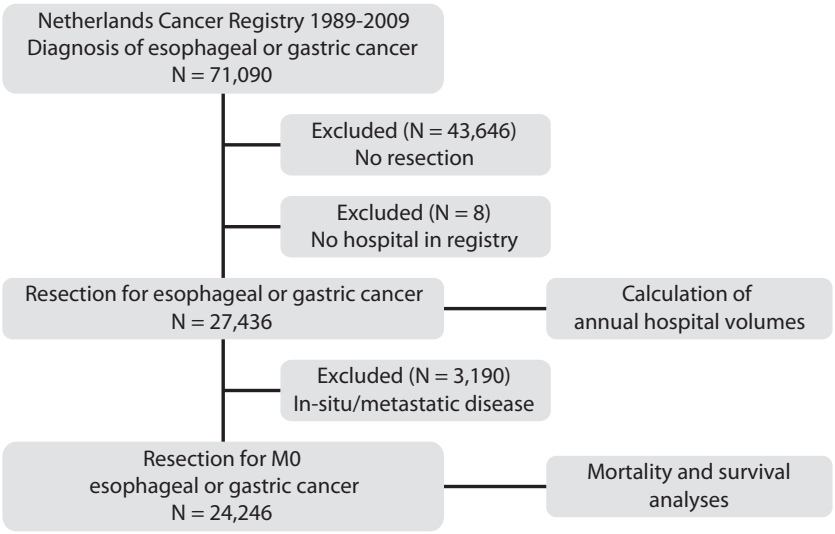

Figure 1. Study profile.

Surgery

Since the NCR is a topography-based registry, and the type of surgery was not specified for every patient, the distinction between esophageal and gastric cancer surgery was based on tumor location. Esophagectomies were defined as resections for cancers of the esophagus (C15.0-15.9) and gastric cardia (C16.0), whereas gastrectomies were defined as resections for non-cardia gastric cancer (C16.1-16.9). To ensure this distinction did not influence the results, volume-outcome analyses were repeated with cardia cancer coded as gastric cancer. Yearly resection rates were calculated as the number of resections relative to the number of cancers diagnosed in a year.

Hospital volumes

Annual hospital volumes were defined as the number of esophagectomies or gastrectomies per hospital per year. Clinically relevant volume categories were defined as very low (1-5/year), low (6-10/year), medium (11-20/year), and high (≥21/year). From 2005-2009, the hospital where surgery was performed was registered for all patients. Before 2005, the hospital were surgery was performed was only registered in 53% of the cases, and showed an 80% overlap with the hospital of diagnosis. For the remaining 47%, with an unknown surgical hospital, the hospital of diagnosis was used to calculate hospital volume.

Statistical analysis

Esophagectomy and gastrectomy were analyzed separately. Resection rates and hospital volumes over time were analyzed with the Chi-square test. Changes in six-month mortality and three-year survival were analyzed with stratified Cox regression, adjusted for sex, age, socio-economic status [14], stage, morphology, preoperative therapy use, and postoperative therapy use (only for three-year survival). Overall survival (OS) was calculated from the day of diagnosis until death, because the date of surgery was not available before 2005. Six-month OS was calculated unconditionally, while 3-year OS was calculated conditionally on surviving the first six months after diagnosis. Lymph node yields over time were adjusted for sex, age, stage, and morphology.

For volume-outcome analyses, the patient was considered the unit of analysis, with hospital volume as the exposure factor. Differences in survival estimates were calculated with Cox regression, stratified for hospital volume and adjusted for the factors used to analyze changes over time, and for clustering of deaths within hospitals [15]. Differences in lymph node yields were analyzed with generalized estimated equations, adjusted for the factors used to analyze changes over time, and for clustering within hospitals.

Besides analyzing hospital volume in categories, annual volume was analyzed as a linear variable. Analyses were performed with SPSS (version 17.0.2) and R (version 2.12.2).

RESULTS

Patient characteristics

Between 1989 and 2009, 24,246 patients with resectable, non-metastatic esophageal (N = 10,025) or gastric cancer (N = 14,221) underwent a resection in the Netherlands. Patient characteristics (Table 1 and 2) varied between the different volume categories.

Table 1. Patient characteristics for all surgically treated patients with non-metastatic invasive esophageal cancer in the Netherlands between 1989 and 2009 (N = 10,025)

	VLV (1-5)		LV (6-10)		MV (11-20)		HV (≥21)		P
	N	%	N	%	N	%	N	%	
Total	2914	*100*	2695	*100*	1494	*100*	2922	*100*	
Sex									
Male	2213	*76*	2058	*76*	1130	*76*	2249	*77*	0.73
Female	701	*24*	637	*24*	364	*24*	673	*23*	
Age Category									
<60	936	*32*	956	*35*	515	*34*	1032	*35*	0.002
60-75	1630	*56*	1456	*54*	814	*54*	1632	*56*	
>75	348	*12*	283	*11*	165	*11*	258	*9*	
SES									
Low	274	*9*	308	*11*	165	*11*	259	*9*	<0.001
Medium	2415	*83*	2124	*79*	1208	*81*	2131	*73*	
High	135	*5*	123	*5*	53	*4*	115	*4*	
Unknown	90	*3*	140	*5*	68	*5*	417	*14*	
Morphology									
Adenocarcinoma	2288	*79*	2006	*74*	1113	*74*	2134	*73*	<0.001
SCC	554	*19*	628	*23*	341	*23*	732	*25*	
Other	72	*2*	61	*2*	40	*3*	56	*2*	
TNM stage									
I	622	*21*	512	*19*	285	*19*	522	*18*	<0.001
II	1161	*40*	1093	*41*	576	*39*	1068	*37*	
III	988	*34*	940	*35*	535	*36*	1112	*38*	
IV*	30	*1*	30	*1*	23	*2*	25	*1*	
unknown	113	*4*	120	*4*	75	*5*	195	*7*	
Preoperative therapy									
Yes	165	*6*	244	*9*	357	*24*	938	*32*	<0.001
No	2749	*94*	2451	*91*	1137	*76*	1984	*68*	
Postoperative therapy									
Yes	144	*5*	145	*5*	91	*6*	151	*5*	0.43
No	2770	*95*	2550	*95*	1403	*94*	2771	*95*	

VLV: Very Low Volume (1-5 resections/year) LV: Low Volume (6-10 resections/year), MV: Medium Volume (11-20 resections/year), HV: High Volume (≥21 resections/year)
SES: Socio Economic Status, Preoperative/postoperative therapy: chemotherapy with/without radiotherapy.
* T4N1-3M0 and T1-4N3M0 gastric cancers were assigned stage IV in the 6th edition TNM-classification

Table 2. Patient characteristics for all surgically treated patients with non-metastatic invasive gastric cancer in the Netherlands between 1989 and 2009 (N = 14,221)

	VLV (1-5)		LV (6-10)		MV (11-20)		HV (≥21)		P
	N	%	N	%	N	%	N	%	
Total	3411	*100*	6099	*100*	4356	*100*	355	*100*	
Sex									
Male	1987	*58*	3707	*61*	2646	*61*	224	*63*	0.045
Female	1424	*42*	2392	*39*	1710	*39*	131	*37*	
Age Category									
<60	689	*20*	1270	*21*	837	*19*	53	*15*	0.016
60-75	1606	*47*	2917	*48*	2074	*48*	165	*46*	
>75	1116	*33*	1912	*31*	1445	*33*	137	*39*	
SES									
Low	378	*11*	783	*13*	560	*13*	53	*15*	<0.001
Medium	2665	*78*	4846	*79*	3559	*82*	294	*83*	
High	118	*3*	230	*4*	106	*2*	8	*2*	
Unknown	250	*7*	240	*4*	131	*3*	0	*0*	
Morphology									
Adenocarcinoma	3336	*98*	5985	*98*	4287	*98*	352	*99*	0.11
Other	75	*2*	114	*2*	69	*2*	3	*1*	
TNM stage									
I	1299	*38*	2279	*37*	1687	*39*	147	*41*	0.014
II	898	*26*	1675	*27*	1187	*27*	78	*22*	
III	936	*27*	1718	*28*	1204	*28*	111	*31*	
IV*	181	*5*	248	*4*	154	*4*	11	*3*	
unknown	97	*3*	179	*3*	124	*3*	8	*2*	
Preoperative therapy									
Yes	167	*5*	303	*5*	138	*3*	8	*2*	<0.001
No	3244	*95*	5796	*95*	4218	*97*	347	*98*	
Postoperative therapy									
Yes	139	*4*	236	*4*	122	*3*	12	*3*	0.009
No	3272	*96*	5863	*96*	4234	*97*	343	*97*	

VLV: Very Low Volume (1-5 resections/year) LV: Low Volume (6-10 resections/year), MV: Medium Volume (11-20 resections/year), HV: High Volume (≥21 resections/year)

SES: Socio Economic Status, Preoperative/postoperative therapy: chemotherapy with/without radiotherapy.

* T4N1-3M0 and T1-4N3M0 gastric cancers were assigned stage IV in the 6th edition TNM-classification

For esophageal cancer, high-volume hospitals treated more patients with squamous cell carcinoma and more advanced tumor stages. For gastric cancer, patients treated in high-volume hospitals were older and had more advanced tumors.

Hospital volumes over time

From 1989 to 2009, the annual number of esophagectomies doubled (from 352 to 723), and the annual number of gastrectomies steadily decreased (from 1107 to 495) (Figure

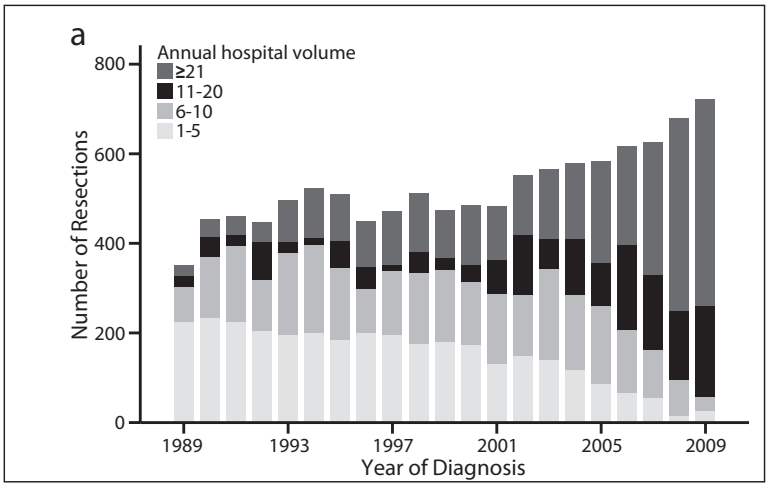

Figure 2a. Number of esophagectomies per hospital volume category.

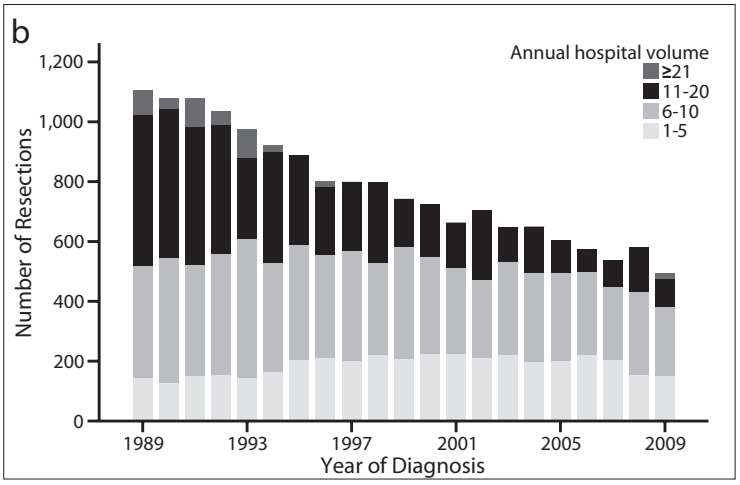

Figure 2b. Number of gastrectomies per hospital volume category.

2). The percentage of esophagectomies performed in high-volume hospitals increased from 7% to 64%, while the number of gastrectomies performed in high-volume hospitals decreased from 8% to 5%. In 2009, 44 of the 92 hospitals (48%) in the Netherlands performed esophagectomies, and 91 of the 92 hospitals performed gastrectomies.

Resection rates, mortality, survival and lymph node yields over the years

Resection rates slightly decreased for esophageal cancer (from 1989-2009: 31% - 29%, $P < 0.01$), and strongly decreased for gastric cancer (56%-37%, $P < 0.01$). Adjusted six-month mortality after esophagectomy decreased from 14.8% in 1989 to 7.1% in 2009 ($P < 0.001$), while adjusted six-month mortality after gastrectomy decreased to a lesser extent: from 15.2% in 1989 to 9.9% in 2009 ($P < 0.001$) (Figure 3a). Adjusted three-year conditional survival significantly increased after esophagectomy: from 41.0% in 1989 to

52.2% in 2009 ($P < 0.001$). Adjusted three-year conditional survival after gastrectomy increased to a lesser extent: from 55.0% in 1989 to 58.4% in 2009 ($P < 0.01$) (Figure 3b). The improvement in six-month mortality and three-year survival over time was significantly stronger after esophagectomy, when compared to gastrectomy (both $P < 0.01$). Mean lymph node yield after esophagectomy increased from 10.1 in 1999 to 16.2 in 2009 ($P < 0.001$), and mean lymph node yield after gastrectomy increased from 8.1 in 1999 to 12.4 in 2009 ($P < 0.001$).

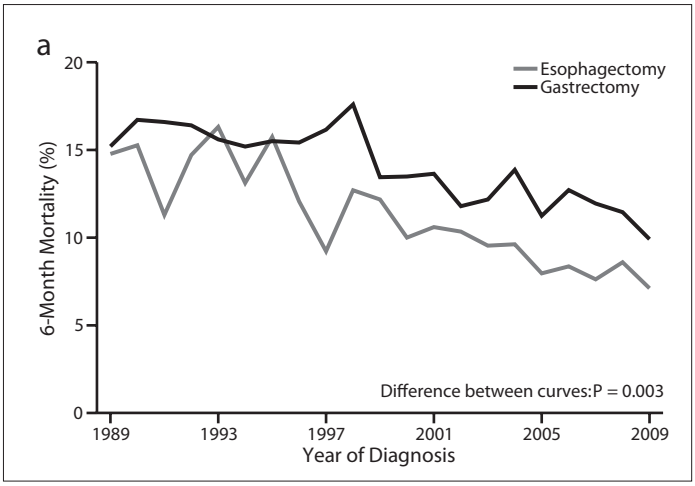

Figure 3a. Six-Month mortality for esophagectomy and gastrectomy, adjusted for sex, age, socioeconomic status, stage, morphology, and use of preoperative therapy (1989-2009). Esophagectomy, HR 0.96 for each year, P < 0.001. Gastrectomy, HR 0.98 for each year, P < 0.001. Difference between esophagectomy and gastrectomy: P = 0.003

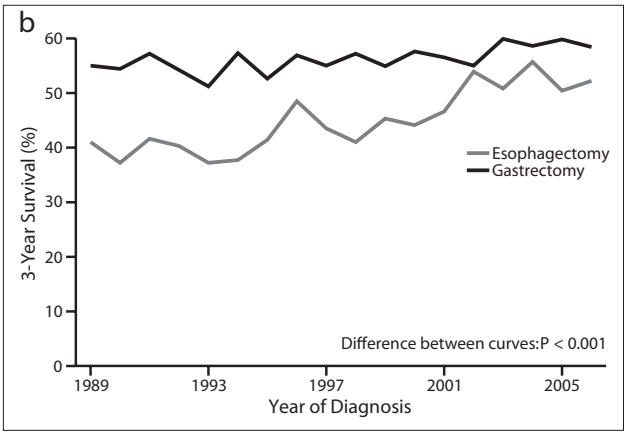

Figure 3b. Three-Year survival rate conditional on surviving the first 6 months for esophagectomy and gastrectomy, adjusted for sex, age, socio-economic status, stage, morphology, and use of preoperative and postoperative therapy (1989-2006).Esophagectomy, HR 0.97 for each year, P < 0.001. Gastrectomy, HR 0.99 for each year, P < 0.001. Difference between esophagectomy and gastrectomy: P < 0.001

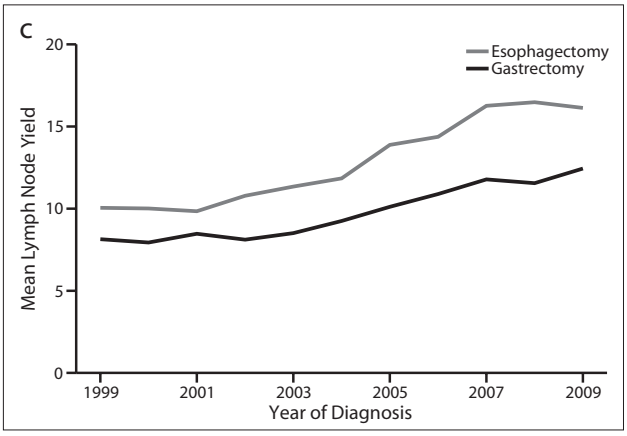

Figure 3c. Median lymph node yield for esophagectomy and gastrectomy, adjusted for sex, age, stage and morphology (1999-2009). Esophagectomy: P < 0.001. Gastrectomy: P < 0.001

Volume-outcome relations

Results from the multivariable analyses on volume-outcome relations are shown in Table 3a&b. After esophagectomy, medium and high volume hospitals were associated with lower six-month mortality and longer three-year conditional survival when compared to very-low volume hospitals (Figure 4). After gastrectomy, neither six-month mortality, or three-year conditional survival were associated with hospital volume category (Figure 5). High hospital volume was associated with high lymph node yield both after esophagectomy and gastrectomy.

Table 3a. Volume-outcome relations for esophagectomy (1989-2009). Mortality and survival were calculated with multivariable Cox regression, nodal yield was calculated with generalized estimated equations.

	Esophagectomy					
	6-month mortality		3-year survival*		LN yield**	
	HR	*95% CI*	HR	*95% CI*	OR	*95% CI*
Hospital Volume						
Very Low(1-5/yr)	1.00		1.00		1.00	
Low (6-10/yr)	0.90	0.78-1.03	1.01	0.94-1.10	1.00	0.91-1.09
Medium (11-20/yr)	**0.78**	**0.62-0.97**	**0.90**	**0.81-0.99**	1.10	1.00-1.22
High (≥21/yr)	**0.48**	**0.38-0.61**	**0.77**	**0.70-0.85**	**1.50**	**1.25-1.80**
Year of Diagnosis						
1989-1993	1.00		1.00			
1994-1997	0.91	0.78-1.07	0.92	0.83-1.01		
1998-2001	**0.82**	**0.68-0.98**	**0.88**	**0.79-0.97**	1.00	
2002-2005	**0.69**	**0.55-0.86**	**0.69**	**0.63-0.75**	**1.18**	**1.10-1.25**
2006-2009	**0.67**	**0.52-0.85**	**0.75**	**0.67-0.83**	**1.42**	**1.27-1.60**
Sex						
Male	**1.00**		**1.00**		**1.00**	
Female	**0.75**	**0.66-0.86**	**0.83**	**0.78-0.89**	**1.04**	**1.00-1.08**
Age category						
<60	**1.00**		**1.00**		**1.00**	
60-75	**1.83**	**1.56-2.14**	**1.14**	**1.07-1.21**	**0.97**	**0.94-1.00**
>75	**3.10**	**2.54-3.79**	**1.41**	**1.25-1.59**	**0.87**	**0.82-0.92**
SES						
Low	**1.00**		**1.00**			
Medium	**0.76**	**0.64-0.90**	**1.05**	**0.96-1.16**		
High	**0.54**	**0.38-0.78**	**1.00**	**0.85-1.17**		
Unknown	**0.53**	**0.38-0.74**	**1.04**	**0.86-1.26**		
TNM Stage						
I	**1.00**		**1.00**		**1.00**	
II	**1.28**	**1.08-1.52**	**2.74**	**2.46-3.04**	**1.15**	**1.09-1.21**
III	**1.73**	**1.41-2.13**	**5.20**	**4.46-6.05**	**1.39**	**1.31-1.47**
IV	**3.85**	**2.55-5.81**	**9.76**	**7.43-12.81**	**1.93**	**1.70-2.20**
unknown	**1.92**	**1.41-2.62**	**2.37**	**2.00-2.81**	**1.04**	**0.92-1.17**
Morphology						
Adenocarcinoma	**1.00**		**1.00**		**1.00**	
SCC	**1.26**	**1.11-1.43**	**1.09**	**0.98-1.21**	**1.05**	**0.99-1.11**
Other	**1.28**	**0.94-1.75**	**1.05**	**0.84-1.33**	**1.00**	**0.88-1.12**
Preoperative therapy						
No	**1.00**		**1.00**			
Yes	**0.32**	**0.23-0.43**	**0.84**	**0.76-0.93**		
Postoperative therapy						
No	**1.00**		**1.00**			
Yes			**1.07**	**0.94-1.21**		

*conditional on surviving the first six months **1999-2009

HR: Hazard Ratio, OR: Odds Ratio, SES: Socio Economic Status, SCC: Squamous Cell Carcinoma, CI: Confidence Interval, Bold: significant ($P < 0.05$)

Table 3b. Volume-outcome relations for gastrectomy (1989-2009). Mortality and survival were calculated with multivariable Cox regression, nodal yield was calculated with generalized estimated equations.

	Gastrectomy					
	6-month mortality		3-year survival*		LN yield**	
	HR	*95% CI*	HR	*95% CI*	OR	*95% CI*
Hospital Volume						
Very Low(1-5/yr)	1.00		1.00		1.00	
Low (6-10/yr)	0.95	0.84-1.07	0.99	0.91-1.07	1.02	0.96-1.08
Medium (11-20/yr)	0.95	0.83-1.08	0.99	0.90-1.08	0.99	0.90-1.10
High (≥21/yr)	1.10	0.82-1.49	0.98	0.86-1.12	**1.93**	**1.81-2.04**
Year of Diagnosis						
1989-1993	1.00		1.00			
1994-1997	0.96	0.86-1.07	0.98	0.90-1.05		
1998-2001	0.89	0.79-1.01	0.94	0.87-1.02	1.00	
2002-2005	**0.74**	**0.65-0.85**	**0.88**	**0.81-0.96**	**1.08**	**1.02-1.16**
2006-2009	**0.70**	**0.60-0.81**	**0.78**	**0.72-0.86**	**1.42**	**1.32-1.52**
Sex						
Male	1.00		1.00			
Female	**0.79**	**0.73-0.85**	**0.91**	**0.85-0.97**	**1.10**	**1.05-1.14**
Age category						
<60	1.00		1.00		1.00	
60-75	**2.03**	**1.78-2.30**	**1.27**	**1.18-1.37**	**0.88**	**0.82-0.93**
>75	**3.94**	**3.47-4.49**	**1.57**	**1.44-1.71**	**0.75**	**0.69-0.81**
SES						
Low	1.00		1.00			
Medium	0.92	0.81-1.04	1.01	0.92-1.12		
High	**0.70**	**0.55-0.91**	1.00	0.84-1.20		
Unknown	0.94	0.73-1.21	1.03	0.85-1.24		
TNM Stage						
I	1.00		1.00		1.00	
II	**1.46**	**1.31-1.63**	**2.99**	**2.78-3.22**	**1.23**	**1.16-1.31**
III	**2.15**	**1.93-2.38**	**5.37**	**5.01-5.75**	**1.55**	**1.46-1.66**
IV	**3.50**	**3.00-4.08**	**8.45**	**7.43-9.61**	**2.23**	**2.05-2.42**
unknown	**1.91**	**1.40-2.60**	**2.36**	**1.96-2.84**	1.01	0.82-1.24
Morphology						
Adenocarcinoma	**1.00**		**1.00**		1.00	
SCC						
Other	**1.18**	**0.86-1.64**	**0.58**	**0.44-0.78**	0.94	0.71-1.25
Preoperative therapy						
No	**1.00**		**1.00**			
Yes	**0.27**	**0.17-0.43**	**1.05**	**0.84-1.31**		
Postoperative therapy						
No			**1.00**			
Yes			**1.01**	**0.85-1.21**		

*conditional on surviving the first six months **1999-2009

HR: Hazard Ratio, OR: Odds Ratio, SES: Socio Economic Status, SCC: Squamous Cell Carcinoma, CI: Confidence Interval, Bold: significant ($P < 0.05$)

When analyzing hospital volume as a linear covariate, volume-survival results remained the same. No changes in the results were found when volume-outcome relations were analyzed with surgery for cardia cancer coded as gastrectomy (data not shown).

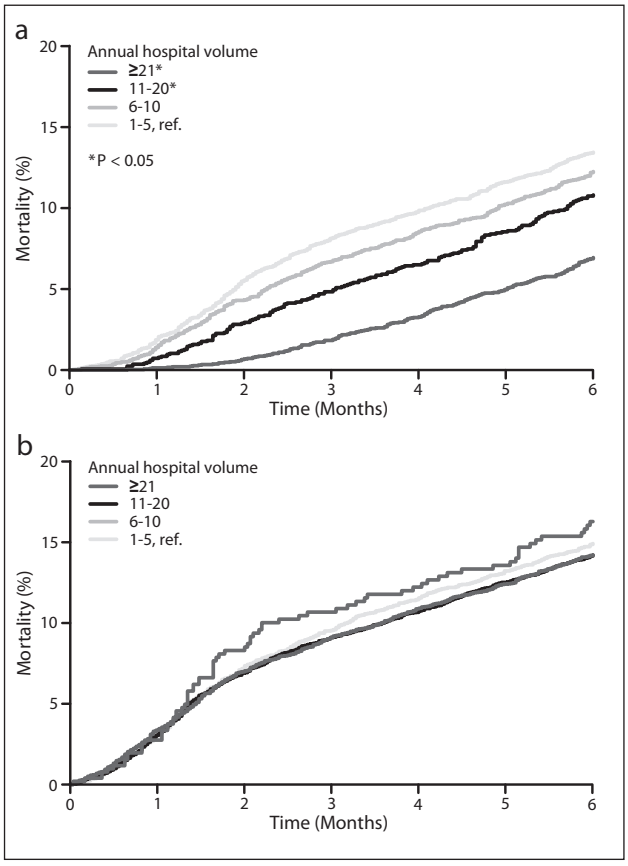

Figure 4. Volume-outcome relations for esophagectomy.
a. Relation between volume and 6-month survival, adjusted for year of diagnosis, sex, age, socio-economic status, stage, morphology, and preoperative therapy use.
* P < 0.05 compared to Very Low Volume.
b. Relation between volume and 3-year survival, conditional on surviving the first 6 months, adjusted for year of diagnosis, sex, age, socio-economic status, stage, morphology, and preoperative and postoperative therapy use.
* P < 0.05 compared to Very Low Volume.

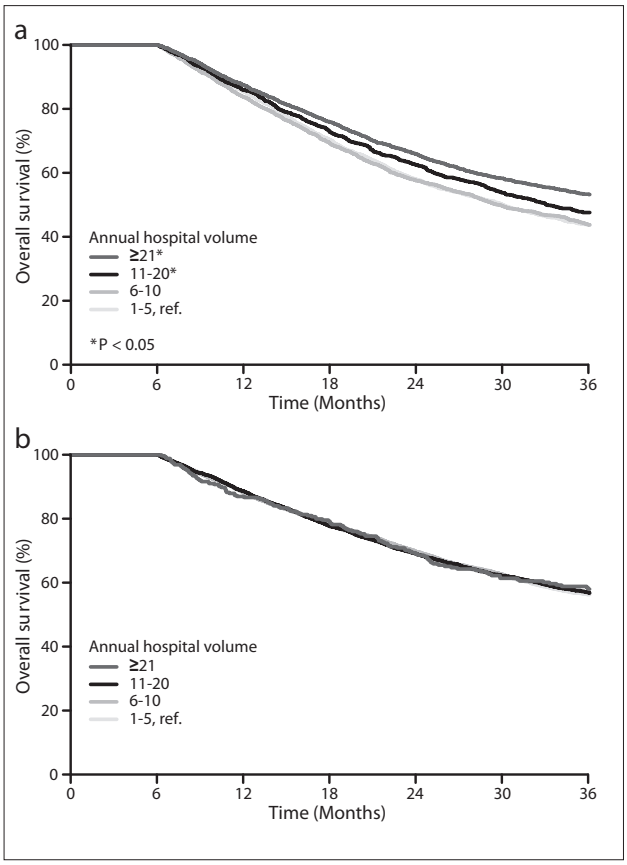

Figure 5. Volume-outcome relations for gastrectomy.

a. Relation between volume and 6-month survival, adjusted for year of diagnosis, sex, age, socio-economic status, stage, morphology and preoperative therapy use.

* P < 0.05 compared to Very Low Volume.

b. Relation between volume and 3-year survival, conditional on surviving the first 6 months, adjusted for year of diagnosis, sex, age, socio-economic status, stage, morphology, and preoperative and postoperative therapy use.

* P < 0.05 compared to Very Low Volume.

DISCUSSION

Over the study period, the number of esophagectomies performed in high volume hospitals considerably increased, while in 2009 most gastrectomies were performed in low volume hospitals. Both six-month mortality and three-year survival improved after esophagectomy, but to a lesser extent after gastrectomy. In the current dataset, a volume-survival relation was revealed for esophagectomy, but not for gastrectomy.

Since Luft et al. published the first study on volume-outcome relations for surgery [16], many studies have emerged investigating the effect of hospital and surgeons volume on short term and long term outcomes for a variety of diseases, including resections for esophageal and gastric cancer. Several large studies have shown an association between high hospital volume and low postoperative mortality both for esophagectomy [17-20], and gastrectomy [17;20-22], but other studies did not find an association [23-25]. In a meta-analysis exploring volume-outcome relations, high volume surgery was associated with lower postoperative mortality after both esophagectomy and gastrectomy [9]. A limited number of studies investigate the relation between hospital volume and *long*-term survival after esophagectomy and gastrectomy, with conflicting results [7;17;24;26].

Over the past two decades, the number of esophagectomies in the Netherlands has increased, corresponding with an increasing incidence of esophageal cancer [27]. The decreasing incidence of gastric cancer explains the low number of gastrectomies currently performed in the Netherlands [28]. Furthermore, the resection rate for gastric cancer dropped significantly, most likely the result of improved preoperative staging. Combined with the almost complete disappearance of surgery for reflux disease and ulcers, surgeons are decreasingly exposed to gastrectomies. This might partly be compensated by increasing volumes of bariatric surgery for obesity, but the surgical techniques used differ significantly.

In the current study, increasing hospital volume was associated with lower mortality and increased long-term survival after esophagectomy, but not after gastrectomy. This observation for gastrectomies might be explained by the low number of high-volume gastrectomies (2.5% of all gastrectomies in the current dataset), and the low threshold for what was considered high volume surgery. In other studies that did find an association between gastrectomy in high volumes and good outcomes, the lower limit of high-volume surgery varied from 20/year up to 264/year [17;26].

The current study covers an extensive period of two decades of esophago-gastric cancer surgery in the Netherlands, and analyzes a significant population of about 25,000 patients. Unlike many of the large volume-outcome studies, the current study uses a clinical database with highly reliable data, providing complete coverage of all diagnosed cancers in the Netherlands. Furthermore, outcomes are case-mix adjusted, increasing

reliability of the results [29]. The absence of comorbidity in the current dataset was partly compensated by the use of SES, which can be considered a proxy for comorbidity [7].

A potential bias when analyzing outcomes over a long period is that preoperative staging and (perioperative) care generally improve over time. For example, endoscopic ultrasound, multislice high resolution computed tomography, and PET computed tomography were introduced resulting in improvement of staging. Hospital volumes for esophagectomy significantly changed during the study period, with most high-volume resections performed in the more recent years. Therefore, high volume resections are intrinsically associated with better outcomes. However, adjusting for year of diagnosis offsets this effect. Another potential weakness is the unavailability of the surgery hospital for part of the patients treated before 2005. Instead, the hospital of diagnosis was used. However, this only happened in the first years of the study, when hospitals less frequently referred patients to another hospital for surgery.

A point of discussion might be that volumes are analyzed on hospital level, rather than surgeon level [26;30;31]. Quality of care, however, consists of more than an individual surgeon's performance. Perioperative care, anesthesia, ICU staffing, experience of the nursery staff, and collaboration between different disciplines all contribute to outcomes associated with the performed procedure [32]. The role of the surgeon is only one, yet important, factor contributing to outcome.

Initiatives to improve medical and especially surgical care are legion. Randomized trials improve care by selecting appropriate treatments for certain indications [3;33], and by educating surgeons participating in the trial [34;35]. However, the majority of cancer patients are treated outside trials, and especially improvements in the process and structure of care on a nation-wide level will bring benefit to this group of patients. Many studies have advocated the centralization of low-volume, high-risk operations, thereby improving nationwide quality of care [11;26]. Centralization of esophageal and gastric cancer is currently performed in several European countries, whereas referral to high-volume centers is also advocated in the United States by the Leapfrog group [36]. In Denmark, centralization of gastric cancer surgery from 37 to 5 hospitals leaded to a drop in postoperative mortality from 8.4% to 2.1% over a period of 5 years [37].

Unlike the Netherlands, which is a relatively small country with good infrastructure, centralization of care in countries with large rural areas might lead to unreasonable travel burdens and problems with continuity of care after surgery. Therefore, others have advocated implementing processes that are related to excellent outcomes in low volume hospitals, but identification of these processes remains challenging [38].

Meanwhile, using hospital volume as the sole basis for referral to improve outcomes is criticized [17]. Although hospital volume can reliably identify groups of hospitals with better results on average, individual low volume hospitals can have excellent outcomes and vice versa. In contrast to volume-based referral, outcome based-referral avoids this

problem, and has proven its value for esophagectomy in the Western part of the Netherlands. In this area, a prospective audit was conducted to identify hospitals with excellent performance in esophagectomy. During the five-year audit, a gradual concentration towards centers with excellent performance occurred, leading to a drop in postoperative mortality (12% to 4%) and an improvement in survival [39].

Combining centralization with auditing substantially adds to improvement of care [40]. With auditing, providers of care are monitored and their performance is benchmarked against their peers. Auditing is performed on a national level for esophagogastric cancer in Denmark [37], Sweden and the United Kingdom. A nationwide audit for both esophageal and gastric cancer surgery has started in the Netherlands as of 2011 aiming for complete coverage of all esophagectomies and gastrectomies.

In conclusion, enforcing centralization for esophagectomy in the Netherlands has resulted in a shift in annual hospital volumes: most resections are currently performed in high volume centers. For gastrectomy, no minimum number of resections was required, and the majority of gastric cancer resections were performed in low volume hospitals. However, as of 2012 gastrectomies in the Netherlands will be centralized to a minimum of 10/year, and as of 2013 to a minimum of 20/year. Esophagectomy in high volume hospitals is associated with improved outcomes. No such relation for gastric cancer could be established in the current dataset, but only a minority of patients was treated in high volume hospitals. Over the past two decades, short-term mortality and long-term survival after esophagectomy decreased significantly, while outcomes after gastrectomy improved to a lesser extent, indicating an urgent need for improvement in quality of surgery and perioperative care for gastric cancer in the Netherlands.

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Chapter 9

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

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ABSTRACT

Background

Studies investigating perioperative chemo- 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 cancer.

Results

In stage I and II disease most patients underwent surgery. Since 2005 more patients are treated with (neo)adjuvant chemotherapy. Postoperative mortality ranged from 1% to 7% and 0.4% to 12.2% in cardia and non-cardia cancer (<55 - 75+ yr). 5-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.

Conclusion

Administration of (neo)adjuvant chemotherapy has increased. No improvement in long term survival could yet be seen, though it is still too early to expect an improvement in survival as a result of the use of chemotherapy.

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 (neo)adjuvant 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 is 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 Do 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 tumour-positive (R1), adjuvant chemo-radiotherapy is recommended (http://www.oncoline.nl).

The aims of this unique population-based 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, haematology departments and radiotherapy institutions. Completeness is estimated to be at least 95% [10]. 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.

All consecutive patients diagnosed between January 1st 1989 and December 31st 2008 with a tumour located in the stomach according to the International Classification of Diseases (ICD) were included in the current study. No patients were excluded. To evaluate trends over time, the study period was divided in five intervals of four years. Tumours 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 tumour characteristics were analyzed with the Chi square test. Trends in treatment, including the use of (neo)adjuvant chemotherapy, and resection, were analyzed as proportional distributions.

The chance to undergo surgery and receive (neo)adjuvant chemotherapy for patients with stage I-III and X (unknown stage) gastric cancer was analyzed with multivariable logistic regression. For (neo)adjuvant 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 tumour characteristics was calculated by means of multivariable relative survival analysis with Poisson regression.

RESULTS

Patients

Between 1989 and 2008, 10294 patients were diagnosed with cardia cancer, and 30017 patients were diagnosed with non-cardia cancer in the Netherlands. Patient and tumour 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 of male gender compared to patients with non-cardia cancer.

Table 1. General characteristics of all patients diagnosed with gastric cardia and non-cardia cancer between 1989 and 2008 in the Netherlands.

	Cardia		**Non-cardia**		
	N	**%**	***N***	**(%)**	***P-value***
Total	*10294*	-26	*30017*	-74	*n.a.*
Age (yrs)					
<55	*1557*	-15	*3260*	-11	
55-64	*2263*	-22	*4894*	-16	
65-74	*3298*	-32	*9086*	-30	
75+	*3176*	-31	*12795*	-43	*<0.0001*
Gender					
Males	*7942*	-77	*17888*	-60	
Females	*2352*	-23	*12129*	-40	*<0.0001*
TNM-stage					
I	*1188*	-12	*5603*	-19	
II	*1408*	-14	*3913*	-13	
III	*1805*	-18	*5014*	-17	
IV	*3815*	-37	*10701*	-36	
X	*2078*	-20	*4786*	-16	*<0.0001*
Period of diagnosis					
1989-1992	*2001*	-19	*7260*	-24	
1993-1996	*2134*	-21	*6490*	-22	
1997-2000	*2192*	-21	*5804*	-19	
2001-2004	*1991*	-19	*5435*	-18	
2005-2008	*1976*	-19	*5028*	-17	*<0.0001*

Table 1. *Continued*

		Cardia		Non-cardia		
		N	**%**	***N***	**(%)**	***P-value***
Region						
	1	*1819*	-18	*4931*	-16	
	2	*466*	-5	*1971*	-7	
	3	*799*	-8	*1973*	-7	
	4	*2211*	-21	*6932*	-23	
	5	*856*	-8	*2294*	-8	
	6	*1718*	-17	*4888*	-16	
	7	*1116*	-11	*2779*	-9	
	8	*1309*	-13	*4249*	-14	*<0.0001*
Tumour differentiation grade						
Well/moderately		*3191*	-31	*7277*	-24	
Poor/undifferentiated		*4636*	-45	*15305*	-51	
Unknown		*2467*	-24	*7435*	-25	*<0.0001*
Tumour sublocation						
Middle part of stomach		*n.a.*		*8470*	-28	
Pylorus				*10596*	-35	
Unknown/overlapping				*10951*	-37	*n.a.*
Histology						
Adenocarcinoma		*9604*	-93	*25965*	-87	
Other		*690*	-7	*4052*	-13	*<0.0001*

n.a. = not applicable

Changes in treatment

Trends in treatment over time are depicted in Figure 1a, b and c, 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 <0.0001*). The proportion of patients treated with (neo) adjuvant chemotherapy increased significantly in every stage group (*P <0.0001*).

In Table 2a, 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's (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 resection rates for stage III cardia and non-cardia gastric cancer were significantly lower (OR cardia: 0.3, OR non-cardia: 0.2, *P <00001*). For non-cardia gastric cancer, the chance of undergoing surgery decreased over time (2005-2008 OR 0.6, *P <0.001*). Resection rates

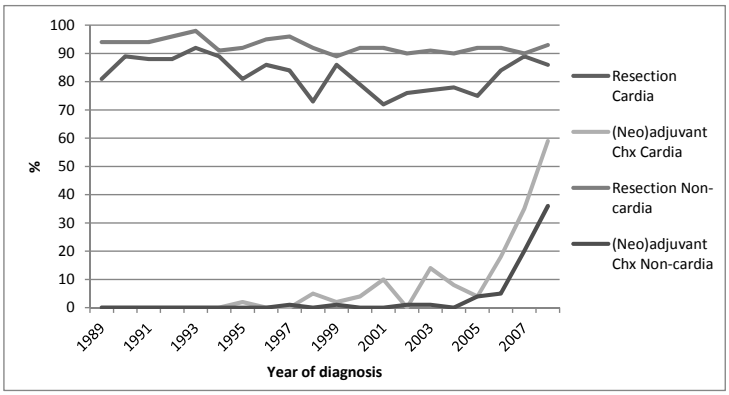

Figure 1A. Trends in treatment of patients with cardia and non-cardia cancer, diagnosed between 1989 and 2008 in the Netherlands. Stage I

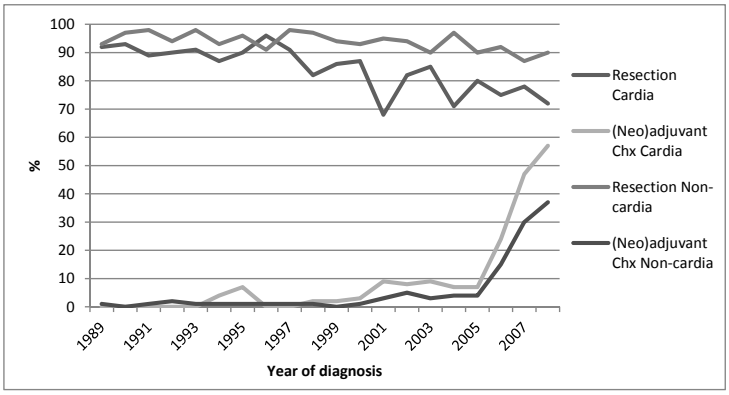

Figure 1B. Trends in treatment of patients with cardia and non-cardia cancer, diagnosed between 1989 and 2008 in the Netherlands. Stage II

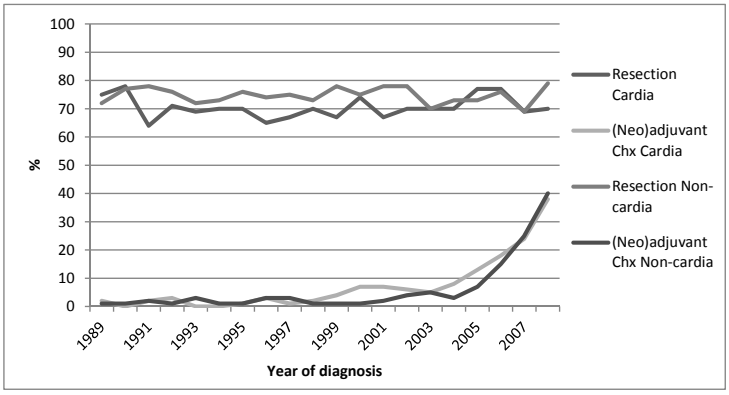

Figure 1C. Trends in treatment of patients with cardia and non-cardia cancer, diagnosed between 1989 and 2008 in the Netherlands. Stage III

Table 2a. Resection percentages and logistic regression of the chance to undergo a resection, stage I-III and X, patients *diagnosed* with cardia and non-cardia cancer

	Cardia			Non-cardia		
	% Resection	OR	P-value	% Resection	OR	P-value
Total						
Age (yrs)						
<55 [a]	79	1		85	1	
55-64	75	0.8	*0.133*	82	0.7	*0.003*
65-74	64	0.6	*<0.0001*	77	0.5	*<0.0001*
75+	26	0.2	*<0.0001*	52	0.3	*<0.0001*
Gender						
Males [a]	58	1		69	1	
Females	44	0.9	*0.075*	65	1	*0.498*
TNM-stage						
I [a]	82	1		92	1	
II	84	0.9	*0.483*	94	1.1	*0.177*
III	71	0.3	*<0.0001*	75	0.2	*<0.0001*
X	5	0.02	*<0.0001*	7	0.01	*<0.0001*
Year of diagnosis						
1989-1992 [a]	58	1		71	1	
1993-1996	57	1	*0.956*	68	0.7	*<0.0001*
1997-2000	52	0.8	*0.097*	66	0.7	*<0.0001*
2001-2004	51	0.7	*0.002*	65	0.7	*<0.0001*
2005-2008	57	1	*0.891*	62	0.6	*<0.0001*
Region						
1 [a]	57	1		67	1	
2	59	0.8	*0.294*	74	1.1	*0.379*
3	62	0.9	*0.595*	69	1	*0.774*
4	49	0.5	*<0.0001*	66	0.7	*<0.0001*
5	50	0.5	*<0.0001*	68	0.7	*0.009*
6	57	1	*0.890*	66	0.7	*0.007*
7	56	1	*0.881*	63	0.7	*<0.0001*
8	55	0.6	*0.002*	67	0.9	*0.111*
Tumour differentiation grade						
Well/moderately [a]	62	1		75	1	
Poor/ undifferentiated	62	0.8	*0.032*	72	0.9	*0.1*
Unknown	27	0.2	*<0.0001*	47	0.3	*<0.0001*
Tumour location	n.a.	n.a.				
Middle part of stomach [a]				71	1	
Pylorus				77	1.2	*0.002*
Unknown/overlapping				51	0.5	*<0.0001*

[a] Reference category. OR=odds ratio. n.a.=not applicable

Table 2b. Percentage of patients treated with (neo)adjuvant chemotherapy and logistic regression of the chance to receive (neo)adjuvant chemotherapy (with or without radiotherapy), stage I-III and X, patients *resected* for cardia and non-cardia cancer in the Netherlands.

	Cardia			Non-cardia		
	% (neo)-adjuvant	OR	*P-value*	% (neo)-adjuvant	OR	*P-value*
Total	29			21		
Age (yrs)						
<55 [a]	44	1		52	1	
55-64	33	0.5	*0.037*	35	0.4	*0.0002*
65-74	29	0.4	*0.0004*	21	0.3	*<0.0001*
75+	10	0.1	*<0.0001*	4	0.0	*<0.0001*
Gender						
Males [a]	30	1.0		20	1.0	
Females	28	0.8	*0.398*	22	0.7	*0.885*
TNM-stage						
I [a]	31	1		17	1	
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	*<0.0001*
Year of diagnosis						
2005 [a]	10	1		5	1	
2006	21	2.8	*0.004*	12	3.2	*<0.0001*
2007	36	6.7	*<0.0001*	26	9.1	*<0.0001*
2008	54	14.0	*<0.0001*	40	20.1	*<0.0001*
Region						
1 [a]	23	1		25	1	
2	37	1.9	*0.222*	23	1.2	*0.627*
3	22	0.9	*0.849*	25	1.0	*0.946*
4	22	0.7	*0.220*	16	0.4	*<0.0001*
5	20	0.7	*0.461*	19	0.7	*0.338*
6	39	2.6	*0.007*	17	0.5	*0.010*
7	58	4.5	*0.0001*	25	1.1	*0.761*
8	23	0.6	*<0.0001*	22	0.7	*0.153*
Tumour differentiation grade						
Well/moderately [a]	22	1		11	1	
Poor/ undifferentiated	23	1.1	*0.739*	20	1.5	*0.069*
Unknown	60	3.5	*<0.0001*	36	3.3	*<0.0001*
Tumour location	n.a.	n.a.				
Middle part of stomach [a]				20	1	
Pylorus				20	1.0	*0.936*
Unknown/overlapping				23	1.1	*0.567*

[a] Reference category. OR=odds ratio. n.a.=not applicable.

Table 3. Thirty-day mortality in percentages and logistic regression analysis for 30-day mortality after resection for cardia and non-cardia cancer *between 2005 and 2008* in the Netherlands.

	Cardia			Non-cardia		
	% 30 day mortality	OR	P-value	% 30 day mortality	OR	P-value
Total	4			7		
Age (yrs)						
<55 [a]	1	1		0.4	1	
55-64	2	2.1	*0.536*	3	6	*0.083*
65-74	8	8.9	*0.043*	7	11	*0.020*
75+	7	6.4	*0.099*	12	23	*0.002*
Gender						
Males [a]	5	1.0		8	1.0	
Females	3	0.7	*0.478*	6	0.7	*0.060*
TNM-stage						
I [a]	6	1		6	1	
II	4	0.6	*0.324*	5	0.9	*0.769*
III	3	0.4	*0.093*	9	1.6	*0.047*
X	0	n.a.		0	n.a.	
Year of diagnosis						
2005 [a]	6	1		8	1	
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						
1 [a]	5	1		9	1	
2	15	3.3	*0.152*	5	0.5	*0.203*
3	7	3.2	*0.124*	6	0.5	*0.150*
4	2	0.6	*0.560*	7	0.6	*0.081*
5	4	1.6	*0.461*	9	1.1	*0.878*
6	3	0.9	*0.612*	6	0.5	*0.051*
7	4	0.6	*0.943*	11	1.5	*0.273*
8	5	0.5	*0.645*	7	0.9	*0.790*
Tumour differentiation grade						
Well/moderately [a]	5	1		8	1	
Poor/undifferentiated	4	0.5	*0.167*	7	1.0	*0.987*
Unknown	5	1.7	*0.370*	7	0.8	*0.568*
Tumour location	n.a.	n.a.				
Middle part of stomach [a]				8	1	
Pylorus				5	0.6	*0.031*
Unknown/overlapping				11	1.5	*0.126*

Table 3. *Continued*

	Cardia			Non-cardia		
	% 30 day mortality	OR	P-value	% 30 day mortality	OR	P-value
Neoadjuvant treatment						
None	5	1		8	1	
Chemotherapy	2	0.2	*0.087*	3	0.7	*0.344*
Radiotherapy	4	0.9	*0.873*	0	n.a.	
Chemoradiation	5	1.0	*0.939*	0	n.a.	

[a] Reference category. OR=odds ratio. n.a.=not applicable

significantly differed between regions, from 49% to 62% for cardia cancer and from 63 to 74% for non-cardia cancer.

In Table 2b, the proportion of patients treated with (neo)adjuvant chemotherapy and the adjusted chance to receive (neo)adjuvant 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 (neo) adjuvant chemotherapy. Again, large regional variations could be noted, ranging from 20% to 58% for cardia cancer and from 16% to 25% for non-cardia cancer.

Short-term mortality

In Table 3, 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.

Survival

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 2).

After adjustment for available patient and tumour 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 3). Thirty-day mortality rates were lower for females compared to males after resection for non-cardia cancer. Statistically, there were no regional differences.

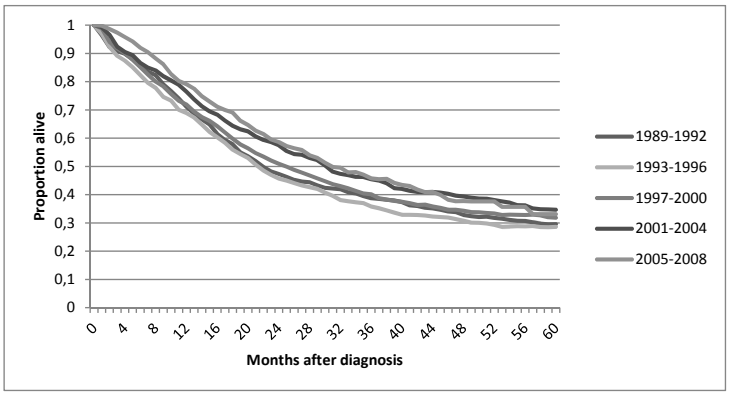

Figure 2A. Cardia. Five-year relative survival of patients after resection for gastric cancer, stage I-III and X, diagnosed between 1989 and 2008 in the Netherlands, by period of diagnosis.

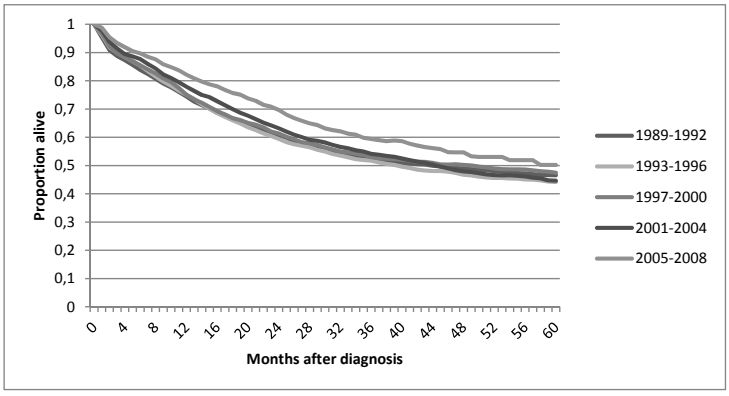

Figure 2B. Non-cardia. Five-year relative survival of patients after resection for gastric cancer, stage I-III and X, diagnosed between 1989 and 2008 in the Netherlands, by period of diagnosis.

DISCUSSION

Over the study period, resection rates for both cardia and non-cardia cancer remained relatively stable. The administration of (neo)adjuvant 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 tumour stage, more recent period of diagnosis, interregional variation and unknown tumour differentiation grade. In non-cardia cancer the location of the tumour was a factor of influence as well.

Before the introduction of the national guideline for treatment of gastric cancer in 2009 the administration of (neo)adjuvant 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 (http://www.nccn.org) [11;12]. In the latest period, after 2005, there was a significant increase in the number of patients treated with (neo) adjuvant chemotherapy, both for cardia and non-cardia cancer. Even in stage I cardia and non-cardia cancer there was a remarkable increase in (neo)adjuvant 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 exact 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 (http://www.oncoline.nl) [13-15]. 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 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;16;17].

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 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 [18], 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% [19] compared to a survival rate of 33% in cardia and 50% in non-cardia cancer in the Netherlands. One of

the most important factors influencing survival is lymph node (N) stage [20]. A minimum of 15 lymph nodes is recommended for gastric cancer (UICC/AJCC) [21]. Studies performed in the Netherlands show that this criterion is still not met [22;23]. 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 [24]) 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;25].

CONCLUSION

Despite a strong increase in the use of (neo)adjuvant 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 (neo)adjuvant chemo- and/or radiotherapy and the effect of centralization on mortality and survival for patients with resectable gastric cancer.

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Part IV

DoCCS-study

Chapter 10

D1*extra* lymphadenectomy in gastric cancer; high lymph node yield and low mortality in a phase II feasibility study

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Submitted

ABSTRACT

Background

Survival after curative treatment for gastric cancer remains low. Currently, only a D1 lymphadenectomy or less is performed in the Netherlands, with an inadequate lymph node yield. This phase II study describes the feasibility of a D1*extra* lymphadenectomy after neoadjuvant chemotherapy in patients with stage IB-IVA gastric cancer.

Patients and Methods

Patients with curable gastric carcinoma (including Siewert 2 and 3 tumours) who met the inclusion criteria, were intended to undergo 4 cycles of docetaxel, cisplatin and capecitabine, followed by a standardized (partial) gastric resection and lymphadenectomy. In principle, lymph node stations 3-9 were removed and depending on the location of the tumour, also stations 1, 2, 10 and 12 (Japanese classification). Pathologic investigation was performed according to a standardized protocol in 3 pathology laboratories. Thereafter, all specimens were revised by an independent pathology department.

Primary endpoint was development of major surgical complications, secondary endpoints were the rate of successful D1*extra* lymphadenectomy and the lymph node yield. Descriptive statistics were used for the primary and secondary endpoints.

Results

In total, 51 patients were included, 48 proceeded to surgery, 42 received a gastric resection with the intention of D1*extra* lymphadenectomy. A mean of 26 nodes (median 25.5 (range 4-52)) was harvested; after revision a mean of 29 (median 28 (range 6-58)). Postoperative morbidity was 31%, in-hospital mortality 2.4%. One patient, who had left the hospital reasonably well, died in a nursing home within 30 days.

Conclusion

The yield of lymph nodes after a D1*extra* resection met up with the national guidelines. Morbidity and mortality were acceptable. Although long-term survival rates have to be awaited, it seems to be feasible to implement a D1*extra* lymphadenectomy in current surgical gastric cancer treatment.

INTRODUCTION

Although incidence and mortality rates are declining for gastric cancer in Europe, it still ranks 5th in incidence and 4th in mortality rates for males, with a somewhat lower ranking for females. In the Netherlands, every year 1.960 patients are diagnosed with gastric cancer, and 1.390 die because of this disease [1,2]. Five year survival rates remain dismal [3]. Several surgical and oncological trials have been performed to improve the survival of curable gastric cancer. The D1 lymphadenectomy (according to the Japanese Classification of Gastric Cancer [4]) has been compared to the D2 lymphadenectomy in several studies in the West but survival rates did not improve. In contrary, morbidity and mortality in the D2 group were so high that nowadays it is not recommended to perform such an extended lymphadenectomy [5]. In the Netherlands, a mean of 8-12 lymph nodes is yielded [6,7], while national guidelines recommend of at least 15 lymph nodes to be removed [8]. Although surgery remains the cornerstone of treatment, perioperative chemotherapy and radiotherapy have proved to be of additional value in improving 5-year survival rates [9,10].

We therefore conducted a multi-centre phase II study to investigate the feasibility of a scheme of neoadjuvant chemotherapy consisting of Docetaxel, Cisplatin and Capecitabine (DCC) followed by a new developed standardized D1*extra* lymphadenectomy in gastric cancer. We hereby describe the results of the study concerning postoperative morbidity and mortality and lymph node yield.

PATIENTS AND METHODS

Patient selection

Inclusion criteria were histologically proven gastric adenocarcinoma (including gastro-oesophageal junction/cardia carcinoma (Siewert 2 and 3 [11])), stage Ib-IVa (6th TNM classification [12]), WHO performance state ≤ 1, age ≥ 18 years, adequate haematologic, renal and hepatic function, patients informed consent and expected compliance with treatment, management of toxicity and scheduled follow-up. Exclusion criteria were inoperability, previous or current malignancies, other serious illness or medical conditions, known hypersensitivity to any of the chemotherapies used, contraindication for the use of corticosteroids, use of immunosuppressive or antiviral medication and pregnant or lactating women. The protocol was approved by a certified ethics committee (METOPP) and by the institutional review board of each center. All patients underwent a history and physical examination, assessment of malnutrition, oesophagoduodenoscopy, blood sampling and radiological imaging consisting of CT scan of the chest and abdomen and a PET-CT scan. After inclusion, all patients signed a written informed consent.

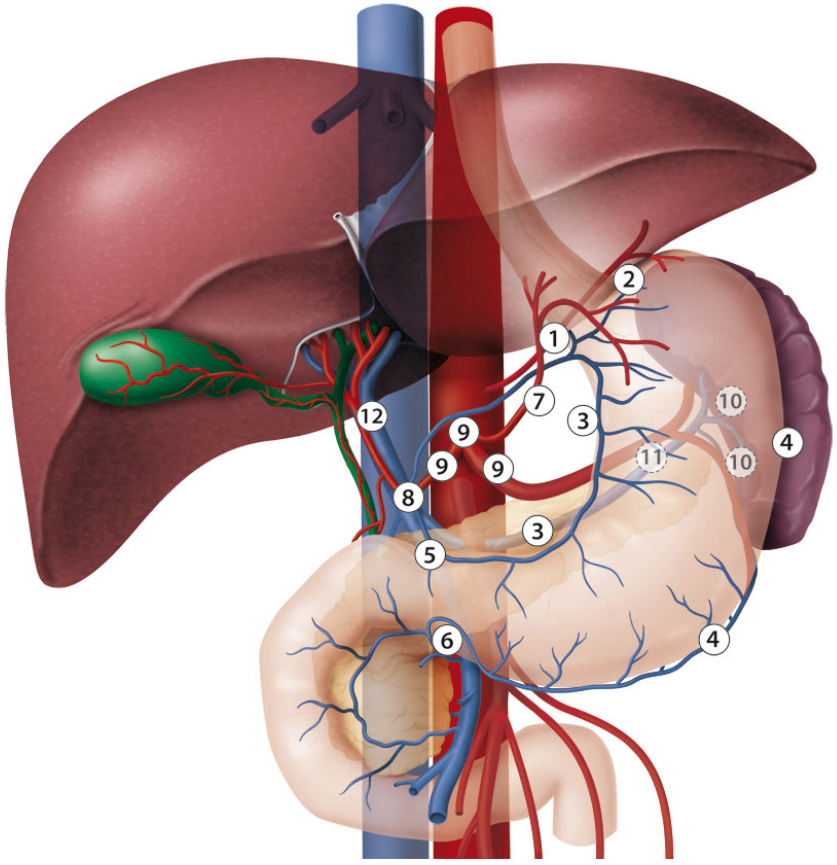

Figure 1. Classification of lymph node stations according to the Japanese Classification
1, right paracardial; 2, left paracardial; 3, along the lesser curvature; 4, along the greater curvature; 5, suprapyloric; 6, infrapyloric; 7, along the left gastric artery; 8, along the common hepatic artery; 9, around the celiac artery; 10, the splenic hilum; 11, along the splenic artery; 12, hepatoduodenal ligament

Treatment

Chemotherapy

Patients were intended to receive four cycles of 21 days each with 60 mg/m^2 docetaxel IV infusion and 60 mg/m^2 cisplatin IV infusion on day 1, and capecitabine 1.875 mg/m2 PO on day 1-14. Dose modification criteria were predefined. Patients were scheduled for surgery after approximately four to six weeks after the last day of chemotherapy.

Surgery and pathology

A local surgeon experienced in gastrointestinal surgery was assisted by a surgeon from the study team to assure adherence to the surgical protocol. In case of a tumour located to the cardia or proximal stomach a total gastrectomy was advised, in case of a tumour located to the mid 1/3 a subtotal gastric resection distally from the cardia was advised, and in case of a tumour located in the distal 1/3 a distal gastric resection was advised. A D1*extra* lymphadenectomy specified to tumour location was performed. The lymph node stations (according to the Japanese Classification [13]) prone to metastasis were removed [14]. Lymph node stations 1-10 were removed in case of proximal gastric cancer combined with a total gastric resection, lymph node stations 1, 3-10 were removed in case of a tumour located to the middle 1/3 of the stomach with a subtotal gastric resection, and lymph node station 3-9 and 12a were removed in case of a tumour located to the distal 1/3 of the stomach accompanied by a distal gastric resection (figure). The surgeon was asked to document the extent of the lymph node dissection on a case record form (CRF). The specimen with the lymph nodes divided per station was sent to the pathologist together with the completed surgical CRF. Pathological examination was documented on a CRF and sent for second evaluation to an independent pathological department. Protocol adherence was determined based on the surgical CRF.

Outcome and Statistical analyses

The primary endpoint of the surgical part of this study was development of major surgical complications (grade 4/5). The secondary endpoints were rate of successful D1*extra*-resection and amount of number of patients with R0 resection. Numbers and proportions of patients reaching the primary endpoint and secondary endpoints will be described in statistical analysis.

RESULTS

In total, 53 patients were included in the study, in 5 hospitals in the Southern part of the Netherlands. Two patients enrolled in the study had distal oesophageal cancer (Siewert 1) and were therefore excluded. Patients characteristics are depicted in table 1. All patients were diagnosed with locoregional disease without distant metastases. Location of tumour was only available for patients who had surgery. From the 51 patients who were included, 48 patients underwent surgery (3 patients died during treatment with chemotherapy, one of them refusing further treatment). Of those 48 patients, one patient had surgery in a hospital not participating in the trial due to his own wish, 2 patients had peritoneal carcinomatosis and therefore had a palliative resection, 1 patient had a palliative resection due to disease progression, 1 patient was treated with ECF

Table 1. General patient characteristics

Age	Median (y)	64,5
	Mean (y)	63,8
	Range (y)	34-84
		N (%)
Gender	Male	36 (70.6)
	Female	15 (29.4)
Tumour site	proximal 1/3	19 (37.3)
	middle 1/3	13 (25.5)
	distal 1/3	12 (23.5)
	Unknown	7 (13.7)
Histology	Intestinal	5 (9.8)
	Diffuse	2 (3.9)
	Tubular adenoca	2 (3.9)
	Moderately differentiated adenoca	9 (17.6)
	Poorly differentiated adenoca	17 (33.3)
	Mucinous adenoca	2 (3.9)
	Signet ringcell adenoca	9 (17.6)
	Diffuse and signet ringcell adenoca	2 (3.9)
	Unknown	2 (3.9)
TNM[a]	IA	1 (2.0)
	IB	8 (15.7)
	II	11 (21.6)
	IIIA	9 (17.6)
	IIIB	2 (3.9)
	IV	3 (5.9)
	Unknown	17 (33.3)

[a] According to the 6th UICC/AJCC TNM classification

(epirubicine, cisplatin and 5-FU) after one cycle of DCC and was therefore excluded from further analyses and 1 patient had multiple myocardial infarctions during chemotherapy and had surgery one year after the administration neoadjuvant treatment. Furthermore, one patient had progressive disease with distant metastasis. Due to his age (34 year) he still had a modified extended lymphadenectomy and was analyzed in the surgery/pathology group. In total, 42 patients had a gastric resection and lymphadenectomy. Surgical and pathological results are shown in table 2.

The precise protocol for the D1*extra*-lymphadenectomy was followed in 21 patients. Contamination, defined by removing more resected stations than necessary, was described in 13 (31%) patients (9 patients 1 station extra, 4 patients 2 stations extra). Station 11 and 12a were the main extra stations that were removed. Non-compliance, defined by less resected stations than required, was described in 8 (19%) patients, but in all of

Table 2. Surgical and pathological results

		N
Radical resection		39
Total gastrectomy		28
Subtotal gastrectomy		7
Distal gastrectomy		3
Proximal gastrectomy		3
Time surgery (minutes)	mean	204
	median	199
	range	113-308
Time hospital stay (days)	mean	17,2
	median	14
	range	7-59
Blood tranfusion		10
D1*extra* lymphadenectomy[a]		21
	contamination	13
	non-compliance	8
Lymph nodes excised	mean	26,2
	median	25,5
	range	4-52
Lymph nodes excised (revision)	mean	28,8
	median	28
	range	6-58
Metastatic lymph nodes	mean	2,6
	median	1
	range	0-15
Metastatic lymph nodes (revision)	mean	2,6
	median	0
	range	0-15

[a] Forty-two patients received a D1*extra* lymphadenectomy with one patient having metastatic disease

them more than 15 lymph nodes were found during pathological examination. Reasons for not complying to the protocol were a formal proximal gastric resection (resection of the proximal 1/3 of the stomach, 3 patients, due to surgeon's preference), emergency surgery due to tumour bleeding (one patient), hemorrhage near the spleen which made the surgeon decide not to remove station 10 (one), and unknown reason (3 patients). Only in 1 patient more than 1 lymph node station was not removed, this patient was the abovementioned patient with distant metastases. In six patients, less than 15 lymph nodes were removed, after 2nd revision this was the case in 4 patients. N stage changed in 7 patients after 2nd revision; 4 patients were downstaged and 3 patients were upstaged.

Table 3. Major surgical complications according to Dindo et al [20]

Type of complication	N	Grade
Small bowel necrosis	2	4 & 5
Anastomotic bleeding	2	3
Anastomotic leakage	2	3
Diaphragmatic hernia	1	3
Umbilical hernia (pre-existing)	1	3
Pneumonia	1	3
Pancreatic fistula	1	3
Duodenal stump leakage	1	3
Subphrenic abscess	1	3
Postoperative ileus	1	3
Clinical deterioration	1	3

From the 41 patients who underwent an operation with curative intent, 39 patients had a radical resection. Two patients had an irradical resection at the distal cutting surface. One of them was admitted to a hospice nineteen days after the operation at his own wish. He died later on within 30 days postoperatively. There were another 14 major surgical complications reported in 13 patients (table 3). One patient died due to small bowel necrosis probably caused by enteral tube feeding, the other 13 complications all resolved without sequelae. Ten patients required a reoperation (24%). This resulted in a postoperative morbidity of 31%, an in-hospital mortality of 2.4% and a 30-day mortality of 4.8%.

DISCUSSION

Gastric cancer still remains a disease with poor survival results, even though several attempts have been made to improve treatment and thereby survival. Surgery remains the only curative treatment option in gastric cancer. In Japan, where gastric cancer is endemic and many resections are performed, extended lymphadenectomies are standard of care, where at least a D2 resection should be performed for T2-T4a and N+ tumours [4]. Studies in the West have not shown improvement in 5-year survival rates comparing D1 and D2 lymph node dissections, while postoperative morbidity and mortality were higher in the D2 group. Analysis of the results 15 years after the Dutch D1/D2 trial showed, however, lesser local recurrence rates and lower gastric-cancer related mortality rates for patients with a D2 resection [15]. In the two trials conducted in the past century, a D2 dissection was also accompanied by a splenectomy or distal pancreaticosplenectomy which showed to be associated with higher postoperative mortality and morbidity [16;17]. In Japan, a D2 resection is nowadays performed without a pancreaticosplenectomy

unless the pancreas or spleen is involved [4]. It is therefore suggested that an extended lymphadenectomy without a pancreaticosplenectomy would be feasible in the West as well. The average amount of examined lymph nodes in the Netherlands is still below the recommended 15 [6;7], with poor survival rates for stage I-III cardia (33%) and non-cardia (50%) cancer [18]. This study showed that with a D1*extra* lymphadenectomy a mean of 26 lymph nodes per patient can be reached, well above the recommended 16 retrieved lymph nodes. In-hospital mortality rate of 2.4% is comparable to the mortality rate of a D1 dissection [16;17;19]. The amount of serious adverse events, defined by grade 3-5 postoperative complications [20], rate was normal to high in comparison with results described in literature [9;16;17;21]. This could be a disadvantage of a D1*extra* lymphadenectomy, although most were grade 3 complications and resolved without sequelae. Ten patients required a reoperation, although only two patients needed an extra organ resection, both due to small bowel necrosis (SBN), probably caused by enteral tube feeding. In both patients, enteral feeding was applied through a jejunostomy catheter. At reoperation, stasis of enteral nutrition in the small bowel was seen distal from the tip of the feedingtube , with bowel distention and patchy ischemia. In both patients resection of affected small bowel was performed. One patient died a couple of days later because of ongoing sepsis, the other one eventually recovered. SBN is a very rare but often fatal complication very likely to be related to enteral feeding, mostly described in patient who were treated with enteral feeding via a jejunostomy catheter [22;23]. After these complications, the study protocol was changed and patients were fed via a nasojejunal catheter. Since then, this complication did not appear again. It is still unclear if neoadjuvant chemotherapy and/or extended lymphadenectomy in gastric cancer is associated with SBN.

For protocol adherence and quality control of the operation, each surgery was performed by two gastrointestinal surgeons. Longer operation time and hospital stay predispose a patient to a higher complication rate. In this study, operation time, the amount of patients who needed a blood transfusion, and length of hospital stay of a D1*extra* lymphadenectomy are comparable to those of a D1 lymphadenectomy [16;17;21;24].

Violation of protocol for lymphadenectomies in gastric cancer are more often described. In this study, violations of in most cases only 1 lymph node station per patient were reported. In comparison to protocol violations reported in the Dutch D1/D2 study and the MRC study, these protocol violations are minor and the percentage of violations were less [17;25]. To adequately perform a D2 lymph node dissection, learning curves of 23 to 200 resections have been reported [26;27]. The D1*extra* lymphadenectomy is likely to be easier to learn and to perform compared to a real D2. In the Netherlands, where curable gastric cancer has a low incidence, it is difficult to achieve an amount of 200 resections. Although a recent study did not show better survival rates in high volume hospitals [7], centralization of the surgical treatment of gastric cancer has been implemented, where

at least 20 resection each year must be performed. Considering the results of this study and the ongoing centralization further implementation of the D1*extra* lymphadenectomy in the Netherlands will probably be feasible.

Higher survival rates after an extended lymphadenectomy can be explained by stage migration for patient groups and a therapeutic effect for the individual patient. In the 6th TNM classification [12], N3 stage was defined by a metastatic lymph node count of 15 or more. With a D1 resection, as practiced nowadays in the Netherlands, no patient will be categorized as N3, due to an insufficient lymph node harvest. This can lead to understaging, with contamination of lower stage groups and thereby decreasing survival rates for lower N-stage group. By resecting more lymph nodes tumour burden can decrease. Furthermore, by resecting more lymph nodes, also lymph nodes bearing micrometastases can be removed thereby decreasing the possibility of local recurrence [28]. However, it is unknown if the higher survival rates after an extended lymphadenectomy are caused by decrease of stage migration or by decrease of tumour burden. Although a D2 resection (including splenectomy and distal pancreatectomy) has no positive impact on survival, the amount of retrieved lymph nodes and the amount of resected negative lymph nodes do have. The latter depicts a therapeutic effect of an extended lymphadenectomy instead of a stage migration effect [19;28-30]. In the 7th TNM classification N stage is changed [31], where N stage 3a is defined as 7-15 metastatic lymph nodes and 3b as ≥ 15 metastatic lymph nodes. Although N3 stage is not subdivided in the TNM classification, stage N3a and N3b have different survival rates [32;33]. It is therefore still imperative to harvest more than 15 lymph nodes to reduce tumour load. With the D1*extra* dissection, the disadvantages of a D2 dissection can be evaded and still an adequate lymph node harvest can be achieved. Long-term survival rates still have to be awaited. It is questionable if a phase III trial comparing a D1 with a D1*extra* lymphadenectomy should be conducted. Accrual in studies for the treatment of curable gastric cancer takes several years at least due to the low incidence of curable gastric cancer in the Netherlands. Looking at current daily practice in the Netherlands where the number of lymph nodes to be retrieved does not meet up to the national and international guidelines, implementation of a D1*extra* lymphadenectomy seems very advisable, leading to a satisfactory nodal yield and acceptable morbidity and mortality.

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Chapter 11

Phase II study of Docetaxel, cisplatin and Capecitabine as preoperative chemotherapy in resectable gastric cancer

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ABSTRACT

Background

Survival for patients with resectable gastric cancer is still dismal. To improve survival several strategies have been explored. Perioperative chemotherapy has improved survival. However, the postoperative part of the regimen is often not started or completed due to toxicity. Docetaxel and capecitabine have been proven to be effective in the advanced gastric cancer with an acceptable safety profile. We conducted a phase II trial exploring the feasibility of a preoperative combination chemotherapy regimen including docetaxel, cisplatin and capecitabine in patients with resectable gastric cancer.

Patients and methods

Patients with resectable gastric cancer (including Siewert 2 and 3 tumours) fulfilling the inclusion criteria, received 4 cycles DCC, docetaxel (60 mg/m^2), cisplatin (60 mg/m^2) and capecitabine (1.875 mg/m^{2}orally on day 1-14 divided into two daily doses) followed by protocolized surgery. Each cycle was repeated every three weeks. Primary end point was the feasibility and toxicity/safety profile of DCC, secondary endpoints were pathological complete resection rate and pathological complete response (pCR) rate.

Results

All of the patients (51) were assessable for the feasibility and safety of the regimen. The entire preoperative regimen was completed by 68.6% of the patients and a total of 169 courses were administered. Grade III/IV febrile neutropenia occurred in 10% of all courses and in 31% of all patients. Three patients died due to treatment related toxicity (5.9%). Four of the 45 patients, who were evaluable for secondary endpoints, developed metastatic disease. A curative resection rate was achieved in 76.5% of the patients and in 3 patients a pCR was seen (5.9%). Two patients underwent a R1 resection (3.9%).

Conclusion

The high occurrence of febrile neutropenia in this preoperative DCC chemotherapy regimen is of concern. To decrease the occurrence of febrile neutropenia the prophylactic use of G-CSF should be explored. A curative resection rate of 76.5% is acceptable.

INTRODUCTION

Although declining, gastric cancer is still ranking in the top 5 of incidence and mortality rates of malignancies in Europe [1]. Loco-regional and metastatic recurrence rates are high and prognosis remains poor, with a 5-year survival rate of 20-31% for stage I-III disease [2]. Surgery is still the cornerstone of treatment of gastric cancer, although survival can be improved by adding perioperative treatment. In 2006, the results of the MAGIC trial were published showing that perioperative chemotherapy with epirubicin-cisplatin-5-FU (ECF) improved survival compared to surgery alone (5-year survival 36% vs 23%, respectively). Although most patients assigned to the perioperative chemotherapy tolerated the preoperative chemotherapy well, only 55% of them started the postoperative chemotherapy due to postoperative complications with only 42% of the patients completing the entire regimen [3]. These results demonstrate the problems encountered with the perioperative approach,i.e. many patients do not complete the full number of post-operative chemotherapy cycles.

In an attempt to increase efficacy and tolerability of chemotherapy regimen in gastric cancer other cytotoxic agents have been explored. The combination of docetaxel, cisplatin and fluorouracil has shown to be effective in advanced gastric cancer with reported overall response rates of 37-43% and an acceptable safety profile [4-6]. Capecitabine, an orally substitute of 5-fluorouracil (5-FU), offers a clear advantage in terms of convenience and safety without compromising efficacy [7]. The combination of cisplatin and capecitabine showed an overall response rate of 46-54.8% in advanced gastric cancer [8;9]. In addition, in a phase II study using preoperative docetaxel and capecitabine in initially locally advanced unresectable gastric cancer a Ro resection could still be achieved in 63% of the patients with an acceptable toxicity (febrile neutropenia 4%, no treatment related mortality) [10].

Taking these promising results into consideration we decided to conduct a phase II trial investigating the feasibility of 4 cycles of preoperative chemotherapy with combination of docetaxel, cisplatin and capecitabine in patients with resectable gastric cancer, followed by a standardized gastric resection and lymphadenectomy.

PATIENTS AND METHODS

Patient selection

Inclusion criteria were histologically proven gastric cancer (including gastro-oesophageal junction/cardia carcinoma (Siewert 2 and 3 [11])), stage Ib-IVa (6th TNM classification), WHO performance s 0-1, age ≥ 18 years and adequate hematologic, renal and hepatic function. All patients signed an informed consent and were expected to comply with

treatment, management of toxicity and scheduled follow-up. Exclusion criteria were inoperability, previous or current malignancies, other serious illness or medical conditions, known hypersensitivity to any of the chemotherapies used, contraindication for the use of corticosteroids, use of immunosuppressive or antiviral medication, and pregnant or lactating women. A certified ethics committee (METOPP) and the institutional review board at each centre approved the protocol. Screening included a history and physical examination, structural assessment of malnutrition, oesophagoduodenoscopy, blood sampling and CT scan of the chest and abdomen Evaluation CT-scans were performed after the second and fourth cycle of chemotherapy.

Treatment

Chemotherapy

Preoperative chemotherapy was administered for four cycles. Each 3-week cycle consisted of docetaxel 60 mg/m^2 IV infusion and cisplatin 60 mg/m^2 IV infusion on day 1, and capecitabine 1.875 mg/m^2 orally on day 1-14 divided into two daily doses (DCC). Prior to each cycle a full physical examination was performed, and a full blood count and chemistry was obtained. The neutrophil count had to be ≥ 1.5 x 10^9/l and the platelet count ≥ 100 x 10^9/l. Dose reductions and delays were predefined for granylocytopenia, thrombocytopenia, and non-hematological toxicity. Secondary use of growth factors was not part of the protocol. Any adverse event was collected and registered according to Common Toxicity Criteria (CTC, version 3). A serious adverse event (SAE), defined as an event that is either fatal, life-threatening, requiring or prolonging hospitalization or resulting in persistent or significant disability or incapacity, was reported to the study coordination centre, and evaluated by the principle investigators. Furthermore, these SAE's were reported to the central medical ethics committee.

Surgery and pathology

Patients were scheduled for surgery approximately four to six weeks after the last cycle of chemotherapy. A (partial) gastric resection and a standardized lymphadenectomy, the so-called D1*extra* lymphadenectomy specified to tumour location was performed by a local surgeon specialized in gastrointestinal surgery, assisted by a surgeon of the study team. The D1*extra* lymphadenectomy is a newly defined dissection in which lymph node stations 1-10 and/or 12 (according to the Japanese Classification [12]) prone to metastases [13] are removed.

Evaluation and outcome

The primary endpoint of the medical oncology part of this study was the toxicity and safety profile of 4 courses of DCC in patients diagnosed with primary resectable gastric

cancer. The secondary endpoint of this study was the determination of pCR and pathological resection rate (R0). Numbers and proportions of patients reaching the primary and secondary endpoints will be described in the statistical analysis.

RESULTS

Patient Characteristics

Between November 2008 and November 2012, fifty-three patients were included in the study from five participating hospitals. Two patients were excluded as they were diagnosed with distal oesophageal cancer. In table 1 the patient characteristics are outlined. The mean age was 64 years (range 34-84), and 75% of the patients exhibited an WHO performance state of 0.

Table 1. Patient characteristics at baseline

Characteristics	No. of patients	%
Age, years		
Median	64	
Range	34-84	
Age, category		
< 50 yr	5	9.8
50-59 yr	8	15.7
60-69 yr	22	43.1
70-79 yr	15	29.4
> 80 yr	1	2.0
Sex		
Male	36	70.6
Female	15	29.4
WHO Performance Status*		
0	37	72.5
1	13	25.5
2	1	2.0
Clinical T stage**		
T1	5	9.8
T2	12	23.5
T3	21	41.2
T4	2	3.9
Unknown	11	21.6

Table 1. *Continued*

Characteristics	No. of patients	%
Clinical N stage**		
N0	16	31.4
N1	19	37.3
N2	4	7.8
N3	2	3.9
Unknown	10	19.6

* WHO Performance status of 0 denotes asymptomatic, 1 symptomatic but fully ambulatory and 2 symptomatic but less < 50% in bed during the day

** Clinical stage according to the 6th edition UICC/AJCC TNM classification, determined by endoscopy, CT scan and PET-CT scan

Table 2. Feasibility: treatment cycles delivered

Cycles received	No. of patients	%
1	51	100.0
2	44	86.3
3	39	76.5
4	35	68.6
Percentage of intended dose delivered (per evaluable patient, ITT)		
Docetaxel		78.9%
Cisplatin		78.7%
Capecitabine		78.3%

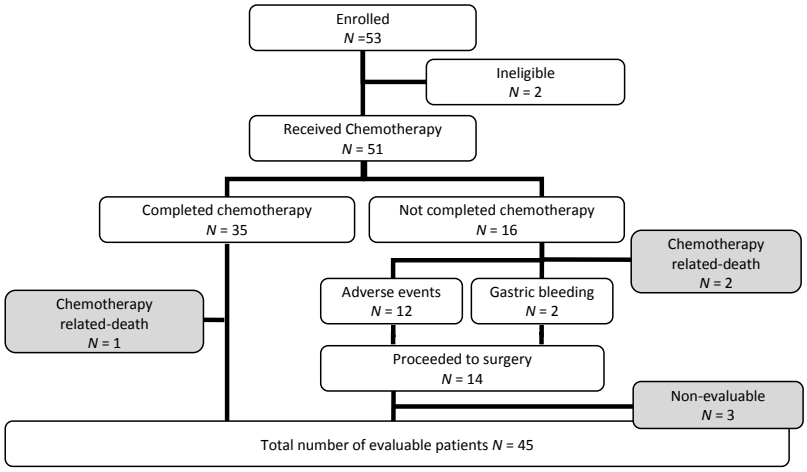

Figure 1. Flow diagram of enrolled patients

Feasibility

All 51 patient started preoperative chemotherapy. In total, 35 patients completed 4 cycles of chemotherapy (68.6%). In table 2 the feasibility results are outlined. A total of 169 cycles of chemotherapy were administered. The percentage of intended dose delivered in the intention-to-treat group was 78-79% for each drug. Reasons for dose reduction and discontinuation were treatment related toxicity, including two deaths and a tumour related bleeding in two patients (figure 1).

Safety

All patients were evaluable for safety. Grade III/IV toxicity is summarized in table 3. The most common toxicitiy was febrile neutropenia and diarrhea occurring in 9.5 and 10.1% of the cycles. There were 3 chemotherapy related deaths, resulting in a mortality rate of 5.9%. In two patients, treatment-related death was infection concomitant with grade III/IV neutropenia. One patient died after refusing further therapy of an initially successful treatment of febrile neutropenia.

Table 3. Grade 3-4 adverse events related to chemotherapy

			Grade III/IV	
Toxicity	No of patients	%	No of cycles	%
Hematologic				
Anemia	3	5.9	3	1.8
Neutropenia	25	49	32	18.9
Febrile neutropenia	16	31.4	17	10.1
Non-Hematologic				
Gastro-intestinal				
Anorexie	8	15.7	10	5.9
Constipation	1	2.0	1	0.6
Diarrhea	13	25.5	16	9.5
Dysphagia	1	2	1	0.6
Mucositis	6	11.8	6	3.6
Nausea	5	9.8	5	2.9
Vomiting	5	9.8	8	4.7
Constitutional				
Fatigue	4	7.8	4	2.4
Hand-foot syndrome	4	7.8	6	3.6
Neurosensory				
Hearing impairment	1	2.0	1	0.6
Neuropathy	2	3.6	2	1.2
Renal impairment	3	5.9	3	1.8

Efficacy

Of the remaining 48 patients, 3 patients were considered non-evaluable for the secondary endpoints because of major protocol violation (one patient was operated one year later after completion of the preoperative regimendue to myocardial infarction, one patient switched to another chemotherapy regimen, and one patient was operated in a non-participating hospital). Of the remaining 45 patients 39 patients underwent a Ro resection. Two patients developed distant metastases assessed prior to surgery, two patients had peritoneal carcinomatosis diagnosed during surgery and two patients had a R1 resection. Thus, 76.5% of the intention to treat population and 86.7% of the evaluable patients had a Ro resection with curative intend. The surgical results are described elsewhere.

A pCR was reported in 3 patients (5.9%).

DISCUSSION

Overall survival of gastric cancer after a curative resection can be improved with perioperative chemotherapy as shown in the MAGIC trial. The additional benefit of perioperative ECF on survival is probably for the larger part attributed to the preoperative part of the treatment [3]. Postoperative chemotherapy in this patient category is challenging since a high percentage of the patients is not fit enough or willing to start and complete the full postoperative part of the regimen [3]. To improve the adherence and increase the benefit of preoperative chemotherapy in resectable gastric cancer we designed this phase II study investigating the feasibility of a preoperative regimen of four cycles of docetaxel, cisplatin and capecitabine. To increase the efficacy of the preoperative regimen, we replaced epirubicin by docetaxel, since docetaxel containing combination regimens have shown to be feasible and superior in locally-advanced and metastatic gastric cancer [4-6]. In our trial however, four cycles of DCC as a preoperative regimen showed to be highly demanding for patients with primarily resectable gastric cancer. Only sixty-eight percent of the patients completed all 4 cycles of DCC, the other patients discontinued mainly due to treatment related toxicity. In comparison with results from other trials this percentage is rather low. In a German phase II trial investigating the same regimen as perioperative chemotherapy, with a higher dosage of docetaxel of 75 mg/m^2, 94% completed all three preoperative cycles [14]. In the MAGIC trial, 86% completed the intended three preoperative cycles of ECF [3]. In a French trial the rate of patients completing two cycles of preoperative chemotherapy was 87% [15], while in an Italian study the rate of completing 4 preoperative docetaxel based cycles was 74% [16]. Four cycles of preoperative DCC chemotherapy, therefore, might be too demanding whereas 86% and 76% of the patients in our study completed 2 and 3 cycles respectively

which is comparable to the results described above. On the other hand, completing postoperative chemotherapy is even more difficult. In the aforementioned Italian study feasibility of preoperative chemotherapy was compared to the feasibility of the same regimen as postoperative chemotherapy. The rate of completing 4 postoperative cycles was 34% in this arm [16]. In the previous mentioned German and MAGIC trials only 53% and 42% respectively completed the postoperative scheme [3;14]. Although the rate of completing all 4 cycles was relatively low in our study, the intended delivered dose was reasonable with percentages of 78 for all drugs individually [7;14]. Accurate monitoring and early intervention in case of deterioration is imperative to prevent a high amount of patients failing to complete a full chemotherapy regimen.

Treatment related mortality was 5.9% being comparable to mortality rates reported in literature (0-6%) [4;5;7;17]. Febrile neutropenia occurred in 10% of all cycles (versus 2-15% found in other trials [4;5]), being the cause of death in three patients. The prophylactic or secondary use of G-CSF was not part of the protocol as no data were available at the time of the study design about the interaction between G-CSF and capecitabine in case of simultaneous administration. In theory, the proliferative activity of bone marrow after the administration of G-CSF might increase the myelotoxicity of capecitabine. In literature, only scarce data are known about the simultaneous use of G-CSF and capecitabine. In a phase II trial in breast cancer, the use of pelfilgastrim was evaluated in a small subset of patients receiving docetaxel and capecitabine based chemotherapy regimen. Minimal grade III/IV neutropenia and no febrile neutropenia was observed [18]. In one phase II trial in metastatic gastric cancer with a comparable DCC regimen as in our study, patients were treated successfully with G-CSF in case of febrile neutropenia and no toxicity related deaths were reported [19]. The use of G-CSF as primary or secondary prophylaxis for (febrile) neutropenia in a docetaxel and capecitabine based chemotherapy scheme is therefore promising, and should be further investigated.

Other main toxicities we encountered were grade III/IV hand-foot syndrome, diarrhea and anorexia. The rate of hand-foot syndrome of 7.8% in this study is acceptable compared to other studies [7-10;14]. Many patients with gastric cancer experience difficulties with eating. With addition of the toxicity of chemotherapy gastric cancer patients are prone to anorexia and weight loss. It is therefore imperative to monitor their intake and weight to be able to act in time when this is deteriorating. A dietician should be consulted and enteral feeding should be started in an early phase.

In gastric cancer, clinical tumour staging faces several difficulties. The current imaging modalities have low sensitivity rates for T- and N-stage[20;21]. It is therefore difficult to clinically assess the efficacy of chemotherapy in these patients. In literature, many modalities have been used to determine response rate [4;7;15], which makes it difficult to compare ORRs. In our study, we therefore only determined pathological response rate. A pCR was found in 3 patients (5.9%) which is lower than expected looking at other studies

investigating DCF or DCC in gastric cancer in which pCRs of 6.1% [10], 11.7% [16] and 13.7% [14] are reported. On the other hand, in the MAGIC trial using ECF as a treatment regimen no pCR was seen [3].

Thirty-nine (76.5%) patients received an Ro resection. This is in line with rates found in the MAGIC trial (69.3%) [3], although it is lower compared to other trials using a docetaxel based regimen in which a Ro resection was achieved in 84% [15], 85% [16], and 90.2% [14] of patients. The long-term effects of this docetaxel based scheme and protocolized D1*extra* lymphadenectomy have to be awaited.

In conclusion, in our study the benefits defined as Ro resection and complete pathological response rate of four cycles of DCC are lower than expected, although the effects on long-term results have to be awaited. Moreover, this is coupled with a high grade III/IV toxicity, especially febrile neutropenia. The use of simultaneous G-CSF and capecitabine should be further investigated to decrease toxicity-related non-adherence and mortality.

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Chapter 12

Acute small bowel necrosis after upper gastrointestinal surgery; a very rare but often fatal complication

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Submitted

ABSTRACT

Objective

To demonstrate the rapid deterioration in case of acute small bowel necrosis (ASBN) induced by enteral feeding after upper gastrointestinal surgery and the imperative need of early diagnosis and therapy.

Patients

Three patients with small bowel necrosis due to early enteral feeding after an upper gastrointestinal resection are described. Two patients were treated with neoadjuvant chemotherapy. After surgery all three showed cramping abdominal pain and an ileus. They rapidly deteriorated and needed extensive surgery. Two patients died, one survived after multiple operations.

Conclusion

Small bowel necrosis is an often fatal but rare diagnosis. Early symptoms are non-specific but rapidly progress into sepsis and multi-organ failure. If a patient with enteral feeding after abdominal surgery develops cramping abdominal pain and abdominal distention,followed by rapid deterioration, this diagnosis should be kept in mind. Early diagnosis and treatment are imperative to save a patient's life.

INTRODUCTION

ASBN induced by postoperative enteral feeding after surgery or major trauma is a very rare, but often fatal complication, Most of the time patients develop this complicationon the 4^{th} to 7^{th} postoperative day . It is characterized bya sudden abdominal distension, cramping pain and loss of bowel function and sometimes increase of gastric tube production. It is rapidly followed by septic shock and multisystem organ failure. Without early intervention death will follow.

In our hospital two patients developed ASBN after a total gastrectomy for gastric cancer followed by enteral feeding via a jejunostomy catheter. One patient evolved ASBN after an extensive resection of a GIST (gastrointestinal stromacell tumour) located in the radix mesenterii followed by enteral feeding via a triple lumen catheter. One patient died; the other two patients survived initially, one died a couple of weeks laterdue to a pneumonia. In this case report we would like to illustrate the difficulty of diagnosing ASBN and the imperative need of an early intervention to save a patient's life.

Case 1

A 66-year old male presented with gastric cancer without distant metastases. He was treated with four cycles of neoadjuvant chemotherapy, consisting of cisplatin, docetaxel and capecitabine, followed by a total gastric resection and an extended lymphadenectomy approximately six weeks after finishing chemotherapy treatment.. Enteral continuity was restored with an oesophagojejunostomy and a jejunojejunostomy. A nasojejunal tube was placed through the proximal anastomosis and a jejunostomycatheter was placed distally from the distal anastomosis. On the first postoperative day 670 ml HP Energy per 24 hrs. was given through the jejunostomy catheter, on the second day he received 1090 ml per 24 hrs, on the 3rd postoperative day he received in total 1470 ml HP Energy.

In the evening of the 3rd postoperative day, after cessation of epidural analgesia, he developed a sudden progressive cramping abdominal pain and abdominal distention. Vital functions were normal and at palpation theabdomen was tenderwithout signs of peritoneal excitation. Enteral feeding was stopped, the epidural analgesia was restarted and the pain resolved. His vital functions remained stable and no further action was taken. During the night, however, he developed fever and hypotension and his diuresis decreased to 20 ml/hour. Because of further clinical deterioration, the patient was transferred to the ICU. A X-ray of the thorax suggested an infiltrate in the right upper and lower lobe of the lung. The next morning, a CT scan of the abdomen showed an ileus of the small bowel with aerobilia. Surgery followed and a patchy necrosis of the jejunum and ileum distally from the jejunostomy catheter was seen. Three segments of small bowel were resected and the remaining jejunal and ileal segments were left in the abdomen. At a second look a day later the remaining small bowel was vital and anastomoses were made. On day 6, he again developed a severe sepsis leading to a decision not to operate again. He died after several hours.

Case 2

A 73-year old male was diagnosed with gastric cancer without distant metastases. He received 4 cycles of neoadjuvant chemotherapy, consisting of cisplatin, docetaxel and capecitabine, followed by a total gastric resection and an extended lymphadectomy approximately six weeks after the last cycle of chemotherapy. Enteral continuity was restored with an oesophagojejunostomy and a jejunojejunostomy, a nasojejunal tube was placed through the proximal anastomosis. A jejunostomy catheter for feeding was placed distally of the distal anastomosis. On the second day enteral feeding was started through the jejunostomy catheter (500 ml/24 hours Fresubin Original, 3rd day 1040 ml/24 hours HP Energy, 4th day 1475 ml/24 hours HP Energy).

On the fourth postoperative day the patient was nauseous and he vomited alongside the nasojejunal tube. Vital functions remained stable except for an oxygen saturation of

93% with 2 l O_2. A X-ray of the abdomen showed distention of the small bowel. A CT-scan of the abdomen showed intestinal pneumatosis and aerobilia. Surgery was performed and showed an ileus with stasis of enteral nutrition. The small bowel showed diffuse patchy ischemia. The small bowel was desoufflated via the terminal ileum and a loop-ileostomy was made. At a second look the day after 1 meter of jejunum was resected because of ongoing patchy ischemia, continuity was not restored. Two days later an additional small resection of jejunum was performed and continuity was restored. The patient stabilized and could be discharged from the hospital 5 weeks later. His ileostomy was replaced a couple of months later.

Case 3

A 82-year old male presented with nausea and vomiting due to a tumour in the radix mesenterii located near the duodenum. He received a resection of the tumour with a pancreastail resection, splenectomy and a left-sided nefrectomy. Continuity was restored with a duodenojejunostomy located at the horizontal part of the duodenum. A jejunal feeding tube was placed with the distal lumen distally from the anastomosis and enteral feeding was started according to local protocol. After 8 days he developed a pneumonia which was treated with antibiotics. Six days later he deteriorated suddenly and CPR was started. He was admitted to the ICU. A CT-scan of the abdomen was performed which showed multiple fluid collections. A radiological drain was placed but due to further clinical deterioration surgery was performed. At surgery ischemia of the proximal jejunum 10 centimeters distal of the duodenojejunostomy was found with stasis of enteral feeding. A resection of the ischemic small bowel was performed, without restoration of continuity. Two days later a second look was performed and a gastrojejunostomy was made. Postoperative he developed acute tubular necrosis for which he needed dialysis. Due to loss of strength he had difficulty with swallowing and coughing, resulting in aspiration. He received a tracheostomy but after a long course of weaning he developed a new aspiration pneumonia. Eventually he and his family decided to stop all treatment after which he died promptly.

DISCUSSION

Early enteral feeding is beneficial after major surgery and trauma[1]. It ameliorates immunity and wound healing and it diminishes the catabolic stress response and the amount of septic complications [2;3]. Complications due to enteral feeding via a jejunal tube are nausea, cramping abdominal pain, diarrhea and distension. Reported incidence of these complications is5-40% [4]. A serious complication like ASBN is less common with reported incidences of 0.14% to 4% [5;6]. Mortality rates vary from 0% to 100% [6-12]. Early symptoms

are non-specific, consisting of abdominal distension, cramping pain and sometimes an increase of gastric tube contents. Eventually, septic shock and multisystem organ failure develop, which, without intervention, will be followed by death. CT scan of the abdomen shows small bowel distension without obstruction and sometimes stasis of enteral nutrition. Findings at laparotomy are a distended jejunum with patchy necrosis or segmental full thickness necrosis, beginning at or just distally from the jejunal tube or catheter. Stasis of enteral nutrition is mostly seen in the affected segment [6;11;13].

Causes are probably multifactorial. Several hypotheses have been suggested for the pathogenesis of acute small bowel necrosis after early enteral feeding. A low flow state of the small bowel with a higher demand of oxygen with continuous enteral feeding could be a cause, although in our patients, as in all patients reported in literature, there were no signs of arterial occlusive disease of the splanchnic vessels [6;14;15]. Enteral feeding can result in an unphysiologic hyperosmolar content in the jejunum and can cause bacterial overgrowth. This can lead to bowel distension and decreased mucosal perfusion, and finally, gross ischemia of the small bowel [16;17]. Although the reported incidence of small bowel necrosis as a complication of early enteral feeding is low, mortality rates are very high. More patients with ASBN are reported as having a jejunostomy catheter rather than a nasogastric or duodenal feeding tube. In literature, no evidence for occlusive arterial or venous disease and obstruction and/or torsion are reported. Only one patient was described with ASBN after chemotherapy prior to oesophagectomy [6]. Although cisplatin is known to give vascular complications, no association between neoadjuvant chemotherapy and ASBN has been mentioned.

As shown in the reported cases, it is difficult to predict whether normal complications like nausea, cramping abdominal pain, diarrhea and distention will develop intoASBN. Although this complication is very rare, it is imperative to keep this in mind when a patient after upper gastrointestinal surgery and enteral feeding is showing non-specific septic symptoms associated with abdominal distention. Enteral feeding should be immediately ceased, early imaging by means of CT is designated and early surgery to resect the affected segment should be performed [18].

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Chapter 13

Discussion

Gastric cancer trends and treatment strategies in the Netherlands: challenges ahead

- **CHANGES IN INCIDENCE OF GASTRIC CANCER**
- **SURVIVAL AFTER GASTRIC CANCER**
- **STAGING OF GASTRIC CANCER**
  - **Preoperative staging**
  - **Peroperative staging**
  - **Postoperative staging**
- **TREATMENT OF CURABLE GASTRIC CANCER**
  - **Surgery**
  - **Perioperative treatment**
  - **Treatment in non-curable gastric cancer**
- **FUTURE PERSPECTIVES**
  - **Increase of the role of laparoscopy**
  - **Gastric cancer in the elderly**
  - **Improvement of care**
- **PERORATION**

CHANGES IN INCIDENCE OF GASTRIC CANCER

Gastric cancer can be subdivided in cardia and non-cardia cancer, the latter being proportionally more frequent in populations with a high incidence. Both types have different etiological, epidemiological, pathological and clinical features. Since the beginning of the 20th century, the incidence of gastric cancer, then one of the most frequent cancers worldwide, has dramatically declined, starting in the USA, soon followed in other industrialized countries like the Netherlands, and finally in eastern and southern Europe and in developing countries a few decades later. Its in cancer control unique decline was generally preceded by better food conservation facilitated by the large scale introduction of the refrigerator. This omitted the need of salting as a food conservation technique (for mainly fish and meat) and made fresh fruits and vegetables available the whole year around. A high amount of salt consumption is a risk factor for developing gastric cancer, while a higher consumption of fresh fruits and certain vegetables is often associated with a lower risk of gastric cancer [1-3]. Another causal risk factor for gastric cancer is a chronic infection with *Helicobacter Pylori* (*H.Pylori*) [4]. It is mainly associated with the intestinal type of gastric cancer (according to the Lauren classification [5]) and mostly found in the distal part of the stomach. *H. Pylori* is believed to be transmitted via the oral-fecal route, mainly during childhood. The risk of transmission has decreased with improved hygiene by the combination of smaller families and better housing. Furthermore, eradication of *H. Pylori* is further accomplished with the use of antibiotics since the last decades of the 20th century, when the bacteria was discovered [6]. The decrease in age adjusted incidence has steadily continued from 25 to 14/100,000 in

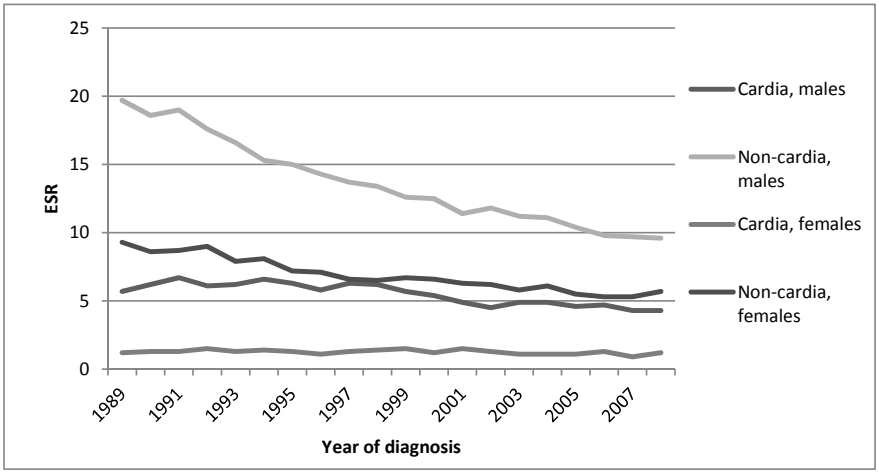

Figure 1. Trends in incidence according to location and gender, the Netherlands 1989 – 2008. ESR, European Standardized Rate per 100 000 inhabitants (source: Netherlands Cancer Registry)

males and from 12 to 7/100,000 in females in 2008 in the Netherlands (data derived from the National Cancer Registry, this thesis).

H. Pylori causes gastritis which can eventually develop in adenocarcinoma via several steps (atrophic gastritis → intestinal metaplasia → dysplasia → cancer), the so-called gastric precancerous cascade [7]. For cardia cancer two different types of etiology have been described, the above mentioned and one associated with high BMI and gastro-oesophageal reflux disease [8;9]. In this thesis we have mainly focused on gastric adenocarcinoma, which comprises 95-99% of all gastric tumours. Other types include gastric lymphoma of which a simultaneous decrease in incidence occurred, also attributed to a decrease in chronic infections with *H. Pylori* [10].

Although decreasing, incidence of gastric cancer is still high in Asian countries as well as in eastern and southern Europe [11]. In Japan, where gastric cancer is endemic, the detection and treatment of gastric cancer still gets a lot of attention. A screening program using photofluorography has been implemented nationwide since 1983. Although no randomized controlled trials (RCTs) have been conducted to prove the benefit of photofluorography or endoscopy, the use of photofluorography is recommended [12]. In the Netherlands, screening has never seemed cost effective and patients will only be diagnosed if they have symptoms that could be associated with gastric cancer. Gastric cancer can cause upper abdominal pain, nausea, vomiting (sometimes haematemesis), weight loss, gastro-oesophageal reflux, fatigue due to occult blood loss causing anemia and dysphagia. All these symptoms are non-specific and might only appear in a late stage. Therefore gastric cancer is usually diagnosed in a late, non-curable stage. In cardia and non-cardia cancer, 40-45% of the patients have reached stage IV disease at initial diagnosis (this thesis). Even if a precursor lesion is found, surveillance is not always performed. A Dutch study assessed the risk of a precursor lesion progressing into gastric cancer within 5 years to be 3% for mild to moderate dysplasia, and 30% for patients with severe dysplasia. For mild to moderate dysplasia, the risk of progressing into gastric cancer after multivariable analysis is 3.9, for severe dysplasia this risk is 40.1 compared to atrophic gastritis. In the aforementioned Dutch study, only 61% of patients had a follow-up gastroscopy after the diagnosis of severe dysplasia [13], showing that there is no national guideline for the follow-up of these patients. To prevent a too late detection of gastric cancer for curative treatment more knowledge of these high risk lesions leading to a more structured follow-up of these patients is needed.

SURVIVAL AFTER GASTRIC CANCER

Mortality rates for gastric cancer have decreased accordingly over the past decades in the Netherlands. This decrease is mainly due to a decrease in incidence of gastric cancer rather than to an improvement in survival rates [14]. Survival after gastric cancer in the Netherlands has remained dismal (this thesis) and differs substantially among the various European countries. Differences in survival rates can be caused by several reasons.

First, epidemiological determinants may play a role. Patients diagnosed in the Netherlands have a higher age at diagnosis. Older age is associated with lower survival rates [15]. Next to age, stage distribution attributes to differences in crude survival rates. As depicted above, more than 40% of the patients are diagnosed with stage IV disease in the Netherlands, with subsequent worse survival rates [15]. Subsite localization, i.e. at the cardia, is another reason for lower survival rates (this thesis). Last, survival is depending on histological type. The differences in survival for gastric cancer between European countries, in up to 60% of cases, could therefore be explained by differences in age, stage distribution, subsite localization, histologic type, [16;17].

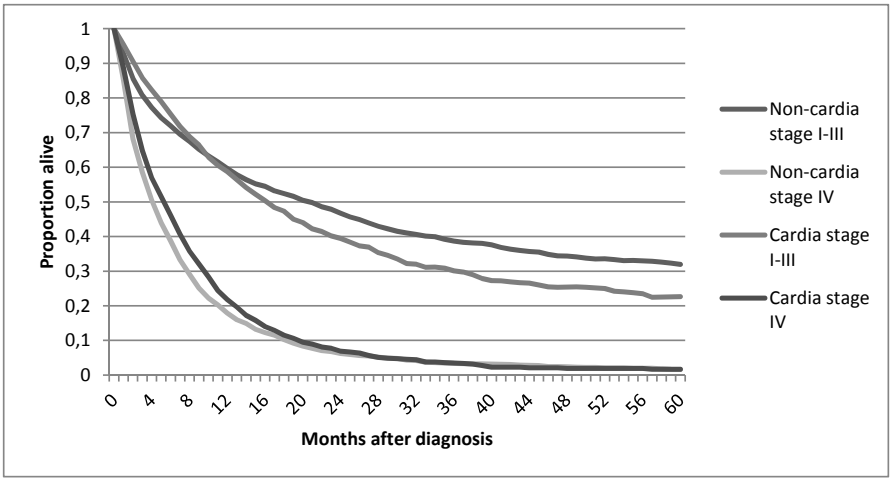

Figure 2. Relative survival for non-cardia and cardia cancer in the Netherlands 2005-2008 (source: Netherlands Cancer Registry)

Second, stage migration could affect stage-specific survival differences. The TNM classification has been accepted as the standard for describing the extent of the disease. In 2010, the 7th edition of the TNM classification was published, a joint effort between the UICC (Union Internationale Contre le Cancre) and the AJCC (American Joint Committee on Cancer) [18]. Compared to the 6th edition from 2002, changes have been made

regarding T, N, and overall TNM stage except for stage IA [19]. In the 6th edition N3 stage was defined as more than 15 positive lymph nodes. In the Netherlands, after resection, a mean of 13 lymph nodes was found in 2009 (this thesis), which, although improved, is still not meeting up with the Dutch national guideline which dictates a yield of at least 15 lymph nodes. Quite a few patients could therefore be classified to stage N3 disease and with a low yield of lymph nodes, the chance of finding positive lymph nodes decreases. Patients with advanced disease can therefore be mixed with those with a lower disease stage, thereby 'polluting' survival rates, which is called stage migration. In the 7th TNM stage, in N3a disease 7-15 positive lymph nodes have to be involved and in N3b disease >15 lymph nodes, although no distinction is made in the overall TNM classification. In Japan and other high frequency countries, a higher amount of lymph nodes is retrieved with a smaller chance of stage migration.

Third, therapeutic differences may explain the survival differences. In Japan and specialized centres extended lymphadenectomies are performed which explains the higher lymph node yield. Besides the effect of stage migration, there is a therapeutic effect of an extended lymphadenectomy, although it is still not clear where the effect of stage migration stops and the therapeutic effect starts. Postoperative mortality rates in high frequency countries and some high volume centres are reported to be lower than 2% [20;21]. In the Netherlands, postoperative mortality rate of 6.7% is found (this thesis).

STAGING OF GASTRIC CANCER

Preoperative staging

Accurate preoperative staging of gastric cancer remains challenging. Precise preoperative staging is necessary for accurate treatment assignment. Gastrectomy and the additional lymphadenectomy have high morbidity and mortality rates and should not be performed in patients with distant metastasis. Furthermore, patients with stage T1 disease can be treated with endoscopic removal of the tumour (endoscopic submucosal resection (ESR) or endoscopic mucosal dissection (EMD)) [22], although Japanese guidelines still recommend a partial gastric resection in these cases [23]. Sensitivity and specificity for T and N stage of current imaging techniques such as ultrasound, CT, MRI and endoscopic ultrasound are insufficient [24;25]. It remains therefore difficult to predict clinical TNM stage, a problem also encountered in the DoCCS-study, in which 14% had an unknown clinical TNM stage (this thesis).

All abovementioned imaging modalities are based on anatomical features. FDG-PET scan (18-F-Fluoro-2-deoxyglucose positron emission tomography) is based on the alteration of glucose metabolism in cells, with a superior sensitivity in detecting lymph node metastases in oesophageal and lung cancer [26;27]. FDG-PET has low sensitivity com-

bined with a high specificity for the detection of gastric cancer (this thesis). The normal gastric wall has a high blood flow and subsequently high uptake of glucose which could give false positive results. The uptake of glucose is regulated by the GLUT-1 receptor. In advanced gastric cancer expression of GLUT-1 receptors is higher due to a higher metabolism compared to early gastric cancer which could explain the higher sensitivity for advanced gastric cancer of ~94% versus ~44% for early gastric cancer (this thesis). Furthermore, the uptake of FDG is dependent on the histological type of gastric cancer. The diffuse type and signet ring cell type have higher mucous contents, more diffuse spreading of tumour cells and less expression of GLUT-1, with subsequent less sensitivity of FDG-PET. For accurate T-staging, FDG-PET is not useful. In detecting lymph node metastasis, sensitivity is low due to low spatial resolution of FDG-PET. On the other hand, when the primary tumour does take up FDG, FDG-PET could play a role in the evaluation of the benefit of (neoadjuvant) chemotherapy. Tumour regression (as shown by CT/MRI) is a relative late effect of chemotherapy compared to the metabolic response. With FDG-PET the altered metabolism could be detected after 1 cycle of chemotherapy, which could prevent patients from receiving toxic treatment when response of the tumour is lacking (this thesis).

Peroperative staging

Although in T1 gastric cancers, EMR or ESD can be performed, it is not widespread available and is only recommended in trial settings according to the Japanese guidelines [23]. These patients may therefore still undergo a resection with a(n extended) lymphadenectomy [22], although lymph node metastases have been reported to be as low as 2-5% in T1a cancer (this thesis). As explained above, the detection of lymph node metastasis in current imaging modalities is unreliable. With sentinel lymph node biopsy (SLNB) a distinction could be made between patients with and without lymph node metastasis, which might affect the extent of the required lymphadenectomy. Current detection rate and sensitivity of SLNB however is too low for implementation of this technique in early gastric cancer (this thesis). Best results are achieved with a combined technique of dye and radio-colloid, although this calls for a two staged procedure, i.e. preoperative endoscopy to apply the radio-colloid with clipping of the tumour when it is small or non-palpable, followed by application of the dye peroperatively. Another issue is the timing of the pathological examination. A peroperative diagnosis would be preferential to prevent a two staged surgical procedure in patients with positive SLNs, but to prevent false negative results, serial sectioning and immunohistochemistry might be needed.

With the aging patient population and hence an increasing amount of patients with comorbidity less extended resections are preferential. Regarding this aspect, the SLNB technique should deserve further attention and future studies should be conducted to evaluate its value, especially in early gastric cancer.

Postoperative staging

Although in the current guidelines postoperative stage has no influence on postoperative treatment, except in a R1 resection where postoperative chemo-radiotherapy is recommended in case preoperative chemotherapy is not administered [28], adequate staging is necessary to determine the exact extent of the disease. T and N stage are the most important prognostic factors (this thesis) [29]. In the current guidelines at least 15 lymph nodes should be resected to adequately determine N stage[28]. This amount is often not retrieved and, therefore, understaging could affect survival rates negatively in the different stages of gastric cancer in the Netherlands (this thesis). The amount of retrieved lymph nodes is both dependent on the extent of lymphadenectomy and on the extent of pathological examination. The two departments of pathology in the Southern part of the Netherlands which found a higher mean of lymph nodes compared to the rest also found a higher percentage of patients with N+ disease (this thesis). This finding is consistent with the results of a study analyzing the amount of harvested lymph nodes in colonic cancer in the same departments of pathology [30]. Furthermore, there was a large variation between the abovementioned departments in the percentage of patients having an unknown amount of lymph nodes, especially in N+ disease (this thesis). Pathological performance results could be ameliorated by the use of serial sectioning and fat clearing techniques [31;32]. Besides the above mentioned aspects of lymph node harvesting, biological features of patients also play a role in the amount of retrieved lymph nodes. A study investigating the amount of lymph nodes in cadavers showed a great variation between individuals [33].

Several new staging systems have been proposed to overcome the effect of stage migration due to insufficient lymph node yield. The lymph node ratio (LNR) has been proposed and is defined as the amount of metastatic lymph nodes divided by the amount of retrieved lymph nodes. It is less influenced by the amount of retrieved lymph nodes compared to the 6th and 7th TNM staging system [18;19], and it has a more homogenous spread looking at 5 year crude survival rates and hazard ratios (this thesis). Furthermore, the LNR has a stronger predictive value for long-term survival [34;35]. However, there are some drawbacks for the lymph node ratio as a new staging system. Lymph node ratios are divided in groups, but there is no standard grouping yet. This implies that LNR groups are divided according to the studied population and may therefore not be reproducible. Another drawback is that most published articles deal with patients who underwent an extended lymphadenectomy, therefore obscuring the prognostic value in patients with less than 15 examined lymph nodes. On the other hand, in patients with a limited lymphadenectomy the LNR is less influenced by the amount of examined lymph nodes compared to the conventional TNM staging system (this thesis). Future studies should focus on standard grouping of LNR and validate its use and predictive value worldwide.

TREATMENT OF GASTRIC CANCER

Surgery

Surgery is still the cornerstone in the treatment of curable gastric cancer, although perioperative treatment seems to improve also long-term survival. For gastric cancer, a (partial) gastric resection and an additional lymphadenectomy are usually performed. Several studies have been conducted to evaluate the extent of the lymphadenectomy. In Japan, perigastric and more distant lymph nodes have been grouped in stations and a standardized lymphadenectomy has been developed [36]. In a D1 resection, lymph node stations surrounding the stomach are removed, in a D2 dissection, additional lymph nodes are removed depending on the location of the tumour. To remove lymph node station 10 and 11 extensively, a pancreatic tail resection and splenectomy had to be performed [37]. In the late '80s and early '90s of the 20th century, two phase III trials have been conducted to evaluate the feasibility of a D2 dissection and to evaluate long-term survival. In both studies, postoperative morbidity and mortality were higher in the D2 group, while 5-year survival rates did not improve. Furthermore, they found that a distal pancreatico- and splenectomy was related to higher postoperative mortality and morbidity, and to a lower long-term survival. However, in both studies surgery was performed in a lot of hospitals with a low case volume [38;39]. In the new Japanese guidelines, a pancreatico-splenectomy is only performed in predefined cases [23]. A more recent study in specialized centres in Italy showed similar low postoperative morbidity and mortality rates for a D1 and a D2 dissection, though long-term results have to be awaited [40]. Another study performed in Taiwan showed a survival benefit of a D3 (D2 plus para-aortic lymph nodes) compared to a D1 dissection with acceptable postoperative morbidity and mortality [41]. In Japan, the benefit of a D2 dissection is since long unabated, although no RCTs have been conducted to evaluate the benefit of a D2 dissection. Two studies comparing a D2 with or without resection of para-aortal lymph nodes found no survival benefit for such an extended resection, although postoperative morbidity and mortality rates were lower than those reported in the European D1 versus D2 trials [21;42]. In the Southern part of the Netherlands, a phase II study conducted to evaluate the feasibility of a D1*extra* lymphadenectomy showed good preliminary results (this thesis). With this technique, irrespective of tumour location lymph node station 3-9 are removed, and depending on location of the tumour, lymph node stations 1,2, 10 and/or 12a. The median amount of lymph nodes removed was 26 (range 4-52), postoperative morbidity rate was 31% with an in-hospital mortality rate of 2.4%. Comparing these results with the literature, a D1*extra* lymphadenectomy could be the solution for the problems encountered performing a D2 lymphadenectomy and the too low retrieved amount of lymph nodes in the Netherlands (this thesis). What the effect is of a D1*extra* lymphadenectomy on long-term survival has to be awaited.

Where does the therapeutic benefit of an extended lymphadenectomy start and where does the effect of stage migration on survival rates end? Many retrospective studies have tried to give an answer to this question, as well as a systematic review [43]. It is apparent that when less than 10 lymph nodes are retrieved, stage migration has a large effect on survival rates for different stages. When more lymph nodes are examined, disease-free survival and overall survival increase. Also in patients with N3 disease survival benefits have been reported when more lymph nodes are assessed (i.e. ≥15 versus ≥ 25 [44], ≤20 versus ≥35 [45]). In No disease also a survival benefit can be seen when more lymph nodes are retrieved. This latter effect can be attributed to a therapeutic effect, i.e. patients with pNo disease can have micro-metastases that are not found during pathological examination. With the removal of these lymph nodes tumour burden is also reduced [43]. Even in patients with less than 7 compared to more than 7 examined lymph nodes and No disease a survival difference can be seen (this thesis). How many lymph nodes should be removed, however, is still not clear, as even a survival benefit can be seen when more than 40 lymph nodes are removed and examined [45]. Furthermore, in stage T1 disease, the lymph node metastasis rate is below 2-5% (this thesis). In case of a gastric resection, the need of an extended lymphadenectomy is arbitrary and a D1 resection could be sufficient [22].The 7th TNM classification recommends removal of at least 16 lymph nodes quite similar to the 15+ nodes of our national guideline [18;28].

Another unanswered question still is what type of gastric resection is preferable. Only 2 RCTs have been conducted in the past century, in a time where surgical techniques and postoperative care were less developed. Both studies were performed in multiple hospitals. In patients with tumours located to the antrum postoperative morbidity (33%) and mortality (1 vs 3%) rates were equal for total (TG) and subtotal gastrectomy (STG). Five-year survival rates were similar as well [46]. The second study investigated and compared STG and TG in patients with a non-cardia tumour. In the TG group more patients developed nonfatal complications (9 vs 13%), although the risk of fatal complications was not different (1 vs 2%). Five year survival rates were similar (65 vs 62%) [47;48]. A prospective observational study conducted in Italy in patients with T3 tumours showed no difference in postoperative complications, but better 5-year disease specific survival rates of 36 in the STG group versus 22% in the TG group (p=0.011) were observed. This difference might be due to less beneficial tumour characteristics in patients in the TG group who had more often extensive lymph node involvement [49]. Quality of life after TG appeared to be inferior compared to STG mainly due to more weight loss and higher frequency of food consumption caused by poor tolerance of food, although daily activity and participation in work and society were not different between the two groups [50;51]. It is therefore recommended to perform a STG if possible [28].

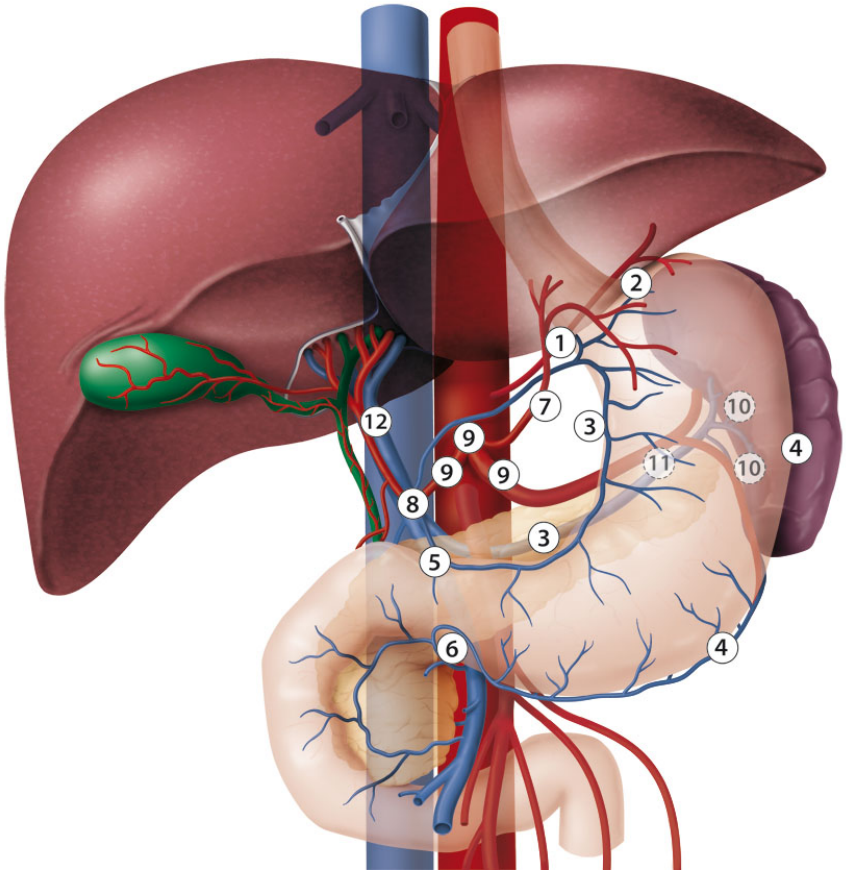

Figure 3. Lymph node stations according to the Japanese Classification
1, right paracardial; 2, left paracardial; 3, along the lesser curvature; 4, along the greater curvature; 5, suprapyloric; 6, infrapyloric; 7, along the left gastric artery; 8, along the common hepatic artery; 9, around the celiac artery; 10, splenic hilum; 11, along the splenic artery; 12, hepatoduodenal ligament; 14, along the superior mesenteric vessels; 15, along the middle colic vessels; 16, paraaortal

Perioperative therapy

The results of the MAGIC trial [52] have changed the guidelines for the treatment of patients with gastric cancer [28]. Those who received perioperative chemotherapy exhibited a 5-year survival rate of 36 versus 23% in the surgery only group. These patients received 3 cycles of epirubicine, cisplatin an 5-FU preoperatively (NAC) and 3 cycles postoperatively, although only 50% completed the whole regimen. The treatment benefit might therefore be due mainly to the preoperative chemotherapy. A review evaluating neoadjuvant chemotherapy found a marginal survival benefit for the NAC group of 1.2%, although progression free survival after 3 years was 41% versus 28%. Numbers needed to treat were 84 [53]. With NAC, tumour response can be assessed and chemotherapy can

be stopped or a regimen switch can be performed. This is important as response rates (complete and partial combined) of 18 to 67% have been reported [54-57]. Furthermore, the proportion of patients who tolerate the treatment well and finish all cycles is high. On the other hand, progression of the disease under chemotherapy and thereby losing the option of curative surgery is a disadvantage of NAC, although a patient with a tumour that does not respond might also have a worse prognosis. Hereby these patients are prevented to undergo a high risk operation with less benefit. In stage T1/T2No disease, the benefit of (neo)adjuvant chemotherapy is debatable. Another disadvantage is the risk of overtreatment in this patient group due to difficulties in preoperative staging. Adjuvant chemotherapy has the advantage that the risk of overtreatment is reduced to almost 0%, although disadvantages are that tumour response cannot be monitored and a higher percentage of patients does not complete the whole regimen. More grade III/IV toxicity is often reported in patients undergoing adjuvant chemotherapy, mainly due to gastro-intestinal complications [58]. Five- year survival rates after adjuvant chemotherapy versus no postoperative treatment have been reported to rise from 50 to 55% [59].

Data on the benefit of perioperative chemotherapy are scarce and no review or meta-analyses can be found in the literature. However, in the Netherlands, perioperative chemotherapy is advised in all patients with resectable gastric cancer higher than stage I (6th TNM classification [19]). With the abovementioned drawbacks of adjuvant chemotherapy, one can debate if postoperative chemotherapy is useful in non-responders or in patients with T2/T3No disease. Tailor made therapy could be of more benefit in these patient categories. An expert panel tried to come to consensus with respect to the treatment of gastric cancer, and they agreed on perioperative chemotherapy for cT4 and cN+ tumours. Differences in opinion existed with regard to cT2N+ and cT3No tumours [22]. The use of perioperative chemotherapy was advocated by most panelist, although a strong minority would drop preoperative chemotherapy in case of cT2N+ and postoperative chemotherapy in case of cT3No tumours. These results further underline the difficulties in treatment strategies in gastric cancer.

In the in this thesis described DoCCS-study, a phase II study investigating the feasibility of neadjuvant docetaxel, cisplatin and capecitabine followed by protocolized surgery, we encountered a complete pathological response in 3 out of 51 patients. This was accompanied by a grade III/IV febrile neutropenia of 31% in 51 patients and 10% in 169 cycles, which was the cause of death in three patients. Total chemotherapy related mortality was 5.9%. The amount of patients with febrile neutropenia was comparable to results in literature [57;60], as well as mortality rates [61]. The encountered toxicity and mortality rates underline the difficulties met in the treatment of gastric cancer, where the potential survival benefits have to be weighed against the price to pay by patients.

The benefit of additional radiotherapy has been subject of clinical trials as well. A study in the US found an absolute survival benefit of 9% after three years for patients who re-

ceived adjuvant chemoradiotherapy (HR 1.35, 95% CI 1.09-1.66, *p*=0.005), although in this study a high percentage of patients underwent a Do resection. The survival benefit of this regimen is probably also substantially compensating for inadequate lymphadenectomy [62]. A meta-analysis analyzing the results of prospective randomized trials found a survival benefit for patients who received either radiotherapy or chemoradiotherapy, either preoperatively or postoperatively. When chemoradiotherapy was compared to chemotherapy alone, the hazard ratio was 0.83 in favour for chemoradiotherapy, although this was not significant (95% confidence interval 0.67-1.03) [63]. Current guidelines in the Netherlands only advise the use of adjuvant (chemo)radiotherapy in case of a R1 resection. The results of the CRITICS [64], a phase III trial comparing adjuvant chemotherapy with chemoradiotherapy after 3 cycles of neoadjuvant chemotherapy, have to be awaited.

Treatment in non-curable gastric cancer

Although surgery remains the only curable treatment option, many patients do not undergo an operation. Of all patients diagnosed with gastric cancer, 45% of patients with cardia and 43% of patients with non-cardia cancer have already reached stage IV disease at presentation. Furthermore, of the patients who have a potential curable disease, resection rates vary between 71 and 82% (stage dependent) for cardia carcinoma; for non-cardia cancer these rates are 75-92% (this thesis). This group of patients comprises the vast majority of patients with gastric cancer. Currently, for these patients palliative chemotherapy, radiotherapy or in selected patients HIPEC (aggressive cytoreductive surgery combined with heated intraperitoneal chemotherapy) is the only treatment available. In the Netherlands, only 36% of these patients receive palliative chemotherapy, which prolongs the median survival to 32-37 weeks, compared to 15-17 weeks if no chemotherapy is administered. The chance of receiving chemotherapy is age dependent, like the chance of undergoing surgery in case of curable disease [65]. In patients with only liver metastases median survival is worse compared to those patients with peritoneal carcinomatosis, although median survival rates are improved with a couple of months after palliative treatment [66]. Overall, efforts to improve survival of gastric cancer through various treatment modalities remain challenging.

FUTURE PERSPECTIVES

Increase of the role of laparoscopy in gastric cancer

The greatest advantage of laparoscopy versus open surgery is avoiding extensive surgical trauma to tissue. In laparoscopic surgery, for access to the abdominal cavity several

small incisions are made, retraction of viscera is avoided, and blood loss is minimized due to meticulous preparation with video-enhanced imaging systems. In colonic cancer, laparoscopic (assisted) resections have made their entry. Long-term survival for laparoscopic and open resections are similar [67], but postoperative hospital stay is shorter for laparoscopic surgery, and passage of stool and intake of solid food is quicker [68;69]. In gastric cancer, however, the short-term and long-term effects have not been widely investigated in RCTs yet. One RCT, dating from the 90's in the past century, included 70 patients and eventually randomized 59 patients [70]. Benefits for laparoscopic surgery in terms of less blood loss, earlier discharge and earlier consumption of food were reported, with equal postoperative morbidity and mortality rates, and equal 5 year survival rates. A study comparing laparoscopic resection of tumours confined to the mucosa with open resection for tumours invading the submucosa, found a benefit looking at use of postoperative analgesics, time to liquid diet and hospital stay for a laparoscopic procedure [71].

Other case controlled studies found similar results [72;73]. In laparoscopic (assisted) gastric surgery, the dissection of lymph node stations 10 and 11 is particularly difficult and has also been reported to give higher postoperative morbidity and mortality rates [72]. The best technique to construct an oesophago-jejunostomy after total gastrectomy in a laparoscopic setting still remains to be established. In the Netherlands, laparoscopic gastric resections have been performed in some hospitals, but its feasibility is still quite uncertain. Its effects on short-term results and the amount of resected lymph nodes have not been evaluated yet. With the current minimal expertise in performing an extended lymphadenectomy, introduction of a laparoscopic (assisted) gastric resection with a D2 dissection would be challenging. Learning curves of 23-200 operations for an open D2 lymphadenectomy have been described [74;75], but none for laparoscopic resection. Experience in laparoscopic gastric surgery could be gained by starting with patients with cT1 disease and/or a well-differentiated, non-ulcerating tumour, without the need of a D2 lymphadenectomy. However, in the Netherlands, the proportion of patients with stage I disease (6th TNM classification [19]), in which only stage IA would qualify for such an approach, is only 10-15% (this thesis). Furthermore, there is no diagnostic tool with a high accuracy to determine T-stage [24;25]. In a D1 *extra* lymphadenectomy, the difficulty of resecting station 11 is avoided, and in case of distal gastric cancer, station 10 is left behind as well. Therefore, in patients with distal gastric cancer and a T2-3 tumour, experience could be gained as well.

Future RCTs are needed to evaluate the benefit of laparoscopic surgery in gastric cancer. In such a trial, only surgeons with experience with laparoscopic gastric resections should be asked to participate to exclude a high level of inexperience as a confounder for results. Gaining experience could start in patients with early gastric cancer or distal gastric cancer as described above.

Gastric cancer in the elderly

The proportion of patients older than 75 years is 33% for cardia cancer and 43% for non-cardia cancer. Due to the high birth rate after the second world war, in the near future, the proportion of people older than 75 years will further rise. This will increase the median age at diagnosis of patients with gastric cancer. Therefore, more elderly will be considered for treatment for gastric cancer. Postoperative mortality rates for elderly were higher for both cardia and non-cardia cancer (this thesis), but not undergoing an operation while having a curable type of gastric cancer results in much lower overall survival rates [15]. In patients with a lower life expectancy due to age and comorbidity it is important to outweigh the benefits of surgery and longer survival versus quality of life. The question is whether comorbidity rather than age is associated with higher postoperative morbidity and mortality rates. The reported resection rates in the elderly reflect the influence of age on the decision to perform an operation or to install a wait and see policy. Resection rates among patients older than 80 years were as low as 35% versus 64% in patients younger than 65 years in the Netherlands in the '80s [76]. These rates have only slightly improved in the following decades with resection rates of 26% for cardia cancer in patients 75 years and older and 52% for non-cardia cancer (this thesis). Furthermore, age influences the chance of undergoing surgery (this thesis), but comorbidity does not in cardia cancer and in non-cardia cancer it has less influence than age (this thesis). Older age is associated with higher comorbidity rates [77-80], so studies investigating the influence of only age on postoperative morbidity and mortality rates could have been biased. Studies investigating the impact of age and comorbidity found an association between postoperative morbidity and comorbidity, but not so much with age. Postoperative mortality in these studies is not influenced by either age or comorbidity [77-79]. In a prospective observational study, length of surgery influenced the postoperative complication rate [77]. Overall survival rates are lower for the older age group compared to the younger patients, but tumour related survival was equal for both groups, meaning that this patient category has a higher chance of dying due to other illnesses [78;79]. One could debate if extended surgery, comprising an extended lymphadenectomy, will be beneficial for overall survival in this patient category, with the added risk of postoperative complications. The benefits of a laparoscopic approach leading to a faster postoperative recovery could be of value in the elderly, especially when a limited lymphadenectomy is considered. Keeping in mind that not offering curative surgery results in a low life expectancy, choice of treatment should be tailor made for the elderly, considering comorbidity more than age in the decision making. The extent of surgery and the use of perioperative therapy should depend on life expectancy and comorbidity.

Improvement of care

Despite all efforts in finding the optimal treatment for gastric cancer, survival rates for patients with curable disease did not improve significantly. Risk of dying, however, has decreased between 2005-2008 and 1989-1993 after adjustment for case mix (RER 0.8 in 2005-2008 compared to 1989-1993, this thesis). To improve care and subsequent outcome, several initiatives have been undertaken in the Netherlands. Since 2012, standards for centralization for gastric cancer are proposed, with a minimum of 10 gastrectomies in 2012, and in 2013 this minimum has increased to 20 resections per year. Results in literature concerning the benefit for centralization of gastric cancer have been somewhat contradicting however [20;81-83]. In the Netherlands, mortality rates and long-term survival were similar between low and high volume hospitals (this thesis). In Denmark, centralization was forced by the government due to a far worse outcome of Danish patients with gastric cancer compared to other European patients in the Eurocare study during the 80's and 90's. After centralization, overall survival rates have increased and mortality rates have declined suggesting a beneficial effect of centralization [20]. In the Netherlands, for patients with oesophageal and pancreatic cancer, centralization has improved outcome (this thesis) [84;85]. It is debated, however, if centralization should be based on volume or outcome. In the Western part of the Netherlands, centralization of oesophageal cancer based on outcome has improved mortality rates and 2 year survival rates [85]. In Canada, centralization of pancreatic cancer in two provinces has led to a higher reduction of postoperative mortality in Ontario but not in Quebec. In Ontario, centralization was implemented based on volume (≥10 operations per year) and postoperative mortality rate (<5% per year), and audited results were shared during feedback sessions with the respective groups of surgeons [86]. In Quebec, no such interventions were made and centralization occurred naturally. This implies that beneficial outcome after centralization not only depends on volume, but also on quality of care.

Although a surgeon plays a substantial role in the outcome for (gastric) cancer, this also depends on multidisciplinary treatment before, during and after surgery. Higher volume can increase the experience in complex treatments among surgeons, anesthesiologists, ICU, nurses and other medical staff engaged in the care of these patients. Centralization can lead to higher awareness of the imperative need to improve care and thereby improving outcome by itself. In the Netherlands, in 1989 a nation-wide cancer registry with clinically relevant data was set up (large part of the data in this thesis consisted of cancer registry data). In addition, in 2011 a clinical nationwide audit has started for gastric and oesophageal cancer. Using the cancer registry and audit data, hospitals (surgeons) can compare their own results with others. The ultimate goal is to improve the quality of care. Transparency of these results has negative influences as well. In a hospital with 'high' volume of 20 gastric resections each year, one death has high impact on postoperative mortality rates. Case mix correction is not possible in these low

numbers, which could lead to a decrease of the amount of patients who will undergo surgery, especially in those with advanced gastric cancer, old age and comorbidity, thus depriving them from the chance of curation.

As mentioned above, a surgeon is not the sole responsible party for the quality of care, and other medical fields should also participate in quality improving initiatives. Since 2009, SONCOS (Foundation Oncological Collaboration) has been set up as a platform for interdisciplinary consultation for physicians engaged in oncological care. A standard for multidisciplinary oncological care is being prepared.

Trials are designed to determine the effect of new treatments compared to standard care for relatively well patients. RCTs (double blind) are the best way to approach such a hypothesis, but especially in gastric cancer, these types of trials have problems with patient enrollment. The incidence of curable gastric cancer in the Western world has become low. Together with inclusion and exclusion criteria not many patients are eligible for trials, while in phase III trials, many patients should be included to find a treatment benefit or disadvantage. In the DoCCS-study, a phase II feasibility study conducted by me, 51 patients were enrolled in 4 years, spread over 5 hospitals (this thesis). The CRITICS trial phase III trial needs 788 patients to be enrolled. This study started in 2008 and is still open for inclusion, while three countries are participating in this study [64]. Several trials investigating the use of preoperative chemotherapy for gastric cancer discontinued due to poor accrual [54;87]. Problems for accrual are physician and patient related. Reasons for patients not to participate are methods of a study (e.g. dislike for randomization or the possibility of treatment with a placebo), side effects and influence on quality of life, trial treatment may not be the best option, and feeling of coercion to participate. For physicians, drawbacks for participation in a trial are the amount of additive (administrative work) and dislike of the trial treatment [88]. In our own experience, problems with enrollment were high age and concomitant comorbidity rate, the awareness of the study among clinicians, the low incidence of curable gastric cancer and the willingness to participate. For adequate control of quality of a trial, high costs with respect to money and effort is needed. In gastric cancer, multi-centre trials are inevitable in case of 20 resections per year per hospital. With centralization and auditing, the participation in clinical trials for gastric cancer might be easier and provide faster accrual. The results of the CRITICS-trial should be awaited for the use of perioperative therapy in gastric cancer. Future trials should be directed at treatment in the elderly and the use of laparoscopic surgery.

PERORATION

Absolute mortality rates for gastric cancer have substantially declined in the past decades, mainly due to the markedly fall in incidence of gastric cancer, the biggest success in cancer control in the Netherlands and most industrialized countries. This fall in incidence is especially attributed to the fall in incidence of non-cardia cancer. The eradication of H. Pylori due to less chance of infection on the one hand and therapeutic treatment on the other hand are the main causes of the decrease of non-cardia cancer incidence. Furthermore, this decrease is further influenced by changes in dietary pattern. Those patients who still develop gastric cancer have a dismal prognosis also related to being a negative selection. This partly explains why numerous studies have not improved surgical and perioperative treatment. For this group, improvement of treatment options and thereby survival rates thus remains imperative.

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Chapter 14

Nederlandse samenvatting

Trends en behandelingsstrategieën bij maagkanker in Nederland: nog vele uitdagingen te gaan

- **VERANDERINGEN IN INCIDENTIE**
- **OVERLEVING VAN PATIËNTEN MET MAAGKANKER**
- **BELANG VAN STAGERING VAN MAAGKANKER**
  - **Voor de operatie**
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- **BEHANDELING VAN MAAGKANKER**
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- **TOEKOMSTPERSPECTIEVEN TEN AANZIEN VAN DE BEHANDELING**
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  - **Meer aandacht voor de oudere patiënt met maagkanker**
  - **Verbetering van de kwaliteit van zorg**
- **PERORATIE**

VERANDERINGEN IN INCIDENTIE

Maagkanker kan worden onderverdeeld naar anatomische locatie in cardia en non-cardia kanker. De cardia bevindt zich direct na de overgang tussen slokdarm en maag, de rest van de maag wordt bestempeld als non-cardia en bestaat. Beiden vertonen verschillende epidemiologische , klinische en biologische eigenschappen. Sinds de jaren '30 van de 20e eeuw is de incidentie, gedefinieerd als het aantal nieuwe patiënten met maagkanker per jaar per 100.000 inwoners, enorm gedaald, eerst in de Verenigde Staten en later in andere geïndustrialiseerde landen. In 2008 was de incidentie voor mannen 14 per 100.000 en voor vrouwen 7 per 100.000 terwijl deze in 1989 nog 25 per 100.000 mannen en 10 per 100.000 vrouwen was (bron: Nederlandse Kanker Registratie, NKR, zie hoofdstuk 2). Deze daling heeft met name te maken met een daling in de incidentie van non-cardia kanker. Door de introductie van de koelkast was het steeds minder noodzakelijk om voedsel met behulp van zout (vooral vlees en vis) te conserveren en is er door het hele jaar heen de mogelijkheid tot het eten van verse groente en vers fruit. Een hoge zout consumptie is een risicofactor voor het ontwikkelen van maagkanker, terwijl sommige soorten groente en fruit een beschermend effect lijken te hebben. Daarnaast is non-cardia kanker, in grotere mate dan cardia kanker, geassocieerd met een infectie met *Helicobacter Pylori* (*HP*), een bacterie die overigens pas in de jaren '80 ontdekt is en die de maag kan infecteren. Het is nog niet helemaal duidelijk hoe een infectie tot stand komt, maar waarschijnlijk via de orale-faecale route tijdens de kindertijd. Kleinere families en betere woonvoorzieningen hebben geleid tot een betere hygiëne hetgeen weer heeft geleid tot een lagere kans op besmetting. Sinds de ontdekking van de bacterie kan deze ook worden bestreden met antibiotica wat verder heeft geleid tot een daling in het aantal infecties met *HP*. Deze bacterie veroorzaakt een ontsteking van het maagslijmvlies, oftewel gastritis, wat zich uiteindelijk via verschillende stappen kan ontwikkelen tot dysplasie (een afwijkende weefselstructuur). Dit kan zich ontwikkelen tot maagkanker. In dit proefschrift is de focus met name op het adenocarcinoom gelegd, een type kanker dat in 95-99% van de gevallen met maagkanker gevonden wordt.

De incidentie van maagcarcinoom is dalende over de hele wereld, al is de incidentie in Japan en enkele andere Aziatische en Zuid-Europese landen nog steeds vele malen hoger dan in ons land. In Japan worden mensen gescreend met behulp van fotofluorografie (hierbij wordt bariumpap geslikt en vervolgens een röntgenfoto gemaakt, waarmee een eventuele afwijking kan worden aangetoond), zonder dat er gerandomiseerde studies zijn gedaan naar de betrouwbaarheid van fotofluorografie ten opzicht van gastroscopie (waarbij de maag met behulp van een videocamera van binnen wordt bekeken). In Nederland zou een dergelijke screening geen voordelen hebben aangezien de kosten niet opwegen tegen een verbetering in overleving van mensen met maagkanker. De symptomen die passen bij maagkanker zijn aspecifiek, zoals pijn boven in de buik, vermoeidheid door bloedarmoede, misselijkheid en braken, passage problemen en

gewichtsverlies. Als een tumor bij de uitgang van de maag gelokaliseerd is kan deze eerder passageproblemen geven. Door deze aspecifieke symptomen, die veelal pas in een laat stadium optreden, wordt maagkanker, met name het cardia carcinoom, vaak in een laat, niet te genezen stadium ontdekt. Dit is het geval in 40-45% van de gevallen van maagkanker in Nederland (zie hoofdstuk 1 en 2). Een Nederlandse studie heeft aangetoond dat in het geval van dysplasie de kans op het ontwikkelen van maagkanker in het 1e jaar ongeveer 30% is, terwijl maar 61% van deze patiënten nogmaals een gastroscopie aangeboden krijgen. Er is geen nationale richtlijn voor de follow-up van deze patiënten. Om een te late detectie van maagkanker in deze groep te voorkomen is betere kennis leidend tot een gestructureerdere follow-up nodig.

OVERLEVING VAN PATIËNTEN MET MAAGKANKER

De mortaliteit (de sterfte in de bevolking) voor maagkanker is aanzienlijk gedaald. Dit is met name toe te schrijven aan een daling van de incidentie van het non-cardiacarcinoom. Enige tijd nam de incidentie van het cardiacarcinoom nog toe, zodat de prognose bij gelijkblijvende behandeling eerder gunstiger werd. Voor de grote verschillen in overleving tussen verschillende landen en delen van de wereld zijn echter meerdere redenen aan te voeren. Epidemiologische verschillen tussen landen zouden voor 60% aan bovengenoemde epidemiologische verschillen toegeschreven kunnen worden vanwege een slechtere overleving bij patiënten met

- een hogere leeftijd
- cardia kanker
- hoger stadium van de ziekte
- met bepaalde histologische typen.

Maagkanker wordt in verschillende stadia ingedeeld volgens de TNM classificatie, waarbij de grootte van de tumor (T), het aantal klieren met uitzaaiingen (N) en uitzaaiingen op afstand (M) worden meegenomen. Hoe hoger het stadium, hoe uitgebreider de kanker is. De 7e editie uit 2010 verschilt behoorlijk ten opzichte van de 6e editie uit 2002. Alleen stadium IA is ongewijzigd gebleven. In de 6e editie werd een N3 stadium toegekend als er ten minste 15 lymfeklieren uitzaaiingen bevatten. In de 7e editie wordt N3b stadium gedefinieerd als 15 of meer positieve lymfeklieren. In Nederland is in de nationale richtlijn aanbevolen ten minste 15 lymfeklieren te verwijderen en te onderzoeken na een maagoperatie voor maagkanker. Dit aantal wordt nog steeds niet overal gehaald, waarbij het gemiddelde aantal klieren dat per patiënt gevonden werd na een operatie 13 per patiënt bedroeg in 2009 (zie hoofdstuk 8). Hierdoor zijn maar weinig patiënten met stadium N3/N3b gediagnosticeerd, terwijl er een grote kans is dat deze

groep groter is. Hierdoor kan de overleving per groep lager zijn dan het daadwerkelijk is, de zogenaamde stadiummigratie. De totale overleving verandert niet tenzij de behandeling verbetert. Door de verandering in TNM classificatie kan stadiummigratie niet alleen vanwege het aantal verwijderde klieren maar ook in de tijd een rol spelen in de overleving.

Als laatste zullen verschillen in stagering en behandeling tot overlevingsverschillen kunnen leiden. In Japan worden veel meer patiënten met maagkanker geopereerd, waardoor de expertise per chirurg en centrum hoger is. Dit geldt ook voor de specialistische centra in het Westen, waar meer uitgebreide lymfeklierresecties plaatsvinden en waar ook nauwkeuriger door de patholoog wordt gekeken naar de aanwezigheid van uitzaaiingen. Hierdoor kan ook de hoeveelheid kanker verminderd worden hetgeen een absolute overlevingswinst voor de patiënt geeft. Het is alleen nog steeds onduidelijk of de uitgebreide lymfeklierresectis alleen een therapeutisch effect hebben of dat stadiummigratie ook nog een rol speelt. Postoperatieve sterfte na zes'n ingreep is in hoog volume landen/centra laag (~2%), terwijl deze in Nederland 6.7% is (zie hoofdstuk 1).

BELANG VAN STAGERING VAN MAAGKANKER

Voor de operatie

Het blijft moeilijk om maagkanker goed te stageren, terwijl dit essentieel is voor de juiste behandeling. Een maagresectie (verwijderen van de maag) en een aanvullende verwijdering van de lymfeklieren geeft een hoge kans op morbiditeit (ziekte) en mortaliteit (sterfte). Dit moet dus vermeden worden bij patiënten met uitzaaiingen op afstand in bijvoorbeeld de lever of longen, aangezien zij alleen maar nadeel zullen hebben van een dergelijke operatie. Ook kunnen patiënten met een kleine maagtumor, gelokaliseerd alleen in het maagslijmvlies, behandeld worden met een beperkte ingreep. De maag-darm- lever arts kan de tumor zelfs via een gastroscopie verwijderen, alhoewel dit nog geen standaard behandeling is. Het T- en N-stadium kan tegenwoordig steeds beter vastgesteld worden met een CT-scan, een MRI scan, en een endo-echo (met behulp van een gastroscopie), maar deze hebben allen een matige sensitiviteit voor het aantonen van de tumor (terecht positieve uitslag), dan wel specificiteit (terecht negatieve, voor de patiënt positieve, uitslag). Dit probleem zijn we ook tegengekomen in de DoCCS-studie, een onderzoek bij patiënten met een te genezen vorm van meer uitgebreide maagkanker (zie hoofdstuk 10).

Buiten de voorgenoemde beeldvormende technieken die allen gebaseerd zijn op anatomische afwijkingen, is het ook mogelijk om de stofwisseling van organen in beeld te brengen. Dit kan gedaan worden met de PET-scan, eventueel gecombineerd met een

CT-scan. Een PET scan is gebaseerd op een verhoogde stofwisseling in kankercellen. Bij een patiënt wordt radioactief glucose ingespoten en vervolgens wordt er een PET-scan gemaakt. Een hogere opname van het radioactief glucose (door de tumor) kan zo worden aangetoond. Bij patiënten met slokdarmkanker en longkanker heeft radioactief glucose een hoge sensitiviteit voor het aantonen van uitzaaiingen in lymfeklieren. Jammer genoeg is dit niet het geval bij maagkanker. Ook voor de tumor zelf is de sensitiviteit en de specificiteit laag. Als de tumor wel 'aankleurt' dan zou een PET-scan een rol kunnen hebben in de evaluatie van de behandeling met chemotherapie. Als de tumor goed reageert op de chemotherapie, is dit vaak eerder terug te zien op een PET-scan dan op een CT-scan welke gebaseerd is op anatomische kenmerken. Hiermee zou het toedienen van toxische chemotherapie bij patiënten die hier geen voordeel van hebben kunnen worden voorkomen (zie hoofdstuk 4).

Tijdens de operatie

Alhoewel gastroscopische verwijdering van een tumor die alleen in de maagwand zit nog niet wordt aangeraden als standaardbehandeling, wordt er wel veel onderzoek naar gedaan. Bij deze patiënten wordt op dit moment veelal nog steeds een maagoperatie met een (uitgebreide) lymfeklier verwijdering verricht terwijl het risico op lymfeklier uitzaaiingen maar 2-5% is (zie hoofdstuk 5). Met een schildwachtklierprocedure (SWKP) zou kunnen worden aangetoond of er lymfeklier uitzaaiingen aanwezig zijn in de klieren waarop de tumor draineert en op basis daarvan zou een uitgebreide of beperkte lymfeklier verwijdering kunnen plaatsvinden. Bij de SWKP wordt radioactief colloïd ingespoten bij/in de tumor en er wordt gekeken welke klier 'heet' is. Tevens wordt een kleurstof ingespoten en wordt er gekeken welke klier aankleurt. De klieren die hiermee ontdekt worden zijn de schildwachters voor de andere klieren. Als er geen uitzaaiingen in de schildwachtklieren zitten, zouden de andere lymfeklieren in theorie ook 'schoon' moeten zijn. Dit is aangetoond voor bijvoorbeeld borstkanker en het melanoom. Op dit moment blijkt de sensitiviteit en specificiteit in ons onderzoek echter te laag om deze techniek bij een vroeg stadium maagkanker te implementeren (zie hoofdstuk 5).

Het is wel belangrijk om deze techniek verder te onderzoeken. Er zullen in de toekomst vooral ouderen maagkanker ontwikkelen. Vanwege andere ziekten en leeftijd heeft het de voorkeur om bij deze groep kleinere operaties met als gevolg minder morbiditeit en mortaliteit te verrichten.

Na de operatie

Op dit moment heeft het stadium van maagkanker geen consequenties voor de behandeling na een operatie, behalve als er nog tumor is achtergebleven. Deze patiënten hebben een overlevingsvoordeel als ze nabestraald worden. Adequate stadiëring is

wel nodig om precies vast te stellen hoe uitgebreid de ziekte is. Het T- en N-stadium blijken de belangrijkste voorspellers voor overleving (zie hoofdstuk 3 en 9). De huidige richtlijn geeft aan dat ten minste 16 klieren moeten worden verwijderd om het exacte N-stadium te kunnen bepalen. Dit aantal wordt vaak niet gehaald in ons Nederland (zie hoofdstuk 6 en 8), zodat er mogelijk sprake is van onderstadiëring, hetgeen weer een negatief effect zou kunnen hebben op de stadium gerelateerde overleving. Het aantal lymfeklieren dat wordt gevonden is afhankelijk van zowel de uitgebreidheid van de operatie verricht door de chirurg als van het naar uitzaaiingen zoekende speurwerk door de patholoog. Een van de onderzoeken beschreven in dit proefschrift heeft laten zien dat in de pathologische centra waar meer klieren per patiënt werden gevonden het percentage patiënten met klieruitzaaiingen ook hoger was (zie hoofdstuk 6). Dit komt overeen met een onderzoek naar lymfeklier uitzaaiingen bij dikke darm kanker dat is verricht in dezelfde regio. Tevens was er ook een grote variatie in het percentage onbekende lymfeklieren per patiënt tussen de verschillende pathologische centra (zie hoofdstuk 6). Naast het effect van de operatie en het pathologische onderzoek spelen ook de biologische verschillen tussen mensen een rol in het aantal gevonden klieren. Het aantal lymfeklieren kan per patiënt zeer verschillen.

Om het effect van stadiummigratie te beperken zijn verschillende andere stageringssystemen voorgesteld. Een daarvan is het stageren volgens de lymfeklierratio. Hierbij wordt het aantal positieve klieren (klieren met uitzaaiingen) gedeeld door het aantal gevonden klieren. Het wordt minder beïnvloed door het aantal gevonden klieren in vergelijking met het conventionele TNM-systeem. De overleving per ratio groep is homogener en het heeft een sterkere voorspellende waarde (zie hoofdstuk 7). Er zijn echter wel enkele kanttekeningen. Er is nog geen gestandaardiseerde ratio groepering. De afkappunten van de verschillende ratiogroepen kunnen daarom worden aangepast aan de data van een onderzoek waardoor de voorspellende waarde van deze groepen in een bepaalde studie op de overleving zo groot mogelijk is. Een andere kanttekening is dat de studies met name verricht zijn bij patiënten waarbij een uitgebreide lymfeklierverwijdering verricht had plaatsgevonden. Het is dus onduidelijk wat het effect is bij patiënten bij wie minder dan 15 lymfeklieren verwijderd zijn. Toekomstige onderzoeken zouden zich moeten richten op het standaardiseren van de ratiogroepen en zouden de inzetbaarheid en voorspellende waarde moeten evalueren.

BEHANDELING VAN MAAGKANKER

Chirurgie

Een operatie is nog steeds de enige optie voor genezing van maagkanker, waarbij toevoeging van chemo- en/of radiotherapie rondom de operatie de overleving positief

beïnvloedt. Een operatie voor maagkanker bestaat uit een (partiële of totale) maagverwijdering en een additionele lymfeklierverwijdering. Er zijn meerdere studies gedaan naar de hoeveelheid klieren die moeten worden verwijderd. In Japan zijn de lymfeklieren in bepaalde stations ingedeeld en is er een gestandaardiseerde lymfeklierverwijdering ontwikkeld. Bij een D1 resectie (verwijdering) worden alleen de klieren direct rondom de maag verwijderd, bij een D2 resectie worden ook klierstations die verder weg zijn gelegen verwijderd (zie figuur 3). Om de stations 10 en 11 te verwijderen werd vroeger ook de nabij gelegen staart van de alvleesklier en de milt verwijderd omdat deze klierstations zeer nauw tegen deze organen aanliggen. In de vorige eeuw zijn twee studies verricht naar de meerwaarde van een D2 resectie ten opzichte van een D1 resectie. In beide studies werd geen overlevingsvoordeel na 5 jaar gezien, maar wel een hogere morbiditeit en mortaliteit na een D2 resectie. Dit heeft tot gevolg gehad dat in ons land meestal een D1 resectie wordt uitgevoerd. De hoge morbiditeit en mortaliteit na een D2 resectie is echter met name te wijten aan het verwijderen van de staart van de alvleesklier en de milt. Klinische studies in specialistische centra waarin een gemodificeerde D2 resectie zonder alvleesklierstaart en milt verwijdering is vergeleken met een D1 resectie, laten een gelijke morbiditeit en mortaliteit zien, al is de overlevingswinst op lange termijn nog niet bekend.

In 5 ziekenhuizen in Zuidoost-Nederland hebben wij een onderzoek verricht naar de behandeling van patiënten met maagkanker die nog te genezen zijn. Bij deze patiënten is preoperatief chemotherapie toegediend (zie hoofdstuk 11) en vervolgens is er een D1*extra* resectie verricht, een resectie waarbij meer klierstations dan bij een normale D1 en minder dan bij een formele D2 resectie worden verwijderd. Hierbij zijn de milt en alvleesklier niet verwijderd. Bij deze patiënten zijn gemiddeld (mediaan) 26 klieren weggehaald, dit ligt ver boven het landelijk gemiddelde. De postoperatieve morbiditeit en mortaliteit zijn gelijk aan gegevens bekend uit de literatuur. Een D1*extra* resectie zou de oplossing kunnen zijn voor bovengenoemde problemen met een D2 resectie en het te lage aantal gevonden klieren in Nederland. De lange termijn resultaten moeten wel nog worden afgewacht (zie hoofdstuk 10).

Het is nog onduidelijk of de uitgebreide lymfeklier verwijdering een effect heeft op de overleving door minder kans op stadiummigratie of dat er ook een duidelijk therapeutisch effect is. Wel is duidelijk dat het effect van stadiummigratie op de overleving heel groot is als er minder dan 10 klieren worden verwijderd. Als er geen uitzaaiingen in de uitgenomen lymfeklieren aanwezig zijn wordt er een beduidend hogere 5-jaars overleving gerapporteerd bij meer gevonden klieren (zie hoofdstuk 6). Dit zou kunnen wijzen op een therapeutisch effect omdat er in deze klieren wel micrometastasen (micro-uitzaaiingen) kunnen zitten. Door het verwijderen van deze klieren wordt de kans op het achterblijven van tumorresten. Zelfs bij patiënten bij wie meer dan 40 klieren worden gevonden wordt nog een overlevingsvoordeel gevonden. Hoeveel klieren er

moeten worden verwijderd is nog niet duidelijk, door sommigen wordt zelfs een oogst van tenminste 25 klieren voorgesteld.

Een andere vraag die nog steeds niet beantwoord is, is of alleen een gedeelte of de gehele maag moet worden verwijderd bij maagkanker. Er zijn maar twee gerandomiseerde studies verricht die het effect van een totale versus een subtotale maagverwijdering hebben vergeleken. Deze studies hebben echter plaatsgevonden in de afgelopen eeuw, toen de chirurgische technieken en de zorg rondom de operatie anders waren dan nu. In beide studies is geen verschil aangetoond in de lange termijn overleving, en de postoperatieve morbiditeit en mortaliteit waren gelijk. Studies die de kwaliteit van leven hebben onderzocht, hebben aangetoond dat patiënten die een totale maagverwijdering hebben ondergaan vaker moeten eten en meer last hebben van gewichtsverlies. Deelname aan werk en het sociale leven waren in beide groepen gelijk. Dit alles heeft ertoe geleid dat er momenteel wordt geadviseerd om een subtotale maagverwijdering uit te voeren indien dit mogelijk is.

Aanvullende therapie rondom de operatie

Het is mogelijk om patiënten voor en/of na de operatie chemotherapie toe te dienen. De resultaten van de MAGIC studie uit Groot-Brittannië hebben de Nederlandse richtlijn voor de behandeling van maagkanker duidelijk veranderd. In de groep patiënten die rondom de operatie chemotherapie hadden gekregen werd immers een overlevingsvoordeel van 9% na chemotherapie gevonden. Patiënten kregen 3 kuren chemotherapie voor en 3 kuren na de operatie toegediend, waarbij maar 42% het hele schema heeft afgemaakt. In de Nederlandse richtlijn voor de behandeling van maagkanker wordt dit schema aangeraden. De chemotherapie voor de operatie zou echter het verschil in overleving ook kunnen hebben veroorzaakt. Een van de voordelen van alleen chemotherapie voor de operatie versus alleen na de operatie is dat het beter mogelijk is om het effect van de chemotherapie op de tumor te evalueren. Bovendien kan als een patiënt niet goed reageert de chemotherapie gestopt worden. Bij patiënten die al geopereerd zijn is er geen mogelijkheid meer om het effect te evalueren aangezien de tumor al verwijderd is. Patiënten wier tumor niet gevoelig is voor de chemotherapie die dus worden behandeld zonder dat ze een therapeutisch voordeel hiervan hebben, manifesteert zich wel de toxiciteit van de chemotherapie. Het nadeel van chemotherapie voor de operatie is dat de tumor van sommige patiënten niet reageert en dat deze zelfs groeit. Hiermee zou de kans dat een patiënt een operatie kan ondergaan verkeken kunnen zijn, doordat de kanker niet meer te verwijderen is. Een ander nadeel van chemotherapie na de operatie is dat patiënten vaak meer moeite blijken te hebben het schema af te maken door de toxiciteit en de problemen (moeite met voedselinname door de maagverwijdering, verlies in conditie) die ze ervaren na de operatie.

In onze DoCCS-studie zijn 51 patiënten voor de operatie systemisch behandeld met docetaxel, cisplatin en capecitabine. Bij 3 patiënten (6%) was de tumor in zijn geheel verdwenen door de chemotherapie. Het toedienen van deze combinatie chemotherapie ging echter wel gepaard met enige morbiditeit en mortaliteit: drie patiënten (6%) zijn overleden door effecten van de chemotherapie. Dit onderstreept de moeilijke afweging voor het geven van chemotherapie, waarbij er op korte termijn patiënten kunnen overlijden door de toxiciteit maar waar tegenover staat dat de overleving op lange termijn wel verhoogd wordt.

Er is ook gekeken naar de waarde van radiotherapie bij maagkanker. Een studie uit de VS bij 556 patiënten liet een hogere 3-jaars overleving van 50% versus 41% zien na postoperatieve chemoradiotherapie. Echter, bij deze patiënten zouden onvoldoende lymfeklieren zijn verwijderd (Do), waarvoor de chemoradiotherapie zou hebben gecompenseerd. In de Nederlandse richtlijn staat alleen vermeld, dat radiotherapie moet worden overwogen indien na een operatie bij pathologisch onderzoek blijkt dat er nog resttumor is achtergebleven. Een lopende studie (CRITICS-studie) in Nederland die continueren van postoperatieve chemotherapie vergelijkt met postoperatief chemoradiotherapie zal wellicht preciezer antwoord kunnen geven op de vraag naar de waarde van radiotherapie bij maagkanker.

Behandeling van maagkanker die niet meer te genezen is

Bij veel patiënten wordt geen operatie meer verricht, omdat zij al te uitgebreide ziekte hebben ten tijde van de diagnose (40-45%, zie hoofdstuk 2 en 3). Daarnaast ondergaan maar 71-95% van de patiënten met een te genezen vorm van maagkanker een operatie, afhankelijk van locatie van de tumor en het stadium (zie hoofdstuk 3 en 9). Deze groep niet-geopereerden betreft het merendeel van de patiënten met maagkanker. Chemotherapie en radiotherapie zijn in deze patiëntencategorie op dit moment de enige ondersteunende behandelingen, maar geven geen genezing. Chemotherapie verdubbelt de mediane overleving van 15-17 naar 32-37 weken. Alles bij elkaar genomen blijft het een uitdaging om de overleving te verbeteren van patiënten met maagkanker.

TOEKOMSTPERSPECTIEVEN

De laparoscopische chirurgie (kijkoperatie) zal waarschijnlijk een grotere rol gaan spelen bij de behandeling van maagkanker. In de toekomst zal het aantal ouderen gediagnosticeerd met maagkanker toenemen. In deze patiëntencategorie is het van belang de voordelen (namelijk genezing) tegen de nadelen (namelijk de hoge morbiditeit en mortaliteit) af te wegen. Met de dalende incidentie van maagkanker is de expertise op

het gebied van behandeling ook afgenomen, waardoor centralisatie van deze groep patiënten zal plaatsvinden. Deze onderwerpen komen hieronder aan bod.

Toename van de rol van laparoscopie bij maagkanker

Het grootste voordeel van laparoscopie ten opzichte van een open operatie is het vermijden van een groot chirurgisch trauma aan de buikwand en de organen. Om toegang te verkrijgen tot de buikholte wordt bij laparoscopie gebruik gemaakt van een aantal kleine incisies, terwijl dit bij een open operatie wordt gedaan met een grote incisie. Al veel patiënten met dikke darmkanker worden laparoscopisch geopereerd. Het is aangetoond dat dit geen negatief effect heeft op de lange termijn overleving, maar er wordt wel een snellere voedselinname en –passage gezien. Daarnaast worden patiënten sneller ontslagen. Bij patiënten met maagkanker is het nut van laparoscopische chirurgie nog niet uitgebreid onderzocht. In de jaren '90 van de vorige eeuw is er wel een buitenlandse gerandomiseerde studie verricht. De patiënten die laparoscopisch geopereerd werden hadden een sneller postoperatief herstel, terwijl de morbiditeit en mortaliteit gelijk waren aan een open operatie. In Nederland worden door enkele chirurgen laparoscopische maagoperaties verricht, maar de waarde hiervan is nog niet duidelijk. Er is nog geen onderzoek gedaan naar de risico's ten opzichte van een conventionele operatie en het is nog onduidelijk of het aantal gevonden klieren voldoende is. Met de huidige minimale ervaring in een uitgebreide lymfeklierresectie bij open chirurgie zou dit een probleem kunnen opleveren bij laparoscopische chirurgie. Er zijn leercurves van 23-200 operaties beschreven voor het adequaat verrichten van een open D2 resectie. Voor het laparoscopisch verwijderen van het laatste deel van de maag wordt een leercurve van 50-60 operaties beschreven, alhoewel deze chirurgen al wel een uitgebreide ervaring hadden in maagchirurgie met D2 resectie. Ervaring met laparoscopische maagchirurgie zou het best kunnen worden opgedaan in patiënten met een laag stadium maagkanker, bij wie een uitgebreide lymfeklierverwijdering niet noodzakelijk is. De incidentie van patiënten met een laagstadium maagkanker is echter erg laag in Nederland (10-15%, zie hoofdstuk 2). Bij patiënten met maagkanker in het laatste 1/3 deel was het bij een D1*extra* resectie niet noodzakelijk om de lymfeklieren bij de alvleesklier en de milt te verwijderen. Dit zijn de stations die met name moeilijk te verwijderen zijn met laparoscopische chirurgie. Bij deze groep patiënten in een goede setting zou daarom ook ervaring kunnen worden opgedaan.

Om het voordeel van laparoscopische chirurgie bij maagkanker te bewijzen moeten gerandomiseerde onderzoeken worden verricht onder ruimschootse voorzieningen. Voor de start van zo'n onderzoek zouden de deelnemende operateurs ervaring moeten hebben met laparoscopische maagchirurgie om bias door onervarenheid te voorkomen.

Meer aandacht voor de oudere patiënt met maagkanker

Het percentage patiënten met maagkanker van 75 jaar en ouder is voor cardia kanker 33 en voor non-cardia kanker zelfs 43. Dit aantal zal alleen maar stijgen aangezien de mensen die geboren zijn na de Tweede Wereldoorlog (baby boom) over 7 jaar 75 jaar zullen zijn. Dit zal ook de mediane leeftijd ten tijde van diagnose verhogen, hetgeen ertoe leidt dat er meer oudere patiënten in aanmerking voor behandeling komen. Postoperatieve mortaliteit is logischer wijze hoger voor oudere dan jongere patiënten (zie hoofdstuk 9), maar het niet behandelen van deze patiëntengroep resulteert in een veel lagere mediane overleving. Bij patiënten met een lagere levensverwachting door leeftijd en co-morbiditeit (bijkomende ziekten zoals hart- en vaatziekten, COPD, diabetes mellitus) moet de overlevingswinst door behandeling af worden afgewogen tegen kwaliteit van leven in de ruimste zin des woords. De vraag is alleen of leeftijd alleen of ook co-morbiditeit invloed heeft op het postoperatieve herstel. In de jaren '80 werd in Nederland maar 35% van de patiënten die ouder dan 80 jaar waren geopereerd, tegenover 64% van de patiënten jonger dan 65 jaar. Deze aantallen zijn maar marginaal toegenomen, 26% van de patiënten ouder dan 75 jaar met cardia kanker wordt nu nog maar geopereerd, en bij non-cardia kanker is dit 52% (zie hoofdstuk 9). Het lijkt erop dat met name leeftijd de kans op het ondergaan van een operatie beïnvloedt en niet zozeer co-morbiditeit (zie hoofdstuk 9). Er zijn enkele studies verricht die met name een associatie vonden tussen co-morbiditeit en postoperatieve mortaliteit en niet zozeer tussen leeftijd en postoperatieve mortaliteit. De kanker-gerelateerde overleving voor ouderen en jongeren was in deze studies gelijk, alhoewel de totale overleving lager was. Dit suggereert dat de oudere patiënt met name overlijdt aan andere ziektes. Bij deze oudere patiënt met een lagere levensverwachting is het van belang de voordelen van een uitgebreide operatie af te wegen tegen het complicatie risico. Bij deze groep patiënten zou een laparoscopische maagoperatie veel voordelen kunnen hebben voor het postoperatieve herstel, met name als er ook een beperkte lymfeklier resectie wordt verricht. In het achterhoofd houdend dat geen operatie leidt tot een veel lagere levensverwachting bij de oudere patiënt moet de behandeling van een 75-plusser worden aangepast aan de patiënt. Hierbij moeten de leeftijd, de levensverwachting, de co-morbiditeit en kwaliteit van leven worden meegenomen in de besluitvorming.

Verbetering van de kwaliteit van zorg

Ondanks alle inspanningen om de overleving van patiënten met maagkanker te verbeteren, is deze gedurende de laatste decennia gelijk gebleven. Het risico om te overlijden aan maagkanker is echter wel gedaald in vergelijking met de vorige eeuw (zie hoofdstuk 9). Om de behandeling en overleving te verbeteren zijn er enkele initiatieven gestart in Nederland. Sinds 2012 wordt nagestreefd om patiënten met maagkanker alleen te opereren in hoog-volume centra. De norm in 2012 was 10 operaties per jaar, in 2013 is

deze 20. Deze centralisatie heeft tot verschillende resultaten geleid in andere landen/gebieden. In Nederland is er geen verschil gevonden in postoperatieve sterfte en overleving van patiënten geopereerd in hoog- versus laag-volume centra (zie hoofdstuk 8). In Denemarken heeft de regering centralisatie opgelegd door de tegenvallende cijfers in vergelijking met Europa. Dit heeft geleid tot een duidelijke verbetering in de overleving. Voor slokdarmkanker en alvleesklierkanker is er al wel een verbetering in overleving gezien na centralisatie in Nederland (zie hoofdstuk 8). Het is echter onduidelijk of centralisatie moet plaats vinden op basis van het aantal operaties of op basis van de kwaliteit van zorg. In West-Nederland heeft centralisatie voor slokdarmkanker op basis van kwaliteit van zorg geleid tot een verbeterde postoperatieve mortaliteit en overleving. In Canada heeft centralisatie voor alvleesklierkanker plaats gevonden in Ontario en Québec waarbij er in Ontario ook kwaliteitsmaatregelen hebben plaats gevonden. Deze centralisatie heeft echter alleen in Ontario geleid tot een lagere postoperatieve sterfte, wat suggereert dat centralisatie alleen niet leidt tot verbeterde postoperatieve sterfte.

Alhoewel een chirurg veel invloed heeft op de postoperatieve mortaliteit en overleving, zijn deze parameters zeker ook afhankelijk van de multidisciplinaire behandeling voor, tijdens en na de operatie. Centralisatie hiervan kan leiden tot een hogere kennis van de complexe behandeling van deze patiënten bij het operatieteam, de intensive care en de paramedici werkzaam op de chirurgische afdeling. Centralisatie kan daarnaast ook leiden tot een hogere gewaarwording voor de noodzaak tot het verbeteren van de kwaliteit van zorg. In 1989 is de Nederlandse Kanker Registratie opgericht die de data van alle patiënten met kanker bijhoudt. In 2011 is een additionele chirurgische klinische audit gestart voor maagkanker. In deze audit worden alle data ingevoerd van patiënten die geopereerd worden vanwege maagkanker. Gebruikmakend van deze data kan een ziekenhuis (en/of chirurg) zijn eigen resultaten vergelijken met de landelijke data. Dit heeft als doel om uiteindelijk de kwaliteit van zorg te bevorderen. Transparantie van deze data heeft echter ook negatieve gevolgen. In 'hoog'-volume centra met 20 operaties per jaar heeft een postoperatief overlijden een grote invloed op de cijfers. Met deze lage aantallen is het lastig te corrigeren voor case-mix wat er toe kan leiden dat bepaalde hoog-risico patiënten (oude leeftijd, zeer uitgebreide ziekte, veel co-morbiditeit) niet meer geopereerd zullen worden.

Zoals hierboven al is aangegeven is de chirurg niet de enige verantwoordelijke voor de behandeling van maagkanker. In 2009 is de SONCOS (Stichting Oncologische Samenwerking) opgericht. Deze stichting dient als platform voor interdisciplinair overleg en professionele samenwerking tussen oncologen, radiotherapeuten en oncologisch chirurgen.

Er worden vele onderzoeken verricht om nieuwe therapieën te vergelijken met de huidige standaard. Om de meest betrouwbare resultaten te verkrijgen is het van belang

gerandomiseerde studies met een controle groep (RCT) te verrichten. In deze studies worden patiënten via loting verdeeld in twee (of meer) groepen waarin de ene groep de standaardbehandeling (dan wel een placebo) krijgt en de andere groep de nieuwe behandeling. Het moeilijke bij maagkanker is echter dat de incidentie erg laag is, terwijl bij RCT's veel patiënten geïncludeerd moeten worden om een verschil tussen de behandelingen te zien. Het heeft 4 jaar geduurd voordat 51 patiënten konden worden geïncludeerd in de DoCCS studie. In de eerder genoemde CRITICS studie moeten 500 patiënten worden geïncludeerd, en alhoewel ook andere landen participeren is deze studie nog steeds open voor inclusie. In de literatuur zijn vele studies beschreven die voortijdig gestopt zijn door een te lage en te trage inclusie. De oorzaken liggen bij de behandelaar en bij de patiënt. Patiënten willen vaak niet meedoen omdat ze niet de mogelijkheid willen hebben om een placebo te krijgen, de bijwerkingen ze tegenstaan en/of ze het gevoel hebben dat ze gedwongen worden om mee te doen. Behandelaars weigeren vaak mee te doen vanwege het extra (administratieve) werk en omdat de behandeling ze eigenlijk tegenstaat. In onze studie lagen de problemen voor de inclusie vooral bij de hoge leeftijd en bijkomende co-morbiditeit van de patiënten met maagkanker, de lage incidentie voor te genezen maagkanker, de bekendheid van de studie bij de behandelaars, en de bereidheid deel te nemen aan de studie door patiënten. Ook dient er aandacht te zijn voor de hoge kosten die gemoeid zijn met een studie en het waarborgen van de kwaliteit van een studie. Met het aantal van 20 maagoperaties per jaar is het onvermijdelijk dat toekomstige onderzoeken in meerdere centra moeten plaatsvinden. Vanwege bovengenoemde redenen kan centralisatie een positieve invloed hebben op het verrichten van deze multi-centra onderzoeken. Toekomstige onderzoeken zouden dus gericht moeten zijn op de waarde van laparoscopische chirurgie en op de behandeling van de oudere met maagkanker.

PERORATIE

De absolute mortaliteitscijfers voor maagkanker zijn de laatste decennia fors gedaald. Dit is grotendeels te danken aan de afname van de incidentie van met name non-cardia kanker. Deze daling wordt vooral veroorzaakt door de daling in infectie met *HP*, welke te danken is aan de kleinere kans op infectie en de mogelijkheid van behandeling van *HP* indien een infectie wel is opgetreden. Daarnaast lijkt de daling in incidentie verder te danken te zijn aan een veranderd eetpatroon. De overleving van patiënten die wel maagkanker hebben gekregen is nog steeds slecht, alhoewel vele studies zijn verricht om de behandeling en hierdoor de overleving te verbeteren. Verdere onderzoeken zullen nodig zijn om maagkanker in een vroeg stadium te ontdekken en om progressie in de strijd tegen maagkanker veilig te stellen.

Curriculum Vitae Autoris

CURRICULUM VITAE AUTORIS

Anneriet Elisabeth Dassen was born in Eindhoven on June 15th, 1980. After graduating from secondary education (VWO at the Lorentz Casimir Lyceum) in Eindhoven she studied medicine at the University of Utrecht. In 2005 she successfully achieved her medical degree. From 2006 to 2007 she worked as a resident not in training at the Beatrix hospital in Gorinchem. During this year she got interested in surgery and in March 2007 she started working as a surgical resident not in training in the Jeroen Bosch hospital. Meanwhile, she started research on gastric cancer under supervision of dr. K. Bosscha, in co-operation with dr. Valery Lemmens (Comprehensive Cancer Centre South, IKZ). In November 2008 she was admitted at the surgical residency program and started her training at the Jeroen Bosch Hospital in 's-Hertogenbosch under the auspices of dr. K. Bosscha. Three years later, she continued her residency at the University Medical Centre of Utrecht (UMCU) under the supervision of dr. M.R. Vriens. In August 2013, she returned to the Jeroen Bosch Hospital to finish her last year of her residency.

Dankwoord

DANKWOORD

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