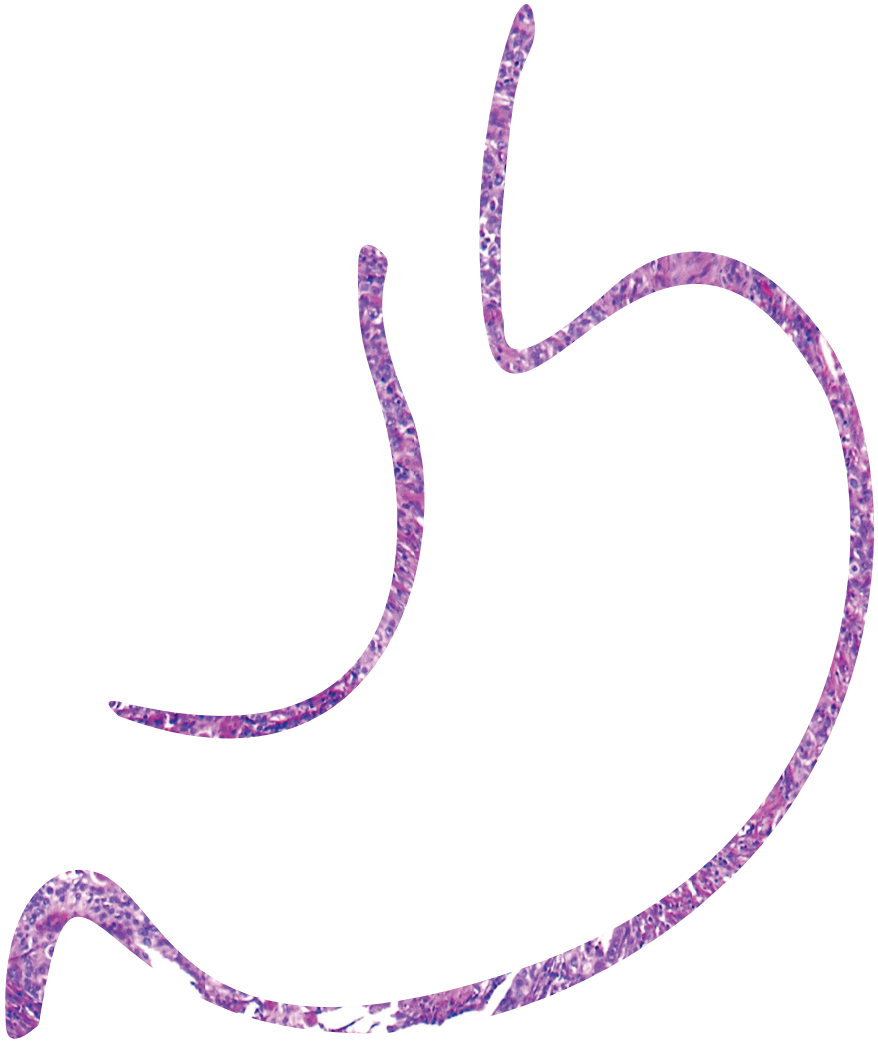
GASTRIC CANCER

STAGING, TREATMENT, AND SURGICAL QUALITY ASSURANCE



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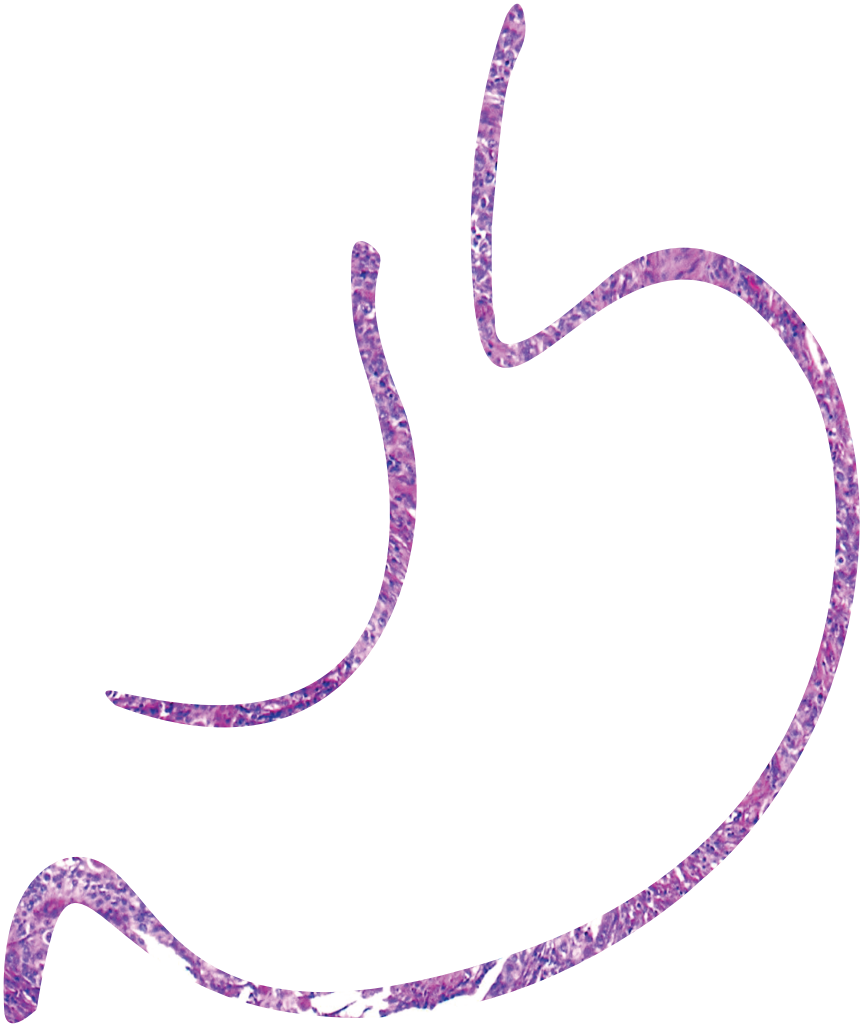

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PROEFSCHRIFT

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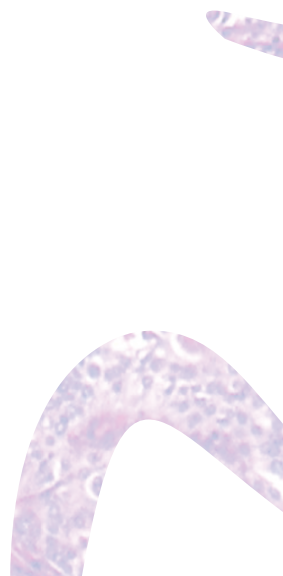
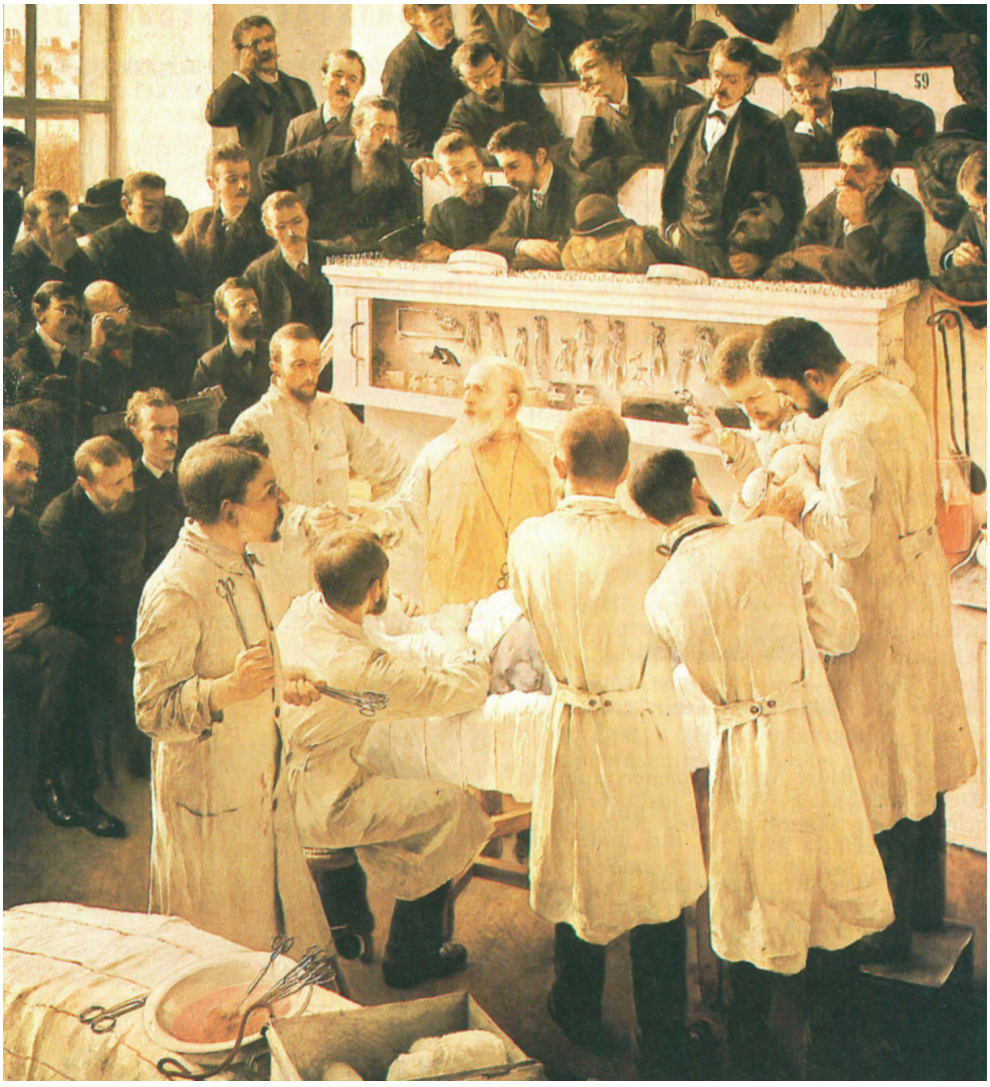
CONTENTS



CHAPTER 1

General introduction and outline of this thesis

Figure 1. Theodor Billroth operating in the auditorium of Vienna General Hospital (Allgemeine Krankenhaus). Painting entitled *Billroth im Hörsaal*, by Adalbert Franz Seligmann, approximately 1890



INTRODUCTION

Since Theodor Billroth (Figure 1) performed the first successful gastrectomy in 1881, many improvements have been made in the treatment of gastric cancer.[1] Postoperative mortality has dropped from nearly a 100% in the early days to below 1% nowadays in experienced hands.[2] Japanese surgeons developed the standardized lymph node dissection.[3] Many trials have been performed on different surgical techniques, including the extent of lymph node dissection.[4] And over the past decade, surgery combined with multimodality therapy has become standard of care for advanced gastric cancer.[5] Another recent development is the introduction of nationwide quality assurance programs and population-based studies investigating the effects of these programs in gastric cancer treatment.[6,7]

Although these improvements have contributed to an increased quality of care, gastric cancer remains the second cause of cancer death worldwide, and yearly approximately one million new patients are diagnosed with gastric cancer.[8] In the Western world, recent survival figures remain dismal. For the approximately 75,000 newly diagnosed European gastric cancer patients each year, 5-year survival is only 24%.[9,10] In the Netherlands, yearly approximately 1,800 patients are diagnosed with gastric cancer, and 5-year survival is 22%.[11] This makes gastric cancer a challenging disease, appealing for maximum effort to improve care. The studies as described in this thesis reflect on several recent developments in the staging and treatment of gastric cancer.

Research as described in part I of this thesis was performed at the *Department of Surgery* at *Memorial Sloan-Kettering Cancer Center in New York, USA*. Research described in part II and III was performed at the *Leiden University Medical Center, Leiden,* and *the Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands*.

PART I - STAGING AND PROGNOSTICATION

For over 50 years, the TNM classification has been a standard in classifying the anatomic extent of disease.[12] In 2010, the 7th edition of the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) TNM staging system was presented.[13] In **Chapter 2**, changes between the 6th and 7th edition of the TNM classification for gastric cancer are evaluated, and both staging systems are compared with regards to complexity and predictive accuracy.

In the 7th edition TNM classification, tumors of the gastroesophageal junction (GEJ) are considered esophageal cancers.[14] Furthermore, for esophageal and GEJ cancers, tumor grade was introduced as an independent determinant of stage grouping in early stage tumors. With the significantly worse prognosis of poorly differentiated early stage adenocarcinomas, these tumors might become candidate for preoperative therapy, given the accurate identification of these tumors with preoperative staging. In **Chapter 3**, preoperatively determined tumor grade is compared to postoperative tumor grade in patients who were treated with surgery alone for adenocarcinoma of the esophagus or

GEJ, in order to assess the feasibility of clinical decision making based on the 7th edition TNM classification for these tumors.[15]

Chapter 4 describes the development of a nomogram - a tool for individual patient prognostication - predicting survival for patients who already have survived a certain period in time after surgery. Another aim of this study was to explore whether variables available with follow-up, such as weight loss and performance status, would improve the predictive accuracy of this nomogram in the follow-up setting. In **Chapter 5**, the performance of the previously published gastric cancer nomogram was assessed in patients who received postoperative chemoradiotherapy.[16]

PART II - MULTIMODALITY TREATMENT

Surgery is the primary curative treatment for locally advanced gastric cancer. A D2 dissection is the recommended type of surgery in Western countries, while in the East at least a D2 lymph node dissection is performed.[17,18] Despite the effort to improve surgical quality, the locoregional relapse rate remains high with consequently a poor prognosis.[19,20] Since publication of the results of the US Intergroup 0116 study, indicating a benefit in survival for postoperative chemoradiotherapy compared to surgery alone, and the British MAGIC study, in which improved survival was found for patients who were treated with perioperative chemotherapy, surgery alone is no longer standard of care for patients with advanced gastric cancer.[21-23]

In **Chapter 6**, an overview of the literature on treatment of resectable gastric cancer is presented, including surgery and multimodality therapy.

In **Chapter 7**, recurrence and survival patterns of patients who received surgery followed by chemoradiotherapy are compared with recurrence and survival patterns of patients who were treated with surgery alone, separately analyzing the effect of the extent of lymph node dissection and whether resection margins were free of tumor cells.[24]

Chapter 8 focuses on another question regarding multimodality therapy use. While it is suggested that more than 15 lymph nodes (LNs) should be evaluated for accurate staging of gastric cancer, LN yield in Western countries is low.[25,26] The effect of preoperative chemotherapy on LN yield in gastric cancer is unknown. The aim of the study described in this chapter is to determine whether preoperative chemotherapy is associated with any difference in the number of LNs obtained from specimens of patients who underwent curative surgery for gastric adenocarcinoma.

In **Chapter 9** the outline of the currently accruing CRITICS trial is described in detail.[27] In this study, patients receive three cycles of preoperative ECC (epirubicin, cisplatin, and capecitabine), followed by D1+ surgery (D2 dissection without splenectomy or pancreatectomy). Postoperative therapy consists of another three cycles of ECC, or chemoradiotherapy with capecitabine and cisplatin.

PART III - SURGICAL QUALITY ASSURANCE

Improving quality of care for patients with resectable gastric cancer is a major challenge, as postoperative mortality is generally high and long term survival leaves room for improvement. In Japan, postoperative mortality rates of 0.8% have been reported.[2] However, in Western countries where the incidence of gastric cancer is much lower, and gastrectomies are performed in lower volume hospitals, mortality rates vary between 2% for specialized centers to above 10% for nationwide cancer registries.[28,29] Although performing randomized studies can significantly improve outcome over a longer period,[30] increasing surgeon and hospital exposure is the key to improvement of treatment results after low volume high-risk surgery such as gastrectomy. Many studies have explored the relation between hospital volume and outcome and found that increasing surgeon and hospital volume are associated with lower postoperative mortality and higher survival rates, both in the Western world and in Asia.[6] Centralization of gastric cancer surgery is currently implemented in the United Kingdom, Sweden, Finland, and the Netherlands. An additional instrument for improvement of care is auditing. With auditing, surgeons can improve their results by learning from their own outcome statistics benchmarked against their peers. Among other variables of interest, in gastric cancer surgery auditing provides the opportunity to analyze differences in hospital mortality, the extent of lymph node dissection, and the use of laparoscopic techniques. Auditing has proven its value in rectal cancer treatment in Europe,[31] and audits for gastric and esophageal cancer are currently present in Denmark, the United Kingdom, and the Netherlands.

As an introduction to part III of this thesis, **Chapter 10** describes the results of a systematic review of the literature on quality of care indicators for gastric cancer surgery. In **Chapter 11** and **Chapter 12**, trends in incidence and survival of gastric, GEJ, and esophageal cancer in the Netherlands are described.

During the past decade, multimodality therapy has become standard of care for the treatment of resectable gastric cancer.[23] In the Dutch guidelines for the treatment of gastric cancer, the use of perioperative chemotherapy is recommended.[32] However, it is unknown how well these evidence-based recommendations are implemented in daily clinical practice. This question is discussed in **Chapter 13**, where the results of a population-based study on the type of treatment for gastric cancer in the Netherlands are described, looking at resection rates and the use of multimodality treatment.

In **Chapter 14**, the results of a study on hospital volumes, mortality, and survival for esophagogastric cancer surgery in the Netherlands are presented. This study also focuses on the relation between annual hospital volume and outcomes after esophagogastric cancer surgery. Another related question is whether the type of hospital where surgery is performed affects outcomes after esophagogastric cancer surgery. This issue is addressed in **Chapter 15**, where outcomes after esophagectomy and gastrectomy are separately analyzed for university, teaching non-university, and non-teaching non-university hospitals in the Netherlands.

In **Chapter 16**, resection rates, outcomes, and annual hospital volumes for esophagogastric cancer surgery in the Netherlands are compared with several other European countries. Furthermore, the relation between annual hospital volume and outcomes is explored in the large dataset used for this study. This study provides the initial step towards a European upper gastrointestinal cancer audit.

Finally, the results of this thesis and future perspectives are discussed in **Chapter 17**.

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PART I

Staging and prognostication

CHAPTER 2

The new American Joint Committee on Cancer/International Union Against Cancer staging system for adenocarcinoma of the stomach: increased complexity without clear improvement in predictive accuracy

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ABSTRACT

BACKGROUND

The objectives of the current study were to evaluate the changes in the 7th edition American Joint Committee on Cancer (AJCC) staging system for stomach cancer compared to the 6th edition and to compare the predictive accuracy of the two staging systems.

PATIENTS AND METHODS

In a combined database containing 2196 patients who underwent an R0 resection for gastric adenocarcinoma, differences between the two staging systems were evaluated and stage specific survival estimates were compared. Concordance probability and Brier scores were estimated for both systems to examine the predictive accuracy.

RESULTS

Nodal status cut-off values were changed, leading to a more even distribution for the redefined N1, N2, and N3 group. AJCC 6th edition stage II reflected a highly heterogeneous population, which is now adequately subdivided in the AJCC 7th edition into stages IIA, IIB, and IIIA. The predictive accuracy of N-classification improved significantly as measured by concordance. Despite increased complexity, the predictive accuracy of AJCC 7th stage grouping was significantly worse than that of the AJCC 6th edition.

CONCLUSIONS

The increased complexity of the 7th edition staging system is accompanied with improvements in the predictive value of nodal staging as compared to the 6th edition, but was no better in overall stage-specific predictive accuracy. Future refinements of the TNM-classification should consider whether increased complexity is balanced by improved prognostic accuracy.

INTRODUCTION

Cancer staging is one of the fundamental activities in oncology.[1,2] For over 50 years, the TNM classification has been a standard in classifying the anatomic extent of disease.[3] In order to maintain the staging system relevant, the International Union Against Cancer and the American Joint Committee on Cancer (AJCC) have collaborated on periodic revisions of this staging system, leading to the 7th edition in 2010.[4]

For gastric cancer, several changes to the 6th edition were made.[5] In the 7th edition, all gastroesophageal junction (GEJ) tumors are staged as esophageal cancers, except tumors arising in the stomach >5cm from the GEJ (Figure 1). The T classification categories have been redefined (Table 1) and the T classification of stomach cancer and esophageal cancer have been harmonized. N-categories have been modified to better represent the distribution of the number of positive lymph nodes. The M1 category has been amended to include positive peritoneal cytology. Stage IV now includes only patients with M1 disease. Finally, new stage groups have been added to the staging system (IIB and IIIC). The 7th edition staging system is more complex, with an increase in the number of permutations of TNM groupings from 56 to 80. There are now nine stage groups, compared to seven in the AJCC 6th edition (Table 2).

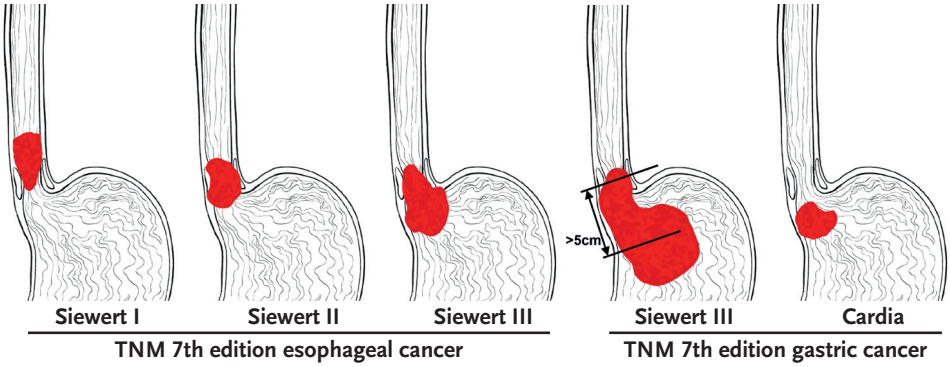
With each staging system revision, there is a tension between improving prognostic value of the staging system by adding subdivisions of existing stage groupings and introducing new predictive parameters, and the desire to keep the staging system intuitive and simple.

Table 1. Changes in the AJCC staging system for gastric cancer

T - Primary tumor (invasion depth)	AJCC 6th edition	AJCC 7th edition
no evidence of primary tumor	T0	T0
carcinoma in situ	Tis	Tis
mucosa[a]	T1	T1a
submucosa		T1b
muscularis propria	T2a	T2
subserosa	T2b	T3
serosa	T3	T4a
adjacent structures	T4	T4b
N - Regional Lymph Node Metastases		
0	N0	N0
1-2	N1	N1
3-6		N2
7-15	N2	N3a
>15	N3	N3b
M - Distant Metastases		
no distant metastases	M0	M0
distant metastases	M1	M1

[a] at least invasion of lamina propria

Figure 1. Definition of esophageal and gastric cancer according to the 7th edition AJCC staging system



The purpose of this study is to compare the 6th to the 7th edition of the AJCC staging system for gastric cancer, first by describing the differences in stage-specific survival, and secondly by examining whether the increased complexity of the 7th edition resulted in improved prognostic accuracy as compared to the 6th edition.

PATIENTS AND METHODS

The dataset used for this study is a combination of two large prospectively collected databases.

MEMORIAL SLOAN-KETTERING CANCER CENTER

Between July 1985 and December 2009, 2589 patients with an adenocarcinoma of the stomach or GEJ underwent a gastrectomy at the Memorial Sloan-Kettering Cancer Center (MSKCC) and were entered in a prospectively maintained database. Patients with tumors of the GEJ (Siewert I-III, N = 669), and patients with a noncurative (R1 or R2) resection, or M1 disease (N = 358) were excluded. As the dataset focused on curative resections, all patients with M1 disease were excluded, all of whom would have been stage IV in the 6th and 7th edition staging system. Three patients with T0N+ disease in their final pathology could not have a stage group assigned and were excluded, leaving 1559 patients for analysis. Most patients underwent a D2 lymph node dissection. Preoperative and postoperative therapy were administered according to the ongoing clinical trials and the standard of care at MSKCC during the study period. Adjuvant chemotherapy was given infrequently from 1985 to 1999. From 2000 to 2009, perioperative chemotherapy became more common for advanced stage tumors, whereas postoperative chemoradiation was also administered between 2000 and 2007. Follow-up was generally conducted according to published NCCN guidelines.[6] Survival data were updated when available until March 2010. This study was approved by the Institutional Review Board of MSKCC. This dataset was used in part to help guide changes to the AJCC 7th edition.

Table 2. Stage grouping according to the 6th and 7th edition AJCC staging system

6th edition AJCC staging system				7th edition AJCC staging system			
Stage	**T**	**N**	**M**	**Stage**	**T**	**N**	**M**
0	**Tis**	**N0**	**M0**	**0**	**Tis**	**N0**	**M0**
IA	**T1**	**N0**	**M0**	**IA**	**T1**	**N0**	**M0**
IB	T1	N1	M0	IB	T1	N1	M0
	T2	**N0**	**M0**		**T2**	**N0**	**M0**
II	T1	N2	M0	IIA	T1	N2	M0
	T2	N1	M0		T2	N1	M0
	T3	N0	M0		T3	N0	M0
				IIB	T1	N3	M0
					T2	N2	M0
					T3	N1	M0
					T4a	N0	M0
IIIA	T2	N2	M0	IIIA	T2	N3	M0
	T3	N1	M0		T3	N2	M0
	T4	N0	M0		T4a	N1	M0
IIIB	T3	N2	M0	IIIB	T3	N3	M0
					T4a	N2	M0
					T4b	N1	M0
					T4b	N0	M0
				IIIC	T4a	N3	M0
					T4b	N3	M0
					T4b	N2	M0
IV	T4	N1-3	M0	IV	**Any T**	**Any N**	**M1**
	T1-3	N3	M0				
	Any T	**Any N**	**M1**				

T: Tumor classification, N: Nodal status, M: Metastases status, **Bold**: No changes in TNM and stage groups

DUTCH GASTRIC CANCER TRIAL

In the Dutch Gastric Cancer Trial (DGCT, 1989-1993), 1078 patients with adenocarcinoma of the stomach were randomized for D1 or D2 lymphadenectomy.[7-9] None of the patients had a tumor of the GEJ, while patients with metastatic disease (N = 367), and patients who underwent a non-curative resection (N = 74) were excluded, leaving 637 patients who underwent an R0 resection for this study. No adjuvant therapy was given to these patients in the curative setting. Follow-up was conducted every 6 months. Recurrent disease was generally confirmed with radiology, endoscopy, and/or histology. Survival data were updated when available until November 2007.

STAGING

Since the UICC and AJCC use the same staging definitions, for purposes of clarity the UICC/AJCC staging system is referred to as AJCC staging system. Tumor, nodal, and metastasis stage and stage grouping are all based on final postoperative pathology. All staging parameters (T, N, M) and stage groupings of the 6th and 7th edition staging system were calculated based on depth of invasion through the gastric wall, the number of positive lymph nodes and the presence or absence of distant metastases. No patients were excluded due to incomplete staging data.

STATISTICAL ANALYSIS

Survival probabilities were estimated with the Kaplan-Meier method, differences in survival curves were assessed using the log-rank test. The endpoint in this study was disease-specific survival (DSS). DSS was recorded from the date of surgery until the date of death of disease, whereas death from other causes and alive at last date of follow-up were recorded as censored events.

The concordance index between survival and stage for the two staging systems was calculated using a methodology previously described.[10] Concordance for a staging system can range from 0% to 100%, with 100% representing absolute concordance, 50% indicating no association (no better than flipping a coin) and 0% perfect discordance. The concordance index for a staging system was calculated by analyzing all possible pairs of two patients in the dataset. A pair of two patients is concordant if the patient with the higher stage has the shorter survival. Concordant pairs are assigned a value of 1, discordant pairs are assigned a value of 0. The concordance of the staging system is the sum of the values of all the individual pairs divided by the total number of pairs in the dataset. For pairs where the shorter survival time was censored, the stage-specific Kaplan-Meier estimate of survival was used. Pairs in which both patients were in the same stage group were assigned a value of 0.5. Therefore, the maximum concordance of the staging system could never be 100%. The maximum potential concordance in our dataset for the 6th edition was 0.818 and for the 7th edition 0.853. Confidence intervals and *P*-values for the difference in concordance indices of the two staging systems were calculated using bootstrap resampling.

To validate the results provided by concordance analysis, the Brier score was used to evaluate the expected error of the predictions in both staging systems. For every patient, the Brier score measures the difference between the survival probability predicted by the staging system, and the observed survival. Kaplan-Meier estimates were used for censored observations. The average squared deviation for all patients gives the Brier score, in which a lower score represents a better predictive accuracy.

RESULTS

PATIENTS

All 2196 patients in this analysis underwent a radical (R0) resection for an adenocarcinoma of the stomach between July 1985 and December 2009, either at MSKCC (N = 1559) or in one of the hospitals participating in the DGCT (N = 637). Patient characteristics are summarized in Table 3. Median follow-up was 98 months.

TNM STAGING

Figure 2 depicts the distribution of T-classification and N-classification of the 6th edition and 7th edition staging system for all patients (N = 2196). The redefined N1, N2, and N3 classification were more evenly distributed. Among 2196 patients, 674 (31%) were

Table 3. Patient characteristics

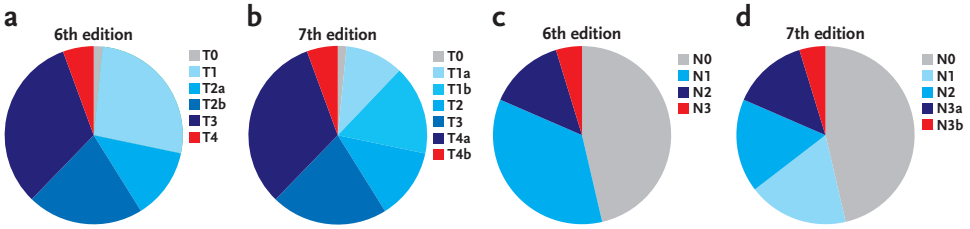
	Total (N = 2196)		MSKCC (N = 1559)		DGCT (N = 637)	
	N	%	N	%	N	%
Sex						
male	1307	*60*	943	*61*	364	*57*
female	889	*40*	616	*39*	273	*43*
Age						
median (range)	67	(22-96)	67	(22-96)	66	(31-84)
Location						
proximal	630	*29*	525	*34*	105	*17*
middle	630	*29*	430	*28*	200	*31*
distal	899	*41*	572	*37*	327	*51*
diffuse	37	*2*	32	*2*	5	*1*
Invasion depth						
no tumor	35	*2*	31	*2*	4	*13*
mucosa	231	*11*	150	*10*	81	*16*
submucosa	355	*16*	255	*16*	100	*15*
muscularis propria	282	*13*	189	*12*	93	*22*
subserosa	464	*21*	322	*21*	142	*20*
serosa	706	*32*	576	*37*	130	*14*
adjacent organs	123	*6*	36	*2*	87	*1*
Number of evaluated nodes						
median (range)	21	(0-106)	21	(0-84)	22	(1-106)
Patients with at least 15 nodes evaluated	1671	*76*	1213	*78*	458	*72*
Number of positive nodes						
median (range)	1	(0-63)	1	(0-63)	1	(0-28)
Type of surgery						
total gastrectomy	562	*26*	359	*23*	203	*32*
proximal gastrectomy	106	*5*	106	*7*	0	
distal gastrectomy	1222	*56*	788	*51*	434	*68*
esophagogastrectomy	291	*13*	291	*19*	0	
wedge/sleeve resection	14	*1*	14	*1*	0	
unknown	1	*0.1*	1	*0.1*	0	
Adjuvant therapy						
preoperative chemotherapy	245	*11*	245	*16*	0	
postoperative chemotherapy	251	*11*	251	*16*	0	
postoperative radiotherapy	80	*4*	80	*5*	0	

Table 4. Distribution of patients according to the 6th and 7th edition AJCC staging system

		AJCC 7th edition								
		0	**IA**	**IB**	**IIA**	**IIB**	**IIIA**	**IIIB**	**IIIC**	**Total**
AJCC 6th edition	**0**	**35**								35
	IA		**476**							476
	IB			**220**	210					430
	II				61	307	99			467
	IIIA						**163**	258		421
	IIIB								181	181
	IV					1	1	44	140	186
	Total	35	476	220	271	308	263	302	321	2196

Bold: patients who stay in the same stage group

Figure 2. Distribution of all patients over the T classification in the 6th edition (a) and the 7th edition (b) AJCC staging system, and N classification in the 6th edition (c) and the 7th edition (d) AJCC staging system



assigned a higher N-classification in the AJCC 7th edition. In the 7th edition staging system, the N3 category is divided into N3a (7-15 positive nodes) and N3b (16 or more positive nodes). This recognized the unique independent prognostic significance of an increasing number of positive nodes, even at the high end.

STAGE GROUPING

Differences in stage distribution between the two systems are shown in Table 4. For stage IB to IV, both T, N and M, as well as stage group definitions were altered leading to a change in stage group for 1302 of 2196 patients (59%). In total, 748 patients (34%) moved to a higher stage group, and 186 patients (9%) moved to a lower stage group. 368 patients (17%) with a stage II tumor in the 6th edition staging system were distributed between stage IIA and IIB in the 7th edition staging system. Of note, stage grouping did not make use of the N3a/N3b classification.

DISCRIMINATION BETWEEN STAGE GROUPS

Five-year survival estimates for both staging systems are shown in Figure 3 and Table 5. In the 6th edition staging system (Figure 3a), Kaplan-Meier survival estimates significantly differed for stage IA-IB, IB-II, II-IIIA and IIIA-IIIB, but not for stage 0-IA ($P = 0.64$) and IIIB-IV ($P = 0.60$). In the new staging system, stage group 0 and IA remain unchanged. Differences between the 7th edition stage groups were significant for stage IA-IB, IIA-IIB, IIB-IIIA and IIIB-IIIC but not for stage 0-IA ($P = 0.64$), IB-IIA ($P = 0.09$) and stage IIIA-IIIB ($P = 0.15$, Figure 3b). Figure 4a shows patients from the 6th edition stage II, which is subdivided into stage IIA, IIB and IIIA in the 7th edition staging system. Differences between the curves were all significant. In Figure 4b the subdivision of 6th edition stage IIIA into 7th edition stage IIIA and IIIB is shown; no significant differences between the two new stage groups were detected ($P = 0.26$). Overall, in the AJCC 6th edition, two out of six consecutive steps between stage groups were not significantly discriminant, while in the AJCC 7th edition, three out of seven consecutive steps were not significantly discriminant, indicating that the discriminant value between stage groups has decreased between the 6th and 7th edition staging system.

Figure 3. Disease-specific survival estimates according to the 6th edition (a) and 7th edition (b) AJCC staging system (N = 2196)

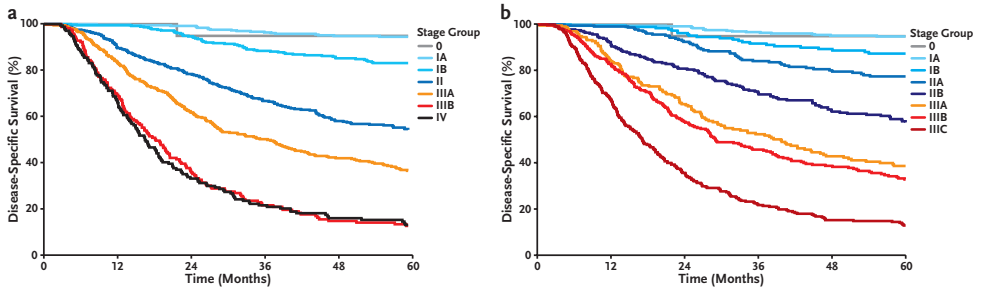
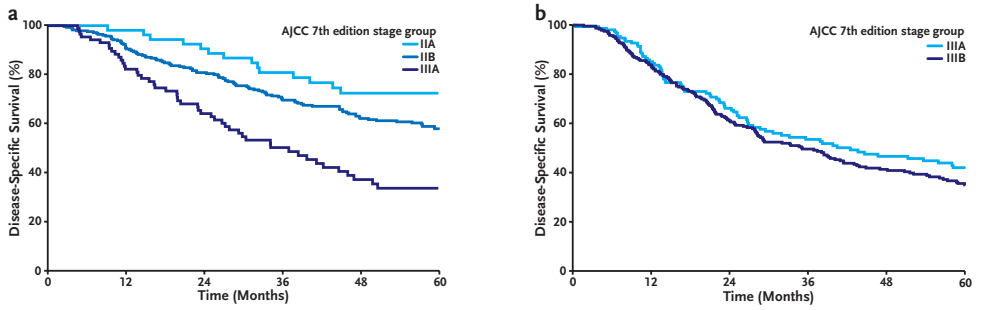


Figure 4. (a) AJCC 6th edition Stage II patients (N = 467) are distributed between stages IIA, IIB, and IIIA in the 7th edition staging system. (b) AJCC 6th edition Stage IIIA patients (N = 421) are distributed between stages IIIA and IIIB in the 7th edition staging system



PREDICTIVE ACCURACY

The concordance index of T staging did not change significantly from the 6th to the 7th edition ($P = 0.36$) (Table 6). The concordance index of N staging showed an increase from 0.659 to 0.665 ($P = 0.03$). Despite the change in definition for almost every stage group and the increased number of stage groups, the concordance estimate for the 7th edition was 0.697, which was significantly inferior to that of the 6th edition staging system (0.711, $P < 0.01$). Brier score for T, N and overall stage groupings showed no significant improvement from the 6th to the 7th edition.

DISCUSSION

The current study describes the impact of the changes made in the 7th edition of the TNM-classification for stomach cancer by comparing stage-specific survival and predictive accuracy of the 6th and 7th edition staging system in a combined dataset with over 2000 patients who underwent an R0 resection for gastric cancer.

Three earlier single institutional Asian studies have compared the 6th with the 7th TNM-classification for gastric cancer.[11-14] The first study analyzed 9998 patients treated at a Korean university hospital and found a more detailed classification of prognosis in the 7th

edition staging system, accompanied with increased homogeneity within stage groups.[11] A Chinese study found better prognostic stratification in the 7th edition staging system.[12] Another Korean study evaluated nodal classification in 295 patients, and found that in multivariable analysis, N-classification was an independent prognostic factor for survival in the 7th edition, but not in the 6th edition staging system.[14]

One strength of the current study is the use of data from multiple institutions, thereby reducing the risk of unique outcome due to single institution bias. However, both series are Western, and no Asian dataset was used. Another advantage of the current study is the high quality of the data: all patients underwent an R0 resection, and disease-specific survival was used as the outcome measure. In the three previously published studies, overall survival instead of disease-specific survival was used, and in one study 14.5% of the patients underwent an R1 resection.[12]

With the redefinition of nodal classification, the distribution of patients among the N1, N2 and N3 categories is more equal (Figure 2b), while many patients are upstaged under the new staging system. A point of discussion on nodal staging in gastric cancer is that in the Western world, lymph node yield is generally low,[15] certainly in comparison with Asian centers.[16] This leads to the potential shift of patients into a more advanced nodal classification simply by investigating more lymph nodes.[17] Several groups have suggested the use of lymph node ratio (metastatic/total lymph nodes) instead of nodal status because of its higher prognostic accuracy and the elimination of the effect of this shift.[18-20] In these studies however, cut-off values for lymph node ratio intervals are often based on the used dataset. This introduces an advantage for lymph node ratio which has a perfect fit on the used dataset, while TNM nodal classification is part of an established system. However, decreasing the threshold for N2 and N3 categories in the 7th edition staging system considerably reduces the shifting effect. A minimum number of 15 nodes, however, remains the recommended threshold for adequate nodal staging.

A limitation of the stage groupings of the 7th edition staging system is that N3a and N3b categories were combined as N3, thereby not recognizing the prognostic significance of having 7-15 positive nodes versus more than 16 positive nodes in overall stage grouping. As the introduction of N3a and N3b as separate categories in overall stage grouping will increase complexity of the staging system, while it is unknown if it will improve overall predictive accuracy, this issue needs to be further addressed in future staging systems.

There are several benchmarks for comparing the performance of two staging systems. First, there should be homogeneity within stage groups; patients within the same stage group should have small differences in survival. Secondly, there should be discrimination between stage groups; patients in different stage groups should have larger differences in survival. Third, a staging system should have good predictive accuracy; patients with a higher stage should have a worse survival. And fourth, a staging system should be as simple and intuitive as possible in clinical practice, as increased complexity impedes clinical utility.

Table 5. Five-year and median disease-specific survival (DSS) estimates for stage groupings of the 6th and 7th edition staging system (N = 2196)

	AJCC 6th edition		AJCC 7th edition	
Stage group	**5-year DSS (%)**	**median DSS (months)**	**5-year DSS (%)**	**median DSS (months)**
0	95.0	not reached	95.0	not reached
IA	94.6	not reached	94.9	not reached
IB	83.4	not reached	87.5	not reached
II	55.3	85		
IIA			77.5	278
IIB			57.6	119
IIIA	37.5	38	38.8	40
IIIB	14.0	19	32.9	29
IIIC			13.0	17
IV	14.4	17		

Table 6. Predictive accuracy of the 6th and 7th edition AJCC staging system

	AJCC edition	T-classification	N-classification	Stage group
Concordance	6th	0.666 ($P = 0.36$)	0.659 ($P = 0.03$)	0.711 ($P < 0.01$)
	7th	0.667	0.665	0.697
Brier score	6th	0.165	0.165	0.158
	7th	0.163	0.164	0.156

Concordance: higher is better, Brier score: lower is better

HOMOGENEITY WITHIN STAGE GROUPS

Establishing homogeneity within stage groups requires grouping of TNM-combinations that have similar survival estimates (Table 2). For homogeneity testing, results are highly dependent on the size of the dataset. Ahn et al. showed improved homogeneity of two homogeneous stage groups in the 7th edition compared to one homogeneous stage group in the 6th edition, using a dataset of nearly 10,000 patients.[11] In the current study, numbers are smaller and therefore significant homogeneity within stage groups is hard to detect (results not shown).

DISCRIMINATION BETWEEN STAGE GROUPS

Heterogeneity between stage groups can be assessed by comparing stage-specific survival estimates for significant differences. Whether differences between stage groups are significant is highly dependent on the size of the dataset. Small differences in survival estimates between stage groups are more likely to be statistically significant in a large dataset. In the current study, stage-specific heterogeneity has decreased in the 7th edition when compared to the 6th edition. Although AJCC 6th edition stage II contained a highly heterogeneous population (Figure 4a), and distributing these patients between stages IIA, IIB, and IIIA in the 7th edition has created three groups with a significantly different prognosis, the distribution of 6th edition stage IIIA patients into AJCC 7th edition stages IIIA and IIIB has created two stage groups with almost identical stage-specific survival (Figure 4b). Wang et al. showed decreased heterogeneity between stage groups in the 7th edition as well.[12]

PROGNOSTIC ACCURACY FOR INDIVIDUAL PATIENTS

Performance of a staging system can also be assessed on the individual patient level, by comparing survival of patients with different stages. Several ways of comparing staging systems on an individual patient level have been proposed, but there is no standard method.[21] Commonly-used methods include explained variation (or Brier score), area under the receiver operating characteristic curve, the concordance index, and a summary measure of separation (SEP). We decided to use the concordance index and Brier score to measure the prognostic accuracy of the staging systems, since they analyze different, complementary measures. Concordance index is a measure of whether ranking of patients by staging is consistent with the ranking of their outcome. Its advantages include interpretation (since it is a probability), robustness (since it is based on ranks, it is not sensitive to small changes in the data) and availability of appropriate statistical methods for estimation. It also incorporates a built-in penalty for staging systems with a higher number of categories, so that with equally performing staging systems, the system with more categories will have a lower concordance probability. It does not penalize possible shifts (miscalibrations) between predicted and observed survival. Therefore, we also used Brier score, since it looks at the actual difference (in months) between predicted and observed survival, taking possible shifts into account.

In the current dataset, concordance analysis showed no difference for T category, an improvement for N category, and a decline for stage grouping. Brier scores consistently showed no significant improvement from the 6th to the 7th edition. Therefore, it can be concluded that for individual patient outcome, no improvements were detected from the 6th to the 7th edition staging system.

Only one of the previously published studies compared the two staging systems on an individual patient level. It found increased predictive accuracy for the 7th edition staging system.[12] A disadvantage of the method employed in that study is that the metric used for comparison, the Akaike Information Criterion, measures how well the staging system fits to the used dataset, without assessing the actual prognostic accuracy.

COMPLEXITY OF THE STAGING SYSTEM

With an increasing number of stage group categories for the 7th edition of the staging system, it has become more complex. Increasing the number of categories of the staging system is not unique to gastric cancer.[4] With the increasing availability of pathologic and molecular data, there is a trend towards incorporating more and more information into newer staging systems. Although these new categories might better reflect the natural history and prognosis of these diseases, there is a limit to the improvement of prognostic accuracy achievable with a categorical anatomic-based staging system like the TNM-classification.[22,23] At the same time, the goal of creating an intuitive, easy to use staging system disappears, and in daily clinical practice, cancer staging consists of using complex tables, if it is used at all.

Meanwhile, tools for individual patient prognostication have been developed that significantly outperform the TNM-classification in prognostic accuracy. For gastric cancer, a nomogram has been developed based on a single US-institution database,[24,25] and has been validated in several international patient cohorts.[26-28] The question is if the TNM-classification should aspire to the same goal of highly accurate individual patient prognostication as these nomograms. Prognostication is only one of the five goals of the TNM-classification, and all other goals are directed towards a simple intuitive international language: to aid the clinician in planning and evaluating treatment, to facilitate the exchange of information, and to contribute to research.[1]

In summary, the 7th edition of the AJCC staging system for gastric cancer has resulted in improved predictive accuracy for the N-classification but decreased heterogeneity among stage groups. The increased complexity of the 7th edition staging system is not accompanied by an improvement in prognostic accuracy of stage grouping. Staging represents a compromise in accounting for the most reproducible and prognostically relevant factors to aim at a simple, intuitive, useful, common language to describe the natural history of a tumor. It should not be confused with more complex multivariable prognostication models, which may be useful in defining groups of patients at homogenous risk of recurrence, regardless of anatomic TNM characteristics.

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PART I

Staging and prognostication

CHAPTER 3

Prospective impact of tumor grade assessment in biopsies on tumor stage and prognostic grouping in gastroesophageal adenocarcinoma: relevance of the 7th edition AJCC staging manual revision

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ABSTRACT

BACKGROUND

In the 7th edition of the AJCC staging system for esophageal cancer, tumor grade was introduced as an independent determinant of stage grouping in early stage tumors. With the significantly lower prognosis of poorly differentiated early stage adenocarcinomas, these tumors might become candidate for neoadjuvant therapy, given an accurate identification of these tumors with preoperative staging. The purpose of this study is to investigate the accuracy of preoperative histopathologic grading and the effect of preoperative grade on tumor stage/prognostic grouping.

PATIENTS AND METHODS

Preoperative tumor grade was compared to postoperative tumor grade in 427 patients who were treated with surgery without neoadjuvant therapy for adenocarcinoma of the esophagus. The impact of preoperative tumor grade on stage/prognostic grouping was investigated.

RESULTS

The overall accuracy of preoperative tumor grade assessment was 76% when unknown differentiation was regarded as well/moderately differentiated as recommended by AJCC, while accuracy was 73% after exclusion of tumors with unknown grade. In patients with T1-2N0 stage tumors, 16% were assigned to a lower stage group based on preoperative pathology, whereas 5% were assigned to higher stage group. In the T1-2N0 group, sensitivity for detecting a poorly differentiated tumor was 0.43 (0.30-0.56), whereas specificity was 0.94 (0.90-0.98).

CONCLUSIONS

With increasing use of neoadjuvant therapy, accuracy of preoperative biopsy assessment has become increasingly important. In the current study, we demonstrate that accuracy of preoperative tumor grade is 73%, leading to changes in AJCC stage/prognostic group in 21% of patients with T1-2N0 esophageal adenocarcinomas. Caution should therefore be exhibited in staging patients with esophageal adenocarcinoma based on preoperative biopsy data.

INTRODUCTION

The seventh edition of the American Joint Committee on Cancer (AJCC) Staging Manual has introduced several major modifications in the staging of gastric and esophageal cancer as compared to its sixth edition.[1-3] Most importantly, all tumors involving the gastroesophageal junction (GEJ) are now classified as esophageal cancers. The only exception is for GEJ tumors with the epicenter >5 cm distal to the GEJ which are coded as gastric cancer. A second important change is the incorporation of histological grade in the stage/prognostic grouping for both adenocarcinoma and squamous cell carcinoma esophageal cancer. For T1-2N0M0 adenocarcinomas, the degree of differentiation is now an independent determinant of stage/prognostic group. Well and moderately differentiated T1N0 adenocarcinomas are staged IA, whereas poorly differentiated T1N0 adenocarcinomas are grouped together with well to moderately differentiated T2N0 tumors in stage IB. Poorly differentiated T2N0 adenocarcinomas are stage IIA. For T3 or higher stage tumors and tumors with positive lymph nodes, the degree of differentiation does not influence stage/prognostic grouping. A third change is the definition of nodal (N) status, which is now based on the absolute number of positive lymph nodes and is synchronized to nodal stage for gastric carcinoma. Additional changes include the definition of tumor stage of Tis (in situ carcinoma), T4, and M classification.

The proposal of the 2010 AJCC staging system for esophageal cancer is based on a combined large international database: the Worldwide Esophageal Cancer Collaboration (WECC).[4] This database contains information of more than 7,000 patients and represents the practice of 13 institutions on 3 continents. However, for the staging system, only data from the 4,627 patients who received surgery without chemotherapy or radiotherapy were used. Therefore, the compliance of the staging system with patients who received preoperative or postoperative treatment is debatable.[5] Another issue with this dataset is the lack of information from preoperative biopsies. The introduction of tumor grade in the staging system is entirely based upon postoperative pathologic evaluation. However, this information is unavailable when a patient is staged prior to surgery to determine the use of neoadjuvant therapy.

Since the use of preoperative chemotherapy and radiation has become increasingly established in the treatment of resectable esophageal and GEJ adenocarcinoma,[6,7] accurate preoperative staging has become an issue of increasing clinical relevance, which is not only limited to locally advanced tumors. In the AJCC 7th ed., poor differentiation/tumor grade is used as an independent predictor of poor survival in early stage tumors. Stage-specific 10-year survival rates are 66%, 51% and 38% for stage IA (T1N0G1,2), IB (T1N0G3/T2N0G1,2), and IIA (T2N0G3), respectively.[8] Provided with these data, the group of patients with T2N0G3 tumors might become candidates for preoperative therapy, given that these tumors can be correctly identified preoperatively.

The purpose of this study was to investigate the accuracy of preoperative assessment of tumor grade of esophageal and GEJ adenocarcinoma by comparing preoperative grading

on biopsies to the postoperative surgical pathology in individuals who did not undergo neoadjuvant therapy. The second purpose was to investigate the impact of preoperative grade on tumor stage/prognostic grouping as detailed in the 7th edition of the AJCC staging manual.

METHODS

PATIENT SELECTION

Patients were identified from two prospectively maintained databases of gastric and esophageal cancer. Between January 1996 and November 2009, 1,440 patients with adenocarcinoma of the distal esophagus or GEJ without metastatic disease underwent potentially curative surgery at Memorial Sloan-Kettering Cancer Center (MSKCC). January 1996 is the time point at which an institutional electronic medical record system was introduced and is, therefore, a date from which additional information to the prospective database can be obtained. Patients who received preoperative chemotherapy or radiation were excluded, leaving 475 patients who did not receive neoadjuvant treatment. Since tumor grade was not assessed in patients with T0 and Tis disease (high grade glandular dysplasia), these patients (N = 48) were also excluded. Overall 427 patients with both preoperative biopsy and postoperative resection material were available for analysis. Patient and pathologic tumor characteristics, treatment, and follow-up data were prospectively recorded. The study was approved by the Institutional Review Board of MSKCC.

PREOPERATIVE STAGING AND HISTOLOGY

Preoperative staging was performed with varying combinations of chest radiograph, computed tomography (CT), positron emission tomography (PET) scan, endoscopic ultrasound (EUS) with biopsies, and diagnostic laparoscopy with biopsies. To avoid influence by imaging modalities on the accuracy of preoperative tumor grade analysis, each patient was assigned a preoperative stage based on the tumor grade assessed from preoperative biopsies, combined with postoperative T-, N- and M-stage. All patients underwent preoperative histopathologic evaluation by an in-house pathologist, either by evaluation of the submitted slides from referring hospitals, or by review of endoscopic biopsy specimens obtained at MSKCC. Whenever possible, all the material from patients who had multiple biopsies was reviewed.

Tumor grade was defined as well, moderately or poorly differentiated and reflected a recording of the poorest grade within the biopsy. In the final analysis, well and moderately differentiated tumors were grouped as one entity. When tumor grade was not mentioned in the pathology report, it was recorded as 'unknown'. In the time period 1996-2003, pathologists of any subspecialty participated in the assessment of these tumors but since 2004, only specialized gastrointestinal pathologists evaluated the esophageal and GEJ tumors.

SURGERY

All patients underwent a potentially curative resection of the esophagus, the GEJ, the stomach or a combination with different types of approaches depending on the tumor location and the preference of the surgeon. Surgical techniques included three-phase esophagectomy (cervico-thoraco-abdominal), Ivor-Lewis esophagectomy (right thoraco-abdominal), (left) thoraco-abdominal esophagectomy, transhiatal (cervico-abdominal) esophagectomy proximal gastrectomy and total gastrectomy.

POSTOPERATIVE HISTOLOGY AND STAGING

Staging was performed according to the new American Joint Committee on Cancer Staging guidelines (7th edition, 2010).[1] Depth of tumor invasion, number of positive lymph nodes, margin status, and the grade of differentiation were prospectively recorded, and used to calculate postoperative AJCC 7th edition T-stage, N-status and stage/prognostic group. According to the AJCC stage-grouping recommendation, tumors with unknown grades were regarded as well/moderately differentiated tumors.

Tumor grade was recorded as well, well to moderately, moderately, moderately to poorly, or poorly differentiated. These were translated to a trichotomous system of well, moderately, and poorly differentiated tumors, recording the poorest grade mentioned. In the final analysis, well and moderately differentiated tumors were grouped into one entity. Adenocarcinomas of the GEJ were classified according to a modification of the Siewert criteria, with type I tumors defined as an adenocarcinoma of the distal esophagus which may extend below the esophagogastric junction by less than 25% of the tumor mass, type II tumors defined as a carcinoma that straddles the esophagogastric junction, and type III tumors as a subcardial gastric carcinoma that involves the GEJ and may extend above the GEJ by less than 25% of the tumor mass.[9]

STATISTICAL ANALYSIS

Accuracy of preoperative staging was calculated by determining the concordance between preoperative and postoperative pathologic grade assessed from biopsies and surgical specimens, respectively. The postoperative pathologic grade was utilized as the gold standard reference point. Accuracy was expressed as the percentage of patients with the correct grade assigned. Although this yields a number that is easy to understand, it fails to reflect on the distribution of patients over different categories. Therefore, Cohen's weighted Kappa test for agreement was used as an additional measurement of accuracy of preoperative tumor grade. In general, values of Kappa from 0.20 to 0.39 are considered fair agreement, 0.40 to 0.59 are considered moderate, 0.60 to 0.79 substantial, and 0.80 outstanding.[10] Differences between groups were calculated by using Pearson's chi-square test. Survival estimates were calculated using the Kaplan Meier method, while differences between survival estimates were analyzed with the Log-Rank test. All statistical analyses were performed with SPSS Statistics 17.0.

Table 1. Patient characteristics, surgical treatment, and pathology data

	N	%
Total	427	*100.0*
Sex		
male	331	*77.5*
female	96	*22.5*
Age		
mean (SD)	66.2	(10.5)
Year of surgery		
1996-1999	147	*34.4*
2000-2004	162	*37.9*
2005-2009	118	*27.6*
Surgery		
three-phase esophagectomy	24	*5.6*
Ivor-Lewis esophagectomy	201	*47.1*
thoraco-abdominal esophagectomy	33	*7.7*
transhiatal esophagectomy	77	*18.0*
proximal gastrectomy	13	*3.0*
total gastrectomy	22	*5.2*
transabdominal	15	*3.5*
esophago/total	4	*0.9*
esophago/proximal	38	*8.9*
Siewert type		
I	125	*29.3*
II	193	*45.2*
III	109	*25.5*
Postoperative stage group		
IA	123	*28.8*
IB	60	*14.1*
IIA	14	*3.3*
IIB	75	*17.6*
IIIA	57	*13.3*
IIIB	41	*9.6*
IIIC	57	*13.3*

RESULTS

Demographic, pathologic and surgical data are summarized in Table 1. Seventy-eight percent of the patients were male and the mean age was 66.2 years. The average number of patients per year who underwent surgery without preoperative therapy decreased over time: 37 patients per year in 1996-1999, 32 patients per year in 2000-2004, and 24 patients per year in 2005-2009. Adenocarcinomas were classified as Siewert I, II or III in 30%, 46% and 24%, respectively. Survival for postoperative T1-2N0 well/moderately/unknown adenocarcinomas was significantly longer as compared to poorly differentiated tumors of the same T1-2N0 stage (Figure 1, 80% versus 56%, $P = 0.005$). Patients with preoperative stage IA, who were upstaged IB on postoperative pathology had a significantly worse prognosis as compared to those who remained stage IA on postoperative pathologic staging ($P = 0.014$, Figure 2), while there was no significant difference in overall survival with patients who were assigned stage IB preoperatively and postoperatively ($P = 0.454$). This analysis could not be performed for patients incorrectly staged between stage IB to IIA, because the number of events in this group was too few.

Figure 1. Kaplan Meier curves for T1-2N0 tumors, separated by postoperative tumor grade (N = 197)

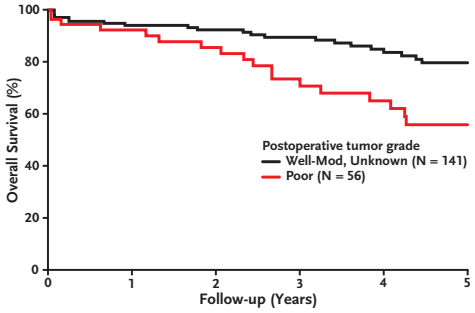
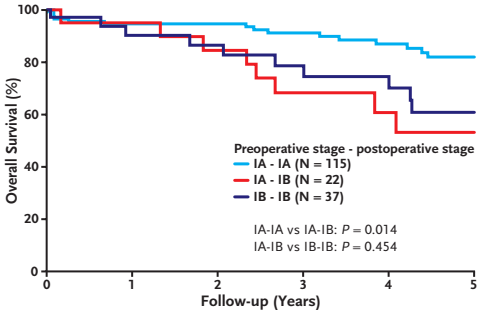


Figure 2. Kaplan Meier curves for T1-2N0 tumors, separated by preoperative and postoperative tumor stage (N = 174)



Postoperative pathology indicated 9% (37/427) of the tumors were well differentiated, 43% (183/427) moderately differentiated and 47% (199/427) poorly differentiated. Postoperative grade was reported in 98% (419/427) of the tumors, and preoperative grade was reported in 71% (302/427) of all tumors (Table 2). Based upon the AJCC staging guidelines, unknown tumor grade was recorded as well/moderately differentiated.

Accuracy of preoperative tumor grade assessment in the entire group (T1-4N0-3 patients) was 76% (324/427, $P < 0.001$) (Table 3). Cohen's kappa test for agreement demonstrated a kappa of 0.50 ($P < 0.001$), which is considered to reflect moderate agreement. Most discordance in preoperative grading in biopsies was a result of under-grading, with 29% (88/301) of all preoperative well and moderately differentiated tumors being poorly differentiated tumors on postoperative surgical pathology (Table 3). After exclusion of the patients with unknown preoperative or postoperative grade, accuracy of preoperative grading was 73% (238/301, $P < 0.001$), with a kappa of 0.58 ($P < 0.001$), indicative of moderate agreement.

The concordance of preoperative grade assessment was comparable when analyzed by specialized gastrointestinal (GI) pathologists (80%) or non-GI-pathologists (78%, P = NS). Differences in accuracy between the different Siewert groups (Siewert I: 72%, Siewert II: 79%, Siewert III: 86%) were borderline significant ($P = 0.06$).

Accuracy slightly increased during the consecutive time periods: accuracy was 73%, 81% and 83% for the periods 1996-1999, 2000-2004, and 2005-2009. This observation did not reach statistical significance.

Since tumor grade only affects stage grouping in T1-2N0 patients, subgroup analyses were performed excluding T3 and T4 tumors and tumors with positive lymph nodes. Accuracy of preoperative grade assessment in T1-2N0 tumors was 79% (156/197, $P < 0.001$), with a kappa of 0.42 (Table 4). Most grading discordance was due to preoperative under-grading. After conversion of T1-2N0 tumors into their corresponding pre and postoperative stage/prognostic groups, 79% (156/197, $P < 0.001$) of the patients were

Table 2. All $T_{1-4}N_{0-3}$ tumors (N = 427)

		Postoperative grade				
		Well	Moderate	Poor	Unknown	Total
Preoperative grade	Well	5	14	6	0	25
	Moderate	7	101	42	1	151
	Poor	1	14	111	0	126
	Unknown	24	54	40	7	125
	Total	37	183	199	8	427

Table 3. All $T_{1-4}N_{0-3}$ tumors (N = 427), unknown grade is coded as well/moderately differentiated
Accuracy: 324/427 = 0.76, Cohen's Kappa: 0.50

		Postoperative grade		
		Well-Mod, Unknown	Poor	Total
Preoperative grade	Well-Mod, Unknown	213	88	301
	Poor	15	111	126
	Total	228	199	427

Table 4. All $T_{1-2}N_0$ tumors (N = 197)
Accuracy: 156/197 = 0.79, Cohen's Kappa: 0.42

		Postoperative grade		
		Well-Mod, Unknown	Poor	Total
Preoperative grade	Well-Mod, Unknown	132	32	164
	Poor	9	24	33
	Total	141	56	197

Table 5. Stage grouping for all $T_{1-2}N_0$ tumors (N = 197)
Accuracy: 156/197 = 0.79, Cohen's Kappa: 0.57

		Postoperative stage group			
		IA	IB	IIA	Total
Preoperative stage group	IA	115	22	0	137
	IB	8	37	10	55
	IIA	0	1	4	5
	Total	123	60	14	197

properly staged (Table 5), with a kappa of 0.57 ($P < 0.001$). Preoperative under-staging occurred in 16% (32/197) of these patients and over-staging in 5% (9/197), respectively. Sensitivity in this group to detect a poorly differentiated tumor was 0.43 (0.30-0.56), whereas specificity was 0.94 (0.90-0.98). This indicates that of all poorly differentiated tumors in the T1-2N0 group, 57% were not identified as such.

DISCUSSION

Although T-stage, N-stage and M-stage are strong independent predictors of survival in esophageal cancer,[11-13] the sixth edition of the AJCC staging system for esophageal cancer has been challenged for its heterogeneity of outcome on survival within the different stage groups.[14] During the past years, several pathologic prognostic factors have been proposed for incorporation into the TNM staging system. These include degree of differentiation,[15] vascular and perineural invasion,[16] extracapsular lymph node invasion,[17] tumor length,[18,19] clearance of the proximal and distal resection margin,[20,21] and status of the circumferential margin.[22] These proposals however, are primarily based on analyses from relatively small series of patients, and in most instances from single institution databases. Incorporation of a new factor into the AJCC staging system not only requires a structured mechanism of the proposed change,[23] but the factor also has to be available in the collaborative WECC database.

In 1991, Robey-Cafferty et al showed in their series of 69 patients with squamous cell carcinoma of the esophagus that the degree of tumor differentiation was an independent prognostic factor.[24] In 2001, Dickson et al. proposed incorporation of tumor grade in the staging system based upon a series of 139 consecutive patients who received surgery for GEJ carcinoma (mostly adenocarcinoma). The authors demonstrated differences in 3-year overall survival for well (33.3%) and moderately differentiated tumors (28.9%) vs poorly differentiated tumors (15.9%) respectively.[15] Khan et al confirmed these results in a series of 219 patients with N0 squamous cell carcinoma and adenocarcinoma of the esophagus, showing that tumor grade was an independent prognostic factor in univariate and multivariate analysis.[25] Other studies also confirmed a correlation between tumor grade and prognosis in univariate analysis, but not in multivariate analysis.[26-28] Recently, Thompson et al reported in a study of 240 patients with mainly adenocarcinoma, that tumor grade was an independent prognostic variable in both univariate and multivariate analysis.[14] In this study, patients were divided into two groups: well and moderately differentiated, and poorly and undifferentiated. Furthermore, the combined data in WECC database also supports the incorporation of tumor grade into the 2010 AJCC staging system for esophageal cancer. The inclusion of postoperatively determined tumor grade into the staging system may provide outcome information and guidance for adjuvant therapeutic strategies. However, the question raised with this addition is how reliable is the assessment of tumor grade in small preoperative biopsies? This is particularly relevant when neoadjuvant options are considered with poorly differentiated adenocarcinomas of T2N0M0 stage.

In the patient group evaluated, the average number of patients without preoperative treatment decreased over the years. This is consistent with increased use of neoadjuvant therapy in locally advanced GEJ carcinoma. Poorly differentiated (G3) and early stage tumors were associated with a significantly lower survival rate as compared to tumors that were graded as well (G1), moderately (G2) or unknown on postoperative pathology

Figure 3. Adenocarcinoma of mixed type with moderately differentiated (lower left) and poorly differentiated component (upper)

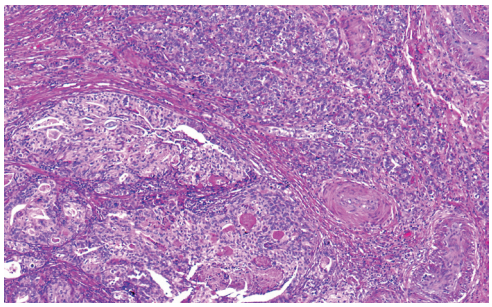
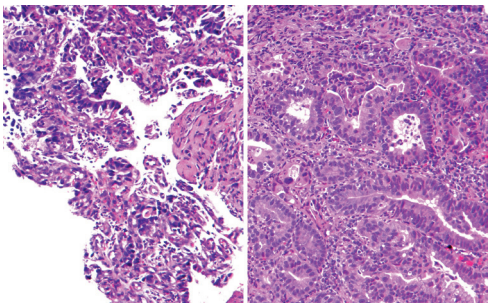


Figure 4. Preoperative biopsy (left) and corresponding surgical resection specimen (right) of a moderately differentiated adenocarcinoma



Biopsy could be upgraded as a poorly differentiated carcinoma due to its proximity to ulcer and the crush artifact

(Figure 1). Preoperatively understaged IB tumors (into preoperative stage IA) were associated with lower survival as compared to correctly staged IA tumors (Figure 2), indicating the significance of accurate tumor grade assessment on preoperative staging. In the entire cohort of this study, including patients with 'unknown' tumor grade, which was regarded as well/moderately differentiated according to AJCC recommendation, preoperative tumor grade assessed in biopsies was concordant with that assessed in surgical specimens in 76% of the patients. After excluding individuals with unknown tumor grade, overall concordance was 73% (kappa value: 0.58) consistent with moderate agreement.

However, not all stage/prognostic groups are affected by tumor grade. In the AJCC 7th Edition only stage T1-2N0 tumors are assigned to three separate stage groups when the tumor is well and moderately or poorly differentiated. In T1-2N0 tumors, the concordance for tumor grade was slightly higher as compared to the entire cohort (79% vs. 76%), and therefore 21% of this group was assigned an "inappropriate" stage group based on preoperative biopsies: under-staging occurred in 16%, and over-staging in 5%.

The differences in concordance of tumor grade assessed by GI-pathologists and non GI-pathologists were not statistically significant. To the authors' best knowledge, this has not been described previously. Siewert type showed borderline significant differences favoring higher accuracy of tumor grade assessment in Siewert III tumors.

A number of factors could account for the discordance in assessment of tumor grade in biopsy and in surgical resection specimens. These include sampling issue, technical quality of the specimen, and, to a lesser extent, the experience of the pathologist. It is of note that a significant number of GEJ adenocarcinomas reveal intratumoral heterogeneity (Figure 3), exhibiting mixed populations of well to moderately and poorly differentiated histopathology within the same tumor. Thus a biopsy specimen may not always represent the dominant component of the tumor grade in the entire lesion. Therefore, sampling bias may be responsible for discordance in both up-grade and

down-grade between biopsy and resection specimens, respectively. A second significant factor responsible for tumor grading discordance is the suboptimal preparation of biopsy specimens, which may include excessive air dry effect before formalin fixation, tumor tissue adjacent to ulcer and necrosis, or thermal/mechanically generated crush artifacts in diminutive specimens. In these situations, an up-grading from a well/moderately to a poorly differentiated tumor is a more likely consequence than down-grading from a poorly differentiated to a well/moderately tumor (Figure 4).

The very recent introduction of the 2010 staging system into clinical practice has precluded the development of treatment algorithms for the different stage/prognostic groups and these remain to be established. No prospective studies have been performed in the subset of early stage poorly differentiated tumors, and most current clinical trials of neoadjuvant therapy for esophageal adenocarcinoma apply different inclusion criteria and usually include patients with cT2-3N0[29] and cT1-3N1 tumors[7]. However, the FFCD 9901 trial showed that preoperative CRT followed by surgery has a negative impact on postoperative mortality in early stage esophageal cancer patients as compared to surgery alone, without a significant difference in overall survival.[30] The majority of patients in this trial however, had squamous cell carcinoma, while no subgroup analyses were performed on poorly differentiated early stage tumors. Furthermore, a WECC database analysis showed that the subgroup of patients with T2N0G3 tumors, when treated with surgery only, has a significantly worse 10-year survival (38%) as compared to other early stage but lower grade tumors (66% and 51%).[8]

Since the new AJCC staging system has revealed a prognostic difference for patients with IA, IB and IIA esophageal adenocarcinoma that is stratified with the combination of tumor stage (T1-2) and tumor differentiation, it is likely that patients with early esophageal and GEJ tumors, which are poorly differentiated, may become candidates for neoadjuvant therapy. However, in our study, we have demonstrated that the sensitivity for grading poorly differentiated early stage tumors correctly is only 0.43. Given this low sensitivity there exists the potential risk that more than half of these patients would not receive therapy that might be otherwise recommended.

With the increasing use of neoadjuvant chemotherapy and radiotherapy in esophageal cancers, it is evident that therapeutic management strategy should be evaluated based on a combination of clinical, radiographic, and pathologic assessments. In future modifications of the AJCC staging system, this might be addressed by capturing clinical staging information in the WECC database. Precise pathological identification is particularly pertinent when assessing tumor differentiation in individuals with early stage and lymph node negative esophageal cancer.

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PART I

Staging and prognostication

CHAPTER 4

Conditional probability of survival nomogram for one, two, and three year survivors after an R0 resection for gastric cancer

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ABSTRACT

BACKGROUND

Survival estimates after curative surgery for gastric cancer are based on AJCC staging, or on more accurate multivariable nomograms. However, the risk of dying of gastric cancer is not constant over time, with most deaths occurring in the first two years after resection. Therefore, the prognosis for a patient who survives this critical period, improves. This improvement over time is termed Conditional Probability of Survival (CPS). Objectives of this study were to develop a CPS nomogram predicting 5-year disease-specific survival (DSS) from the day of surgery for patients surviving a specified period of time after a curative gastrectomy, and to explore whether variables available with follow-up improve the nomogram in the follow-up setting.

PATIENTS AND METHODS

A CPS nomogram was developed from a combined US-Dutch dataset, containing 1642 patients who underwent an R0 resection with or without chemotherapy/radiotherapy for gastric cancer. Weight loss, performance status, hemoglobin, and albumin one year after resection were added to the baseline variables of this nomogram.

RESULTS

The CPS nomogram was highly discriminating (concordance index: 0.772). Surviving one, two, or three years gives a median improvement of 5-year DSS from surgery of 7.2%, 19.1%, and 31.6%, as compared to the baseline prediction directly after surgery. Introduction of variables available at one year follow-up did not improve the nomogram.

CONCLUSIONS

A robust gastric cancer nomogram was developed, to predict survival for patients alive at time points after surgery. Introduction of additional variables available after one year of follow-up did not further improve this nomogram.

INTRODUCTION

Survival estimates for individual gastric cancer patients are usually based on AJCC staging,[1] or on more accurate multivariable nomograms.[2] A 5-year survival estimate based on either AJCC staging or a nomogram, represents the probability for a patient to be alive 5 years after surgery.

However, the risk of dying of gastric cancer is not constant over time, with most deaths occurring in the first two years after a curative resection (Figure 1). Therefore, the prognosis (and the 5-year survival probability from the day of surgery) of a patient who survives this critical period improves conditionally on having survived this period after surgery. This improvement of prognosis over time is termed Conditional Probability of Survival (CPS).

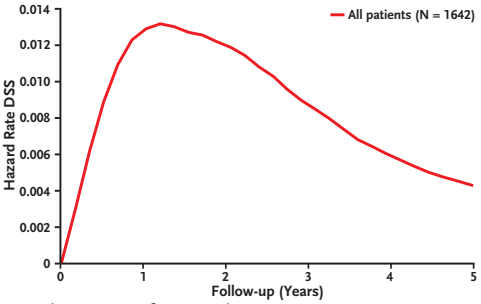
CPS is higher as compared to the survival probability at the time of surgery for a variety of cancers, including melanoma,[3] cancer of the CNS,[4] head and neck,[5] breast,[6] lung,[7] colon,[8,9] ovaries,[10] and stomach.[11] For gastric cancer, the difference between initial and conditional survival probability is greatest in patients with high stages who have a corresponding poor initial prognosis.[11]

Nomograms represent multivariable models predicting survival of individual patients based on several patient-specific parameters.[12] A US-derived nomogram predicting disease-specific survival (DSS) after an R0 resection for gastric cancer showed a high predictive accuracy with internal validation,[2] as well as external validation in Dutch[13], German[14], and Turkish[15] patients. This nomogram is based on patient and tumor characteristics of patients who underwent curative surgical resection alone, without adjuvant therapy. With the increasing clinical practice of preoperative and postoperative therapy for advanced gastric cancer, we felt that these patients should be included in an updated nomogram.

Although the current nomogram accurately estimates 5-year DSS directly after R0 surgery, it does not estimate the improved conditional survival of patients who remain alive at time points following resection, and is therefore not useful in the follow-up setting. Furthermore, we hypothesized that factors representing the patient's clinical status in the follow-up setting, such as weight loss and performance status, might contribute to and influence the estimate of patient prognosis in the follow-up setting in addition to variables available directly after surgery.

The first purpose of the current study is to develop a new, clinically useful nomogram predicting 5-year DSS after an R0 resection for gastric cancer, with or without chemotherapy and/or radiotherapy. The second purpose is to incorporate into this new nomogram the ability to predict conditional 5-year DSS from the day of surgery for patients surviving a specified period of time after an R0 resection for gastric cancer. The third purpose is to see if the introduction of variables available at one year of follow-up improves predictive accuracy of the new nomogram in the follow-up setting.

Figure 1. Hazard of death from gastric cancer for all patients (N = 1642)



DSS: disease-specific survival

PATIENTS AND METHODS

PATIENTS

The final dataset was derived from two prospective clinical databases.

The first database was from Memorial Sloan-Kettering Cancer Center (MSKCC), prospectively maintained since 1985, and the source of data for the initial gastric cancer nomogram.[2] This database contains information on 1473 patients who underwent curative resection for an adenocarcinoma of the stomach with or without (neo)adjuvant therapy, between January 1996 and December 2009. The study was approved by the MSKCC Institutional Review Board.

This dataset was combined with a Dutch dataset on which the original nomogram was validated,[13] containing information on 1078 patients who were randomized to undergo D1 or D2 lymph node dissection for adenocarcinoma of the stomach between 1989 and 1993, without receiving chemotherapy or radiation.[16,17] This study was approved by the principal investigator of the Dutch Gastric Cancer Trial.

From this combined dataset, patients with M1 disease (N = 441), patients with a positive resection margin (R1, R2, N = 216), and patients without all original nomogram variables available (N = 245) were excluded. Of the patients who died of unknown cause (N = 40), 7 were excluded and 33 were included as censored, leaving 1642 patients in the currently reported analyses. When the nomogram was regenerated excluding all 40 patients who died of unknown cause, no differences in CI were detected. The cause of death was based on available information on disease recurrence, which was generally confirmed with radiology, endoscopy, and/or histology.

SURVIVAL ANALYSES

Disease-specific survival (DSS) was calculated from the day of surgery until the day of death of gastric cancer (event), or death of other causes or the last day of follow-up (censored). The day of R0 surgery was chosen as the starting point for survival as this is the moment that all patients were considered 'disease-free'. The DSS hazard curve was plotted using kernel density smoothing.[18]

5-Year DSS in this study is defined as the probability of 5-year DSS *from the day of surgery*. Conditional Probability of Survival (CPS) was defined as the probability of DSS at five years from the day of surgery, given that the patient had not died of gastric cancer at a specified period of time (*x* years) after surgery. Calculations of CPS were performed using the standard definition of conditional probability:[19]

$$CPS\ (5|x) = S\ (5) / S\ (x)$$

in which

CPS (5/*x*) =	DSS probability 5 years after surgery, given the patient did not die of disease *x* years after surgery
S (5) =	DSS probability 5 years after surgery
S (*x*) =	DSS probability *x* years after surgery

For example, a patient's 1-year survival probability is 0.8, whereas his 5-year survival probability is 0.4. The probability of surviving the first 5 years after surgery, given that the patient already has survived the first year, is calculated as follows:

$$CPS\ (5|1) = S\ (5) / S\ (1) = 0.4 / 0.8 = 0.5$$

So, this patient's CS (5|1) is 0.5, which is higher than the originally 5-year survival probability (5|0), which is 0.4.

1. NEW NOMOGRAM PREDICTING 5-YEAR DSS

The first purpose of the study was to develop a new, clinically relevant nomogram, predicting 5-year DSS after an R0 resection for gastric cancer based on patients who underwent curative resection, with or without (neo)adjuvant chemotherapy and/or radiotherapy. Age, sex, primary site (distal, middle, proximal, and gastroesophageal junction), Lauren classification (diffuse, intestinal, mixed), maximum tumor diameter (cm), number of positive lymph nodes resected, number of negative lymph nodes resected and depth of invasion were entered into the Cox proportional hazards model predicting DSS. The effects of age, number of positive and negative lymph nodes, and invasion depth were modeled using restricted cubic splines. Although this new nomogram was initially developed to predict 5-year DSS, it also has the ability to predict DSS for any point in time after surgery, which is necessary for the next step.

As AJCC stage-specific survival is the most common way a prognosis of a patient is assessed, all patients were staged according to the 7th edition of the AJCC staging system.[1] Then, the predictive accuracy of the new nomogram was compared to that of the staging system.

2. PREDICTING CPS WITH THE NEW NOMOGRAM

The second purpose was to use the newly developed nomogram to predict DSS 5-years from the day of surgery, given that the patient had not died of gastric cancer for a specified time (*x* years) after resection. The new nomogram can give a DSS probability for any point in time after surgery. To calculate a CPS prediction for an individual patient, both the 5-year and the *x*-year DSS probability are predicted by the nomogram, followed by dividing the 5-year DSS probability by the *x*-year DSS probability. For patients surviving one, two and three years after surgery, the probability of surviving the first five years after surgery is calculated as follows:

CPS (5|1) = 5-year DSS probability / 1-year DSS probability
CPS (5|2) = 5-year DSS probability / 2-year DSS probability
CPS (5|3) = 5-year DSS probability / 3-year DSS probability

3. INTRODUCTION OF FOLLOW-UP VARIABLES INTO THE NEW DSS-NOMOGRAM

The third purpose of this study was to evaluate if introduction of variables available at follow-up would improve predictive accuracy of the new nomogram. Variables used in this nomogram are all available directly after surgery and do not represent a patient's condition at the moment of follow-up. We hypothesized that weight loss, Eastern Cooperative Oncology Group (ECOG) performance status (PS), hemoglobin (HGB) and albumin (ALB) might have additional predictive value for DSS to the original variables alone, given that the patient had survived a certain period in time.

Weight, PS, HGB and ALB were retrospectively recorded for one year disease-free survivors treated at MSKCC (N = 769), within a time interval of three months before or after one year of follow-up. Although the original aim was to collect these data for one, two and three year survivors, data availability was limited because of retrospective collection and smaller number of patients surviving up to two years after surgery. To calculate weight loss, two independent weights had to be recorded. If a weight was available 1-4 months before the weight measured at follow up, weight loss was calculated. If a patient had remained stable or gained weight, a weight loss of 0 was recorded. ECOG PS was recorded as 0-1 versus 2-3.

First the predictive accuracy of the nomogram using only original variables was assessed in one year disease-free survivors. Secondly, the nomogram was extended with the collected follow-up variables. Different combinations of old and new variables were used to explore whether incorporation of any or all of these variables improved the concordance index.

CALCULATING PREDICTIVE ACCURACY OF THE NOMOGRAMS

The nomogram was validated using two methods. First, discrimination was quantified with the concordance index (CI).[20] CI is a measure of how well the predictions match the

observed outcomes. In particular, CI is the probability that, in a randomly selected pair of patients, the patient with the better prediction also has the longer observed survival. CI of a nomogram is calculated by comparing all possible pairs of patients in the dataset, and adding scores of all individual pairs. The current dataset contains censored patients, who did not die of gastric cancer at the last follow-up. If such a patient has the shorter follow-up in a certain pair, it is impossible to determine which of the two patients had the best outcome. These pairs are called non-informative, and were excluded from the CI calculation. All CIs were corrected for overfit by bootstrapping. A bootstrapped significance test was used to assess differences between CIs.
Secondly, calibration was assessed by grouping patients with respect to their nomogram-predicted probabilities and then comparing the mean of the group with the observed DSS Kaplan-Meier estimate, correcting by bootstrap for overfit. All analyses were performed using R (version 2.11.0).

RESULTS

Patient characteristics are presented in Table 1. Median follow-up of all patients was 66 months, and 565 (34%) events (death of disease) occurred in this population.

1. NEW NOMOGRAM PREDICTING 5-YEAR DSS

A nomogram predicting 5-year DSS after an R0 resection for gastric cancer directly after surgery (0-year survivors) was developed based on the current dataset of 1642 patients (Figure 2). Variables that were used in the original nomogram,[2] are highly predictive in the current dataset. The CI of the new nomogram is 0.772. A calibration plot for this nomogram shows a high correspondence between the predicted and actual survival (Figure 3a).
Chemotherapy with or without radiation was administered to 29.5% of the patients. However, the addition of a variable in the nomogram indicating the use of chemotherapy or radiation did not improve the CI of the new nomogram. When using the current dataset to compare the new nomogram with the previously published nomogram,[2] there was no difference in CI (0.772 versus 0.771, $P = 0.18$).
When comparing this nomogram with the AJCC staging system 7th edition, the nomogram outperformed the staging system in discriminative ability (CI = 0.772 versus 0.766, $P = 0.03$).

2. PREDICTING CPS WITH THE NEW NOMOGRAM

The new nomogram can predict 5-year DSS from the day of surgery for patients alive at time points up to 5 years after an R0 resection for gastric cancer. The probability of 5-year DSS from the day of surgery shows a median increase of 7.2%, 19.1% and 31.6%, respectively for one, two and three-year survivors, as compared to patients for who 5-year DSS was predicted directly after surgery (Table 2).

Table 1. Patient characteristics (N = 1642)

	N	%
Sex		
male	1016	*61.9*
female	626	*38.1*
Age		
mean ± SD	64.9 ± 11.9	
median (IQR)	67 (57-74)	
Primary site		
GEJ	359	*21.9*
proximal	283	*17.2*
middle	415	*25.3*
distal	585	*35.6*
Lauren histotype		
intestinal	1050	*63.9*
diffuse	434	*26.4*
mixed	158	*9.6*
Invasion depth		
mucosa	170	*10.4*
submucosa	325	*19.8*
muscularis propria	243	*14.8*
subserosa	340	*20.7*
serosa	479	*29.2*
adjacent organs	85	*5.2*
Tumor size (cm)		
mean ± SD	4.1 ± 2.9	
No. of nodes evaluated		
mean ± SD	23.6 ± 12.6	
median (IQR)	21 (15-31)	
No. of positive nodes		
mean ± SD	3.0 ± 5.5	
median (IQR)	1 (0-4)	
Preoperative/postoperative chemotherapy/radiotherapy	484	*29.5*

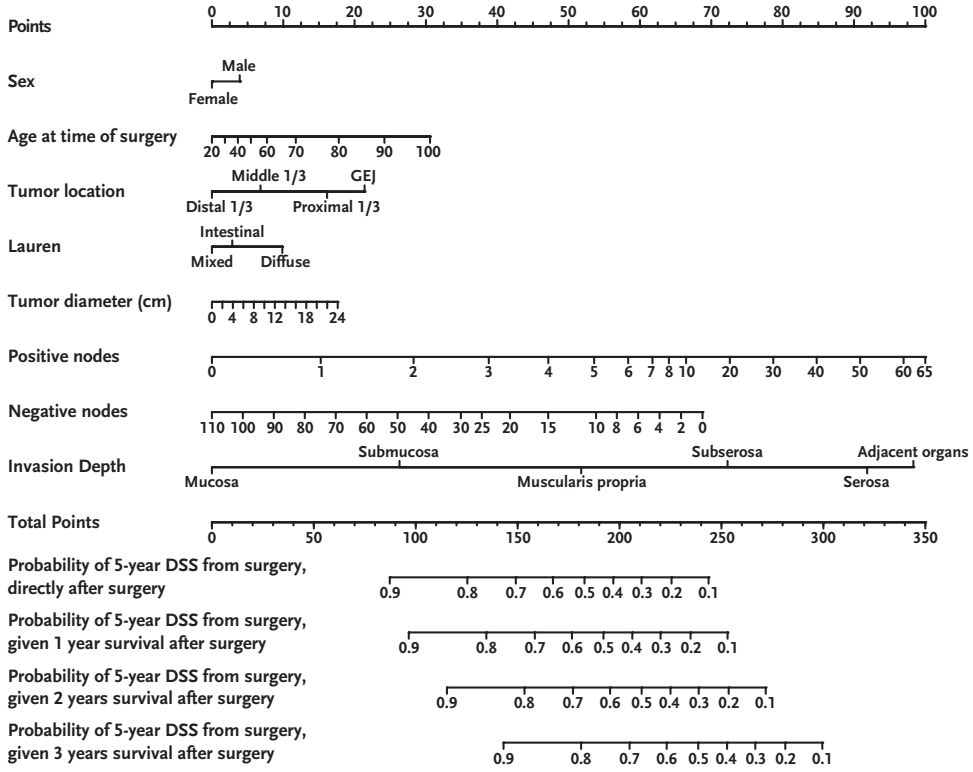
SD: standard deviation, IQR: inter quartile range, GEJ: gastro esophageal junction

This is illustrated in Figure 3b, in which the three curves show the improvement in 5-year DSS probability from the day of surgery for one, two and three year survivors as compared to 0-year survivors.

3. Introduction of follow-up variables into the original DSS-nomogram

Weight loss, performance status, HGB and ALB were retrospectively recorded for patients that were alive and had not recurred one year after surgery. Table 3 compares the CI of the nomogram based on original variables only, with the CI of nomograms with follow-up variables. Addition of weight loss, hemoglobin, albumin, and performance status or a combination of those did not improve the CI of the nomogram that was based on original variables only.

Figure 2. Nomogram predicting 5-year disease-specific survival from the day of surgery based on 1642 patients who underwent an R0 resection for gastric cancer



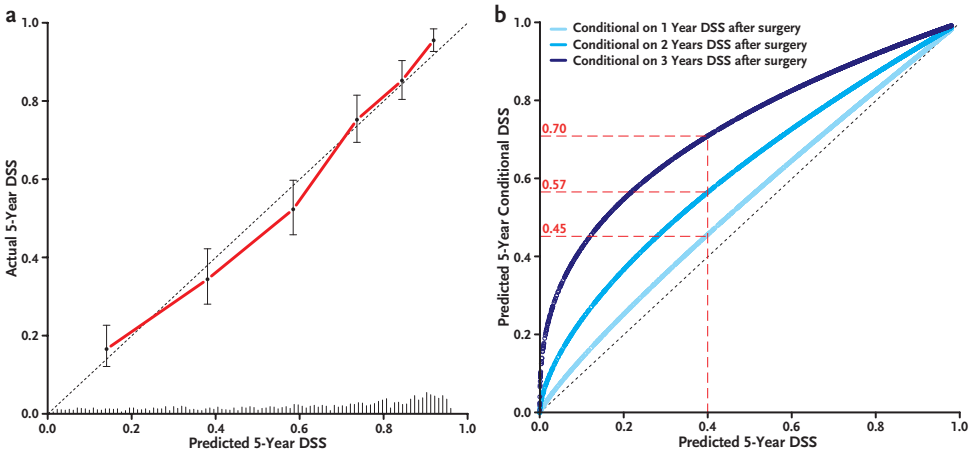
Instructions
Locate the patient's sex on the **Sex** axis. Draw a line straight upwards to the **Points** axis to determine how many points towards gastric cancer-specific death the patient receives for his or her sex. Repeat this process for the other axes, each time drawing straight upward to the **Points** axis. Sum the points achieved for each predictor and locate this sum on the **Total points** axis. Draw a line straight down to the **disease-specific survival** axes to find the patient's probability of 5-year DSS from the day of surgery, directly after surgery, or one, two or three years after surgery.

DISCUSSION

The original gastric cancer nomogram that was published in 2003 predicts five and nine-year DSS after an R0 resection of gastric cancer, based on patients who only received an R0 resection without chemotherapy or radiation.[2] Although this nomogram is highly precise, and has been validated in databases from three different countries in Europe,[13-15] the predictive accuracy in patients who received chemotherapy or radiation has not been investigated.

In the present study, a new nomogram was developed, predicting 5-year DSS for patients who received an R0 resection for gastric cancer, with or without chemotherapy and/or radiation. To increase nomogram accuracy, MSKCC data were combined with data in which the original nomogram has been previously validated[13]. Incidence rates for

Figure 3. Calibration plots for the 5-year disease-specific survival nomogram (N = 1642)
(a) predicting 5-year DSS directly after surgery (0-year survivors)
(b) predicting 5-year DSS conditional on surviving of gastric cancer for 1, 2 or 3 years



Instructions Figure 3b
In the example the nomogram predicts a 5-year DSS of 40%.
- step 1: draw a line from the original (0-year survival prediction) axis.
- step 2: the probability for this patient to survive the first 5 years after surgery, without dying of gastric cancer is:
  - 40% directly after surgery (0 years survival)
  - 45% after surviving 1 year without dying of gastric cancer
  - 57% after surviving 2 years without dying of gastric cancer
  - 70% after surviving 3 years without dying of gastric cancer

gastric cancer are generally comparable between the USA and the Netherlands[21]. When comparing the new with the previously published nomogram, no differences in CI were detected. This attests to the strength of the initial predictive model and indicates robustness of the new nomogram. Overall, the discriminative ability (CI) of the new nomogram is relatively high by standards of cancer prognosis. The calibration plot (Figure 3a), which shows how well the nomogram predictions (x-axis) correspond with the actual unconditional 5-year DSS of the patients in this study (y-axis), reveals a high predictive accuracy. Furthermore, the CI of the new nomogram is higher than the CI of the AJCC staging system, indicating more accurate predictions are provided by the nomogram as compared to the AJCC staging system.

With the original gastric cancer nomogram, there was no accurate way to predict the outcome for patients who had survived over a certain period in time after their surgery for gastric cancer, as the original nomogram prediction is only useful directly after surgery and not after a certain period of follow-up. Using the new nomogram, it is now possible to estimate the (improved) probability of 5-year DSS from the day of surgery for patients alive at time points after an R0 resection for gastric cancer. The improvement in prognosis ranges from a median of 7.2% for 1-year survivors to a median of 31.6% for

Table 2. Increase of 5-year DSS from the day of surgery, when compared with the baseline prediction directly after surgery (0-year survival), using the new nomogram

	Median increase (%)	IQR (%)
1 year after surgery	7.2	2.9-17.6
2 years after surgery	19.1	7.4-50.7
3 years after surgery	31.6	11.9-90.6

IQR: inter quartile range

Table 3. Introduction of follow-up variables into the nomogram. All patients are one-year disease-free survivors from the MSKCC group

Added variables	No. of patients with available data	No. of events in group	Step 1 Nomogram with original variables (CCI)	Step 2 Nomogram with new variables (CCI)[a]
only original variables	769	170	0.721	
PS	485	103	0.731	0.728
WL	377	93	0.712	0.729
HGB	319	83	0.736	0.732
ALB	311	81	0.725	0.734
WL+ALB	249	69	0.702	0.739
HGB+ALB	298	78	0.731	0.734
PA+HGB+ALB	275	71	0.720	0.729
PA+WL+ALB	245	68	0.696	0.729
WL+HGB+ALB	238	66	0.706	0.727
PS+WL+HGB+ALB	235	66	0.705	0.723

[a]None of the differences in CI between step 1 and step 2 were significant
WL: weight loss, PS: performance status, HGB: hemoglobin, ALB: albumin, CCI: corrected concordance index, event: death of disease

3-year survivors (Table 2). The added feature of the nomogram will be useful for patient counseling, as it is now possible to give a patient an accurate estimation of the improved survival probability as time after surgery goes by, and for the timing of surveillance, clinical assessments, and diagnostic tests. For example, patients for whom the CPS after a certain period is nearly a 100% might consider to reduce the follow-up frequency, while patients with a relatively low CPS might have more frequent follow-up visits.

The CPS for an individual patient can be calculated manually with Figure 2, simply by entering the values and reading from the correct DSS axis in the bottom of the figure. CPS can also be calculated with Figure 3b, using the 0-year survival prediction from Figure 2. For example, a patient's 5-year DSS probability derived from the 0-year survival axis in Figure 2 is 0.4. By entering the 5-year DSS probability of 0.4 on the x-axis of Figure 3b, the probability of 5-year DSS conditional on the fact that the patient survives one, two or three years after surgery can be derived from the y-axis and is 0.47, 0.58 and 0.73 respectively. The new nomogram can also be accessed on the internet,[22] and can calculate CPS by entering patient variables and the time of follow-up.

Extending static nomograms to provide conditional survival estimates has been previously illustrated for both prostate cancer and renal cell carcinoma.[23,24] Both studies use variables available directly after surgery. Unique to the approach of the current study

is the use of variables available with follow-up, as it can be assumed that there are clinical markers representing the current status of the patient that ultimately become more important than baseline characteristics and surgical variables.
The third aim of the present study was to explore whether the introduction of clinical variables available at follow-up could improve the accuracy of the 5-year DSS nomogram. This objective was based on the assumption that as time goes by after diagnosis, clinical factors other than surgical and pathological variables available only at the time of surgery may become important in predicting survival in gastric cancer. This approach is entirely novel in the development of nomograms. Introduction of new variables for the nomogram, however, did not improve the CI, as can be seen in Table 3: for most 'cohorts' with a certain newly added variable available, the CI for the nomogram with original variables was essentially equal to the CI of the nomogram with follow-up variables. This might be explained by the limited availability of follow-up variables (weight loss, PS, HGB, ALB), which has led to a relatively low number of one-year survivors that could be included in these analyses. Clinical data on two- and three-year disease-free survivors was even more limited and no analyses on these patients could be performed. Secondly, with the very high CI of the nomogram based on baseline variables, newly added follow-up variables would need to be very strongly predictive in order to improve the CI, which might not be the case with the currently used new variables. In order to reassess this question in a more thorough way, follow-up data should be prospectively collected at fixed time points. The absence of an improvement in CI with the introduction of multimodality therapy use in the nomogram does not necessarily indicate that chemotherapy and/or radiotherapy did not affect survival in the current population. Rather, the predictive accuracy of the current nomogram can be considered very high by means of concordance, and despite a proven effect on survival, multimodality therapy use was simply unable to further improve this concordance.

In conclusion, decisions about postoperative adjuvant therapy, and intensity of follow-up are based on our best risk assessments at the time of surgery. However, follow-up is a dynamic process, with the risk of cancer-related death decreasing over time. The current nomogram has the ability to estimate risk of cancer-related death at time points after initial treatment, and offers useful insight to the patient and clinician about what to expect in the years ahead.

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PART I

Staging and prognostication

CHAPTER 5

Performance of a nomogram predicting disease-specific survival after an Ro resection for gastric cancer in patients receiving postoperative chemoradiotherapy

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ABSTRACT

BACKGROUND

The internationally validated Memorial Sloan-Kettering Cancer Center (MSKCC) gastric cancer nomogram was based on patients who underwent curative (R0) gastrectomy, without any other therapy. The purpose of the current study was to assess the performance of this gastric cancer nomogram in patients who received chemoradiotherapy after an R0 resection for gastric cancer.

PATIENTS AND METHODS

In a combined dataset of 76 patients from the Netherlands Cancer Institute (NKI), and 63 patients from MSKCC, who received postoperative chemoradiotherapy (CRT) after an R0 gastrectomy, the nomogram was validated by means of concordance index and a calibration plot.

RESULTS

The concordance index for the nomogram was 0.64, which was lower than the CI of the nomogram for patients who received no adjuvant therapy (0.80). In the calibration plot, observed survival was about 20% higher than the nomogram predicted survival for patients receiving postoperative CRT.

CONCLUSIONS

The nomogram significantly underpredicted survival for patients in the current study, suggesting an impact of postoperative CRT on survival in patients who underwent an R0 resection for gastric cancer, which has been proved by randomized controlled trials. This analysis stresses the need for updating nomograms with the incorporation of (neo) adjuvant strategies.

INTRODUCTION

Until the late nineties, surgery was considered the only treatment option for resectable gastric cancer.[1] While complete resection remains the only potentially curative treatment, several recent studies have demonstrated that combining surgery with other modalities can improve outcome. The British MAGIC trial showed improved overall survival after perioperative chemotherapy for resectable, advanced gastric and distal esophageal cancer.[2] A Japanese randomized study found improved overall survival after postoperative administration of S-1 (an oral fluoropyrimidine).[3] The US Intergroup 0116 study demonstrated that postoperative chemoradiotherapy (CRT) improves overall survival among patients who have undergone an R0 resection for advanced gastric cancer.[4] As a result of the Intergroup 0116 trial, postoperative CRT is now considered a standard treatment option for patients receiving surgery without preoperative chemotherapy for locally advanced gastric cancer.[5,6]

The identification of patients who should undergo postoperative treatment can be done by postoperative AJCC tumor stage, but also with the use of nomograms. Nomograms are prediction tools that calculate survival probability for individual patients based on patient, tumor and treatment characteristics. These statistically based tools not only use the factors included in a clinical staging system but also incorporate additional factors suspected to have an effect on outcome. The internationally validated MSKCC gastric cancer nomogram predicts disease-specific survival (DSS) after an R0 resection for gastric cancer (Figure 1).[7] Patients included to develop the nomogram underwent surgery only, and did not receive any other therapy. Therefore, the nomogram can be used to identify high-risk patients who underwent surgery only and might be candidates for postoperative therapy. However, it is unknown how well the nomogram will predict survival for patients who underwent surgery followed by postoperative chemoradiotherapy. Based on the survival benefit for postoperative chemoradiotherapy that was shown in the Intergroup 0116 study, it is suspected that the nomogram will underpredict survival for patients receiving postoperative chemoradiotherapy. Therefore, the purpose of the current study was to assess the performance of the gastric cancer nomogram in patients who received postoperative chemoradiotherapy after an R0 resection for gastric cancer.

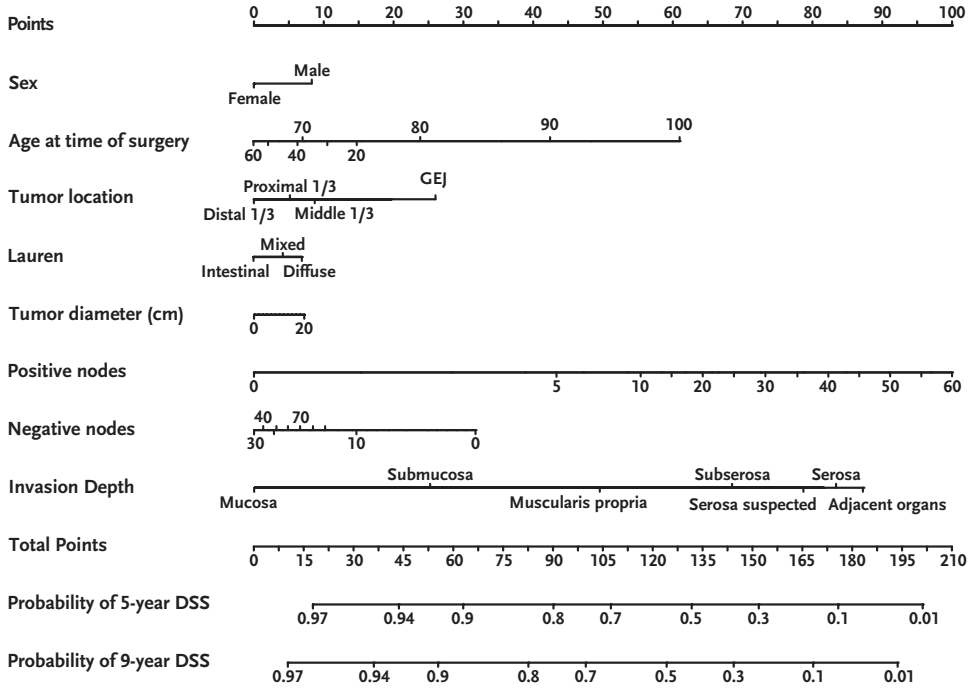
PATIENTS AND METHODS

A combined dataset with patients treated at the Netherlands Cancer Institute and patients treated at Memorial Sloan-Kettering Cancer Center was used for this analysis.

NETHERLANDS CANCER INSTITUTE PHASE I/II STUDIES

From 2000 to 2008, 113 patients with locally advanced adenocarcinoma of the stomach or gastroesophageal junction, stage Ib-IV according to the 6th edition of the American Joint Committee on Cancer (AJCC),[8] underwent gastric resection followed by CRT at the Netherlands Cancer Institute. No patients received preoperative therapy. Patients who

Figure 1. Previously published nomogram predicting disease-specific survival (DSS) after an R0 resection for gastric cancer



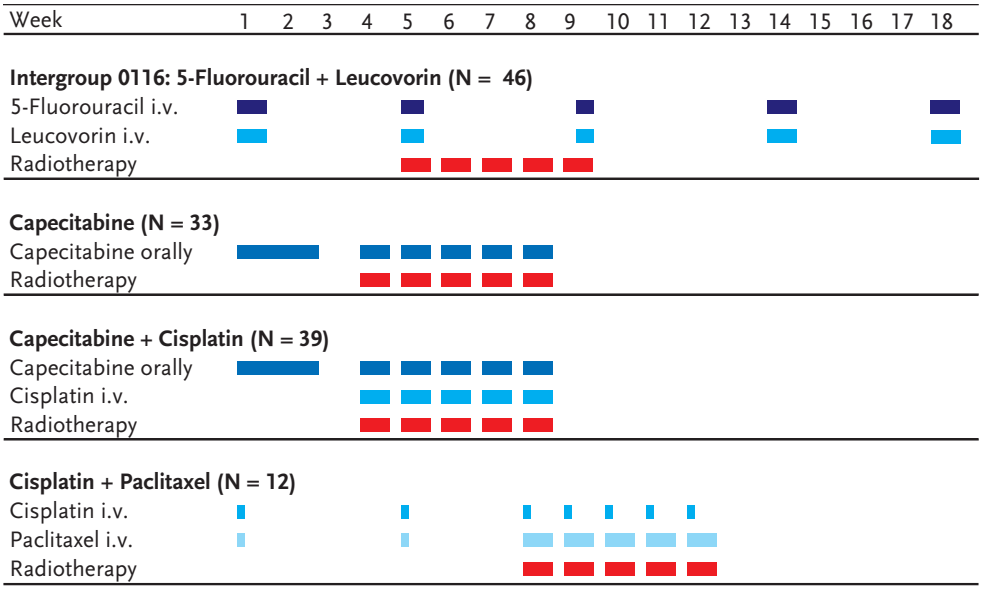
Instructions
Locate the patient's sex on the **Sex** axis. Draw a line straight upwards to the **Points** axis to determine how many points towards gastric cancer-specific death the patient receives for his or her sex. Repeat this process for the other axes, each time drawing straight upward to the **Points** axis. Sum the points achieved for each predictor and locate this sum on the **Total points** axis. Draw a line straight down to the **disease-specific survival** axes to find the patient's probability of surviving gastric cancer assuming he or she does not die of another cause first.

did not undergo an R0 resection (N = 29), and patients for whom not all the nomogram variables were available (N = 8) were excluded, leaving 76 patients for analysis.

All patients underwent R0 gastrectomy with at least a D1 lymph node dissection, without routine splenectomy or pancreatic tail resection. After satisfactory recovery from surgery, patients were offered participation in one of the phase I-II trials of postoperative chemoradiotherapy.

Patients were treated with 25 fractions of 1.8 Gy of radiotherapy to a total dose of 45 Gy (5 fractions/week). The clinical target volume consisted of the gastric bed (with stomach remnant, when present), anastomoses, and draining lymph nodes. Radiotherapy was combined with escalating doses of capecitabine and cisplatin (N = 39),[9] capecitabine (N = 33),[10] or with fluorouracil (5-FU) and leucovorin, according to the Intergroup 0116 scheme (N = 4) (Figure 2). The design of these studies is described in more detail in the original publications.[9,10]

Figure 2. Chemoradiotherapy regimens



Radiotherapy was administered in 5 fractions/week
i.v.: intravenous

MEMORIAL SLOAN-KETTERING CANCER CENTER

Patients treated at Memorial Sloan-Kettering Cancer Center (MSKCC) were selected from a prospectively maintained database containing information on 2590 patients who underwent a resection for an adenocarcinoma of the stomach between 1985 and 2009. Of these 2590 patients, 72 patients received postoperative chemoradiotherapy between 2000 and 2009. Patients who received preoperative chemotherapy (N = 8) and patients who did not undergo an R0 resection (N = 2) were excluded, leaving 63 patients for analysis.

All patients underwent a gastrectomy, usually with D2 lymphadenectomy, without routine splenectomy or pancreatic tail resection. Postoperatively, all patients received 45 Gy of radiotherapy on the gastric bed (with stomach remnant, when present), anastomoses, and draining lymph nodes in 25 fractions of 1.8 Gy.

Radiotherapy was combined with one of several chemotherapy regimens. The majority of patients (N = 43) received 5-FU with leucovorin according to the Intergroup 0116 protocol (Figure 2). The other patients received cisplatin combined with paclitaxel (N = 10), cisplatin, paclitaxel and 5-FU (N = 2), epirubicin, cisplatin and 5-FU (N = 4) single-agent 5-FU (N = 2), or single-agent capecitabine (N = 2). This study was approved by the Institutional Review Board of MSKCC.

Table 1. Patient characteristics (N = 139)

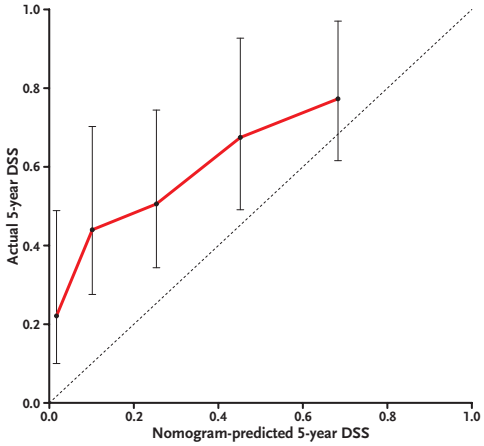
	Total (N = 139)		NKI (N = 76)		MSKCC (N = 63)	
	N	%	N	%	N	%
Sex						
male	96	*69.1*	56	*73.7*	40	*63.5*
female	43	*30.9*	20	*26.3*	23	*36.5*
Age						
median (IQR)	61	(51-68)	57	(49-65)	65	(52-72)
Primary site						
GEJ	16	*11.5*	9	*11.8*	7	*11.1*
proximal	17	*12.2*	9	*11.8*	8	*12.7*
middle	47	*33.8*	26	*34.2*	21	*33.3*
distal	59	*42.5*	32	*42.1*	27	*42.9*
Lauren classification						
intestinal	56	*40.3*	28	*36.8*	28	*44.4*
diffuse	54	*38.9*	31	*40.8*	23	*36.5*
mixed	29	*20.9*	17	*22.4*	12	*19.0*
Invasion depth						
mucosa	1	*0.7*	1	*1.3*	0	*0*
submucosa	7	*5.0*	0	*0*	7	*11.1*
muscularis propria	13	*9.4*	6	*7.9*	7	*11.1*
subserosa	34	*24.5*	24	*31.6*	10	*15.9*
serosa suspected	21	*15.1*	21	*27.6*	0	*0*
serosa	58	*41.7*	21	*27.6*	37	*58.7*
adjacent organs	5	*3.6*	3	*3.9*	2	*3.2*
Tumor size						
median (IQR)	5	(2.9-6.5)	5.0	(3.5-6.8)	4.5	(2.8-6.5)
Positive lymph nodes						
median (IQR)	4	(2-10)	4	(3-11)	5	(2-9)
Negative lymph nodes						
median (IQR)	11	(4-20)	4	(2-11)	17	(13-26)
AJCC 7th edition stage group						
IA	0	*0*	0	*0*	0	*0*
IB	3	*2.2*	1	*1.3*	2	*3.2*
IIA	7	*5.0*	1	*1.3*	6	*9.5*
IIB	20	*14.4*	10	*13.2*	10	*15.9*
IIIA	39	*28.1*	25	*32.9*	14	*22.2*
IIIB	33	*23.7*	20	*26.3*	13	*20.6*
IIIC	37	*26.6*	19	*25.0*	18	*28.6*

STATISTICAL ANALYSIS

Disease-specific survival (DSS) was calculated from the day of surgery until death of gastric cancer (event) or death of other causes, or alive at last follow-up (censored). The Cox proportional hazards model was used to compare DSS between NKI and MSKCC patients adjusted for factors present in the nomogram.

In agreement with our previous report, the following prognostic variables were used for the nomogram: age, gender, primary site (distal one-third, middle one-third, proximal one-third, and gastroesophageal junction), Lauren histologic type (diffuse, intestinal, mixed), number of positive lymph nodes resected, number of negative lymph nodes resected, and invasion depth. For each of the patients, the nomogram 5-year DSS probability was computed.

Figure 3. Calibration plot of the nomogram validated in patients who received postoperative chemoradiotherapy (N = 139)



Nomogram validation comprised two activities. First, discrimination was quantified with the concordance index (CI).[11] The concordance index is similar to the area under the receiver operating characteristic curve, but appropriate for censored data, and ranges from 0.5 (no discrimination) to 1.0 (perfect discrimination). Given a randomly selected pair of patients, the concordance index is the probability that the patient who dies first had the worst predicted outcome by the nomogram. Secondly, calibration was assessed. This was done by grouping patients with respect to their nomogram predicted probabilities and then comparing the mean of the group with the observed Kaplan-Meier estimate of DSS. All analyses were performed using R statistical software package (version 2.11.0).

RESULTS

Table 1 depicts patient characteristics of the 139 patients that were included in the current study. Most patients (69.1%) were male. The median age in the NKI group (57 years) was lower as compared to the median age in MSKCC patients (65 years). In both groups, the majority of patients had a tumor in the middle (33.8%) or distal stomach (42.5%). As suspected, most patients (78.4%) had pathology stage III gastric cancer; this proportion being slightly higher for the NKI group (84.2%) than for the MSKCC group (71.4%).
With a median follow-up of 51 months, 62 patients (44.6%) had died of disease. Median survival was almost 6 years (71 months). On multivariate Cox regression, adjusting for the prediction based on all variables present in the nomogram, no significant difference in DSS was detected between NKI and MSKCC patients (HR 0.996, $P = 0.989$), indicating the feasibility of combining both datasets to assess the performance of the nomogram.
The nomogram performance in the current patient cohort was tested in two ways. First, discrimination between individual patients was assessed with the concordance index (CI). The CI for the nomogram was 0.64, which can be considered moderately predictive.

However, this is lower than the CI for patients who received no adjuvant therapy, which was 0.80.[7] Secondly, the observed and the predicted survival were compared with a calibration plot (Figure 3), which showed that the nomogram significantly underpredicted the 5-year DSS probability in the current patient cohort with about 20%.

DISCUSSION

In the current study, the performance of the existing gastric cancer nomogram was evaluated for patients who received postoperative chemoradiotherapy after an R0 resection for gastric cancer. In the current patient cohort, discriminative ability, which was tested by means of the CI, was lower than the CI for patients who received no adjuvant therapy.[7] As expected based on results from the Intergroup 0116 study, the nomogram significantly underpredicted 5-year DSS in the current patient cohort, indicating the need for updating nomograms with the incorporation of (neo)adjuvant strategies.

Postoperative CRT has proven to improve outcomes for patients with resectable gastric cancer in several early randomized trials in the eighties and nineties.[12-15] However, patient numbers in these studies were small (below 200), limiting the value of this observation. The key trial supporting the use of postoperative CRT in advanced, resectable gastric cancer is the Intergroup 0116 trial.[4] In this study, 556 patients were randomized after surgery for postoperative CRT with 5-FU and leucovorin, or no further treatment. The 5-year overall survival rate was significantly higher in patients receiving chemoradiotherapy (40% vs 28%), which was confirmed in a recent update with follow-up of over 10 years.[16] This trial was criticized because of the low number of D2 dissections (10%), the fact that patients were highly selected (only R0 resections with adequate postoperative recovery), the treatment compliance of 64%, and the complexity of the chemoradiotherapy protocol. Despite this critique, since publication of the Intergroup 0116 results in 2001, postoperative CRT has become a standard treatment option in both Europe and the United States for patients undergoing curative resection of stage Ib-IV gastric cancer who did not receive neoadjuvant therapy.[5,6] This might also be caused by the high number of patients who first receive surgery, after which their postoperative treatment plan is discussed in a multidisciplinary team. A SEER database analysis showed that postoperative radiotherapy use in the United States increased from 6.5% to 13.3% before and after 2000, likely reflecting an increased use of postoperative CRT.[17]

During the past years, the concept of concurrent postoperative CRT has further evolved, with newer, potentially less toxic CRT schedules that have been tested in several studies. A study from Germany in which patients were treated with 45 Gy of radiotherapy plus folinic acid, 5-FU, paclitaxel and cisplatin, showed that this four-drug regimen has an acceptable toxicity profile.[18] In a US Phase II study, a combination of cisplatin, paclitaxel, and radiotherapy showed an acceptable toxicity profile, but failed show a favourable disease-free survival rate.[19] Several phase I/II studies from the Netherlands combining capecitabine with or without cisplatin with radiotherapy revealed feasibility of these

regimens.[9,10,20] A regimen with daily capecitabine and weekly cisplatin that emerged from these studies is currently tested in a phase III randomized trial (CRITICS, clinicaltrials.gov NCT00407186).

Other new regimens that have been tested include irinotecan,[21] docetaxel,[22] and liposomal cisplatin.[23] A US Intergroup trial comparing the Intergroup 0116 regimen with postoperative CRT with epiribicin, cisplatin, and 5-FU (ECF) showed that the ECF regimen has an acceptable toxicity profile, without an improvement in survival compared to 5-FU and leucovorin.[24] In the Korean ARTIST trial, 458 patients were randomized after gastrectomy with a D2 lymphadenectomy for postoperative chemotherapy with cisplatin and capecitabine with or without 45 Gy radiotherapy. Compliance for the postoperative schedule in both arms was high (75% and 82%), but no difference in disease free survival was shown.[25]

The currently available gastric cancer nomogram can be used to estimate 5-year and 9-year DSS after an R0 resection for gastric cancer.[7] The nomogram shows a high predictive accuracy with internal validation, and with external validation in several European datasets.[26-28] This nomogram has two distinct purposes: risk stratification and informing patients. With risk stratification, the survival probability of an individual patient that is predicted by the nomogram can be used to determine if a patient is at high risk of recurrence, and should consider postoperative therapy. Secondly, patients can be informed on their risk of DSS. Because none of the patients from the datasets in which the nomogram was developed received any form of preoperative or postoperative chemotherapy or radiation, the nomogram can very well be used to stratify patients who underwent surgery into a high-risk and a low-risk category. This risk stratification gives a recommendation about postoperative therapy use. As it is expected that postoperative chemoradiotherapy will improve survival, it can be hypothesized that the nomogram will underpredict survival in patients receiving postoperative chemoradiotherapy.

In the current study, the performance of the gastric cancer nomogram was assessed in a cohort of 139 patients who received postoperative CRT after an R0 resection for gastric cancer, without receiving preoperative therapy. Different CRT schedules were used reflecting the ongoing search for better and less toxic CRT regimens over the years. Most patients in the current study had stage III disease based on postoperative pathology, which is expected since these patients are candidates for adjuvant therapy. Neither of the populations (NKI or MSKCC) was significantly associated with better survival after correcting for variables present in the nomogram.

The number of events in this dataset was too small to create a new nomogram specifically for patients who received postoperative CRT. However, the number of events was sufficient to assess the performance of the existing nomogram in this dataset. The concordance index, which indicates discriminative ability, was moderately high in this population. The calibration plot at 5-years, however, showed significant underprediction of the nomogram in this patient cohort of about 20%. Since postoperative CRT has

shown to improve survival compared to surgery alone in a randomized setting, and the nomogram is based on surgery only patients, this was an expected finding. Therefore, the nomogram provided DSS probability should not directly be used in patients who received postoperative CRT. Since it is unlikely that a large group of patients who received chemoradiation and who are sufficiently followed can be assembled to construct a separate nomogram, we recommend that, as a rule of thumb, approximately 20% should be added to the nomogram-predicted 5-year DSS probability.

In conclusion, while the gastric cancer nomogram accurately risk-stratifies patients who received an R0 resection alone for gastric cancer, it significantly underpredicts 5-year DSS for patients who receive postoperative CRT after an R0 resection for gastric cancer.

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PART II

Multimodality treatment

CHAPTER 6

Treatment of resectable gastric cancer

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ABSTRACT

Stomach cancer is one of the most common cancers worldwide, despite its declining overall incidence. Although there are differences in incidence, etiology and pathological factors, most studies do not separately analyze cardia and non-cardia gastric cancer. Surgery is the only potentially curative treatment for advanced, resectable gastric cancer, but the locoregional relapse rate is high with a consequently poor prognosis. To improve survival, several preoperative and postoperative treatment strategies have been investigated. Whereas perioperative chemotherapy and postoperative chemoradiation are considered standard therapy in the Western world, in Asia postoperative monochemotherapy with S-1 is often used. Several other therapeutic options, though generally not accepted as standard treatment are postoperative combination chemotherapy, hyperthermic intraperitoneal chemotherapy and preoperative radiotherapy and chemoradiotherapy. Postoperative combination chemotherapy does show a statistically significant but clinically equivocal survival advantage in several meta-analyses. Hyperthermic intraperitoneal chemotherapy is mainly performed in Asia and is associated with a higher postoperative complication rate. Based on the currently available data, the use of postoperative radiotherapy alone and the use of intraoperative radiotherapy should not be advised in the treatment of resectable gastric cancer. Western randomized trials on gastric cancer are often hampered by slow or incomplete accrual. Reduction of toxicity for preoperative and especially postoperative treatment is essential for the ongoing improvement of gastric cancer care.

INTRODUCTION

EPIDEMIOLOGY

Gastric cancer is a major problem worldwide: it is the second leading cause of cancer death, affecting approximately one million new individuals per year.[1] Whereas the incidence in males is twice as high as in females, there is also a marked geographic variation. Highest incidence rates occur in north-east Asia (up to 70 per 100,000), Eastern Europe and much of the east part of South-America, while lowest incidence rates are seen in North America (8 per 100,000), Africa and South and West Asia.[2] Stomach cancers can anatomically be classified as non-cardia (fundus, corpus and antrum) and cardia cancers, with non-cardia cancers constituting the majority of all gastric cancers worldwide. Whereas the incidence of non-cardia gastric cancer has declined over the past decades,[3,4] there has been a rapid increase in the incidence of cardia gastric cancer until the early nineties, which has not persisted in the current century.[5-7]

CARCINOGENESIS

Two distinct histologic types of gastric cancer have been defined by Lauren: an intestinal type, which is characterized by irregular tubular structures in areas of mucosal inflammation, and a diffuse type, which can be characterized by discohesive cells and pools of mucus.[8] Gastric carcinogenesis of the intestinal type is thought to be a multifactorial process involving irritation of the mucosa by environmental factors, acid secretion and bacterial nitrite and N-nitroso compounds production from dietary nitrates. The intestinal type gastric cancer is mostly found in the distal stomach and typically arises through the Correa's cascade, progressing from the successive steps of normal gastric epithelium infected by *Helicobacter pylori*, leading to acute and chronic gastritis, atrophic gastritis, intestinal metaplasia, dysplasia and finally gastric carcinoma.[9,10] Very little is known about the development of diffuse gastric cancer, although in the autosomal dominantly inherited syndrome of hereditary diffuse gastric cancer (HDGC), loss of polarity of gastric stem or progenitor cells has been suggested to lead to the formation of foci of signet ring cells that invade the lamina propria.[11,12]

ETIOLOGY

Childhood environment is an important factor in the risk of developing gastric cancer.[13,14] Environmental risk factors for non-cardia gastric cancer include *Helicobacter pylori* infection,[15-17] high intake of salt and salt-preserved foods,[18,19] low intake of vegetables and fruits,[20] tobacco smoking,[21,22] and achlorhydria.[23] Gastric atrophy has been positively associated with non-cardia gastric cancer.[17,24] For cardia cancer, described risk factors are male sex, white race,[25] smoking and obesity,[26,27] and gastro-esophageal reflux disease.[24]
Of all cancers of the stomach about 10% arise in individuals with a family history of gastric cancer.[28] HDGC develops in subjects with a germline mutation in one allele of the E-cadherin gene (CDH1).[29] During a recent consensus meeting of the International

Gastric Cancer Linkage Consortium, updated results on carriers of 58 families with a CDH1 mutation showed a more than 80% life-time risk of developing diffuse gastric cancer.[30] Familial preponderance has been described in other familial cancer syndromes, like Lynch syndrome,[31] Li-Fraumeni syndrome,[32] and Peutz-Jeghers syndrome.[33,34] In these families the intestinal type of gastric cancer prevails.

STAGING

In the Western world, staging is performed according to the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC).[35] The Japanese Gastric Cancer Association has its own staging system of gastric carcinoma.[36] Until recently, the Japanese staging of nodal status (N) was based on location of the positive nodes. Nowadays both Japanese and Western systems are based on the number of positive lymph nodes, which seems to be more reproducible, provided that a minimum number of 15 lymph nodes are removed and analyzed.[37]

Tumors of the gastro-esophageal junction (GEJ) are often misclassified as either gastric when they should be esophageal, or vice-versa. In 2000, Siewert et al. proposed a classification based on anatomic location: type I (adenocarcinoma of the distal esophagus), type II (cardia carcinoma, arising from the GEJ), and type III: (subcardial gastric carcinoma infiltrating the GEJ and esophagus from below, Figure 1, page 18).[38] In the latest, 7th edition of the TNM classification, tumors of the GEJ are all classified as esophageal cancer based on the worse prognosis of cardia and GEJ tumors as compared to mid and distal gastric tumors.[39] Differences in stage grouping between the 6th and 7th edition of the AJCC staging system for gastric cancer are shown in Table 1.[40,41]

SURVIVAL

As more than half of the patients in the Western world present with stage III or IV gastric cancer, overall prognosis is poor.[42] A recent survey shows that 5-year survival in all gastric cancer patients in Europe is only 24.1%.[43] Survival for all patients in the US is comparable: in the period 1999-2005, survival was 26.5%. For patients with metastatic disease at initial presentation, 5-year survival is <5%.[44] In patients treated with surgery in the US in the period 1985-1996, stage specific 5-year survival was 58% for stage IB, 34% for stage II, 20% for stage IIIA and 8% for stage IIIB.[42] In contrast, Japan has 5-year survival rates of approximately 60%.[1] This difference has been addressed to mass screening programs using photofluorography,[45] differences in tumor biology and location with more intestinal subtypes and distal locations, and stage migration due to higher lymph node yield in Japanese series.[46] In a comparative analysis between a US and a Korean center, multivariate analysis applying different patient and tumor characteristics and the number of resected lymph nodes shows a higher disease-specific survival for Korean patients as compared to US patients (HR 1.3, $P = 0.008$), suggesting the possibility of an intrinsic biologic difference between gastric cancer in the US and Korea.[47]

Table 1. Stage grouping for gastric cancer according to the 6th (2002) and 7th (2010) edition of the AJCC staging system[40,41]

6th edition AJCC staging system				7th edition AJCC staging system			
Stage	**T**	**N**	**M**	**Stage**	**T**	**N**	**M**
0	**Tis**	**N0**	**M0**	**0**	**Tis**	**N0**	**M0**
IA	**T1**	**N0**	**M0**	**IA**	**T1**	**N0**	**M0**
IB	T1	N1	M0	IB	T1	N1	M0
	T2	**N0**	**M0**		**T2**	**N0**	**M0**
II	T1	N2	M0	IIA	T1	N2	M0
	T2	N1	M0		T2	N1	M0
	T3	N0	M0		T3	N0	M0
				IIB	T1	N3	M0
					T2	N2	M0
					T3	N1	M0
					T4a	N0	M0
IIIA	T2	N2	M0	IIIA	T2	N3	M0
	T3	N1	M0		T3	N2	M0
	T4	N0	M0		T4a	N1	M0
IIIB	T3	N2	M0	IIIB	T3	N3	M0
					T4a	N2	M0
					T4b	N1	M0
					T4b	N0	M0
				IIIC	T4a	N3	M0
					T4b	N3	M0
					T4b	N2	M0
IV	T4	N1-3	M0	IV	**Any T**	**Any N**	**M1**
	T1-3	N3	M0				
	Any T	**Any N**	**M1**				

T: Tumor classification, N: Nodal status, M: Metastases status
Bold: No changes in TNM and stage groups

RECURRENCE PATTERNS

With increasing cancer stage, the risk of locoregional relapse increases, thus diminishing survival. In a combined analysis of several autopsies series, eventually 80-93% of all patients developed locoregional relapse.[48] A retrospective study on 367 patients with clinically complete recurrence data in a single center revealed that 54% of recurrences were locoregional, whereas distant sites were involved in 51%. Of all recurrences, 79% developed within the first two years.[49] In a single-center study performed during 1949-1971, reoperations as second-look procedures in 107 previously resected gastric cancer patients - both symptomatic and asymptomatic – revealed locoregional failure in 23% as the only site of relapse.[50] Data from a US randomized trial showed the highest relapse in locoregional sites, even after postoperative chemoradiation (CRT) had been administered.[51]

SURGICAL TREATMENT

Resection is a prerequisite for the curative treatment of localized gastric cancer. It can be divided into three major approaches: endoscopic (sub)mucosal resection or dissection (EMR or ESD), minimally invasive surgery and open gastrectomy. Endoscopic mucosal

resection is only used for the treatment of early gastric cancer (EGC), which is defined as a tumor of the stomach limited to the mucosa or submucosa regardless of lymph node metastases.[52] This topic will not be further covered in this review.

LAPAROSCOPIC SURGERY

Minimal invasive surgery for the treatment of gastric cancer is mainly performed in Korea and Japan, with the majority of patients treated for early and distal gastric cancer. But with increasing laparoscopic experience and improvement in instrumentation, more extensive procedures and treatment of more advanced gastric cancers is becoming more common. Although laparoscopic gastrectomy has been performed since 1991, only four, mostly single-center, randomized controlled trials comparing the technique with open gastrectomy have been reported.[53-57] Laparoscopic gastrectomy has been discussed in two reviews which indicate oncologic equivalency and safety based on the current small patient numbers.[58,59] Large multicenter randomized controlled trials are necessary to establish the role of laparoscopy in the treatment of gastric cancer.

EXTENT OF GASTRIC RESECTION AND MARGINS

Total gastrectomy is the indicated treatment for tumors located in the proximal or middle third of the stomach.[60] As compared to a total gastrectomy, a proximal gastrectomy for proximal gastric cancer is associated with a markedly higher rate of complications such as anastomotic stenosis and weight loss.[61] For distal gastric cancer, a distal gastrectomy is the recommended therapy provided that an adequate margin can be obtained. Two randomized trials investigated the impact of total versus distal gastrectomy for distal gastric cancer, and showed no difference in postoperative morbidity, mortality, or overall survival with more extensive resection.[62,63]

Microscopically positive resection margins (R1) are associated with a significantly worse prognosis as compared to a microscopically radical (R0) resection, especially in patients with early stage disease.[64,65] An Italian study investigated the minimal margin that should be obtained to ensure radical surgery in T3-4 tumors, and suggested a minimum margin of 6 cm.[66] Dutch data show that survival in patients with an R1 resection is comparable with patients with positive cytology after abdominal washing,[67] indicating that frozen-section examination is mandatory for potentially curative resections of gastric cancer.

LYMPH NODE DISSECTION

As the primary tumor penetrates more deeply through the wall of the stomach, the risk of lymph-node metastases increases. The Japanese Classification of Gastric Carcinoma[36] defined 16 different lymph node stations surrounding the stomach (Figure 2, page 103), which are divided in three groups, each group further away from the primary tumor site. In a D1 dissection, the stomach (total or distal) plus the perigastric lymph nodes are removed. For a D2 dissection, additional removal of the nodes along the left gastric, the

common hepatic, the splenic and the left hepatoduodenal artery is performed as well as some stations that are different for proximal, middle and distal tumors. With a D3 dissection, an even more extended lymphadenectomy is performed, including paraaortic and posterior hepatoduodenal nodes. For adequate staging a minimum of 15 lymph nodes should be evaluated.[37]

Three prospective randomized trials have been performed that compared D1 with D2 lymph node dissection.[68-70] In an early trial, 43 patients were randomized between a D1 or D2 dissection, and with a median follow-up of 3.1 years no differences in survival were detected.[68] A British trial that randomized 400 patients for D1 or D2 dissection showed equal 5-year survival rates (35% versus 33%), but increased postoperative mortality and morbidity in the D2 group (13% versus 7% and 46% versus 28%).[69,71] In the Dutch Gastric Cancer Group Trial (DGCT), 711 patients underwent a D1 or D2 gastrectomy. Initial results showed an increased morbidity (25% versus 43%) and mortality (4% versus 10%) in the D2 group, which could be partially attributed to the higher number of splenectomies and pancreatectomies in this group,[72] while there was no significant difference in 11-year survival rates (30% versus 35%).[70] However, a recent update revealed that gastric cancer-related death rate after a median follow-up of 15.2 years was significantly higher in the D1 group (48%) compared with the D2 group (37%),[73] indicating that a D2 dissection is the recommended type of surgery in Western countries, especially when postoperative mortality can be avoided.

In Japan, a D2 lymph node dissection is seen as standard treatment for curative resections.[74] Convinced of the benefits of extended lymph node dissection, Japanese surgeons consider it generally unethical towards patients to run a randomized trial including an arm with a D1 lymph node dissection. A Japanese trial randomizing 523 patients for D2 alone or D2 combined with paraaortic node dissection showed no significant difference in 5-year survival while there was a trend towards more surgery-related complications in the paraaortic group (28% versus 21%).[75,76] In a Taiwanese study with 221 patients, for the first time the benefit of a D3 over a D1 lymph node dissection was detected: 5 year overall survival was significantly higher in the D3 group (60% versus 54%).[77]

In conclusion, in Western countries there has been an extensive debate on the role of a D2 lymph node dissection, which can now be considered the recommended type of surgery for advanced gastric cancer, with removal of at least 15 lymph nodes for adequate staging. In Asian countries at least a D2 dissection is performed.

ACCEPTED ADJUVANT AND NEOADJUVANT THERAPIES

Because adequate locoregional or systemic control is difficult to obtain with resection alone, surgery can be combined with adjuvant or neoadjuvant treatment. A distinction between accepted and non-standard adjuvant and neoadjuvant therapies is provided in Table 2. Randomized studies on adjuvant and neoadjuvant treatment of gastric cancer are summarized in Table 3 (page 82-83).

Table 2. Currently available treatment strategies for advanced, resectable gastric cancer

	Therapy	Supporting data	Comments
Accepted therapy	postoperative chemotherapy	Sakuramoto[90]	S-1 only in Asia
	postoperative chemoradiotherapy	MacDonald[51], Kim[99]	
	perioperative chemotherapy	Cunningham[109], Boige[111]	low compliance for postoperative chemotherapy
Non-standard or encouraging therapy	preoperative chemotherapy	Hartgrink[112], Schuhmacher[113]	underpowered studies
	postoperative combination chemotherapy	Sun[89]	only positive in meta-analyses, absolute survival benefit ≤ 5%
	hyperthermic intraperitoneal chemotherapy	Yan[119]	small studies, high morbidity, mainly in Asia
	preoperative radiotherapy	Fiorica[101], Valentini[123]	
	preoperative chemoradiotherapy	Ajani[98,130,131]	only phase II studies
No role or inadequate data	postoperative radiotherapy	Valentini[123]	meta-analysis with limited number of studies, heterogeneous design
	intraoperative radiotherapy	Sindelar[124], Kramling[125], Skoropad[126]	underpowered studies

POSTOPERATIVE CHEMOTHERAPY

Adjuvant chemotherapy may eliminate occult residual locoregional or metastatic disease after surgery. More than 30 randomized trials have been performed evaluating adjuvant chemotherapy in gastric cancer over the past two decades. Although the earlier trials were small, during the last decade trials with up to 400 patients have been performed in Southern Europe. Most find a small survival benefit, which is mostly non-significant.[78-82] Different treatment regimens were tested, including 5-fluorouracil-based chemotherapy with or without anthracyclines, with or without mitomycin C, and platinum with etoposide. Most of these studies are included in several meta-analyses,[83-89] which all except for one[84] show a small, significant increase in survival for adjuvant chemotherapy of 3-5 percent point (Table 4). However, the benefit of this increase in daily clinical practice is modest.

Sakuramoto et al. were the first to show a significant benefit in overall survival for postoperative chemotherapy in a large, adequately powered trial performed in an Asian patient population. In this study 1059 patients with stage II/III gastric cancer were randomized following at least D2 and R0 resection between surgery alone or surgery plus S-1 (oral fluoropyrimidine) for 12 months. Compliance after 12 months of chemotherapy was 66%. After 3 years, overall survival (80% versus 70%) and relapse-free survival (72% versus 60%) were significantly higher in the chemotherapy group.[90] Experience with S-1 in Western populations is limited to a combination chemotherapy study in patients with advanced, untreated gastresophageal cancer.[91]

Overall, many early trials showed no or little advantage of postoperative chemotherapy. However, meta-analyses indicate a statistically significant but clinically equivocal survival benefit for adjuvant chemotherapy. Whereas Western trials focus on multi-drug

Table 4. Meta-analyses on adjuvant chemotherapy

	No. of trials	No. of patients	Mortality risk	95% CI	West/East
Hermans 1993[84]	11	2096	0.88 (OR)	0.72-1.08	both
Earle 1999[83]	13	1990	0.80 (OR)	0.66-0.97	West
Mari 2000[87]	20	3658	0.82 (RR)	0.75-0.89	both
Hu 2002[85]	14	4543	0.56 (OR)	0.40-0.79	both
Panzini 2002[88]	18	3118	0.72 (OR)	0.62-0.84	both
Janunger 2002[86]	21	3962	0.84 (OR)	0.74-0.96	both
Sun 2009[89]	12	3809	0.78 (OR)	0.71-0.85	both

95% CI: 95% confidence interval, OR: Odds ratio, RR: relative risk

regimens, in Japan S-1 is considered to be of superior value. Compliance for postoperative chemotherapy remains a problem: in most Western studies 4-6 month of combination chemotherapy gives compliance rates from 87% to 43%, with hematological and gastrointestinal toxicities as the main reasons for not completing the treatment schedule. None of the randomized trials distinguished between cardia or non-cardia cancer.

POSTOPERATIVE CHEMORADIOTHERAPY

Radiosensitizing drugs, such as 5-fluorouracil, have been added to radiotherapy with the intent to enhance the cytotoxic effect of radiotherapy on locoregional occult residual disease and to reduce locoregional relapse. Four early randomized trials showed the benefit of 5-fluorouracil-based CRT over surgery alone,[92-95] while another early study was negative.[96] However, patient numbers in these studies were small (N = 62-191), limiting the value of this observation.

The key trial supporting the role of adjuvant CRT was the US Intergroup 0116 trial,[51] in which 556 patients with stage Ib to IV gastric cancer who had received an R0 resection were randomized to no further treatment or postoperative CRT. Adjuvant treatment consisted of one cycle 5-fluorouracil, leucovorin and 45 Gy of radiation with 7 days of 5-fluorouracil administered in 5 weeks, followed by two more cycles of 5-fluorouracil plus leucovorin. Treatment compliance in the CRT group was 64%; 17% stopped treatment because of mostly haematologic and gastrointestinal side effects. Major reasons for premature discontinuation in the other patients were early disease progression or patient's request. Overall survival at 5 years was significantly higher in the CRT group (40% versus 28%), which was confirmed in a recent update with follow-up of over 10 years.[97] Because of this trial, postoperative CRT is currently a standard option in the United States for patients undergoing curative resection of stage Ib-IV gastric cancer who did not receive neoadjuvant therapy.[98] However, the study has been criticized for the complexity of the CRT protocol, the limited interaction between chemotherapy and radiotherapy, the lack of surgical quality control, and because patients were highly selected (only R0 resections with adequate postoperative recovery). Furthermore, CRT

Table 3. Randomized studies on preoperative and postoperative therapy for advanced, resectable gastric cancer

Trial	N	Stage	Location	Cardia	Intervention arm	Control arm	Treatment compliance	Median follow-up (years)	OS	RFS	Remarks
Postoperative chemotherapy											
Sakuramoto 2007[90]	1059	II-IIIB	stomach	1%[2]	surgery: R0, D2-D3 S-1 for 12 m	surgery: R0, D2-D3	66%	2.9	80% vs 70%[3y] *P* = 0.003	72% vs 60%[3y] *P* < 0.001	
Postoperative chemoradiotherapy											
Macdonald 2001[51]	556	Ib-IV	stomach	7%[3]	surgery: R0, D0-2 5-FU, leucovorin EBRT 45Gy in 5 wks	surgery: R0, D0-2	64%	5	40% vs 28%[5y] *P* = 0.005	31% vs 25%[5y] *P* < 0.001	54% D0 36% D1 10% D2
Kim 2005[99] (observational)	1000	Ib-IV	stomach	10%[3]	surgery: R0, D2 chemotherapy/radiotherapy: same as Macdonald 2001	surgery: R0, D2	75%	5.5	57% vs 51%[5y] *P* = 0.02	55% vs 48%[5y] *P* = 0.016	
Combined preoperative and postoperative treatment											
Cunningham 2006[109]	503	-	esophagus, GEJ, stomach	11.5%[3]	surgery: R0 66%, D2 40% preoperative and postoperative epirubicin, cisplatin, 5-FU	surgery: R0 69%, D1-2	42%	2	36% vs 23%[5y] *P* = 0.009		
Boige 2007[111]	224	-	esophagus, GEJ, stomach	GEJ 64%	surgery: R0 84% preoperative and postoperative cisplatin, 5-FU	surgery: R0 73%	48%	5.7	38% vs 24%[5y] *P* = 0.02	34% vs 19%[5y] *P* = 0.003	
Postoperative/intraoperative radiotherapy											
Halissey 1994[122]	436	II-III	stomach	-	surgery 1. mitomycin-C, doxyfluridine, 5-FU 2. EBRT 45Gy in 35 days + 1x5Gy boost	surgery	1. 42% 2. 66%	7	19% vs 12% vs 20%[5y] (NS)	-	
Sindelar 1993[124]	41	I-IV	stomach	-	surgery IORT 20Gy	stage I-II: surgery stage III-IV: surgery + EBRT 50Gy in 5-6 wk	-	7	25 m vs 21 m (NS)	12 m vs 16 m (NS)	
Krämling 1996[125]	115	-	-	-	surgery IORT 28Gy	SURG	-	2.5	27m vs 31 m (NS)	-	
Skoropad 2000[126]	78	-	GEJ, stomach	23%[3]	surgery: R0, D1 EBRT 20Gy + IORT 20Gy	SURG: R0, D1	100%	-	HR 1.03 (NS)	-	

Trial	N	Stage	Location	Cardia	Intervention arm	Control arm	Treatment compliance	Median follow-up (years)	OS	RFS	Remarks
Preoperative chemotherapy											
Hartgrink 2004[112]	59	I-IV	stomach	-	methrotrexate, 5-FU, leucovorin, doxorubicin surgery: R0 46%	surgery R0 59%	56%	6.9	21% vs 34%[5y] *P* = 0.17	-	closed early
Schuhmacher 2009[113]	144	T3-4	GEJ, stomach	53%	leucovorin, 5-FU, cisplatin surgery	surgery: R0 67%	63%	4.4	HR 0.84 *P* = 0.065	-	closed early
Biffi 2010[114]	69	Ib-IV	stomach	-	preoperative docetaxel, cisplatin, 5-FU surgery	surgery postoperative docetaxel, cisplatin, 5-FU	75% vs 34%	-	-	-	
Preoperative radiotherapy											
Zhang 1998[127]	370	I-IV	cardia	100%[2]	EBRT 40Gy in 4 wk surgery: R0 80%	surgery: R0 62%	-	10	30% vs 20%[5y] *P* = 0.009	-	
Skoropad 2002[128]	102	I-IV	stomach	29%[2]	EBRT 20Gy in 5d surgery: R0 89%	surgery: R0 80%	100%	-	39% vs 30%[5y] (NS)	-	
Shchepotin 1994[129]	293	T2-4 N any	stomach	-	1. EBRT 20Gy in 4d 2. EBRT 20Gy in 4d + hyperthermia surgery	surgery	-	-	45% (1) vs 30% (3) 51% (2) vs 30% (3)[5y]	-	
Preoperative chemoradiotherapy No phase III trials											

Specification of cardia cancer: [2]stomach divided into 2 parts (upper/lower), [3]stomach divided into 3 parts (upper/middle/lower)
[3y]: 3-year survival, [5y]: 5-year survival, GEJ: gastro esophageal junction, EBRT: external beam radiotherapy, IORT: intraoperative radiotherapy, OS: overall survival (intervention vs control), RFS: relapse-free survival (intervention vs control), wk: weeks, y: years, m: months, NS: non-significant

might have compensated for the low number of extended lymph node dissections, with only 10% of the patients undergoing a D2 dissection and 54% receiving a D0 dissection. At the same time, an observational study from South Korea compared 446 patients who underwent D2 gastrectomy with 544 patients who underwent D2 gastrectomy followed by CRT per the Intergroup 0116 protocol.[99] After a median follow-up of 66 months, there was a significant benefit in survival in the CRT group (57% versus 51%), indicating the potentially beneficial role of postoperative CRT also after extended lymphadenectomy. A Dutch observational study comparing 694 patients who underwent D1 or D2 surgery with 91 patients who underwent postoperative fluoropyrimidine-based CRT showed improved local control in the CRT group after a D1 dissection, but not following a D2 dissection.[100] After an R1 resection, postoperative CRT was significantly associated with better survival.

In a meta-analysis of postoperative CRT, 5-year overall survival is significantly higher with CRT as compared to surgery alone (OR 0.45, 95% CI 0.32-0.64). Despite a higher frequency of severe and life-threatening toxicities in the CRT group, overall compliance for the CRT was 73%. The majority of patients in this analysis are nonetheless derived from the Intergroup trial.[101]

Several phase I/II studies on CRT with new types of chemotherapy have been performed to improve the interaction between chemotherapy and radiotherapy. A study from Germany in which patients were treated with 45 Gy of radiotherapy plus folinic acid, 5-fluorouracil, paclitaxel and cisplatin, showed that this four-drug regimen had an acceptable toxicity profile.[102] Three studies from the Netherlands demonstrated the feasibility of radiotherapy combined with daily capecitabine and cisplatin.[103-105] Radiotherapy fields contained the gastric bed and the anastomosis, with lymph node regions depending on the location of the primary tumor. A side-study on renal toxicity in 44 patients from these studies showed that there is a progressive relative functional impairment of the left kidney after postoperative CRT for gastric cancer, emphasizing that radiotherapy doses to the kidney should be minimized by using newer techniques such as intensity modulated radiotherapy (IMRT) in order to reduce toxicity while gaining the full benefit of survival of postoperative CRT.[106]

In conclusion, postoperative CRT shows an advantage in survival over surgery alone, but the question remains whether this effect persists after an extended lymphadenectomy and radical resection. New treatment regimens on CRT opting for equal or better efficacy and reduced toxicity are currently under investigation.

PERI-OPERATIVE CHEMOTHERAPY

The most important limitation of postoperative therapy is the impaired patient performance status after a gastrectomy that can hamper or even prevent delivery of the planned adjuvant treatment.[107] Part of this is caused by the nutritional status and

insufficient nutritional support that is given in this patient group prone to major weight loss.[107,108] For this reason, the concept of neo-adjuvant treatment might be a valuable alternative, while the postoperative therapy still can be administered when tolerated. The main goal of giving neo-adjuvant chemotherapy is to treat micrometastatic disease at an early stage and to improve resectability by tumor downsizing and downstaging.[109]

In the beginning of the 1990s the concept of perioperative chemotherapy was tested for its feasibility in a small study, showing a compliance rate of 72% and an acceptable toxicity profile.[110] The MRC Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial, randomized 503 patients with advanced (more than submucosal), resectable adenocarcinoma of the stomach, esophagogastric junction, or lower esophagus for surgery and perioperative chemotherapy versus surgery alone. Chemotherapy consisted of three preoperative and three postoperative cycles of epirubicin, cisplatin and 5-fluorouracil. R0 resection rates were 66% and 69% for the two groups in favor of the chemotherapy group, and 40% of all resections were D2 lymph node dissections. Whereas 86% of the patients completed the preoperative chemotherapy schedule, only 55% started postoperative chemotherapy and subsequently 42% completed all six courses. The most important reasons for not starting or finishing postoperative chemotherapy were early progressive disease or death, patient's request and postoperative complications. With a median follow-up of 48 months, 5-year overall survival was significantly higher in the chemotherapy group (36% versus 23%) with no differences according to tumor site. No differences in postoperative morbidity and mortality were observed between the two treatment groups.[109]

A French prospective trial randomized 224 patients with adenocarcinoma of the stomach (25%), the GEJ (64%) or lower esophagus (11%) between chemotherapy plus surgery (N = 113) or surgery alone (N = 111). Chemotherapy consisted of 2-3 cycles of preoperative 5-fluorouracil and cisplatin and was continued after surgery in case of response to preoperative chemotherapy or stable disease with pN+. Compliance for the preoperative therapy was 87%, whereas 48% of the patients completed the total regimen. With a median follow-up of 5.7 years, 5-year overall and disease free survival were significantly higher in the chemotherapy group (38% versus 24% and 34% versus 21%).[111] Although the final report of this initially in 2007 presented study has still to be awaited, the results are quite similar to the MAGIC study with better outcomes for peri-operative chemotherapy when compared to surgery alone.

Only a few studies have been performed on preoperative chemotherapy without postoperative treatment. In a Dutch randomized trial 59 patients were treated with surgery alone (N = 30) or chemotherapy with 5-fluorouracil, doxorubicin and methotrexate (FAMTX) followed by surgery (N = 29). This trial was discontinued before total accrual was achieved because of poor accrual and a low R0 resection rate in the neo-adjuvant group. With a median follow-up of 83 months, this study did not show a difference in overall survival.[112] An EORTC study randomized 144 patients between surgery versus

surgery preceded by folinic acid, 5-fluorouracil and cisplatin. Again, due to poor accrual, the trial was closed early. Although the R0 resection rate was actually lower in the neoadjuvant chemotherapy group (82% versus 67%), there was no difference in overall survival.[113] Based on these underpowered studies, it is difficult to draw conclusions about the role of preoperative chemotherapy without postoperative therapy.

THE CHOICE BETWEEN ESTABLISHED TREATMENT PARADIGMS

Whereas adjuvant chemotherapy with S-1 is an established regimen in Japan, the Western debate currently focuses on the use of postoperative CRT versus perioperative chemotherapy. While the Intergroup 0116 study only included patients with an R0 resection and adequate postoperative recovery, the MAGIC study included all patients that were eligible for curative surgery. Therefore, results of the Intergroup 0116 and MAGIC study are incomparable with regards to treatment adherence and survival.[51,109] In both studies, most toxicities were hematological or gastrointestinal, but due to a different way of reporting on the number of adverse effects, toxicity profiles can not be compared either. But what these studies do indicate is that the toxicity profile of the chemotherapy and radiation regimen is critical for the individual patient to complete therapy, and consequently for trials to complete accrual.

To compare preoperative with postoperative chemotherapy, a Swiss/Italian study randomized 70 patients for docetaxel, cisplatin and 5-fluorouracil either before or after surgery. This trial closed early because of poor accrual. In the neoadjuvant group, 75% completed the whole treatment schedule, as compared to 34% in the postoperative group (66% started with postoperative chemotherapy). Neoadjuvant chemotherapy could be delivered with a higher dose intensity without decreasing the chances for radical surgery or an increase in perioperative mortality.[114]

Based on these results, preoperative chemotherapy should be considered standard treatment in patients with advanced (more than submucosal), resectable gastric cancer. With a significantly higher compliance rate as compared to postoperative therapy, it not only reduces tumor burden, but also increases the chance for an R0 resection. When tolerated, adjuvant therapy should also be administered, but no standard regimen for this has been established. Patients with (distant) micrometastases will benefit more from systemic chemotherapy, but so far there is no adequate diagnostic modality or molecular marker to identify distant micrometastases. A different approach on predicting the efficacy of postoperative chemotherapy is grading histological response in the resection specimen after preoperative chemotherapy. Such a response, however, has not proven to be associated with survival in a US study.[115] Patients at high risk for a local recurrence, for example patients who undergo an R1 resection, may benefit most from postoperative CRT,[100] although this has not been addressed in a prospective study yet.

Questions on the use of postoperative chemotherapy or CRT, after preoperative chemotherapy and surgery, are prospectively addressed in the Dutch CRITICS trial,

in which patients receive 3 cycles of preoperative ECC (epirubicin, cisplatin, and capecitabine), followed by D1+ surgery (D2 dissection without a splenectomy or pancreatectomy). Postoperative therapy consists of another three cycles of ECC, or CRT with capecitabine and cisplatin without epirubicine.[116]

NON-STANDARD ADJUVANT AND NEO-ADJUVANT THERAPIES

INTRAPERITONEAL CHEMOTHERAPY

With a curative resection for gastric cancer, positive peritoneal washings occur in 7% of the patients,[117] whereas more than 50% will develop a peritoneal carcinomatosis at some point during follow-up. Risk factors for positive cytology include serosal invasion and lymph node metastases.[118] The concept of intraoperative intraperitoneal chemotherapy (IPC) has been tested in several trials on gastric cancer. IPC can be combined with hyperthermia (HIPC) and can also be administered directly after surgery (early postoperative intraperitoneal chemotherapy, EPIC).

Most trials on IPC are included in a meta-analysis, which reports on studies where patients received normothermic IPC, HIPC, or EPIC with or without postoperative systemic chemotherapy. Patient numbers of the ten included, and mostly Asian, studies varied from 67 to 268. This meta-analysis showed a significant improvement in survival with HIPC alone (Hazard Ratio (HR)=0.60, 95% CI 0.43-0.83) and HIPC combined with EPIC (HR=0.45, 95% CI 0.29-0.68). There was also a trend towards improved survival with IPC, but this was not significant in combination with either EPIC alone or delayed (after recovery from surgery) postoperative intraperitoneal chemotherapy. Intraperitoneal chemotherapy was associated with higher risks of neutropenia and intra-abdominal abscess.[119]

A more recent large Korean study, that was reported in abstract form only and was not included in the meta-analysis, randomized 640 patients with serosa-positive M0 resectable gastric cancer to adjuvant systemic mitomycin C and doxifluridine with or without IPC with cisplatin. With a median follow-up of 3.5 years, overall survival was significantly higher in the IPC group (71% versus 60%).[120] This study can be criticized because of differences in the adjuvant chemotherapy schedule.[121]

Summarizing, HIPC in Asian trials is associated with a significant benefit in survival, at the cost of an increased postoperative complication rate. Therefore, this treatment modality is used with restraint in Western countries, and is considered an investigational strategy, not intended for standard daily practice.

POSTOPERATIVE AND INTRAOPERATIVE RADIOTHERAPY

Several studies investigated the effect of postoperative and intraoperative radiotherapy. A British randomized study with 436 patients found no difference in 5-year survival between surgery alone, surgery plus radiotherapy (45-50Gy) or surgery plus chemotherapy (mitomycin C, doxorubicin, and 5-fluorouracil) postoperatively. Compliance for the

protocol-defined dose in the radiotherapy group was 66%, with poor patient condition and withdrawal of consent as the most important reasons for failure.[122] A meta-analysis reporting on pre- and postoperative radiotherapy also revealed no significant difference for postoperative radiation.[123]

Intraoperative radiotherapy (IORT) has been tested in several relatively small trials. In an American randomized trial, 41 patients were treated with surgery (control arm: early stages) and postoperative radiotherapy (control arm: advanced stages), or with surgery and IORT (experimental arm: all stages). Locoregional recurrence rates were lower for the IORT group (44% versus 92%, $P < 0.001$), but this did not translate in a difference in survival. There were no differences in complication rates.[124] A German study that randomized 115 patients for surgery or surgery plus IORT (1x 28Gy) also did not show a significant difference in overall survival.[125] A Russian study, however, did show longer survival after IORT in a post-hoc subgroup analysis: 78 patients received either preoperative radiotherapy (5x4Gy) followed by surgery with 20Gy IORT, or surgery alone. Although there was no survival difference between the two groups, for patients with T3-4 disease or lymph node involvement a significant benefit in survival for the radiotherapy group was reported.[126]

Based on these underpowered studies, adjuvant radiotherapy as single modality following surgery has no role in routine daily clinical practice. IORT might be further investigated in patients with unfavorable tumor characteristics.

PREOPERATIVE RADIOTHERAPY

In a Chinese prospective randomized trial, 370 patients with cardia gastric cancer were randomized for surgery alone or preoperative radiotherapy (20x 2Gy in 4 weeks) followed by surgery after 2-4 weeks. The 5-year survival rates were 30% for the RT group as compared to 20% for the surgery alone group ($P < 0.01$) with a higher R0 resection rate in the RT group and no statistical difference in postoperative mortality and morbidity. Increased pathologic response rate to radiotherapy correlated with increased survival.[127]

A Russian study randomized 102 patients with resectable gastric cancer to radiotherapy (5x4Gy in 1 week) plus surgery within 5 days or surgery only. Tolerance of the radiotherapy scheme was acceptable. The difference in 5-year overall survival between the two groups (39% versus 30%) did not reach statistical significance. Subgroup analysis showed a tendency towards better survival in the radiotherapy group in locally advanced gastric cancer (T4 and tumor positive lymph nodes).[128] To investigate the effect of hyperthermia added to preoperative radiotherapy, an Ukrainian-American study randomized 293 patients between surgery, surgery preceded by radiotherapy (4x5Gy), and surgery with a similar short course of preoperative radiotherapy and hyperthermia. Radiotherapy showed no significant benefit over surgery alone, but hyperthermia in combination with the radiotherapy significantly improved 5-year survival compared to surgery alone (51% versus 30%).[129]

A meta-analysis based on the abovementioned three trials showed an advantage of neo-adjuvant radiotherapy over surgery alone in 3- and 5-year survival (OR 0.57 and OR 0.62).[101] Another meta-analysis on pre,- intra-, and postoperative radiotherapy showed a significant increase in 3- and 5-year survival as well (RR 1.26) with most survival benefit using the preoperative approach.[123]
In summary, data on neo-adjuvant radiotherapy are still limited, but suggest an advantage in survival over surgery alone. The largest trial has been performed in patients from a high incidence area with exclusively cardia cancer.

PREOPERATIVE CHEMORADIOTHERAPY

Currently, most accruing randomized trials focus on peri-operative chemotherapy and postoperative chemo(radio)therapy. However, several phase I/II studies have combined the administration of neo-adjuvant chemotherapy with neo-adjuvant radiotherapy.[130-133] Although results are promising with different chemotherapy schedules all containing 5-fluorouracil and cisplatin, multicenter phase III trials are necessary in order to evaluate whether this treatment strategy can improve survival.

CONCLUSIONS AND FUTURE PERSPECTIVES

Surgery remains the primary curative treatment for locally advanced gastric cancer. A D2 dissection is the recommended type of surgery in Western countries, while in the East at least a D2 dissection is performed. Despite the effort to improve surgical quality, locoregional relapse rate remains high with a consequent poor prognosis.
Currently accepted adjuvant and neoadjuvant therapies include adjuvant chemotherapy, postoperative CRT, and perioperative chemotherapy. Adjuvant chemotherapy is mainly given in Japan with S-1, but has not been evaluated in the West because of limited experience with S-1 in Western patients. The Western debate focuses on the use of postoperative CRT versus perioperative chemotherapy, but due to different inclusion criteria, the results of the Intergroup 0116 and MAGIC trials are incomparable with regards to treatment adherence and survival. These studies do indicate, however, that the toxicity profile of the chemotherapy and radiation regimen is critical for patient compliance and study accrual. Based on the superior compliance of preoperative chemotherapy as compared to postoperative chemotherapy or radiation, preoperative chemotherapy should be considered standard treatment in patients with advanced, resectable gastric cancer. When tolerated, postoperative treatment should also be administered, but no standard regimen for this has been established. After an R1 resection postoperative CRT might improve survival, but it has not been compared in a prospective randomized manner with postoperative chemotherapy.
Several currently accruing or yet unpublished trials focus on the choice of the optimal postoperative treatment (Table 5). In the Dutch CRITICS trial, patients receive 3 cycles of preoperative chemotherapy (ECC) followed by surgery, after which they receive

another 3 cycles of ECC, or postoperative CRT. The Korean ARTIST trial, which finished accrual, randomized patients who received a D2 dissection between postoperative chemotherapy (cisplatin and capecitabine) and postoperative CRT. No preoperative therapy was administered. Feasibility data of this study were reported at ASCO-GI 2009 showing good toxicity profiles with compliance rates of 75% versus 82%, respectively. Survival data of this trial have to be awaited.[134] With the low cure rates of the currently accepted therapies, several of the currently accruing Western trials focus on improved chemotherapy schedules: in the British MAGIC-B trial, bevacizumab is added to perioperative epirubicin, cisplatin, and capecitabine. A very recent protocol change has included another arm with panitumumab instead of bevacizumab. The US CALGB 80101 compares the Intergroup regimen (radiation, 5-FU, leucovorin) with radiation, epirubicin, cisplatin and 5-FU and has finished accrual, but final outcomes of this study have to be awaited.

Western randomized controlled trials on gastric cancer are often hampered by slow or incomplete accrual. Reduction of toxicity for preoperative and especially postoperative treatment and adequate nutritional support are essential for the ongoing improvement of gastric cancer care. Currently accruing Asian trials mainly focus on improved adjuvant chemotherapy with or without immunotherapy.

Most of the studies covered in the current review mention the rate of cardia cancer in the trial population. However, subgroup analyses for cardia versus non-cardia cancer are rarely performed. Because of the differences in epidemiological, etiological and histological factors, this subject warrants further attention.

Table 5. Current phase III trials for treatment of resectable gastric cancer

Trial	Treatment setting	Treatment arms	No. of patients required
CRITICS Dutch Colorectal Cancer Group	stage Ib-IV gastric cancer	perioperative ECC(three cycles pre- and post-) neo-adjuvant ECC (three cycles), surgery, then adjuvant CC CRT	788
Magic-B British MRC	stage Ib-IV resectable adenocarcinoma of the stomach or Siewert III GEJ	peri-operative ECC (three cycles pre- and post-) peri-operative ECC plus bevacizumab (three cycles pre- and post-) maintenance bevacizumab 6x	1100
ARTIST Samsung Medical Centre NCT00323830	D2 resected stage Ib-IV gastric cancer	postoperative CC postoperative CC CRT	490
Intergroup CALGB 80101 (completed)	stage Ib-IV resected adenocarcinoma of the stomach or GEJ	postoperative 5-FU CRT postoperative ECF CRT	824
Tokyo Metropolitan Oncology Group NCT00687843	stage II-IIIB gastric cancer	postoperative Tegafur-gimeracil-oteracil (TS-1) postoperative TS-1 + PSK (Krestin)	480
Hokuriku-Kinki Immunochemotherapy Study Group NCT00216034	stage II-IIIA gastric cancer	postoperative Tegafur-gimeracil-oteracil (TS-1) postoperative TS-1 + PSK (Krestin)	280
Japan Clinical Oncology Group JCOG 0501 NCT00252161	Borrmann Type 4 and Large Type 3 Gastric Cancer	D2 resection alone neo-adjuvant S-1 plus cisplatin then D2 resection	300
CLASSIC Sanofi-Aventis, South-Korea	stage II-IIIb gastric cancer	D2 resection D2 resection, adjuvant capecitabine, oxiplatin	1024

ECC: epirubicin, cisplatin, capecitabine
CC: cisplatin, capecitabine
CRT: chemoradiotherapy
GEJ: gastresophageal junction
5-FU: 5-fluorouracil
ECF: epirubicin, cisplatin, 5-FU

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PART II

Multimodality treatment

CHAPTER 7

Impact of the extent of surgery and postoperative chemoradiotherapy on recurrence patterns in gastric cancer

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ABSTRACT

BACKGROUND

The Intergroup 0116 trial demonstrated that postoperative chemoradiotherapy (CRT) improves survival in gastric cancer. We retrospectively compared survival and recurrence patterns in two phase I-II studies evaluating more intensified postoperative CRT with those from the Dutch Gastric Cancer Group Trial (DGCT) that randomized patients between D1 and D2 lymphadenectomy.

PATIENTS AND METHODS

Survival and recurrence patterns of 91 patients with adenocarcinoma of the stomach who had received surgery followed by radiotherapy combined with fluorouracil and leucovorin (N = 5), capecitabine (N = 39), or capecitabine and cisplatin (N = 47) were analyzed and compared with survival and recurrence patterns of 694 patients from the DGCT (369 D1, 325 D2). For both groups, the Maruyama Index of Unresected Disease (MI) was calculated and correlated with survival and recurrence patterns.

RESULTS

With a median follow-up of 19 months in the CRT group, local recurrence after 2 years was significantly higher in the surgery only (DGCT) group (17% versus 5%, *P* = 0.0015). Separate analysis of CRT patients who underwent a D1 dissection (N = 39) versus DGCT-D1 (N = 369) showed fewer local recurrences after chemoradiation (2% versus 18%, *P* = 0.001), while comparison of CRT-D2 (N = 25) vs DGCT-D2 (N = 325) demonstrated no significant difference. CRT significantly improved survival after a microscopically irradical (R1) resection. The MI was found to be a strong independent predictor of survival.

CONCLUSION

Following D1 surgery, the addition of postoperative CRT had a major impact on local recurrence in operable gastric cancer.

INTRODUCTION

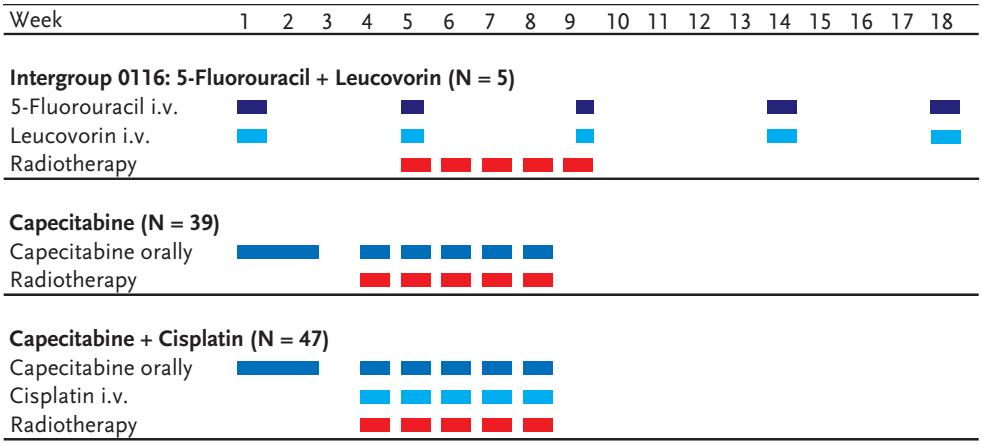
Gastric cancer is the second leading cause of cancer death worldwide,[1] and responsible for 8.1% of all cancer deaths in Europe.[2] Surgery is the only possible curative treatment, and results of gastrectomy with respect to survival, morbidity, and mortality have improved through the years.[3] Despite these improvements, up to 80% of the patients who undergo a resection with curative intent develop locoregional recurrences.[4] Although extended surgery has been associated with better staging and lower locoregional recurrence rates, randomized studies in the Western world have failed to show an improvement in survival with extended lymph node dissection.[5-7] In one of these studies, the Dutch Gastric Cancer Group Trial (DGCT), 711 patients were randomized for gastrectomy between a D1 and D2 lymphadenectomy. Long-term results of this study showed no significant benefit in survival after a D2 lymphadenectomy, which was mainly due to increased postoperative morbidity and mortality.[5] Only recently, a retrospective analysis on survival rates in the Netherlands before, during, and after the DGCT, showed that survival of patients with curatively resected non-cardia gastric cancer has improved over the last several years, which is most likely the result of standardization and surgical training.[8]

The high recurrence rate makes gastric cancer a disease difficult to cure by surgery alone, with 5-year survival rates after surgery of 34% to 70% for patients with stage I and II, and 7% to 20% for stage III and IV disease.[9] Recent data show that 5-year overall survival for all diagnosed patients in Europe is only 24.5%.[10] Considering the recent advantages in survival that have been achieved with postoperative chemoradiotherapy (CRT)[11] and perioperative chemotherapy,[12] surgery alone is no longer the standard treatment for patients with resectable (more than T2N0) gastric cancer.[13]

The Intergroup 0116 randomized study of 556 patients with resectable adenocarcinoma of the stomach or gastroesophageal junction demonstrated that postoperative CRT with fluorouracil and leucovorin improved 5-year overall survival (40% versus 22%), and local recurrence rate (19% versus 29%), compared to surgery alone.[11] A recent update on this study confirmed these results with hazard ratios (HR) for survival (HR 1.32, $P = 0.004$) and disease-free survival (HR 1.51, $P < 0.001$) favoring chemoradiation, after a median follow-up of more than ten years.[14] Based on these results, postoperative CRT has become standard treatment for gastric cancer in the United States. In a side study, the investigators calculated the Maruyama Index of Unresected Disease (MI) for each patient to predict the likelihood that the remaining lymph nodes were tumor positive. The MI was found to be a powerful independent predictor of survival.[15,16]

From 2000 to 2008, several phase I/II trials with intensified postoperative CRT (as compared to the Intergroup 0116 trial) were performed in the Netherlands, and all these trials established the feasibility of these regimens.[17-19] From these studies, a CRT regimen with daily capecitabine and weekly cisplatin has emerged, and is currently being tested in a phase III trial (CRITICS; clinicaltrials.gov NCT00407186). The objective of these

Figure 1. Treatment design phase I/II studies



Radiotherapy was administered in 5 fractions/week

adjuvant strategies is to reduce the locoregional recurrence rate and improve survival. Therefore, in the current retrospective study, the patterns of recurrence and survival of patients in the phase I/II CRT studies were compared to patterns of recurrence and survival of patients in the DGCT, in which patients were treated with surgery only. In addition to these analyses, the correlation between MI and survival and recurrence patterns in these groups was investigated.

PATIENTS AND METHODS

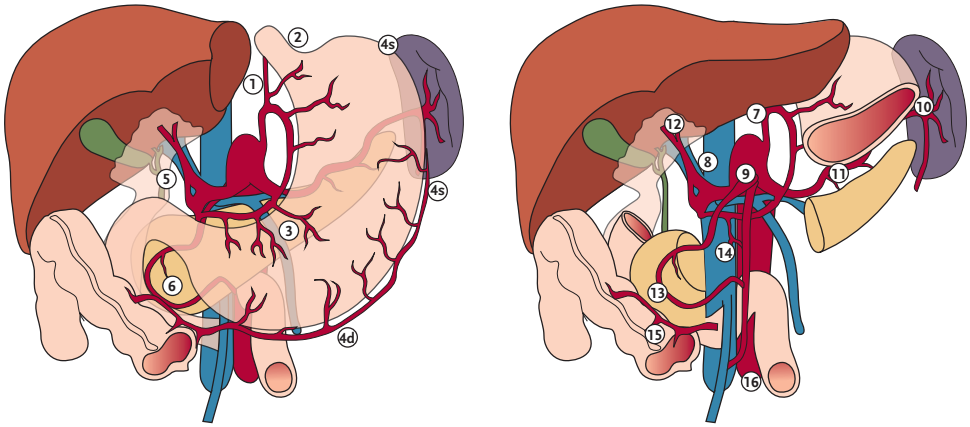
PHASE I/II CHEMORADIOTHERAPY STUDIES

From 2000 to 2008, 113 patients with histologically confirmed adenocarcinoma of the stomach or gastroesophageal junction, stage Ib-IV according to the American Joint Committee of Cancer,[20] underwent gastric resection followed by CRT at the Netherlands Cancer Institute. For a detailed description of the study design, please refer to the original publications.[17,18]

In summary, all patients underwent (partial) gastrectomy with preferably at least a D1 lymph node dissection, without routine splenectomy or pancreatic tail resection. After macroscopically radical gastric surgery, patients were asked to participate in the phase I-II studies. All patients were treated with 25 fractions of 1.8 Gy radiotherapy to a total dose of 45 Gy (5 fractions/week). The clinical target volume consisted of the gastric bed (with stomach remnant, when present), anastomoses, and draining lymph nodes. Radiotherapy was combined with escalating doses of fluorouracil and leucovorin (Intergroup 0116 scheme), capecitabine,[18] or capecitabine and cisplatin[17] (Figure 1).

Follow-up after completion of treatment consisted of physical examination, lab tests including tumor markers every 3 months and computed tomography (CT) of the abdomen every 6 months.

Figure 2. Lymph node stations as defined by the Japanese Research Society for Gastric Cancer[24]



N1 Lymph nodes (perigastric)
1 Right cardiac nodes
2 Left cardiac nodes
3 Nodes along the lesser curvature
4 Nodes along the greater curvature
5 Suprapyloric nodes
6 Infrapyloric Nodes

N2 Lymph nodes (branches coeliac axis)
7 Nodes along root left gastric artery
8 Nodes along common hepatic artery
9 Nodes around celiac axis
10 Nodes at splenic hilum
11 Nodes along splenic artery

N3 Lymph nodes
12 Nodes at the hepatoduodenal ligament
13 Retropancreatic (perioduodenal) nodes
14 Nodes at the root of the mesentery

N4 Lymph nodes
15 Nodes along the middle colic vein
16 Para-aortic nodes

D1 resection: removal of the N1 lymph nodes. D2 resection: removal of the N1 and N2 lymph nodes.

DUTCH GASTRIC CANCER GROUP TRIAL, D1 VERSUS D2

From 1989 to 1993, 1078 patients with histologically confirmed adenocarcinoma of the stomach without evidence of distant metastases were randomly assigned for D1 or D2 lymph node dissection if, at laparotomy, no signs of distant lymph node, hepatic, or peritoneal metastases were found.[5,21] D1 and D2 dissection were defined according to the guidelines of the Japanese Research Society for the Study of Gastric Cancer (JRSGC) (Figure 2).[22] In D2 dissections, resection of the spleen and pancreatic tail were only performed in proximal tumors to achieve adequate removal of D2 lymph node stations 10 and 11.

All patients were evaluated every 3 months during the first year and every 6 months thereafter. If history and physical examination were suspicious for the diagnosis of a relapse, this was considered sufficient. However, for the majority of patients, the diagnosis of recurrent disease was confirmed by radiology, endoscopy, and/or histology. For further details on study design, please refer to the original publications.[5,21]

DEFINITION OF RECURRENCE

Recurrences were categorized as local, regional or distant. Local recurrence was defined as recurrence in the gastric bed, regional gastric lymph nodes, or at the esophago/gastrojejunal anastomosis. This corresponds with the clinical target volume of radiotherapy. Peritoneal carcinomatosis was scored as regional recurrence. Distant recurrence was defined as liver or lung metastases or metastases in other organs (bone, brain, ovaries).

MARUYAMA INDEX OF UNRESECTED DISEASE

The MI was calculated using the Maruyama Computer Program,[23] which contains data of 4702 patients with gastric cancer treated at the National Cancer Center Hospital, Tokyo. The program matches a given case with the database in order to estimate the likelihood (percentage) of nodal disease for each of the 16 JRSGC-defined[24] lymph node stations (Figure 2), using 7 variables: age, sex, Borrmann type of tumor, tumor size, location, depth, and histology. The program has shown to be highly accurate in Japanese, German, and Italian series.[25-27] To quantify the likelihood of unresected nodal disease, the MI has been defined[15] as the sum of nodal disease percentages for each of the regional node stations (1-12) not removed by the surgeon. For example, a given patient undergoes a gastrectomy with removal of lymph node stations 1-10. The MI of this patient is calculated by adding up the likelihood of disease percentages of station 11 and 12, which are left *in situ*. Previous publications have shown superior survival for patients with a MI < 5.[15,16]

For the DGCT, detailed lymphadenectomy data for each patient were reported. For the CRT group, however, only the type of lymph node dissection (D0, D1, D2) was registered. Therefore, we derived the resected lymph node stations from the Japanese Classification of Gastric Carcinoma,[24] based on surgical and pathology reports.

STATISTICAL ANALYSIS

In order to account for intrinsic differences between populations, rather than matching, groups were adjusted for covariates in multivariate Cox proportional hazards models. Used covariates were: age (≥70/>70 years), sex, localization of tumor (proximal/middle/distal/diffuse), Lauren classification (intestinal/diffuse/mixed) T-stage, N-stage, gastrectomy (total/subtotal), pancreatectomy, splenectomy, type of dissection (D0/D1/D2), and radicality (R0/R1). Survival curves for the two populations are model-based curves evaluated at the mean of the covariates used in the multivariate proportional hazards models. For the pooled MI survival analysis, Kaplan-Meier survival curves were calculated and the log-rank test was used to test for differences between high and low MI groups.

Patients from the DGCT were entered in this study if they had survived surgery, while patients from the phase I/II trials were only entered into this study if they had survived surgery and completed chemoradiotherapy. To account for the fact that patients in the phase I/II trials who died before entering the trial would not be present in the CRT group, delayed entry techniques were used for all survival and recurrence analyses.[28]

For both groups, overall survival was calculated from surgery until death of any cause (event) or last follow-up contact (censored). Disease-free survival was calculated from surgery until recurrence or death (event) or the day of last follow-up without recurrence (censored). Times to recurrence (local, regional, distant) were calculated from surgery until recurrence (event) or the day of last follow-up without recurrence (censored).

All survival and recurrence analyses were performed using R software (version 2.9.1).

Table 1. Patient characteristics

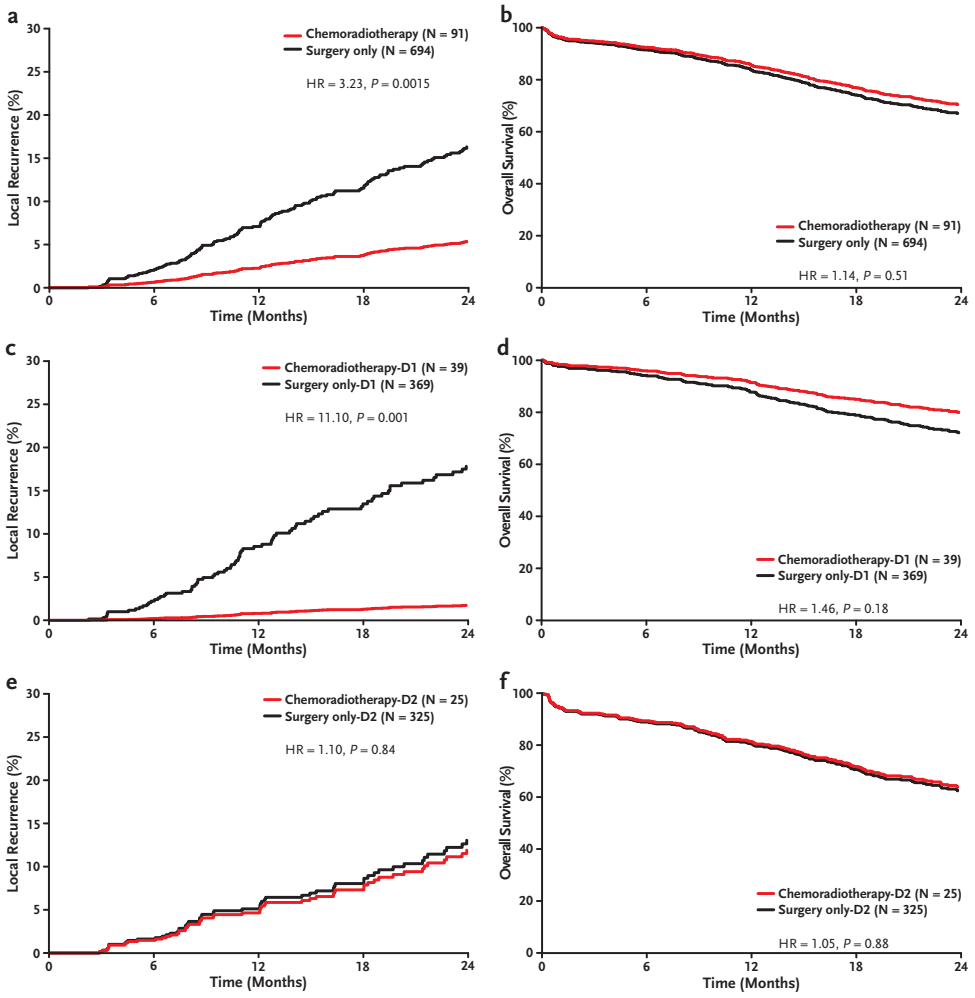
	Chemoradiotherapy		Surgery only		*P*
	N	%	N	%	
Total	91	*100*	694	*100*	
Sex					
male	63	*69.2*	392	*56.5*	0.021
female	28	*30.8*	302	*43.5*	
Age					
<70	81	*89.0*	469	*67.6*	<0.001
≥70	10	*11.0*	225	*32.4*	
Location					
proximal	11	*12.1*	91	*13.1*	0.415
middle	31	*34.1*	217	*31.3*	
distal	41	*45.1*	377	*54.3*	
diffuse	8	*8.8*	9	*1.3*	
Gastrectomy					
total	32	*35.2*	237	*34.1*	0.848
distal	59	*64.8*	457	*65.9*	
Spleen and pancreas					
not removed	74	*81.3*	529	*76.2*	0.016
spleen removed	12	*13.2*	57	*8.2*	
pancreas removed	2	*2.2*	1	*0.1*	
both removed	3	*3.3*	107	*15.4*	
Lymph node dissection					
D0	27	*29.7*			<0.001
D1	39	*42.9*	369	*53.2*	
D2	25	*27.5*	325	*46.8*	
Tumor stage					
T1	2	*2.2*	182	*26.2*	<0.001
T2	17	*18.7*	331	*47.7*	
T3	66	*72.5*	169	*24.4*	
T4	6	*6.6*	12	*1.7*	
Nodal status					
N0	6	*6.7*	309	*44.7*	<0.001
N1	45	*50.0*	248	*35.9*	
N2	27	*30.0*	93	*13.5*	
N3	12	*13.3*	41	*5.9*	
Nx	1	*0.1*	3	*0.1*	
Lauren classification					
intestinal	21	*23.1*	309	*44.5*	<0.001
diffuse	24	*26.4*	129	*18.5*	
mixed	8	*8.8*	21	*3.0*	
unknown	38	*41.8*	235	*33.9*	
Radicality					
R0	69	*75.8*	633	*91.2*	<0.001
R1	22	*24.2*	61	*8.8*	

RESULTS

PATIENT CHARACTERISTICS

Ninety-one of 113 patients from the CRT group were suitable for analysis. Patients who underwent an esophageal-cardiac resection or patients with an adenocarcinoma of the gastroesophageal junction (N = 22) were excluded. Of the 711 patients of the DGCT (surgery only) who underwent a curative resection, 17 patients were excluded because

Figure 3. Multivariate analyses of local recurrence (LR) and overall survival (OS), (a) LR all patients, (b) OS all patients, (c) LR D1 patients, (d) OS D1 patients, (e) LR D2 patients, (f) OS D2 patients, HR = Hazard Ratio



they were classified as 'T_o' or had metastatic disease, leaving 694 patients for comparative analysis.

Baseline characteristics are summarized in Table 1. D2 lymphadenectomy was performed in 46.8% of the surgery-only group compared to 27.5% in the CRT group. There were more microscopically irradical (R1) resections in the CRT group. Although Lauren classification was not available for all patients, in the CRT group there were less intestinal-type and more diffuse-type tumors. Tumor and nodal stages were more advanced in the CRT group.

Figure 4. Kaplan-Meier survival curves for MI < 5 versus MI ≥ 5, pooled data from all 716 patients in which the Maruyama Index was calculated

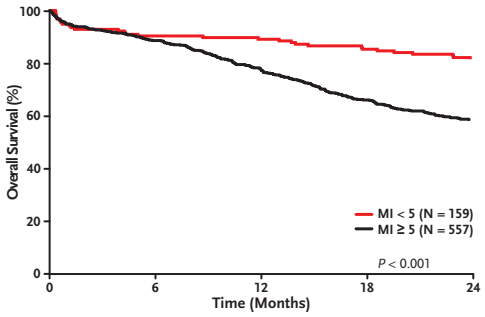
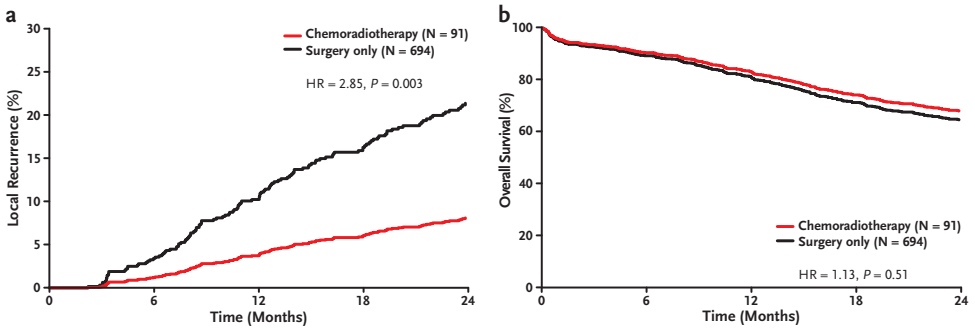


Figure 5. Multivariate analysis with adjustment for Maruyama Index, (a) local recurrence, (b) overall survival



OVERALL SURVIVAL, RECURRENCE-FREE SURVIVAL, AND RECURRENCE RATES

At time of analysis, median follow-up in the CRT group was 19 months, as compared to 51 months in the surgery only group.

Survival and recurrence analyses revealed a significant decrease in local recurrence rate in the CRT group as compared to the surgery only group (HR 3.23, $P = 0.0015$, Figure 3a). Model-based local recurrence percentages after 2 years were 5% for the CRT group, and 17% for the surgery only group. This, however, did not translate into a significant difference in 2-year overall survival (71% versus 67%, HR 1.14, $P = 0.51$, Figure 3b) or recurrence-free survival (HR 0.86, $P = 0.53$, not shown). Analysis of the regional recurrence rate (peritoneal carcinomatosis) showed an advantage for the surgery only group (6% versus 3%, HR 0.48, $P = 0.05$, not shown). There was no significant difference in distant recurrence rate (HR 0.98, $P = 0.95$, not shown).

Subgroup analysis for the extent of lymphadenectomy revealed that the decrease in local recurrence rate was largest in patients who underwent a D1 lymphadenectomy. The rate of local recurrence after 2 years was significantly lower in the CRT-D1 group compared to the surgery-only-D1 group (2% versus 18%, HR 11.10, $P = 0.001$, Figure 3c). However,

overall survival again was not different between these two groups (80% versus 72%, HR 1.46, $P = 0.18$, Figure 3d). There were no differences between patients who underwent a D2 resection followed by chemoradiation or a D2 resection alone with regards to local recurrence rate (12% versus 13%, HR 1.10, $P = 0.84$, Figure 3e) and overall survival (64% versus 63%, HR 1.05, $P = 0.88$, Figure 3f).

Subgroup analyses of radical (R0) and microscopically irradical (R1) gastrectomies demonstrated a significant improvement in 2-year overall survival in the CRT group following an R1 resection as compared to the surgery-only-R1 group (66% versus 29%, HR 2.91, $P = 0.002$). This coincided with a significant decrease in the local recurrence rate in the CRT-R1 group (6% versus 26%, HR 5.36, $P = 0.02$) and no significant differences in regional and distant recurrence rates. Although the local recurrence rate was significantly lower in the CRT-R0 group compared to the local recurrence rate for the surgery-only-R0 group (5% versus 13%, HR 2.53, $P = 0.03$), there was no significant difference in survival for patients in this subgroup.

MARUYAMA INDEX

The MI was calculated for 78 out of 91 patients in the CRT group, and for 638 out of 694 patients in the surgery-only group. Median MI in the CRT group was 74.5 compared to 25.5 in the surgery-only group. This difference is mainly explained by the low number of D2 dissections in the CRT group, in which only 6 patients had an MI < 5 (7.6%), compared to 153 (24.0%) with an MI < 5 in the surgery-only group.

Using pooled data from the CRT and the surgery-only group, comparison of patients with MI < 5 versus MI ≥ 5 shows that survival is superior for patients with an MI < 5 with 2-year survival rates of 82% versus 59% ($P < 0.001$, Figure 4). In this analysis, only the predictive power of MI is tested. The number of patients in the CRT group was too low to test the predictive value of MI within this group.

To assess the probability that patients who receive postoperative chemoradiation benefit over patients with the same MI who receive only surgery, a multivariate analysis between the two groups, with only MI as a linear covariate, was performed. This analysis revealed a significant benefit in time to local recurrence for the CRT group (8% versus 22%, HR 2.85, $P = 0.003$), and, again, no significant difference in 2-year overall survival between the groups (68% versus 65%, HR 1.13, $P = 0.51$) (Figure 5).

DISCUSSION

Extended lymph node dissection in resectable gastric cancer has never been indisputably proven to increase survival significantly in Western studies.[5-7] Several (neo)adjuvant treatment strategies have been studied in order to improve outcome for patients with gastric cancer,[29,30] but it was not until 2001, and again in 2006, that two studies revealed that patients with gastric cancer could actually benefit from such a treatment strategy.[11,12] The Intergroup 0116 trial, which now has a median follow-up of more than 10 years,

showed a significant benefit in overall survival and locoregional recurrence after postoperative CRT.[11,14] This study has received major criticism because 54% of all patients underwent a D0 gastrectomy instead of the recommended D2 gastrectomy, leading to the hypothesis that postoperative CRT might have compensated for suboptimal surgery. Notwithstanding this, no significant differences in relapse-free survival or overall survival could be detected according to the extent of the dissection.[31] Moreover, a Korean observational study did show an advantage in overall survival of 95.3 months versus 62.6 months, respectively, in 990 patients who underwent a D2 lymphadenectomy plus postoperative chemoradiation (Intergroup 0116 scheme) or D2 dissection alone.[32]

In the present retrospective study, we demonstrate that postoperative chemoradiation leads to a reduction in the local recurrence rate (5% versus 17% after 2 years), without an advantage in regional or distant recurrence rate. This difference in recurrence does not lead to a significant decrease in 2-year overall survival. This may be due to the relatively short median follow-up period of 19 months. The effect on local recurrence persists when adjusting for MI, which has shown to be a strong independent predictive parameter for relapse-free and overall survival.[15,16] The effect of CRT on local recurrence is especially strong in patients who received a D1 lymphadenectomy (2% versus 18% after 2 years), with possibly a trend towards longer overall survival.

In contrast to the benefit of chemoradiotherapy for patients receiving a D1 gastrectomy, subgroup analysis of patients who underwent a D2 lymph node dissection shows no advantage for postoperative CRT. Although the limited number of patients in the CRT-D2 group could have influenced this moderate effect of chemoradiation in the D2 group, it suggests that, in the Western population, postoperative chemoradiotherapy has a higher impact following a D1 dissection than a D2 dissection. And consequently, one questions whether a limited D1 dissection combined with CRT is equal to an extended nodal resection and/or a more extensive gastric resection.

Another subgroup that seems to particularly benefit from CRT is the subgroup of patients with an R1 resection. In this group, CRT improves both local recurrence rate and overall survival.

Despite the benefit of CRT on local recurrence, the regional recurrence rate (peritoneal carcinomatosis) is higher in the CRT group. As the multivariate analyses were adjusted for Lauren classification, the higher number of diffuse tumors in the CRT group cannot explain this observation. A possible explanation might be the more intensive follow-up with bi-annual CT scanning in the CRT group, which could have led to the earlier detection of asymptomatic ascites or peritoneal thickening. If this would be the case, this would underscore the power of local recurrence analyses as well, since the lowest local recurrence rates were found in a more intensively monitored group.[17-19] There is no significant difference in the number of distant recurrences, which might be explained by the fact that the more aggressive locoregional treatment has limited effect on systemic recurrences.

For the Intergroup 0116 study and the DGCT, MI has shown to be a strong independent predictor of survival and recurrence, whereas thus far the type of lymph node dissection has not. In the current study, MI shows to have a strong predictive value, as patients with an MI < 5 have superior 2-year overall survival rates.

We emphasize that only a prospective randomized trial can provide definite answers to the question whether postoperative CRT has a clinical benefit over surgery with extended lymphadenectomy. Currently two such studies aim to answer this question. In a Korean trial, all patients will undergo D2 lymphadenectomy, followed by postoperative chemotherapy with or without concurrent radiotherapy (clinicaltrials.gov NCT00323830). In the second study, performed in the Netherlands and Sweden, patients will receive 3 courses of ECC (epirubicin, cisplatin, capecitabine) followed by D2 lymphadenectomy without splenectomy and pancreatectomy, followed by either 3 additional courses of ECC or chemoradiation (capecitabine and cisplatin) (CRITICS, clinicaltrials.gov NCT00407186).

In conclusion, postoperative chemoradiation following surgery has a major impact on local recurrence in operable gastric cancer, while there seems to be no additional benefit on regional and distant recurrences. Especially patients with a limited D1 resection and patients with a microscopically irradical resection seem to benefit from CRT following surgery. Patients with a microscopically irradical (R1) resection also have a better overall survival following CRT.

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PART II

Multimodality treatment

CHAPTER 8

Preoperative chemotherapy does not influence the number of evaluable lymph nodes in resected gastric cancer

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ABSTRACT

BACKGROUND

While it is suggested that more than 15 lymph nodes (LNs) should be evaluated for accurate staging of gastric cancer, LN yield in western countries is generally low. The effect of preoperative chemotherapy on LN yield in gastric cancer is unknown. The aim of the present study is to determine whether preoperative chemotherapy is associated with any difference in the number of LNs obtained from specimens of patients who underwent curative surgery for gastric adenocarcinoma.

PATIENTS AND METHODS

In 1205 patients from Memorial Sloan-Kettering Cancer Center (MSKCC) and 1220 patients from the Netherlands Cancer Registry (NCR) who underwent a gastrectomy with curative intent for gastric adenocarcinoma without receiving preoperative radiotherapy, LN yield was analyzed, comparing patients who received preoperative chemotherapy and patients who received no preoperative therapy.

RESULTS

Of the 2425 patients who underwent a gastrectomy, 14% received preoperative chemotherapy. Median LN yields were 23 at MSKCC and 10 in the NCR. Despite this twofold difference in LN yield between the two populations, with multivariate Poisson regression, chemotherapy was not associated with LN yield of either population. Variables associated with increased LN yield were institution, female sex, lower age, total (versus distal) gastrectomy and increasing T-classification.

CONCLUSIONS

In this patient series, treatment at MSKCC, female sex, lower age, total gastrectomy and increasing primary tumor classification were associated with a higher number of evaluated LNs. Preoperative chemotherapy was not associated with a decrease in LN yield. Evaluating more than 15 LNs after gastrectomy is feasible, with or without preoperative chemotherapy.

INTRODUCTION

In addition to the number of lymph node (LN) metastases,[1,2] the total number of evaluated LNs is a strong predictor of survival after a curative resection for gastric cancer.[3] In node-negative patients a larger number of evaluated LNs is associated with better survival.[4] Although the minimum number of LNs that should be evaluated for definitive staging has not been defined,[5] a LN yield of 15 or more has been associated with improved overall survival.[6] More than 15 lymph nodes should be evaluated for accurate staging according to the American Joint Committee on Cancer (AJCC) staging manual.[7,8] A lower number of evaluated nodes could lead to *stage migration*, i.e. the migration of patients into a less advanced nodal stage by investigating fewer lymph nodes. When fewer nodes are examined, lymph node metastases could be missed that would have been demonstrated when more lymph nodes would have been investigated.[9] In Western countries, nodal yields are generally low. Studies report that only 29-32% of US patients who undergo a resection with curative intent have 15 or more nodes evaluated.[6,10]

With the increasing use of neoadjuvant therapy in the treatment of resectable gastric cancer,[11-13] the question arises whether lymph node yield is influenced by the use of preoperative chemotherapy. If preoperative chemotherapy decreases the number of evaluable lymph nodes, retrieval of more than 15 nodes would be more difficult to achieve. Retrospective analysis of a series of patients who underwent a curative resection for gastric cancer prior to 1999 showed that preoperative chemotherapy (cisplatin, leucovorin, fluorouracil) had a marked effect on tumor cells in regional lymph nodes, and that the extent of this effect could be correlated with the degree of pathologic response of the primary tumor to chemotherapy.[14] The MAGIC study, in which patients were randomized between surgery with preoperative and postoperative chemotherapy, or surgery alone, also showed that preoperative chemotherapy was associated with a lower number of tumor positive lymph nodes.[11] Neither study reported on differences in total LN yield.

In other malignancies, including rectal[15-17] and breast cancer,[18] preoperative therapy has been associated with a lower number of evaluated lymph nodes. For gastric cancer, data on this topic are not available. The aim of the present study was to determine if preoperative chemotherapy is associated with any change in the number of lymph nodes retrieved from surgical specimens of patients undergoing resection with curative intent for gastric cancer.

PATIENTS AND METHODS

MEMORIAL SLOAN-KETTERING CANCER CENTER

From a prospectively maintained database, 1921 patients were identified who underwent surgery for adenocarcinoma of the stomach (excluding tumors of the gastroesophageal junction) at Memorial Sloan-Kettering Cancer Center (MSKCC) between 1985 and 2009. Patients who underwent surgery other than total or distal gastrectomy (N = 516), patients

with metastatic (M1) disease identified before or during surgery (N = 161), patients without tumor identified on postoperative pathology (N = 26; group was too small to analyze separately) and patients who received preoperative radiotherapy (N = 9) were excluded from the analyses. Of the remaining 1209 patients, 1205 (99.7%) had available information on the number of evaluated LNs. Data on individual patient and tumor characteristics, treatment, and survival were entered into the database.

Neoadjuvant chemotherapy was administered according to hospital practice or active trial protocols. Patients were registered to have received preoperative chemotherapy if they received at least one cycle of treatment. All patients were scheduled for a D2 lymphadenectomy with spleen preservation. Perigastric soft tissues were thoroughly examined in order to identify all possible lymph nodes, and multiple attempts were made in an effort to achieve more than 15 LNs in all specimens. The study was approved by the MSKCC Institutional Review Board.

NETHERLANDS CANCER REGISTRY

The Netherlands Cancer Registry (NCR) is a registry of all newly diagnosed malignancies in the Netherlands. Information in the NCR is routinely collected by trained registrars who extract this information from the hospital records. In the registry, information on patient and tumor characteristics is available as well as data on treatment and survival. Since the date of resection was not registered in the cancer registry, the date of histologically confirmed diagnosis was used to calculate patient's age at operation. Before 2005, no data were collected on the type of gastrectomy.

From the cancer registry, 1934 patients were selected who underwent resection for a primary adenocarcinoma of the stomach between 2005 and 2007. After exclusion of patients who underwent surgery other than total or distal gastrectomy (N = 460), patients with M1 disease (N = 107), patients without tumor identified on postoperative pathology (N = 16), patients without available data on the number of evaluated LNs (N = 89), unknown T-stage and stage group (N = 13) and unknown tumor location (N = 29), 1220 patients were available for analysis.

If a patient had received any preoperative chemotherapy, this was considered sufficient to register 'preoperative chemotherapy' use. Patients received surgery according to clinical guidelines for the treatment of gastric cancer in the Netherlands, advising at least a D1 lymphadenectomy. TNM classification and stage group were recorded by the registrar based on the 6th edition (2002) of the AJCC staging system. Since data in the NCR could not be fully translated into the 7th edition (2010), in this study, the 6th edition is used.

In the Netherlands, an official pathology guideline has been approved only last year. Before that, no official Dutch guideline was available. However, in the Netherlands the 6th edition of the AJCC staging manual was used in the study period, requiring more than 15 lymph nodes for accurate staging. The study was approved by the NCR Review Board.

Table 1. Patient characteristics

	MSKCC (N = 1205)		NCR (N = 1220)		*P*
	N	%	N	%	
Sex					
male	660	*55*	762	*62*	<0.001
female	545	*45*	458	*38*	
Age at diagnosis					
mean	65.3		68.5		
median (IQR)	68	*(57-75)*	70	*(61-77)*	<0.001
Type of surgery					
distal gastrectomy	812	*67*	729	*60*	<0.001
total gastrectomy	393	*33*	491	*40*	
Preoperative chemotherapy					
no	1020	*85*	1065	*87*	0.06
yes	185	*15*	155	*13*	
Tumor location					
proximal	151	*13*	144	*12*	<0.001
middle	413	*34*	277	*23*	
distal	593	*49*	563	*46*	
multiple	48	*4*	236	*19*	
Invasion depth					
T1	335	*28*	200	*16*	<0.001
T2	389	*32*	622	*51*	
T3	444	*37*	341	*28*	
T4	37	*3*	57	*5*	
Nodal status					
N0	541	*45*	487	*40*	<0.001
N1	400	*33*	488	*40*	
N2	182	*15*	194	*16*	
N3	82	*7*	51	*4*	
Number of nodes evaluated					
median (IQR)	23	*(16-32)*	10	*(6-16)*	<0.001
median positive (IQR)	1	*(0-5)*	1	*(0-5)*	0.21
>15 nodes evaluated	929	*77*	312	*26*	<0.001
Tumor differentiation grade					
well-moderate	350	*29*	301	*25*	*<0.001*
poor-undifferentiated	837	*69*	710	*58*	
unknown	18	*2*	209	*17*	
Stage Group AJCC 6th ed.					
I	499	*41*	443	*36*	<0.001
II	249	*21*	341	*28*	
III	351	*29*	341	*28*	
IV	106	*9*	95	*8*	

AJCC: American Joint Committee on Cancer, IQR: Inter Quartile Range, MSKCC: Memorial Sloan-Kettering Cancer Center, NCR: Netherlands Cancer Registry

STATISTICAL ANALYSIS

Differences between the MSKCC and NCR populations were analyzed with the Chi-square test for categorical variables, and the Mann-Whitney U test for continuous variables. LN yields were expressed as the mean and standard deviation of the number of LNs evaluated. Because of a twofold difference in LN yield between the two populations, separate analyses were performed for the MSKCC and NCR groups. Differences in LN yield between groups were calculated with two-sample t-tests. When more than

two subgroups were tested, for ordinal subgroups t-tests were performed between the consecutive groups, whereas for nominal variables the first subgroup was used as reference for the other groups. Multivariate Poisson regression was used to model the number of LNs retrieved as a function of demographic and clinical factors and to identify significant predictors of LN retrieval. Factors that were significant in univariate analysis were included in the multivariate model, except tumor location (which determined the type of surgery that was performed), nodal status (because it is dependent on the number of evaluated nodes), and stage group (because it is dependent on nodal status).
In the MSKCC group, patients with unknown differentiation grade (N = 18) were excluded from the multivariate analysis, because of overdispersion of the multivariate model with these patients included. Since preoperative chemotherapy might decrease the depth of invasion on postoperative pathology, a second multivariate analysis without tumor stage was also performed. All analyses were performed using SPSS (version 17.0.0).

RESULTS

A total of 2425 patients underwent a total or distal gastrectomy with curative intent for M0 gastric adenocarcinoma between 1985 and 2009 at MSKCC (N = 1205) or between 2005 and 2007 in the Netherlands (N = 1220). Patient characteristics are summarized in Table 1. Fifty-nine percent of the patients were male and the mean age was 66.9 years. About two-thirds of the patients underwent a distal gastrectomy. Preoperative chemotherapy was administered in 15% of the MSKCC patients, and in 13% of the NCR patients (P = 0.06). In the MSKCC population, 45% of the patients were node negative, and 55% had positive LNs. In the NCR population, 40% of all patients were node negative, and 60% of the patients had positive lymph nodes ($P < 0.001$). Large differences in LN yield were observed between MSKCC patients, with a median of 23 sampled nodes (Inter Quartile Range 16-32), and NCR patients, with a median number of 10 (IQR 6-16) sampled nodes ($P < 0.001$). The percentage of patients with more than 15 LNs examined was 77% in the MSKCC group, and 26% in the NCR group ($P < 0.001$). Stage group distributions were similar between MSKCC and NCR patients.

Table 2 summarizes differences in LN yield by patient, tumor, and treatment characteristics. Despite significant differences in nodal yield between the two populations, chemotherapy was associated with very little difference in the total number of nodes analyzed. The mean difference of two nodes in each population was significant in the NCR population, but not in the MSKCC group. Differences in LN yield per T-stage based on univariate analysis are depicted in Figure 1. Only in the NCR T2 tumor patient subgroup the number of evaluated lymph nodes was significantly higher after preoperative chemotherapy, likely a random observation. Figure 2 indicates a decrease in LN yield with increasing patient age, which is underscored for both groups in the multivariate analysis.
Despite wide variations in LN yield between the populations, on multivariate Poisson

Table 2. Univariate analysis on the number of evaluated lymph nodes for different patient characteristics, separately analyzed for the MSKCC and NCR population

	MSKCC (N = 1205)			NCR (N = 1220)		
Number of nodes	**Mean**	**± SD**	***P***	**Mean**	**± SD**	***P***
Sex						
male	23.8	± 12.6		11.2	± 7.7	
female	26.4	± 13.1	<0.001	12.0	± 8.7	0.09
Age at diagnosis						
<50	27.6	± 13.2		14.2	± 9.0	
50-69	25.1	± 12.5	0.03	12.5	± 8.2	0.08
≥70	24.0	± 13.1	0.17	10.4	± 7.7	<0.001
Type of surgery						
distal gastrectomy	23.5	± 12.3		10.3	± 7.5	
total gastrectomy	27.9	± 13.5	<0.001	13.3	± 8.6	<0.001
Preoperative chemotherapy						
no	24.7	± 13.0		11.3	± 8.1	
yes	26.1	± 12.3	0.18	13.3	± 7.8	0.004
Tumor location						
proximal	26.1	± 13.1		13.8	± 8.5	
middle	26.0	± 13.7	0.95 [a]	12.1	± 8.7	0.06[a]
distal	23.5	± 12.0	0.62 [a]	10.9	± 7.6	<0.001[a]
diffuse	29.0	± 14.2	0.18 [a]	10.8	± 8.0	<0.001[a]
Tumor stage						
T1	22.9	± 12.7		8.8	± 7.0	
T2	25.2	± 12.4	0.02	11.3	± 7.9	<0.001
T3	26.0	± 12.9	0.36	13.3	± 8.6	<0.001
T4	28.4	± 16.8	0.28	12.5	± 7.7	0.47
Nodal status						
N0	23.1	± 12.7		8.9	± 7.7	
N1	23.9	± 12.5	0.36	10.9	± 6.7	<0.001
N2	27.2	± 11.8	0.003	15.8	± 6.0	<0.001
N3	37.1	± 11.0	<0.001	26.3	± 8.6	<0.001
Tumor differentiation grade						
well-moderate	24.7	± 13.6		10.5	± 7.6	
poor-undifferentiated	25.1	± 12.6	0.60	12.0	± 8.3	0.008
Stage group AJCC 6th ed.						
I	22.9	± 12.5		9.0	± 7.5	
II	25.0	± 13.0	0.04	10.6	± 7.1	0.002
III	24.5	± 11.7	0.68	13.2	± 7.1	<0.001
IV	35.7	± 13.2	<0.001	20.2	± 10.2	<0.001

P-values are based on comparison of consecutive categories, except for *Tumor Location*
MSKCC: Memorial Sloan-Kettering Cancer Center, NCR: Netherlands Cancer Registry
[a] as compared to proximal

regression (Table 3), preoperative chemotherapy was not associated with a significant difference in LN yield in either population. Factors that were associated with a significant increase in LN yield were the same for the MSKCC and NCR groups: female gender (+13.2% and +9.0%), decreasing age (+3.7% and +7.1% per 10 years), total gastrectomy (+17.4% and +20.8%) and increasing tumor stage. Excluding tumor stage from the multivariate model (not shown) only changed the effect of tumor grade in the NCR group: this became significant.

Figure 1. Univariate comparison of lymph node yield per T category, (a) MSKCC patients, (b) NCR patients

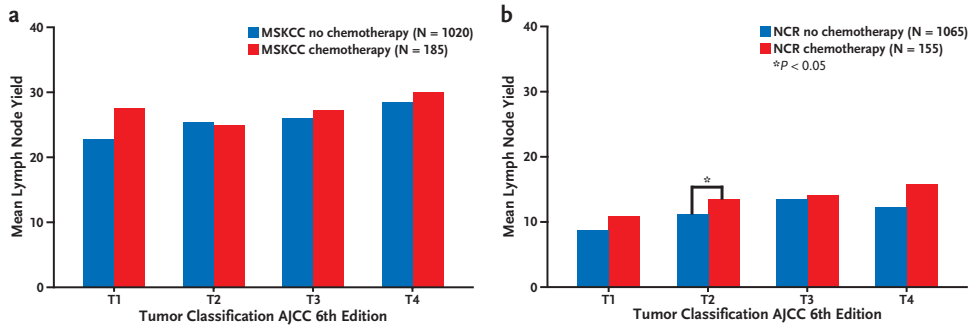
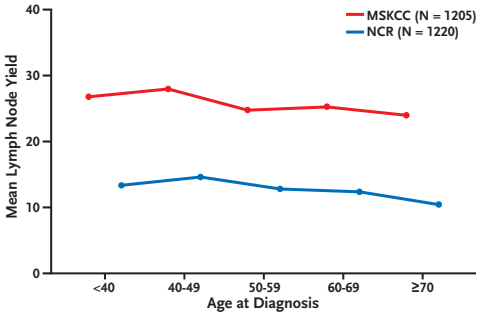


Figure 2. Univariate comparison of lymph node yield per age category



DISCUSSION

Although the use of preoperative chemotherapy has been associated with a decrease in tumor cells in regional lymph nodes in gastric cancer,[14] and has been associated with nodal downstaging in one recent randomized study,[11] there are no reports available on the association of preoperative chemotherapy on the total number of evaluated lymph nodes in gastric cancer.

In the present study, preoperative chemotherapy was not associated with any change in the number of evaluated lymph nodes in gastric cancer, either in a high-volume US center, or a population-based cancer registry. Performing this analysis in two entirely different populations increases the robustness of the results, given the comparable outcomes in both groups.

Comparing LN yield between the two populations reveals a large difference in the median number of evaluated nodes. Median LN yield is 23 in the MSKCC group and 10 in the NCR group. A US-population-based study on gastric cancer patients also found a median number of 10 evaluated nodes.[10] While for adequate staging more than 15 LNs should be evaluated,[7] in the current study, the percentage of patients with more than 15 LNs examined was 77% in the MSKCC group, but only 26% in the NCR group. These findings

Table 3. Multivariate Poisson regression on the number of evaluated lymph nodes, separately analyzed for the MSKCC and NCR population

	MSKCC (N = 1187)			NCR (N = 1220)		
	RR[a]	95% CI	*P*	RR[a]	95% CI	*P*
Sex						
male (ref)	1.000			1.000		
female	1.132	1.069-1.199	<0.001	1.090	1.009-1.178	0.03
Age at diagnosis[b]	0.963	0.942-0.985	<0.01	0.929	0.900-0.959	<0.001
Type of surgery						
distal gastrectomy (ref)	1.000			1.000		
total gastrectomy	1.174	1.104-1.248	<0.001	1.208	1.118-1.305	<0.001
Preoperative chemotherapy						
no (ref)	1.000			1.000		
yes	0.994	0.917-1.076	0.87	1.046	0.934-1.171	0.44
Tumor classification						
T1 (ref)	1.000			1.000		
T2	1.111	1.029-1.200	<0.01	1.274	1.130-1.437	<0.001
T3	1.118	1.035-1.209	<0.01	1.455	1.280-1.654	<0.001
T4	1.184	1.006-1.394	0.04	1.327	1.087-1.621	<0.01
Tumor differentiation grade						
well-moderate (ref)	1.000			1.000		
poor-undifferentiated	0.937	0.876-1.002	0.06	1.062	0.966-1.168	0.21
unknown	[c]			1.013	0.895-1.147	0.83

ref: reference category

[a] The RR (relative risk) of an increase in the lymph node yield for the covariate. For example, an RR of 1.132 means that females in the MSKCC group had 1.132 times as many lymph nodes examined (ie, a 13.2% increase).

[b] Estimates the ratio of a 10-year incremental increase in age

[c] 18 patients were excluded because the multivariate model was unable to fit this small group

reflect the experience of gastric cancer surgery and specimen processing of a dedicated cancer hospital in comparison to a nationwide group of academic and general hospitals where gastric cancer surgery is not centralized and is performed in lower volumes. A recent survey in Denmark, where gastric cancer surgery was centralized from 37 to 5 hospitals in 2003, showed an increase in the number of patients with at least 15 LNs evaluated from 19% to 75% in five consecutive years.[19]

In the current study, on univariate analysis, preoperative chemotherapy was associated with a statistically significant higher LN yield in the NCR (+2 nodes), but not in the MSKCC group. This is not a biologically significant difference, but a consequence of the smaller standard deviation in the NCR group.

With multivariate analysis, which adjusts for the other demographic and tumor characteristics, preoperative chemotherapy was not associated with a change in LN yield in either the high-volume center or the population-based registry. The difference with the univariate analysis may be explained by the higher percentage of patients receiving chemotherapy in the younger age group (<50: 29%) as compared to the older groups (50-69: 19% and ≥70: 6%), while the younger patients also have a higher LN yield. Adjusting for age group in the multivariate analysis offsets this effect. In the multivariate analysis,

female gender remained associated with an increase in LN yield in both groups, with 13% more nodes in the MSKCC group and 9% more nodes in the NCR population. This has previously been reported for gastric[10] and rectal cancer.[20] It can be hypothesized that differences in immune system that exist between males and females[21] might be responsible for this difference. Increased age was associated with a decrease in lymph node yield, also previously described for gastric,[10,22] colorectal,[15] and breast cancer.[23] This might be explained by a less aggressive lymph node dissection in elderly patients, or possibly a lower absolute number of lymph nodes present in the elderly, due to age-associated changes in the immune system.[24] The increase in LN yield from total as compared to a distal gastrectomy is an expected finding given the more extended operation. Increasing T-stage was also associated with an increasing LN yield. It has been suggested that larger tumors may cause a more intense immune response within the regional LNs, making them more visible to pathologic examination and possibly leading to higher LN yields.[25]

The relation between nodal status and LN yield is complex and is influenced by multiple factors. First, nodal status can have an effect on LN yield: LN metastases are often enlarged and easier to find during surgery and specimen processing by the pathologist. On the one hand, the presence of LN metastases could therefore lead to an increased LN yield; on the other hand, it could decrease LN yield if the surgeon or pathologist limits the search for extra nodes once positive nodes are identified.[26] The relatively uniform D2 dissection performed in the MSKCC dataset argues against this latter possibility. This problem might be overcome by using fat dissolving techniques to identify all LNs present in a specimen,[27] but this very labor intensive technique was not regularly performed in either of our patient populations. Secondly, LN yield determines AJCC N status (instead of nodal status determining LN yield), because the number of positive nodes can never be higher than the total number of LNs. Therefore, nodal status was left out of the multivariate regression model.

Similar studies have been performed for other cancer types. One study has analyzed the effect of preoperative chemoradiotherapy on nodal yield in adenocarcinoma and squamous cell carcinoma of the esophagus. No differences were detected in the number of lymph nodes sampled.[28] For rectal cancer, several studies report a lower total number of lymph nodes after preoperative (chemo)radiotherapy.[15-17,20,29] For breast cancer, conflicting results are found: some studies report a decrease in nodal yield after preoperative chemotherapy,[18,30] while others find no difference.[31,32] Overall, no uniform relation between preoperative therapy and nodal yield can be defined for all cancer types. It can however be hypothesized that preoperative radiotherapy does have an effect on LN yield, while for preoperative chemotherapy this effect might be dependent on the type of chemotherapy administered. Furthermore, different surgical and specimen processing techniques might influence the effect of preoperative therapy on nodal yield for different cancer types.

The number of evaluated LNs in a specimen is influenced by three main factors: First, patient and tumor-related factors contribute to LN yield. Age, gender, activity of the immune system all contribute to the absolute number of LNs present in a patient. Enlarged, tumor positive nodes will be found more easily, thereby increasing LN yield. Secondly, the surgeon determines the number of nodes that are dissected, by defining both the extent of gastrectomy, and the extent of the lymph node dissection performed. The third and potentially most important factor is the pathologist, who will find a certain number of LNs based on specimen processing protocols, and available resources. The only available pathologist related factor in the current series is the study population. By separately analyzing the two populations, an adjustment is made for high versus low volume center.

In conclusion, the increasing use of systemic therapy raises the question if preoperative chemotherapy reduces the number of evaluated lymph nodes in gastric cancer resection specimens. The current study was performed in two entirely different populations: a high-volume cancer center and a nationwide cancer registry. In both populations, the administration of preoperative chemotherapy was not associated with a difference in LN yield. Therefore the threshold of what is considered an adequate assessment of regional nodes in gastric cancer should not be changed for patients who have received neoadjuvant chemotherapy.

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PART II

Multimodality treatment

CHAPTER 9

Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS)

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ABSTRACT

BACKGROUND

Radical surgery is the cornerstone in the treatment of resectable gastric cancer. The Intergroup 0116 and MAGIC trials have shown benefit of postoperative chemoradiation and perioperative chemotherapy, respectively. Since these trials cannot be compared directly, both regimens are evaluated prospectively in the CRITICS trial. This study aims to obtain an improved overall survival for patients treated with preoperative chemotherapy and surgery by incorporating radiotherapy concurrently with chemotherapy postoperatively.

METHODS AND DESIGN

In this phase III multicenter study, patients with resectable gastric cancer are treated with three cycles of preoperative ECC (epirubicin, cisplatin and capecitabine), followed by surgery with adequate lymph node dissection, and then either another three cycles of ECC or concurrent chemoradiation (45 Gy, cisplatin and capecitabine). Surgical, pathological, and radiotherapeutic quality control is performed. The primary endpoint is overall survival, secondary endpoints are disease-free survival (DFS), toxicity, health-related quality of life (HRQL), prediction of response, and recurrence risk assessed by genomic and expression profiling. Accrual for the CRITICS trial is from the Netherlands, Sweden, and Denmark, and more countries are invited to participate.

CONCLUSION

Results of this study will demonstrate whether the combination of preoperative chemotherapy and postoperative chemoradiotherapy will improve the clinical outcome of the current European standard of perioperative chemotherapy, and will therefore play a key role in the future management of patients with resectable gastric cancer.

BACKGROUND

In the Western world, most patients with gastric cancer present with advanced stages of disease, leading to a low 5-year survival of around 25%.[1,2] After surgical resection, the majority of patients will develop a locoregional recurrence.[3] Many different strategies have been evaluated to improve the outcome of gastric cancer surgery. Randomized trials investigating the role of a more extended lymph node dissection (D2) in comparison with the standard D1 lymphadenectomy found no difference in overall survival, while a D2 dissection was associated with increased postoperative mortality and morbidity.[4-7]

Two Western studies have changed current clinical practice in the treatment of resectable gastric cancer. The Intergroup 0116 study showed a significant benefit in overall survival with adjuvant chemoradiotherapy (CRT) consisting of 45 Gy of radiotherapy combined with fluorouracil (5-FU) and leucovorin, compared to surgery alone.[8] In the British MAGIC (Medical Research Council Adjuvant Gastric Infusional Chemotherapy) study, a significant overall survival benefit was found favoring perioperative chemotherapy (epirubicine, cisplatin, and continuous 5-FU infusion, ECF-regimen) versus surgery alone.[9]

Taken the abovementioned pivotal studies together, the important question that needs to be answered is whether postoperative chemoradiotherapy improves survival as compared to postoperative chemotherapy in patients who are treated with neoadjuvant chemotherapy followed by gastric resection. Due to differences in study design and eligibility criteria between the Intergroup 0116 and the MAGIC study, comparing results of these trials is intrinsically not possible (Table 1). Therefore, the two regimens should be compared in a prospective, randomized manner. This is performed in the currently accruing CRITICS trial (ChemoRadiotherapy after Induction chemoTherapy In Cancer of the Stomach). In the present manuscript, we describe the study protocol of this trial and reflect on the possible implications.

METHODS AND DESIGN

STUDY DESIGN AND OBJECTIVES

The CRITICS study is an international, multicenter, randomized phase III trial. The primary objective is to compare overall survival between patients treated with neoadjuvant chemotherapy followed by surgery and either postoperative chemotherapy or postoperative chemoradiotherapy for resectable gastric cancer (Figure 1). Secondary endpoints include disease-free survival, toxicity, health-related quality of life (HRQL), prediction of response and recurrence risk assessed by genomic and expression profiling. Randomization is performed directly after entering the study, before the administration of preoperative chemotherapy.

The study started in January 2007 and as of May 2011, 350 patients have been included, while a total of 788 is required to meet the H0 hypothesis that the experimental arm with adjuvant chemoradiotherapy improves overall survival by 10% or more. In the first

Table 1. Comparison of Intergroup 0116, MAGIC and CRITICS trials

General	Intergroup 0116[8]	MAGIC[9]	CRITICS
Accrual	1991 – 1998	1994 - 2002	2007 -
N	556	503	788 (needed)
Randomization	after R0 surgery	after diagnosis (before any treatment)	after diagnosis (before any treatment)
Inclusion			
Histology	adenocarcinoma	adenocarcinoma	adenocarcinoma
Location	GEJ / stomach	lower 1/3 esophagus / GEJ / stomach	GEJ / stomach (bulk in stomach)
Stage	IB-IV (M0)	II-IV (M0)	IB-IV (M0)
Preoperative therapy			
Schedule	not applicable	A: ECF (3 courses) B: none	A: ECC/EOC (3 courses) B: ECC/EOC (3 courses)
Compliance	not applicable	86%	ongoing
Surgery			
Type	D0 gastrectomy: 54% D1 gastrectomy: 36% D2 gastrectomy: 10%	esophagogastrectomy: 23% D1 gastrectomy: 19% D2 gastrectomy: 40% non-curative/unknown: 18%	ongoing
R0 resection	100% (if R1/R2: no inclusion)	A: 69.3% B: 66.4%	ongoing
Postoperative Therapy			
Schedule	A: 5-FU/LV/RT (45Gy) B: none	A: ECF (3 courses) B: none	A: CC/RT (45Gy) B: ECC/EOC (3 courses)
Compliance	64%	42%	ongoing
Quality Assurance			
Surgery	D2 recommended postoperative analysis of extent of LN dissection	not reported	D1+ resection regular feedback to individual surgeons and pathologists
Radiotherapy	central review of RT plan major deviations corrected	not applicable	central review of at least first 3 RT plans of each center CTV contouring atlas
Results			
Primary endpoint	overall survival	overall survival	overall survival
Results	A: 42% 5-year OS B: 25% 5-year OS	A: 36% 5-year OS B: 23% 5-year OS	ongoing

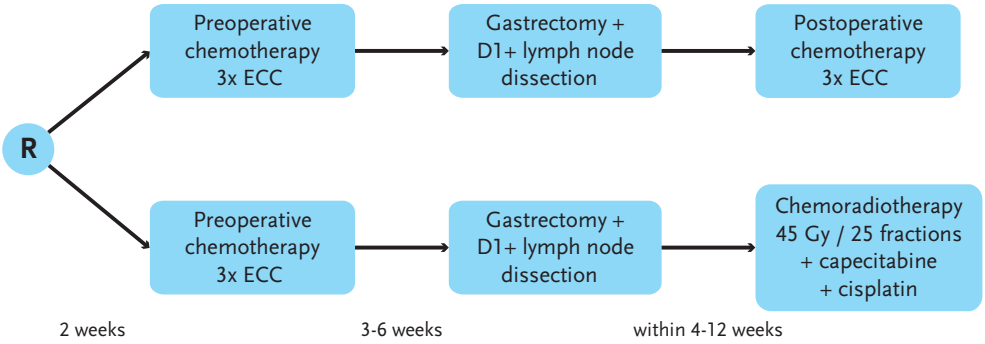
A: experimental arm, B: control arm, CTV: clinical target volume, GEJ: gastroesophageal junction, OS: overall survival
5-FU: 5-fluorouracil, LV: leucovorin, CC: capecitabine/cisplatin, ECC: epirubicin/cisplatin/capecitabine, EOC: epirubicin/oxaliplatin/capecitabine, RT: radiotherapy (always 25 x 1.8 Gy in 5 weeks)
D1+ resection: removal of stations 1-9 and 11, at least 15 lymph nodes, no routine splenectomy

two years only a few centers in the Netherlands included patients in this trial. At current times, about 50 centers are collaborating, and, besides the Netherlands, Sweden and Denmark are participating countries (clinicaltrials.gov NCT00407186).

PATIENT SELECTION AND PREOPERATIVE STAGING

Patients with histologically proven stage Ib-IVa (UICC 6th edition) gastric adenocarcinoma

Figure 1. Randomization scheme



R: randomization
ECC: epirubicin, cisplatin, capecitabine

are eligible for this study. The gastroesophageal junction (GEJ) may be involved, but the bulk of the tumor has to be in the stomach. Patients should be at least 18 years old and WHO performance status should be 0 or 1. Patients must have adequate hematological, renal and liver functions as defined in the study protocol. Left ventricular ejection fraction should not be lower than 50%. Exclusion criteria include: previous malignancy, inoperability due to technical surgery-related factors or general condition, and a solitary functioning kidney within the potential radiation field.

Baseline investigations consist of blood tests, an esophagogastroduodenoscopy with tumor biopsy samples, computed tomography (CT) of the chest and abdomen, renography, cardiac ejection-fraction scan, electrocardiography, and when the preoperative CT-scan suggests peritoneal carcinomatosis, diagnostic laparoscopy. Endoscopic ultrasonography and a PET-scan are optional.

Randomization is performed with stratification for Lauren classification (intestinal, diffuse, or mixed type adenocarcinoma, or unknown), localization (GEJ, proximal, mid, or distal stomach) and hospital.

PREOPERATIVE CHEMOTHERAPY

Within two weeks after randomization, preoperative chemotherapy is started. All patients are treated with 3 cycles of epirubicin, cisplatin, and capecitabine (ECC). Epirubicin 50 mg/m^2 and cisplatin 60 mg/m^2 are administered on day 1 intravenously every three weeks, with adequate hydration. Capecitabine is given orally on days 1-14 in a dose of 1000 mg/m^2 bid. In Sweden, oxaliplatin 130 mg/m^2 is administered instead of cisplatin in order to facilitate chemotherapy administration in the outpatient clinic setting without the need for prehydration. At the start of the study no reimbursement was available for oxaliplatin in the treatment of gastric cancer in the Netherlands. Response evaluation with CT-scan after two cycles of chemotherapy is aimed primarily to identify patients with early progression.

SURGERY

Surgery is planned 3-6 weeks after the last chemotherapy course. The definitive decision to proceed to surgery is taken based on the absence of signs of progressive disease and an ASA classification of 1 or 2.

Under general anaesthesia supported by epidural anaesthesia, a midline laparotomy is performed, followed by a complete exploration of the abdomen including peritoneal surfaces, liver, and in women, the ovaries. Any free abdominal fluid is aspirated for cytological examination. A curative resection is not possible in case of tumor infiltration into the head of the pancreas requiring a Whipple procedure, para-aortic lymph node metastases below the renal arteries, tumor positive cytology of free peritoneal fluid, or peritoneal metastases that cannot be included in the planned local resection. If curative resection is not possible, the best palliative surgical option is to be decided upon by the surgeon.

Principle of surgery is a wide resection of the tumor bearing part of the stomach (total, subtotal or distal gastrectomy) en bloc with the N1 and N2 lymph nodes (stations 1-9 and 11, Figure 2, page 103) with a minimum of 15 lymph nodes, without routine splenectomy and resection of the pancreatic tail (D1+ lymph node dissection).[10] If possible, a macroscopic proximal and distal margin of 5 cm should be obtained. Adjacent organs are only removed when there is suspicion on tumor involvement.

The continuity of the gastrointestinal tract is restored by a Billroth II reconstruction or with the use of a Roux-en-Y loop. Whether the anastomosis is hand-sutured or stapled is left up to the surgeon. A feeding jejunostomy is strongly advocated and is left *in situ* until postoperative treatment has been completed and oral intake is adequate.

PATHOLOGY

The specimen is sent to the pathologist, preferably fresh and unopened to enable the collection of fresh frozen tissue, followed by processing and reporting of the specimen according to the study protocol. The pathology report includes a minimal dataset containing the following items: type of tumor, localization and size of tumor, invasion depth, surgical margins, and number of (tumor positive) lymph nodes. All specimens undergo additional central pathology review for grading of histological response.[11]

POSTOPERATIVE TREATMENT

Between 4-12 weeks following surgery, patients in the control arm are given another 3 courses of ECC. Patients in the experimental arm are treated with radiotherapy combined with capecitabine and cisplatin during five weeks. Capecitabine in this group is administered in a dose of 575 mg/m^2 bid from Monday to Friday. Cisplatin is administered at a dose of 20 mg/m^2 intravenously with pre- and posthydration weekly. The chemotherapy doses are based on previous dose-finding studies in The Netherlands Cancer Institute (see discussion).[12,13]

Radiotherapy consists of 45 Gy in 25 fractions of 1.8 Gy with a frequency of five fractions a week. External beam therapy is used to irradiate the tumor bed, anastomoses and regional lymph nodes. The *clinical target volume* (CTV) has to be delineated on CT-images based on all diagnostic information available. In defining a *planning target volume* (PTV), the CTV has to be expanded in all directions with a margin of 10 mm, except towards the vertebrae and kidneys, where a margin of 5 mm is applied. All 3D conformal (or IMRT, *intensity modulated radiotherapy*) techniques are allowed to get a homogeneous dose distribution in the PTV. AP-PA techniques are judged to be suboptimal and are therefore not allowed. Target volume delineation manuals and workshops are offered to all participating radiation oncologists. A digital CTV contouring atlas is made available for all local investigators by the study coordinators. Furthermore, all centers are asked to provide CTV contouring and treatment plans of the first three included patients (or of consecutive patients if considered necessary) to the study coordinators before start of treatment, as interobserver variability in CTV delineation for postoperative radiotherapy after gastric resection is large.[14]

TOXICITY AND ADVERSE EVENTS

Toxicity is measured according to NCI Common Toxicity Criteria (CTC), version 3.0. When preoperative chemotherapy is postponed for more than two weeks consecutively, chemotherapy should be discontinued and the patient should proceed to surgery when possible. Dose modification rules are defined in the study protocol.[15] Serious adverse events are defined according to the rules of good clinical practice and must be reported within one working day.

FOLLOW-UP

After treatment, patients are followed by a medical oncologist or gastroenterologist (and radiation oncologist when they received radiotherapy) on a monthly basis during the first three months, followed by three-monthly visits during the rest of the first year and visits every six months until five years of follow-up. Beyond the initial postoperative period, follow-up by the surgeon is planned every 6 months. CT-scanning and renography are performed every 6 months, followed by yearly scans after 2 years of follow-up.

STATISTICS

Based on results from the Intergroup 0116[8] and MAGIC[9] trials, it is estimated that 5-year overall survival in the perioperative chemotherapy group is 40% and in the chemoradiotherapy group 50%. In order to detect a difference between 40% and 50% in 5-year overall survival with a power of 80% and a significance level of 0.05, about 430 events are required, which corresponds to a total of 788 patients. Data analysis will be performed according to the intention to treat principle. An interim analysis is performed when half of the required number of events have been observed.

ETHICS

All patients receive both oral and written information about the study. Randomization can only take place when patients have signed an informed consent. The study is carried out in agreement with the declaration of Helsinki. The study has been approved by the Medical Ethical Committee of the Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital.

QUALITY ASSURANCE

Local monitoring has been performed for the first three patients in the first ten participating centers and continuation of the monitoring will be performed. Furthermore, surgical and pathological quality is monitored for every patient, and feedback to the individual surgeons and pathologists on their own performance is used to improve surgical and pathological quality.

SIDE STUDIES

Patients fill out quality of life questionnaires EORTC QLQ-C30 and STO22 five times after randomization: before treatment, after preoperative chemotherapy, after surgery, after postoperative therapy and during follow-up after 12 months. After finishing accrual and survival analysis, the value of the Maruyama Index of unresected disease[16] and the Memorial Sloan-Kettering Cancer Center (MSKCC) predictive nomogram[17] will be investigated. Furthermore, collected tumor tissue and serum will be used for genomic profiling and further translational research focussing on prognostic and predictive biomarkers.

DISCUSSION

SURGERY

In both the British MRC trial[4,5] and the Dutch Gastric Cancer Trial (DGCT)[6,7] that randomized gastric cancer patients for a D1 or D2 lymph node dissection, overall survival was not statistically different between the two groups, while a D2 dissection was associated with increased postoperative mortality and morbidity. This might be partially attributed to the higher number of splenectomies and pancreatectomies with a D2 dissection. Another study showed that splenectomy is associated with a twofold risk of postoperative complications.[18] Therefore, it is suggested that performing a gastrectomy with dissection of at least 15 (N1 and N2) lymph nodes, but without routine splenectomy and resection of the pancreatic tail, a so called D1+ resection, can result in a better outcome.[19] The rationale for a minimum of 15 nodes has been the observation that patients with at least 15 nodes examined have superior survival compared to patients with fewer nodes examined.[20,21]

While the Intergroup 0116 study, which had no strict surgical quality protocol, was criticized for its low number of per protocol prescribed D2 dissections,[16] in the MAGIC

study the percentage of D2 dissections was higher, although no surgical or pathological quality measurements were performed. In the CRITICS study, the Maruyama Index (MI) of unresected disease is used to estimate surgical quality.[16] Also, feedback to individual surgeons and pathologists on their own performance is used to improve surgical and pathological quality.

POSTOPERATIVE CHEMORADIOTHERAPY

The Intergroup 0116 study is the key trial supporting the use of postoperative chemoradiotherapy in the potentially curative treatment of gastric cancer.[8] Because of this trial, postoperative CRT is currently a standard option in the United States for patients undergoing curative resection of stage Ib-IV gastric cancer.[22] However, the study has been criticized because it had no strict surgery and pathology quality protocol, suboptimal surgery (with 54% D0 resections while at least a D1 resection should be recommended), a complex, toxic and nowadays outdated chemotherapy schedule with minimal room for interaction with the daily radiation sessions, and the fact that patients were highly selected (only R0 resections with adequate postoperative recovery). In addition, toxicity in the chemoradiotherapy arm was substantial, with only 64% of the patients completing the planned treatment. In a Dutch retrospective study, postoperative chemoradiation after a D2 dissection was not associated with improved survival,[23] in contrast to the results of a large observational Korean study.[24]

Since the Intergroup 0116 study was initiated in the early 90s, the concept of concurrent chemoradiotherapy has nowadays been further developed. Capecitabine, an oral prodrug of 5-FU, mimics continuous infusion of 5-FU, and has proven its feasibility in combination with cisplatin and radiotherapy in several phase I/II studies in advanced, resectable gastric cancer,[12,25] while its systemic exposure was not found to be compromised by the radiation treatment.[26] In these studies, acute toxicity was low, and compliance to the treatment protocol was high (89-100%). The maximum tolerable doses that evolved from these studies are currently used in the CRITICS study. Renal toxicity was addressed in a prospective fashion, showing a reduction in contribution of the left kidney to total renal function in more than half of the patients, especially after 2D radiotherapy techniques.[27] This illustrates the need for precise modern radiotherapy techniques to minimize renal toxicity.

CHEMOTHERAPY

Many studies have been performed with adjuvant chemotherapy in resectable gastric cancer. These studies have been part of several meta-analyses, which could demonstrate no, or at the most a modest survival benefit for adjuvant chemotherapy.[28-33] Newer chemotherapy schedules, with capecitabine and oxaliplatin, have shown to be as least as effective as schedules with 5-FU and cisplatin, with respect to overall survival (REAL-2 study).[34]

The combination of adjuvant with neo-adjuvant chemotherapy has proven its value in two randomized studies. In the MAGIC study, perioperative chemotherapy resulted in a reduction of the tumor stage, a 10% higher resectability rate and a significant survival benefit of 13% at 5 years.[9] It should be noted that only 55% started postoperative chemotherapy and 42% of the patients completed the entire treatment. The major reasons for a premature treatment stop were tumor progression, postoperative complications, patients' refusal and toxicity. A French prospective trial showed comparable results with 48% of the patients completing the total regimen.[35] The final report of this study has to be awaited. A recent EORTC study comparing preoperative chemotherapy and D2 surgery with D2 surgery alone was stopped early because of poor accrual. A higher R0 resection rate was found in the chemotherapy arm, but no benefit in survival was detected in this underpowered study.[36]

Due to the strong position of perioperative chemotherapy with tumor downsizing and downstaging the CRITICS investigators were reluctant towards a randomization arm without preoperative chemotherapy. Therefore, both arms have the same preoperative chemotherapy schedule. This also leads to comparable resection rates thus eliminating the effect of surgery (and preoperative therapy) on a potential survival difference between the two treatment arms.

FUTURE PERSPECTIVES

With the CRITICS trial, several other studies on the treatment of resectable gastric cancer are ongoing or have just finished. In the currently accruing MAGIC-B study, patients are randomized between perioperative ECC courses with or without bevacizumab. In the Korean ARTIST trial, which finalized accrual, patients were randomized between postoperative chemotherapy with cisplatin and capecitabine versus chemoradiotherapy after a D2 gastric resection. No preoperative therapy was administered. Feasibility data of this study were reported at ASCO-GI 2009 showing good toxicity profiles with compliance rates of 75% versus 82% respectively. Survival data of this trial have to be awaited.[37]

An interesting development is the use of trastuzumab for Her2 positive tumors, which has shown an impressive survival benefit in metastatic gastric cancer.[38] This raises the question if trastuzumab is a valuable addition to the currently used chemotherapy regimens for Her2 positive, resectable gastric cancer. But so far, no such trials have been initiated.

FINAL REMARKS

Accrual for the CRITICS study has been expanded to Sweden and Denmark and more countries are invited to participate. It is expected that the results of this study will play a key role in the future treatment of patients with resectable gastric cancer.[39]

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PART III

Surgical quality assurance

CHAPTER 10

Quality of care indicators for the surgical treatment of gastric cancer: a systematic review

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ABSTRACT

BACKGROUND

Quality assurance is increasingly acknowledged as a crucial factor in the (surgical) treatment of gastric cancer. The aim of the current study was to define a minimum set of evidence-based quality of care indicators for the surgical treatment of locally advanced gastric cancer.

METHODS

A systematic review of the literature published between January 1990 and May 2011 was performed, using search terms on gastric cancer, treatment, and quality of care. Studies were selected based on predefined selection criteria. Potential quality of care indicators were assessed based on their level of evidence, and were grouped into structure, process, and outcome indicators.

RESULTS

A total of 173 articles were included in the current study. For structural measures, evidence was found for the inverse relationship between hospital volume and postoperative mortality as well as overall survival. Regarding process measures, the most common indicators concerned surgical technique, perioperative care and multimodality treatment. The only outcome indicator with supporting evidence was a microscopically radical resection.

CONCLUSIONS

Although specific literature on quality of care indicators for the surgical treatment of gastric cancer is limited, several quality of care indicators could be identified. These indicators can be used in clinical audits and other quality assurance programs.

INTRODUCTION

Quality assurance is increasingly acknowledged as a crucial factor in the (surgical) treatment of gastric cancer, mainly because outcomes between different providers and different countries vary considerably.[1-3] In Europe, mortality rates after gastric cancer resections range from below 2% in specialized centers,[4] to above 10% in certain nationwide registries,[2] while in Japan mortality rates below 1% are achieved in specialized centers.[5] Also, long term survival rates in Asian centers are superior to those in Western centers, and even within Europe long-term survival shows substantial differences.[3,6,7] In an attempt to reduce these variations in outcomes and to pursue delivery of high quality oncologic care, the European Organisation for Research and Treatment of Cancer (EORTC) has advocated quality assurance programs for radiotherapy and medical oncology.[8,9] More recently, surgical audits for gastric cancer treatment were initiated in the United Kingdom, Denmark, and the Netherlands.[10-12]

Evidence-based treatment guidelines provide a framework for clinical decision making, but seldom incorporate all available quality indicators. Donabedian has proposed a model to evaluate patient care in terms of structure, process, and outcome measures.[13] With this model, quality of care indicators can be assessed in a structural and uniform way. This has been performed for esophageal cancer and breast cancer.[14,15] As yet, no systematic assessment of quality of care indicators for gastric cancer treatment has been performed.

The aims of the present study were to identify evidence-based standards for the surgical treatment of locally advanced gastric cancer, based on a systematic review of the literature, and to construct a minimum set of quality of care indicators for registration and benchmarking in gastric cancer surgery.

METHODS

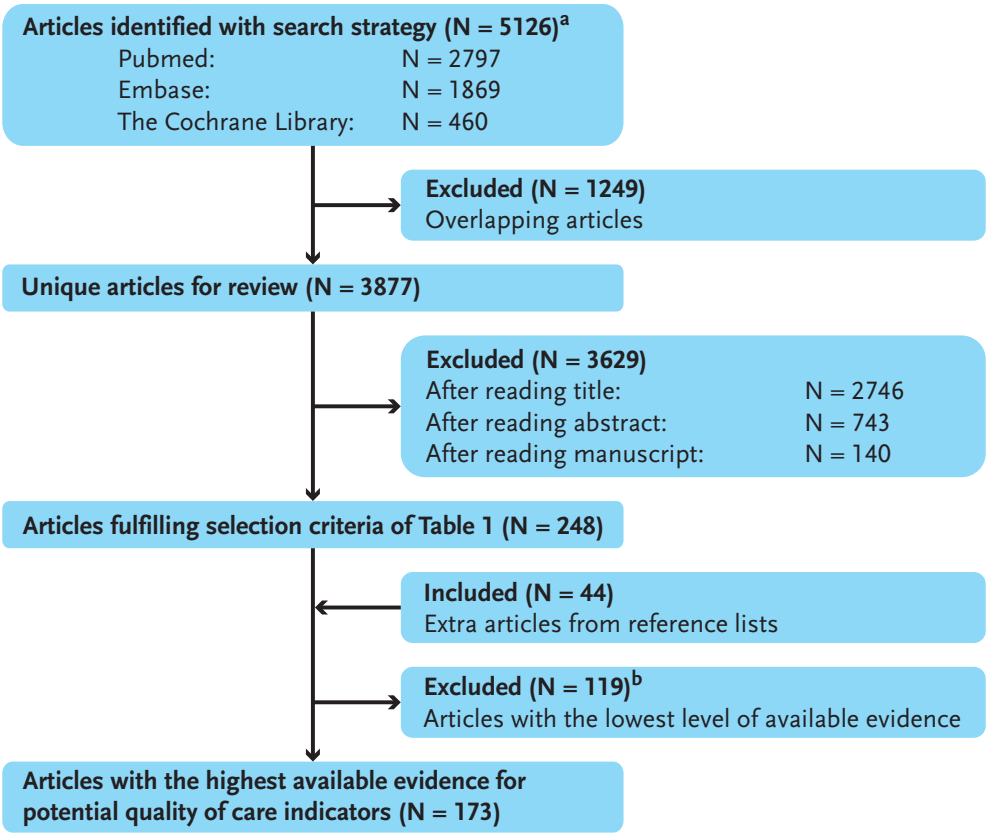
SEARCH STRATEGY

Literature that was published between January 1990 and May 2011 was assessed through Pubmed, Embase, and the Cochrane library, using a search strategy that was constructed by a specialized librarian (Appendix). Search terms on gastric neoplasms were combined with treatment-related search terms (surgery, chemotherapy, and radiotherapy). Because there is no universal Medical Subject Headings (MeSH) term available to identify studies on quality of care, a variety of search terms related to this subject was used to select studies appropriate for this review.

SELECTION OF STUDIES

Study selection criteria were created using a Delphi technique[16] with four authors (JLD, JS, JWvS and MWJMW) and are shown in Table 1. Only comparative studies on locally advanced (at least T2), non-metastatic gastric cancer were selected. Treatment should

Figure 1. Selection process



[a] The used search strategy is outlined in the Appendix
[b] Levels of evidence are described in the Methods section (Selection of studies)

consist of a gastric resection, with or without chemotherapy and/or radiotherapy before and/or after the operation. Two investigators (JLD and JS) independently reviewed each title, abstract, and manuscript (Figure 1). Disagreements on selecting a study were solved by discussion, or by consulting a third reviewer (JWvS). Reference lists of the selected articles were then searched for additional studies.

Different levels of evidence were distinguished. A meta-analysis of at least 2 randomized controlled trials (RCTs) was considered the highest level of evidence. The next level of evidence consisted of one or more RCTs, and the lowest level of evidence comprised non-randomized studies (prospective or retrospective). When at least five meta-analyses were available for a certain indicator, RCTs on the same subject were not included in the current review. When at least one RCT with at least 100 patients was available for a certain indicator, non-randomized studies on the same subject were not included.

Table 1. Inclusion and exclusion criteria

	Included	Excluded
Publication	January 1990 - May 2011 English language	before 1990, after May 2011 non-English language
Study design	In order of availability: meta-analysis RCT[1] non-randomized comparative study[2]	non-comparative study (including systematic reviews, non-systematic reviews, case reports, phase I/II studies)
Study population	≥50 gastric cancer patients at least T2 tumor	gastric cancer patients with: T1 tumor metastatic disease recurrent disease
Treatment	open or laparoscopic gastric cancer surgery with or without (neo)adjuvant chemo- and/ or radiotherapy	palliative treatment salvage surgery emergency surgery esophageal-cardia resection endoscopic (sub)mucosal resection intraperitoneal chemotherapy intraoperative radiotherapy targeted therapy

RCT: Randomized Controlled Trial
[1] when at least five meta-analyses were available for a certain indicator, RCTs on the same subject were not included in the current review
[2] when at least one RCT with at least 100 included patients was available for a certain indicator, non-randomized studies on the same subject were not included in the current review

QUALITY OF CARE INDICATORS

Potential quality of care indicators were grouped into the three categories as defined by Donabedian: structure, process, and outcome.[13] *Structure* indicators relate to the setting in which care takes place. *Process* indicators refer to the actual medical treatment that is applied to the patient. *Outcome* indicators reflect the outcome of healthcare.

To be entered into a minimum set of evidence-based quality of care indicators for gastric cancer surgery, indicators needed support of at least one meta-analysis, two RCTs, or one RCT either with at least 100 patients or with an adequate power analysis supporting less than 100 included patients, or at least three non-randomized studies with multivariate analysis. In case of conflicting evidence for a certain indicator, RCTs were considered decisive over non-randomized studies. For conflicting studies with equal levels of evidence, the number of non-supporting studies was subtracted from the number of supporting studies.

RESULTS

A total of 3.877 unique articles published between January 1990 and May 2011 was identified with the literature search. These articles were reviewed, and 248 articles fulfilled the selection criteria shown in Table 1. In the reference lists of the selected articles, 44 studies matched with the selection criteria for this study. Articles were then grouped by subject and categorized based on their level of evidence. In the final selection step, articles with the highest level of evidence for a certain indicator were separated from

those with lower levels of evidence on that subject. In total, 173 articles were included in the current review (Figure 1).

STRUCTURE INDICATORS (TABLE 2)

Many studies have been performed analyzing possible volume-outcome relations in gastric cancer surgery (Table 2). In the majority of these studies, the effect of hospital volume on postoperative mortality was investigated, with variable results.[12,17-33] Of note, in most large studies, a benefit for high annual hospital volume was found, while in smaller studies no difference between high volume and low volume hospitals was detected (Figure 2). In none of these studies, high hospital volume was associated with poor outcomes. In the studies that did find a relation between volume and outcomes, there was no uniform threshold for what should be considered high volume surgery, although it was most frequently set at 20 per year.

In a limited number of studies surgeon volume and surgeon experience were investigated, with a benefit for increasing surgeon volume,[17,20,23,34,35] but no benefit for increasing surgeon experience.[20,36] In two studies, outcomes between university/teaching and non-university/non-teaching hospitals were compared, but no difference in survival was documented.[26,37]

PROCESS INDICATORS – SURGERY (TABLE 3)

EXTENT OF LYMPH NODE DISSECTION

Numerous studies have been performed in which a limited lymph node dissection (D1) was compared with an extended lymph node dissection (D2), but only four of these studies were RCTs.[4,38-40] None of these RCTs revealed a difference in overall survival, except for a small, early study.[39]

The increased postoperative mortality in the D2 group is likely the result of the high number of splenectomies and distal pancreatectomies, combined with a lack of experience with D2 lymph node dissections in Europe. As gastric-cancer specific survival in the Dutch D1D2 study was higher after a D2 dissection, it has been suggested that a D2 dissection without splenectomy, performed in an experienced center will lead to improved survival as compared to a D1 dissection.[40] In a Taiwanese RCT performed in specialized centers, a D3 dissection led improved overall survival over a D1 dissection.[41] Combining an extended lymph node dissection with removal of the paraaortic nodes did not result in a survival benefit.[5,42,43]

LAPAROSCOPIC RESECTION

Laparoscopic resections for gastric cancer are mainly performed in Asia, where the incidence of early gastric cancer is high. In the majority of studies on laparoscopic surgery, only patients with early gastric cancer were included. There is one RCT comparing laparoscopic distal gastrectomy (LDG) with open distal gastrectomy in

Table 2. Structure Measures

Structure measure	End point	Indicator	MA (+/-/=)	RCT (+/-/=)	NRS (+/-/=)	Ref.
Hospital volume (high versus low)	overall survival	high volume	NA	NA	5/0/2	17,28,31,33,138-140
	postoperative mortality	high volume			11/0/8	12,17-33
	postoperative morbidity	high volume			2/0/2	25,29,141,142
	length of hospital stay	high volume			0/0/1	29
	number of lymph nodes	high volume			2/0/0	12,143
Surgeon volume (high versus low)	postoperative mortality	high volume	NA	NA	3/0/1	17,20,23,34
	postoperative morbidity	high volume			1/0/0	34
	overall survival	high volume			0/0/2	17,35
Surgeon experience (experienced versus non-experienced)	postoperative mortality	experienced	NA	NA	0/0/2	20,36
	postoperative morbidity	experienced			0/0/1	36
	peroperative blood loss	experienced			0/0/1	36
University/teaching hospital	overall survival	university/teaching hospital	NA	NA	0/0/2	26,37
NCI-NCCN Center[a]	postoperative mortality	NCI-NCCN Center	NA	NA	1/0/0	143
	number of lymph nodes	NCI-NCCN Center			1/0/0	143

[a]only in United States

Legend to Tables 2-7

+	number of studies indicating a positive effect of the indicator on the endpoint listed
-	number of studies indicating a negative effect of the indicator on the endpoint listed
=	number of studies with no significant difference between the indicator and its opposite with regard to the endpoint listed
Excl.	excluded
LDG	laparoscopic distal gastrectomy
LG	laparoscopic gastrectomy
LMWH	low molecular weight heparin
LN	lymph nodes
LND	lymph node dissection
MA	meta analysis
NA	not available
NCI-NCCN Center	National Cancer Institute - National Comprehensive Cancer Network Center
NRS	non randomized study
ODG	open distal gastrectomy
OG	open gastrectomy
PAND	paraaortic lymph node dissection
R0	microscopically radical resection
R1	microscopically irradical resection
RCT	randomized controlled trial
Ref.	references
RY	roux-en-y reconstruction
SG	subtotal gastrectomy
TG	total gastrectomy
TG-PS	total gastrectomy + pancreaticosplenectomy
TG-S	total gastrectomy + splenectomy

patients with advanced gastric cancer.[44] LDG was associated with less blood loss, earlier resumption of food intake and shorter hospital stay (*postoperative recovery* in Table 3), but postoperative mortality and morbidity, and overall survival were comparable between the two groups. Likewise, in most non-randomized comparative series, laparoscopic gastric cancer surgery was comparable to open surgery with respect to both short- and long-term results.[45-53] In several non-randomized studies, one should be aware of a significant difference in disease stage between the laparoscopic and open surgery group.

Table 3. Process Measures - surgery

Process measure	End point	Indicator	MA (+/-/=)	RCT (+/-/=)	NRS (+/-/=)	Ref.
Extent of lymph node dissection						
D1 versus D2 LND	overall survival	D2 LND	0/0/2	0/1/2	Excl.	38-40,144,145
	disease-specific survival		NA	1/0/0		40
	recurrence rate		1/0/0	0/0/1		40,144
	postoperative mortality		0/2/0	0/2/1		4,40,144-146
	postoperative morbidity		0/0/1	0/2/1		39,40,144,146
	transfusion requirement		NA	0/1/0		39
D1 versus D3 LND	overall survival	D3 LND	NA	1/0/0	Excl.	41
	postoperative morbidity			0/1/0		147
	operating time			0/1/0		147
	quality of life			0/0/1		148
D2 versus D2+PAND	overall survival	D2+PAND	0/0/1	0/0/2	Excl.	5,42,43
	postoperative mortality		0/0/1	0/0/2		42,149,150
	postoperative morbidity		0/0/1	0/1/1		42,149,150
	body weight		NA	0/0/1		151
	functional outcomes			0/0/1		151
	operating time			0/1/0		152
	blood loss			0/1/0		152
Removal of celiac nodes	long term complaints	celiac node removal	NA	NA	0/1/0	153
D1/2 versus D3/4	lymphorrea	D1/2	NA	NA	1/0/0	154
Laparoscopic resection						
LDG versus ODG	overall survival	LDG	NA	0/0/1	0/0/2	44,47,52
	postoperative mortality			0/0/1	0/0/5	44,47-49,52,53
	postoperative morbidity			0/0/1	0/0/5	44,47-49,52,53
	postoperative recovery			1/0/0	5/0/0	44,47-49,52,53
	number of lymph nodes			0/0/1	0/0/2	44,48,52
LG versus OG	overall survival	LG	NA	NA	0/0/2	46,50
	postoperative mortality				0/0/3	46,50,51
	postoperative morbidity				0/1/3	45,46,50,51
	postoperative recovery				2/0/0	46,51
	number of lymph nodes				1/0/1	46,50
	resection margins				0/0/2	46,50
	intraperitoneal cancer cells				0/0/1	155
Type of resection						
Total versus subtotal gastrectomy	overall survival	SG	NA	0/0/1	1/0/6	54,156-162
	postoperative mortality			0/0/1	0/0/6	55,156,159-163
	postoperative morbidity			0/0/1	0/0/6	55,156,159-163
	postgastrecomty symptoms			1/0/0	NA	164
	weight			NA	2/0/0	159,163
	quality of life			1/0/0	2/0/0	163-165
TG versus TG-S	overall survival	TG	0/0/1	0/0/2	NA	56,166,167
	postoperative mortality		0/0/1	0/0/2		56,166,167
	postoperative morbidity		0/0/1	0/1/1		56,166,167
	number of harvested LNs		0/0/1	0/0/1		166,167

Table 3 (continued)

Process measure	End point	Indicator	MA (+/-/=)	RCT (+/-/=)	NRS (+/-/=)	Ref.
TG-S versus TG-PS	overall survival	TG	NA	0/0/1	0/1/2	57,58,168,169
	postoperative mortality			0/0/1	0/1/2	57,58,168,169
	postoperative morbidity			0/0/1	0/3/0	57,58,168,169
	number of harvested LNs			0/0/1	1/0/0	57,168
	glucose intolerance			0/1/0	0/2/0	57,58,168
TG versus TG-PS	overall survival	TG	NA	NA	0/1/2	59-61
	postoperative mortality				0/0/3	59-61
	postoperative morbidity				0/3/0	59-61
Bursectomy	postoperative mortality	bursectomy	NA	0/0/1	NA	62
	postoperative morbidity			0/0/1		62
Multiorgan resection (yes versus no)	overall survival	multiorgan resection	NA	NA	0/1/2	170-172
	postoperative mortality				0/0/2	171,172
	postoperative morbidity				0/0/2	171,172
Type of reconstruction						
Pouch reconstruction after total gastrectomy (yes versus no)	postoperative mortality	pouch	0/0/2	0/0/3	Excl.	63,64,66,173,174
	postoperative morbidity		0/0/2	0/0/3		63,64,66,173,174
	post gastrectomy symptoms		1/0/1	0/0/2		63,64,173,174
	quality of life		2/0/0	2/0/1		63-66,174
	weight		1/0/1	1/0/3		63-66,173,174
Billroth I versus Billroth II reconstruction	overall survival	Billroth II	NA	0/0/1	NA	67
	postoperative mortality			0/0/1	NA	67
	postoperative morbidity			1/0/0	0/0/1	67,70
	hospital stay			NA	0/0/1	70
Billroth I/II versus RY reconstruction	postoperative morbidity	RY	NA	0/0/1	0/0/1	68,69
	hospital stay			0/0/1	1/0/0	68,69
	bile reflux			0/0/1	NA	68
Hand sewn versus stapled anastomosis	postoperative mortality	stapled	NA	0/0/1	0/0/2	71-73
	postoperative morbidity			0/0/1	0/0/2	71-73
	delayed gastric emptying			NA	0/1/0	71
	operation time			0/0/1	1/0/0	71,72
Other surgery-related factors						
Use of Ligasure (yes versus no)	postoperative mortality	Ligasure	NA	0/0/1	NA	175
	postoperative morbidity			0/0/1		175
	operating time/blood loss			1/0/0		175
	number of harvested LN			0/0/1		175
Seprafilm versus no seprafilm	postoperative mortality	Seprafilm	NA	0/0/1	NA	176
	postoperative morbidity			0/0/1		176
	small bowel obstruction			0/0/1		176
Duration of surgery	surgical site infection	shorter operation time	NA	NA	1/0/0	177
Ligation versus cauterization of lymphatic vessels	postoperative lymphorroea	ligation	NA	NA	1/0/0	154
Transverse versus midline incision	postoperative morbidity	transverse	NA	0/0/1	NA	178
	intestinal obstruction			0/0/1		178
	postoperative pain			0/0/1		178
Prophylactic drain versus no drain	postoperative morbidity	no drain	NA	0/0/2	NA	179,180
	postoperative mortality			0/0/1		180
	analgesic use			1/0/0		179
	hospital stay			1/0/1		179,180
Intra-operative blood loss	peritoneal recurrence	< 475 ml blood loss	NA	NA	1/0/0	181

TYPE OF RESECTION

In the largest RCT on subtotal versus total gastrectomy for distal gastric tumors, no difference was observed in overall survival or postoperative mortality or morbidity.[54,55] Routine (pancreatico)splenectomy has been advocated to obtain a more thorough lymph node dissection. However, a survival benefit has never been shown. In contrast, routine splenectomy increased the number of postoperative septic complications in a Chile RCT.[56] The addition of a pancreatectomy also increased postoperative morbidity in a number of studies.[57-61] A bursectomy did not result in increased postoperative morbidity and mortality, but a survival analysis is yet to be performed in the single RCT on this subject.[62]

TYPE OF RECONSTRUCTION

A benefit of creating a reservoir or pouch after total gastrectomy was found in two meta-analyses and two RCTs.[63-66] Studies on reconstructive techniques after subtotal gastric resection have shown varying results, and no large RCTs are available on this subject.[67-70] In two studies comparing a stapled with a hand-sewn anastomosis, no difference was found in postoperative mortality or morbidity, while in one retrospective study, stapler use was associated with an increase in delayed gastric emptying.[71-73]

Several other subjects related to surgical technique are shown in Table 3.

PROCESS INDICATORS – PERIOPERATIVE CARE (TABLE 4)

The administration of perioperative parenteral nutrition reduced postoperative morbidity in malnourished patients in one retrospective study.[74] In another study, there was no significant difference between the groups with and without enteral and/or parenteral nutritional support.[75] In three RCTs, immunonutrition was associated with less infectious complications and a shorter hospital stay.[76-78] Due to its high costs, shorter hospital stay did not lead to less overall costs.[77]

In earlier days, nasogastric decompression has been used routinely to prevent anastomotic leakage, enhance bowel function and shorten hospital stay. However, in none of the studies, a benefit in postoperative morbidity or mortality of routine nasogastric or nasojejunal decompression was documented. In contrast, in three RCTs, hospital stay increased with the use of nasogastric decompression.[79-81]

In both RCTs on fast-track gastric cancer surgery, fast-track care improved postoperative recovery (return to normal gastro-intestinal function, analgesic use, mobilization, and hospital stay) as compared to conventional care.[82,83] Both RCTs were performed in China. One of the two studies also showed a significant decrease in medical costs with fast-track care.[83]

Randomized studies on the prognostic impact of perioperative blood transfusions in gastric cancer surgery are not available, and non-randomized studies show conflicting results. In nine retrospective series, an association was found between no blood

Table 4. Process Measures - perioperative care

Process measure	End point	Indicator	MA (+/-/=)	RCT (+/-/=)	NRS (+/-/=)	Ref.
Perioperative nutritional support versus normal diet	postoperative mortality	nutritional support	NA	NA	0/0/2	74,75
	postoperative morbidity				1/0/1	74,75
Immunonutrition	postoperative mortality	immunonutrition	NA	0/0/3	NA	76-78
	postoperative morbidity			3/0/0	NA	76-78
Nasogastric decompression	postoperative mortality	nasogastric decompression	0/0/1	0/0/6	Excl.	79-81,182-185
	postoperative morbidity		0/0/1	0/0/6		79-81,182-185
	time to flatus/intake		0/1/0	0/3/3		79-81,182-185
	hospital stay		0/0/1	0/3/3		79-81,182-185
Early versus traditional oral feeding	postoperative mortality	early feeding	NA	NA	0/0/1	186
	postoperative morbidity				0/0/1	186
	postoperative recovery				1/0/0	186
Fast track care versus conventional care	postoperative mortality	fast track	NA	0/0/2	NA	82,83
	postoperative morbidity			0/0/2		82,83
	postoperative recovery			2/0/0		82,83
Perioperative transfusion versus no transfusion	overall survival	no transfusion	NA	NA	4/0/5	84-92
	postoperative mortality				0/0/2	92,187
	postoperative morbidity				0/0/2	92,187
LMWH prophylaxis vs no prophylaxis	postoperative morbidity	LMWH prophylaxis	NA	NA	0/1/0	188
	postoperative recovery				0/0/1	188
Selective bowel decontamination	anastomotic leakage	selective bowel decontamination	NA	1/0/0	NA	93
Single versus multiple dose antibiotics	surgical site infection	multiple dose antibiotics	NA	1/0/0	NA	94

transfusion and a better survival rate in univariate analysis.[84-92] In four of these studies, this adverse effect remained significant in multivariate analysis considering other prognostic factors.[85,88,90,91]

In one RCT on selective bowel decontamination, a decreased anastomotic leakage rate was found.[93] In another study, the use of multiple dose antibiotics was associated with less surgical site infections than the use of single dose antibiotics.[94]

PROCESS INDICATORS – MULTIMODALITY THERAPY (TABLE 5)

NEOADJUVANT THERAPY

In several studies, the role of preoperative chemotherapy was assessed, but in none of these individual studies a benefit compared to surgery alone was found.[95-97] However, in a recent meta-analysis on preoperative chemotherapy, a benefit in survival was documented.[98] In the British MAGIC study, perioperative chemotherapy improved overall survival.[99] In a study comparing preoperative with postoperative chemotherapy, a higher treatment compliance was observed in the preoperative chemotherapy group.[100] Preoperative radiotherapy has only been tested positive in a study with gastric cardia cancer patients.[101]

Table 5. Process Measures - multimodality treatment

Process measure	End point	Indicator	MA (+/-/=)	RCT (+/-/=)	NRS (+/-/=)	Ref.
Neo-adjuvant treatment						
Preoperative chemotherapy	overall survival	preoperative chemotherapy	1/0/0	0/0/3		95-98
	R0 resection rate		1/0/0	1/0/1	Excl.	95,96,98
	morbidity		NA	1/0/0		96
Preoperative versus postoperative chemotherapy	treatment compliance	preoperative chemotherapy	NA	1/0/0	Excl.	100
	morbidity			0/0/1		100
Perioperative chemotherapy	overall survival	perioperative chemotherapy	NA	1/0/0	Excl.	99
	R0 resection rate			0/0/1		99
Preoperative radiotherapy	overall survival	preoperative radiotherapy	NA	0/0/1	Excl.	189
	mortality			0/0/1		189
	morbidity			0/0/1		189
Adjuvant treatment						
Adjuvant chemotherapy	overall survival	adjuvant chemotherapy	9/0/1	Excl.	Excl.	102-111
Single-agent versus combination chemotherapy	overall survival	combination chemotherapy	1/0/0	Excl.	Excl.	111
Postoperative chemoradiotherapy	overall survival	postoperative chemoradiotherapy	NA	1/0/0	Excl.	112
Postoperative radiotherapy	overall survival	postoperative radiotherapy	NA	0/0/1	Excl.	190
Postoperative chemotherapy versus postoperative chemoradiotherapy	overall survival	postoperative chemoradiotherapy	NA	0/0/2	Excl.	191,192
Postoperative D-galactose	overall survival	postoperative D-galactose	NA	1/0/0	NA	193
	hepatic metastases			1/0/0		193

ADJUVANT THERAPY

Many studies have been performed on adjuvant chemotherapy after a gastric cancer resection, and most of these studies have been incorporated in several meta-analyses.[102-111] In all but one of the meta-analyses, a small, but significant benefit for the use of adjuvant chemotherapy was shown. Multi-drug regimens have been associated with better survival when compared to single-drug regimens.[111] In the Intergroup 0116 study, overall survival was higher in the postoperative chemoradiotherapy group when compared to the surgery alone group.[112]

OUTCOME INDICATORS (TABLE 6)

In many studies, the prognostic benefit of a microscopically radical (R0) resection over microscopically irradical (R1) resection has been shown.[35,113-128] Patients who have clear resection margins have a higher survival, and fewer local recurrences. In three studies, an association between an increasing number of removed lymph nodes and higher survival was reported.[129-131]

Table 6. Outcome Measures

Outcome measure	End point	Indicator	MA (+/-/=)	RCT (+/-/=)	NRS (+/-/=)	Ref.
R0 versus R1 resection	overall survival	R0 resection	NA	NA	15/0/1	[35,113-128]
	local recurrence				1/0/0	[113]
Clear versus involved esophageal margin	overall survival	clear margin	NA	NA	0/0/1	[114]
	local recurrence				1/0/0	[114]
	postoperative morbidity				0/0/1	[114]
	postoperative mortality				0/0/1	[114]
Number of lymph nodes evaluated (<15 versus >15)	overall survival	>15 nodes	NA	NA	2/0/0	[129,130]
Number of lymph nodes evaluated (<26 versus >26)	overall survival	>26 nodes	NA	NA	1/0/0	[131]
	postoperative mortality				0/0/1	[131]
	postoperative morbidity				0/0/1	[131]

MINIMUM SET OF QUALITY OF CARE INDICATORS

After applying the predefined selection rules as outlined in the Methods section (subheading Quality of care indicators), thirteen evidence-based quality of care indicators were identified (Table 7). Hospital volume was the only indicator on the structure of healthcare. As high annual hospital volume was defined as at least 20 resections per year in the majority of positive studies, this number has been added to the indicator. The majority of indicators in the set reflect the process of care. A microscopically radical resection was the only outcome indicator.

DISCUSSION

In this systematic review of the literature, evidence-based quality of care indicators for the surgical treatment of gastric cancer were identified. Possible indicators were evaluated in terms of structure, process and outcome measures as proposed by Donabedian.[13]

STRUCTURE INDICATORS

High volume gastrectomy was associated with lower postoperative mortality in most large studies (>5,000 patients included), but not in the smaller studies (Figure 2). This indicates that sufficient patient numbers are needed in order to show a significant volume-outcome relation. Limited evidence was found for surgeon volume as a quality indicator. This underlines the importance of the multidisciplinary and perioperative team in the (surgical) treatment of gastric cancer. Both findings are in concordance with a recent meta-analysis on hospital and surgeon volume in the surgical treatment of esophageal cancer.[132] Nevertheless, results of volume – outcome analyses need to be interpreted with caution. Heterogeneity in patient population and treatment can introduce bias in such studies and ideally, outcome data are adjusted for case-mix factors. Nationwide registries in which patient and treatment characteristics are prospectively collected will give further insight in structure of care indicators in the future.

Table 7. Minimum set of evidence-based quality of care indicators for gastric cancer surgery

Type	Quality of care indicator	Improved end points	Level of evidence
Structure	high hospital volume (>20/year)	overall survival postoperative mortality	NRS
Process	D2/3 lymph node dissection[a]	disease specific survival overall survival	RCT
	no routine (pancreatico)splenectomy	postoperative morbidity	NRS
	pouch reconstruction	quality of life	MA
	fast-track care	postoperative recovery	RCT
	no perioperative blood transfusion	overall survival	NRS
	selective bowel decontamination	anastomotic leakage rate	RCT
	multiple dose antibiotics	surgical wound infection rate	RCT
	preoperative chemotherapy	overall survival	MA
	perioperative chemotherapy	overall survival	RCT
	adjuvant (combination) chemotherapy	overall survival	MA
	postoperative chemoradiotherapy	overall survival	RCT
Outcome	R0 resection	overall survival	NRS

[a]in centers with low postoperative mortality

PROCESS INDICATORS

In the published literature on quality of gastric cancer surgery, a broad variety of process indicators has been analyzed.

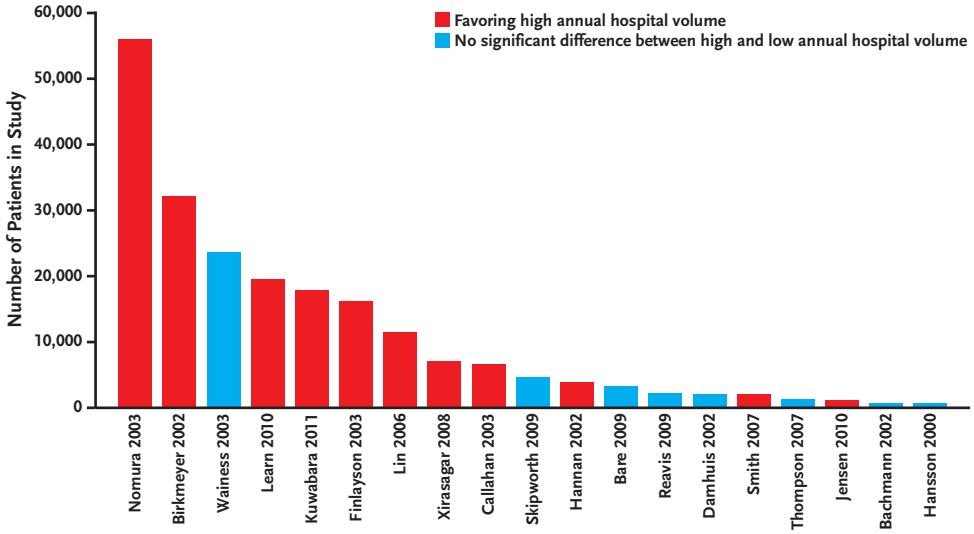
SURGICAL TECHNIQUE

The extent of lymph node dissection has been the subject of many studies. In initial reports, a D2 lymph node dissection was associated with increased postoperative mortality without a survival benefit as compared to D1 surgery.[38,133] Long term results from the Dutch D1D2 study, however, revealed an improved gastric cancer specific survival after a D2 dissection.[40] From this, it can be concluded that, when postoperative mortality can be avoided, a D2 lymphadenectomy should be recommended. In experienced centers, postoperative mortality after a D2 lymph node dissection is low.[4] Additional (pancreatico) splenectomy has been associated with increased postoperative morbidity without any survival benefit.[59-61]

PERIOPERATIVE CARE

While fast-track surgery has proven its benefit in colorectal cancer surgery, the number of studies in gastric cancer is limited. In two recent RCTs, fast-track care was shown to be feasible (in China) and was associated with a shorter hospital stay, less medical costs, and improved quality of life at discharge when compared to conventional care.[82,83] The widespread introduction of fast-track surgery programs or clinical care pathways in the management of gastric cancer patients deserves further attention as it potentially contributes to a higher level of care.

Figure 2. Studies on the relation between annual hospital volume and postoperative mortality, ordered by the number of included gastric cancer patients[12,14-30]



A negative impact of perioperative blood transfusion on overall survival was seen in univariate analysis in nine studies. In only four studies, blood transfusion remained an adverse prognostic factor in multivariate analysis, and it should be avoided without jeopardizing best supportive care.[85,88,90,91] Similar results have been observed in colorectal cancer surgery.[134] Selective bowel decontamination emerged as a quality of care indicator as it decreased the risk of anastomotic leakage and its clinical sequelae in a large RCT.[93] In a more recent RCT, preoperative intravenous administration of multiple dose antibiotics was associated with less surgical wound infections than the use of single dose antibiotics.[94]

MULTIMODALITY TREATMENT

In a recent meta-analysis, preoperative chemotherapy was associated with improved survival.[98] In this meta-analysis, patients from trials on perioperative chemotherapy were also included. Adjuvant chemotherapy has been administered for many years, and its survival benefit has been confirmed in several meta-analyses.[102-111] In the Western world however, an optimal regimen for postoperative chemotherapy has not been yet established. In Japan, postoperative chemotherapy is standard of care. Following the results of the Intergroup 0116 study, postoperative chemoradiotherapy is currently standard of care in the United States.[112,135] In Europe, perioperative chemotherapy has been advocated, according to the results of the MAGIC study.[99] The international multicenter CRITICS study will give an answer to the question whether postoperative chemoradiotherapy improves survival as compared to postoperative chemotherapy in patients who undergo gastric cancer resection after preoperative chemotherapy.[136]

OUTCOME INDICATORS

Radicality of the resection and the number of resected lymph nodes are frequently used as outcome parameters when measuring quality of oncologic surgery. In gastric cancer surgery, a large number of studies support a microscopically radical resection to be considered as a quality of care indicator.[35,113-128] The number of studies on the number of evaluated lymph nodes in relation to outcomes was too small to identify this factor as an evidence-based quality of care indicator.[129-131]

CONCLUSIONS

From the current review, it becomes clear that improving the quality of care in the treatment of gastric cancer is a multidisciplinary team effort in which surgical technique is only one of the contributing factors. High quality perioperative care asks for well trained nurses, experienced anesthesiologists, and ICU staff.[137] Furthermore, outcome of gastric cancer surgery is obviously dependent on the experience of other specialists in the multidisciplinary team (i.e., medical oncologists, gastroenterologists, radiation oncologists).

The set of indicators that was derived from the current study can be used for registration and benchmarking in gastric cancer surgery. Most indicators in clinical audits, as established in the United Kingdom, Denmark, Sweden, and the Netherlands are derived from expert panel discussions. With the current review, the datasets in these audits may be supplemented with evidence-based quality of care indicators. Furthermore, the proposed minimum set of indicators can be used for uniform reporting in future studies on quality of gastric cancer surgery.

A limitation of the current study is the absence of a MeSH search term for studies related to 'quality of care'. Therefore, the search strategy included a variety of search terms for different aspects of care. This might have influenced the set of studies in the final selection. Furthermore, due to the large number of studies that emerged from the search strategy, stringent criteria for inclusion were used. Approximately 60% of included manuscripts in the current literature review are from Western countries, whereas approximately 40% of the included manuscripts are from Asia. A large amount of literature from Asia was excluded from the current review because part of these studies are written in non-English languages, while another large part focused on early gastric cancer, which was not the subject of the current review. Therefore, quality of care indicators derived from the current study are likely to be more applicable to Western countries than to Asian countries. Finally, although the identified quality of care indicators reflect best practice for gastric cancer surgery, none of the studies actually validated a best practice indicator as a tool to measure differences in quality of care between different providers.

Appendix. Pubmed, Embase, and Cochrane search terms

Pubmed
Limits activated: English, Publication Date from 1990
("stomach neoplasms"[mesh] OR (stomach[All Fields] OR gastric[all fields]) AND (neoplasms[all Fields] OR neoplasm[all fields] OR tumor[all fields] OR tumors[all fields] OR tumor[all fields] OR tumors[all fields] OR cancer[all fields] OR cancers[all fields] OR carcinoma[all fields] OR carcinomas[all fields])))
AND
("gastrectomy"[mesh] OR "gastrectomy"[all fields] OR "gastrectomies"[all fields] OR "gastric resection"[all fields] OR "Stomach Neoplasms/surgery"[mesh] OR "Lymph Node Excision"[mesh] OR "Surgical Procedures, Operative"[mesh:noexp] OR "Neoadjuvant Therapy"[mesh] OR "Chemotherapy, Adjuvant"[mesh] OR "Radiotherapy, Adjuvant"[mesh] OR adjuvant[tiab] OR neoadjuvant[tiab])
AND
("quality indicators, health care"[mesh] OR ("quality"[all fields] AND ("indicators"[all fields] OR indicator[all fields])) OR "health care quality indicators"[all fields] OR "Quality Assurance, Health Care"[mesh] OR "health care quality assessment"[all fields] OR "benchmarking"[mesh] OR "benchmarking"[all fields] OR "Outcome and Process Assessment (Health Care)"[mesh:noexp] OR "outcome assessment"[all fields] OR "Process Assessment"[all fields] OR "Delivery of Health Care"[mesh] OR "Risk Adjustment"[mesh] OR "risk adjustment"[all fields] OR "Clinical Audit"[mesh] OR "audit"[all fields] OR "Quality of Health Care"[mesh:noexp] OR "Quality Control"[mesh] OR "Guideline Adherence"[mesh] OR "Clinical Competence"[mesh] OR "Hospital Mortality"[mesh] OR "Mortality"[mesh:noexp] OR "Mortality"[ti] OR "Morbidity"[mesh:noexp] OR "Postoperative Complications"[mesh] OR "Complications" [ti] OR "Treatment Outcome"[mesh])
NOT
((animals[mesh] NOT humans[mesh]))

Embase
Limits activated: English, Publication Date from 1990
(exp *"stomach tumor"/ OR ((stomach.ti. OR gastric.ti.) AND (neoplasms.mp. OR neoplasm.mp. OR tumor.mp. OR tumors.mp. OR tumor.mp. OR tumors.mp. OR cancer.mp. OR cancers.mp. OR carcinoma.mp. OR carcinomas.mp.)))
AND
(exp *gastrectomy/ OR "gastrectomy".mp. OR "gastrectomies".mp. OR "gastric resection".mp. OR exp *stomach tumor/su OR "Lymph Node Excision".mp. OR exp *lymphadenectomy/ OR *surgery/ OR surgical.mp. OR adjuvant.ti,ab. OR exp *ADJUVANT CHEMOTHERAPY/ OR neoadjuvant.ti,ab. OR exp *adjuvant therapy/)
AND
(exp *health care quality/ OR (quality.ti,ab. AND indicators*.ti,ab.) OR "quality assurance".ti,ab. OR exp *quality control/ OR "health care quality assessment".ti,ab. OR benchmark*.ti,ab. OR exp *outcome assessment/ OR "outcome assessment".ti,ab. OR "Process Assessment".ti,ab. OR "delivery of health care".ti,ab. OR exp *health care delivery/ OR exp *risk assessment/ OR "risk adjustment".ti,ab. OR exp *medical audit/ OR "audit".ti,ab. OR "health care quality access evaluation".ti,ab. OR exp *health care access/ OR exp *"evaluation and follow up"/ OR exp *clinical assessment/ OR exp *clinical evaluation/ OR exp *evaluation/ OR exp *evaluation research/ OR exp *outcome assessment/ OR "quality control".ti,ab. OR exp *quality control/ OR "guideline adherence".ti,ab. OR "guidelines as topic".ti,ab. OR "clinical coti,abetence".ti,ab. OR exp *clinical competence/ OR "hospital mortality".ti,ab. OR *mortality/ OR morbidity.ti,ab. OR *morbidity/ OR complication*.ti,ab. OR exp *postoperative complication/ OR treatment outcome.ti,ab. OR exp *treatment outcome/)
AND
(exp human/)

Cochrane Library
Limits activated: English, Publication Date from 1990
"stomach neoplasms"
AND
(gastrectomy OR "lymph node excision" OR adjuvant OR neoadjuvant)

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PART III

Surgical quality assurance

CHAPTER 11

Increased incidence and survival for esophageal cancer but not for gastric cardia cancer in the Netherlands

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ABSTRACT

BACKGROUND

A worldwide increasing incidence is seen for esophageal adenocarcinoma, but not for esophageal squamous cell carcinoma (SCC) and gastric cardia adenocarcinoma. Purposes of the current study were to evaluate the changing incidence rates of esophageal and gastric cardia cancer, and to assess survival trends.

PATIENTS AND METHODS

Patients diagnosed with esophageal adenocarcinoma (N = 12,195) or SCC (N = 9,046), or gastric cardia adenocarcinoma (N = 9,900) between 1989 and 2008 in the Netherlands were included. Changes in European Standard Population (ESP) and relative survival over time were evaluated.

RESULTS

Incidence rates for esophageal adenocarcinoma increased in males (+7.5%, $P < 0.001$) and females (+5.2%, $P < 0.001$), while the incidence for esophageal SCC remained stable in males (-0.2%, $P = 0.6$) and slightly increased in females (+1.7%, $P = 0.001$). The incidence for gastric cardia cancer decreased in males (-1.2%, $P < 0.006$), and remained stable in females (-0.2%, $P = 0.7$). Five-year survival for both M0 and M1 esophageal carcinoma doubled over the last 20 years. No significant changes in survival were found for M0 and M1 gastric cardia carcinoma.

CONCLUSIONS

In the Netherlands, a rising incidence is seen for esophageal adenocarcinoma, but not for gastric cardia adenocarcinoma. This finding most likely reflects true changes in disease burden, rather than being the result of changes in diagnosis or classification. The increased survival for esophageal carcinoma can be attributed to centralization of surgery, and an increased use of multimodality therapy, factors hardly acknowledged for gastric cancer.

INTRODUCTION

Esophageal and gastric cancer are, respectively, the sixth and second causes of cancer death worldwide, with an estimated 500,000 new cases of esophageal cancer and one million new cases of gastric cancer each year.[1]

Esophageal cancer is primarily composed of two histological types, adenocarcinoma and squamous cell carcinoma (SCC), each with a distinct etiology and specific risk factors.[2] Subtypes of gastric cancer are often based on topology, distinguishing cardia and non-cardia gastric cancer. Most gastric cancers are adenocarcinomas.

Worldwide, there has been a marked increase in the incidence of esophageal cancer over the last decades, which is mainly attributed to an increase in the incidence of adenocarcinoma of the esophagus in North America,[3,4] Europe[5] and Japan.[6] The incidence of SCC of the esophagus has remained stable or is declining.[3,5] For gastric cardia cancer, two studies have reported a rising incidence in the United States in the seventies and eighties, while the incidence since then has stabilized.[4,7] In the Netherlands, a rising incidence of adenocarcinoma of the esophagus has been reported as well from 1989 to 2003, while the incidence of esophageal SCC hardly increased, and gastric cardia cancer incidence rates were declining.[8,9] However, these data did not include a comprehensive analysis of incidence and survival for esophageal adenocarcinoma, esophageal SCC, and gastric cardia adenocarcinoma.

The first purpose of the current study was to give an update on incidence rates and stage distribution for esophageal adenocarcinoma and SCC, and gastric cardia adenocarcinoma in the Netherlands from 1989 to 2008. The second purpose was to evaluate survival patterns for these cancers during the same period.

PATIENTS AND METHODS

NETHERLANDS CANCER REGISTRY

Data were obtained from the Netherlands Cancer Registry (NCR), in which data is collected on all newly diagnosed malignancies in the Netherlands, a country of 16.7 million inhabitants. The NCR receives data from eight regional cancer registries, covering all hospitals in the Netherlands. Information on patient and tumor characteristics and treatment is routinely collected by trained registrars who extract this information from the hospital records 6-18 months after diagnosis. Topography and morphology are coded according to the International Classification of Diseases for Oncology (ICD-O)[10], based on information from the medical files, including the pathology report. Tumors are staged according to the International Union Against Cancer (UICC) TNM classification. Until December 1996, the UICC 4th edition was used,[11] from 1997 until 2001 the UICC 5th edition was used,[12] and as of January 2002, all tumors were coded according to the UICC 6th edition.[13] For esophageal carcinoma, the 4th, 5th, and 6th UICC TNM classifications were not different, except for a minor modification in the 5th edition with the introduction of the M1a and M1b classification. For gastric cardia cancer, 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. Vital status in the NCR is extracted from the medical records or is obtained by record linkage with the Dutch Central Bureau of Statistics, which registers all deceased persons in the Netherlands. As the NCR does not capture the cause of death, mortality rates were extracted from the Dutch Central Bureau of Statistics, separately for esophageal and gastric cancer. The study was approved by the NCR Review Board.

PATIENTS

Between January 1989 and December 2008, 22,530 cases of primary invasive esophageal (C15.0-15.9) and 9,963 cases of primary invasive gastric cardia cancer (C16.0) were diagnosed in the Netherlands. For the current study, adenocarcinomas (ICD-O morphology codes 8140-8142, 8144, 8145, 8190, 8200, 8210, 8211, 8230, 8255, 8260-8263, 8310, 8130, 8180, 8481, 8490, 8510, 8560, 8570, 8573-8576) of the esophagus or gastric cardia, and SCCs (ICD-O morphology codes 8051, 8052, 8070- 8076, 8078) of the esophagus were selected. Tumors with other or unknown histology (including 'No Otherwise Specified') of the esophagus (N = 1289) or gastric cardia (N = 63) were excluded, leaving 21,241 patients with esophageal cancer, and 9,900 patients with cardia cancer for analysis.

STATISTICAL ANALYSIS

Separate analyses were performed for esophageal adenocarcinoma (C15.0-15.9), esophageal SCC (C15.0-C15.9), and gastric cardia adenocarcinoma (C16.0). To evaluate trends over time, the study period was divided in four intervals of five years.

Incidence rates were calculated as the number of new patients per 100,000 inhabitants per year, and are age-standardized using the European Standardized Population (ESP).[14] The ESP reflects the incidence as if the population of the Netherlands would have the same age-composition as a hypothetical European population. Changes in incidence were evaluated with the estimated annual percentage change (EAPC), fitting a regression line to the natural logarithm of the rates using calendar year as a regressor variable.[15]

Differences in stage distribution between the various time-periods were calculated with a chi-square test. Stage IV gastric cardia adenocarcinoma comprises not only M1 disease but also locally advanced (T4N1-3, T1-3N3) M0 disease.[13] Therefore, stage IV-M0 and stage IV-M1 gastric cardia adenocarcinomas were analyzed separately.

Follow-up was complete until December 31st, 2009. Survival was calculated from the date of diagnosis until death of any cause (event) or alive at last follow-up (censored) by using the life-table method. Then, relative survival was calculated correcting for age- and gender-specific background mortality.[16] Mortality rates were obtained directly from the Dutch Central Bureau of Statistics as the absolute number of deaths per 100.000. All analyses were performed with SAS statistical software (version 9.2).

Table 1. Patient and tumor characteristics (N = 31,141)

	Esophageal adenocarcinoma (C15.0-15.9)		Esophageal SCC (C15.0-15.9)		Gastric cardia adenocarcinoma (C16.0)	
	N	%	N	%	N	%
Total	12195	*100.0*	9046	*100.0*	9900	*100.0*
Sex						
male	9566	*78.4*	5429	*60.0*	7640	*77.2*
female	2629	*21.6*	3617	*40.0*	2260	*22.8*
Age at diagnosis						
<60	2952	*24.2*	2661	*29.4*	2452	*24.8*
60-74	5124	*42.0*	4062	*44.9*	4380	*44.2*
≥75	4119	*33.8*	2323	*25.7*	3068	*40.0*
Tumor location						
cervical esophagus	52	*0.4*	400	*4.4*		
intrathoracic upper 1/3	182	*1.5*	1106	*12.2*		
intrathoracic middle 1/3	1003	*8.2*	3148	*34.8*		
intrathoracic lower 1/3	10211	*83.7*	3509	*38.8*		
other/unknown	747	*6.1*	883	*9.8*		
gastric cardia					9900	*100.0*
Tumor grade						
well/moderate	3706	*30.4*	3651	*40.4*	3047	*30.8*
intermediate/poor	4669	*38.3*	2790	*30.8*	4465	*45.1*
unknown	3820	*31.3*	2605	*28.8*	2388	*24.1*

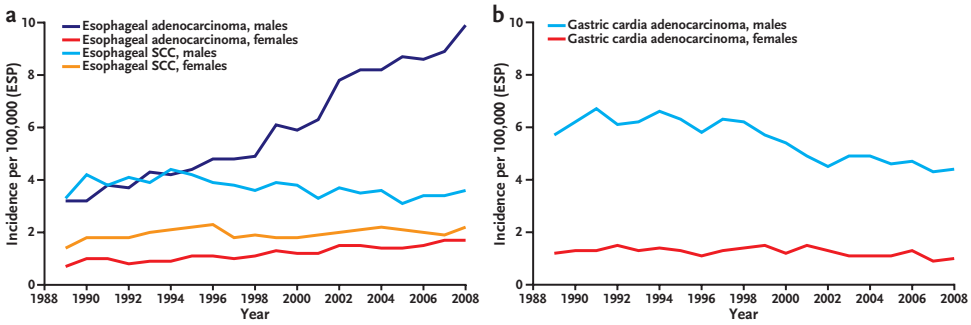
SCC: Squamous Cell Carcinoma

RESULTS

Between January 1st, 1989 and December 31st, 2008, 12,195 patients with esophageal adenocarcinoma, 9,046 patients with esophageal SCC, and 9,900 patients with gastric cardia adenocarcinoma were diagnosed in the Netherlands. Patient and tumor characteristics are summarized in Table 1. The number of males exceeded the number of females in all three subgroups. Median age at diagnosis was 69.6 years for esophageal adenocarcinoma, 66.9 years for esophageal SCC and 69.3 years for gastric cardia adenocarcinoma. The majority (83.7%) of esophageal adenocarcinomas were located in the lower esophagus. Esophageal SCC was more evenly distributed throughout the esophagus.

The incidence of esophageal adenocarcinoma increased in males in the period 1989-2008 (Figure 1a): the ESP increased from 3.2 per 100,000 inhabitants per year in 1989 to 9.9 in 2008 with an estimated annual percentage change (EAPC) of +7.5 (95% CI +6.8 to +8.2, $P < 0.001$). In females, the ESP of esophageal adenocarcinoma also increased, but to a lesser extent: from 0.7 in 1989 to 1.7 in 2008, with an EAPC of +5.2 (95% CI +4.2 to +6.2, $P < 0.001$). For esophageal SCC, no significant change was detected in males (EAPC -0.2, 95% CI -1.0 to 0.6, $P = 0.6$), while in females the incidence slightly increased (EAPC +1.7, 95% CI +0.8 to +2.7, $P = 0.001$). The incidence of gastric cardia carcinoma decreased over the years in males but did not significantly change in females (Figure 1b): in males, the ESP decreased from 5.7 in 1989 to 4.4 in 2008, with

Figure 1. Incidence of (a) esophageal carcinoma and (b) gastric cardia adenocarcinoma in the Netherlands, 1989-2008



ESP: European standardized population
SCC: squamous cell carcinoma

an EAPC of -1.2 (95% CI -2.0 to -0.4, $P = 0.006$), and in females, the ESP decreased from 1.2 in 1989 to 1.0 in 2008, with an EAPC of -0.2 (95% CI -0.9 to 1.2, $P = 0.7$).

Differences in stage distribution were noted (all $P < 0.001$), but in all three tumor types about 40% of all tumors were diagnosed in a non-metastatic stage. The other 60% of tumors were either staged as M1 disease, or did not have a stage group assigned. Changes in stage distributions over the years for esophageal adenocarcinoma and SCC showed a similar pattern over time (Figures 2a and 2b). The percentage of patients with an unknown stage steadily decreased, with a corresponding increase in the proportion of stage IV patients. Comparing changes in tumor location for esophageal adenocarcinoma versus SCC, there was a relative increase in distally located tumors for adenocarcinoma (77.2% - 87.7%), without major changes in the distribution of SCCs (Figures 3a and 3b). For gastric cardia adenocarcinoma (Figure 2c), the proportion of patients with no stage assigned also decreased, but this was less prominent (from 19.8% to 15.0%). With the incorporation of the absolute number of metastatic lymph nodes into the TNM classification as of 1997, differences in stage distribution for gastric tumors might very well reflect a staging difference rather than a true shift in stage distribution.

Mortality rates per 100.000 inhabitants in the Netherlands increased for esophageal carcinoma, both for males (from 6.8 to 13.9) and females (3.1 to 5.1). Mortality rates for gastric cancer decreased for males (18.6 to 10.7) and females (11.5 to 6.6). Survival estimates for esophageal and gastric cardia carcinoma are shown in Table 2. Five-year relative survival significantly increased from 12.2% to 25.3% for M0 esophageal adenocarcinoma and from 11.6% to 18.9% for M0 esophageal SCC. No significant increase in survival was detected for M0 gastric cardia carcinoma (19.0% to 20.6%). In the metastatic setting, 2-year relative survival significantly increased for esophageal carcinoma, but not for gastric cardia carcinoma. Survival curves are depicted in Figure 4.

Figure 2. Stage distribution of (a) esophageal adenocarcinoma, (b) esophageal squamous cell carcinoma, and (c) gastric cardia adenocarcinoma in the Netherlands, 1989-2008

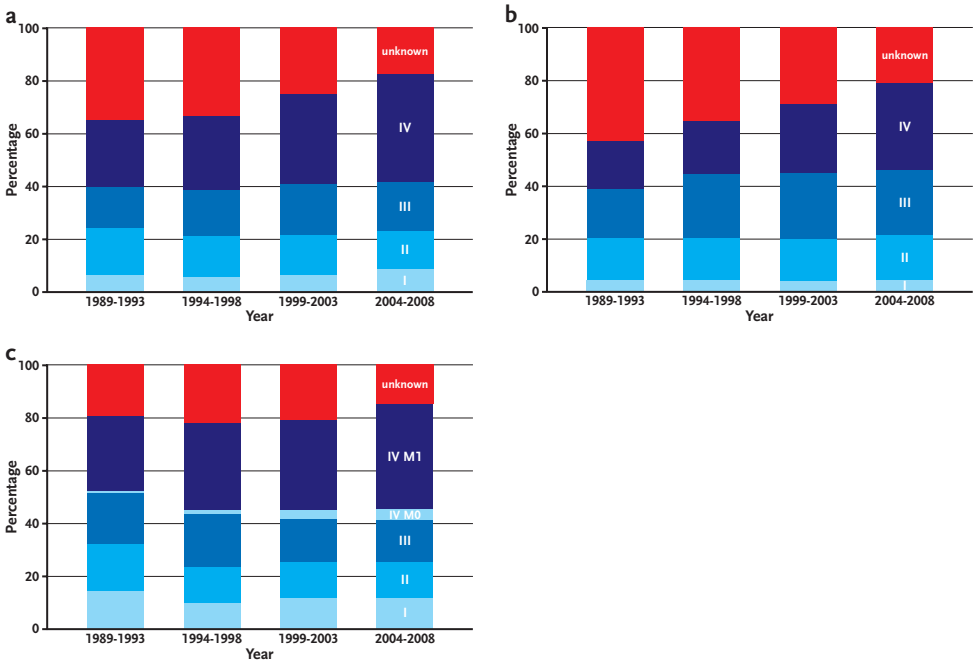
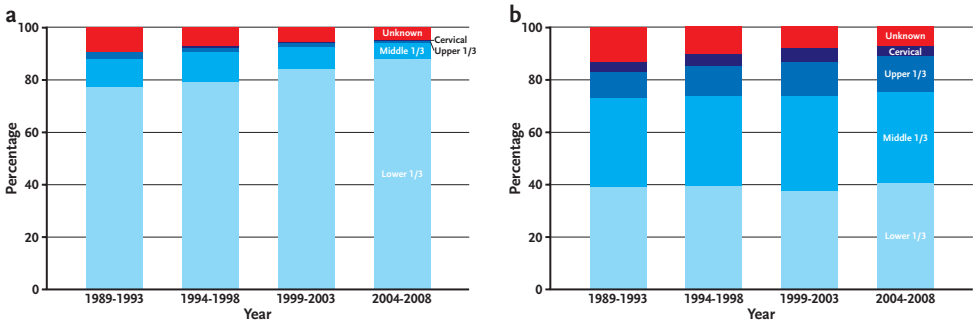


Figure 3. Relative distribution of location for (a) esophageal adenocarcinoma and (b) esophageal squamous cell carcinoma



DISCUSSION

Worldwide, the incidence of esophageal cancer is increasing. In the United States, the incidence of esophageal cancer has shown a six-fold rise over the last three decades.[4] This is entirely caused by a rise in the incidence of esophageal adenocarcinoma, primarily in white males.[3] In Europe, mainly the Northern part, there has also been an increase in the incidence of esophageal adenocarcinoma in men, but not in women.[5] The incidence of SCC has remained stable in Europe and the United States.[3,5] In the current study, similar

patterns were found. The incidence of esophageal adenocarcinoma in males showed a three-fold increase over two decades (1989-2008), with a smaller increase in females. For SCC, the incidence remained constant in males, and slightly increased in females, who increased their smoking habits over the past decades.

For gastric adenocarcinoma, there has been a worldwide decrease in the incidence of non-cardia gastric cancer over the past decades.[17,18] For gastric cardia cancer, early studies report an increasing incidence in the West Midlands (England),[19] Connecticut (US),[20] and the SEER regions (US),[21] but none of these studies report data after 1989. More recent studies from the United States,[4,7] Sweden,[22] and Spain[23] confirmed this increase until the early nineties, after which the incidence for gastric cardia cancer reached a plateau followed by a slow decrease as of the late nineties. Other studies, including the current study, report a stable or decreasing incidence of gastric cardia cancer over the last decades.[24,25] Therefore, the often cited[17,26,27] increasing incidence of cardia gastric cancer in developed countries should be considered carefully, and be judged in the light of more recent observations.

In the current study, incidence rates significantly changed over time for adenocarcinoma of the esophagus in both males and females, for SCC in females, and for gastric cardia carcinoma in males. Time trends in disease incidence should be interpreted cautiously, because they might reflect changes in diagnostics or reclassification of tumors, rather than representing a true change in disease burden. With the refinement of various diagnostic modalities in general, and the increased use of endoscopy in patients with reflux disease or Barret's esophagus, improved diagnosis might be a reason for the increased incidence of esophageal adenocarcinoma in the Netherlands. However, improved diagnosis would be present in all disease entities, in both sexes and throughout the entire esophagus in a comparable way. Furthermore, improved diagnosis would mainly lead to an increased incidence of early stage tumors, but this is not observed in the current study.

Another explanation for changes in incidence is reclassification. Because there are no clear morphologic differences that distinguish adenocarcinomas of the lower esophagus from those of the cardia, tumors of the gastro-esophageal junction are vulnerable to reclassification. And although the registry's topography classification rules have remained unchanged over the study period, clinical classification of tumors of the gastro-esophageal junction might have shifted towards esophageal cancer. However, the six-fold increase in the incidence of esophageal adenocarcinoma is not fully compensated by the decrease in gastric cardia adenocarcinomas. Furthermore, reclassification would be equally present in males and females. Therefore, although reclassification might partly explain the increase in esophageal adenocarcinoma, it is likely that the greater part of the increase in esophageal adenocarcinoma is a true rise in disease burden.

Table 2. Five-year relative survival of non-metastatic (M0) and metastatic (M1) esophageal and cardia carcinoma in the Netherlands, 1989-2008

	Esophageal adenocarcinoma		Esophageal SCC		Cardia adenocarcinoma	
	%	95% CI	%	95% CI	%	95% CI
M0 disease						
1989-1993	12.2	10.0-14.6	11.6	9.9-13.6	19.0	16.7-21.3
1994-1998	14.9	13.0-16.9	11.9	10.3-13.6	15.5	13.7-17.4
1999-2003	17.4	15.8-19.2	13.3	11.7-15.1	18.4	16.4-20.5
2004-2008	25.3	22.9-27.8	18.9	16.5-21.5	20.6	17.7-23.8
M1 disease						
1989-1993	3.3	1.8-5.7	6.0	3.6-9.2	4.2	2.8-6.0
1994-1998	5.3	3.7-7.3	4.7	2.9-7.0	3.1	2.1-4.5
1999-2003	5.7	4.5-7.1	5.4	3.8-7.4	4.1	2.8-5.5
2004-2008	9.0	7.7-10.4	10.1	8.0-12.4	6.0	4.6-7.7

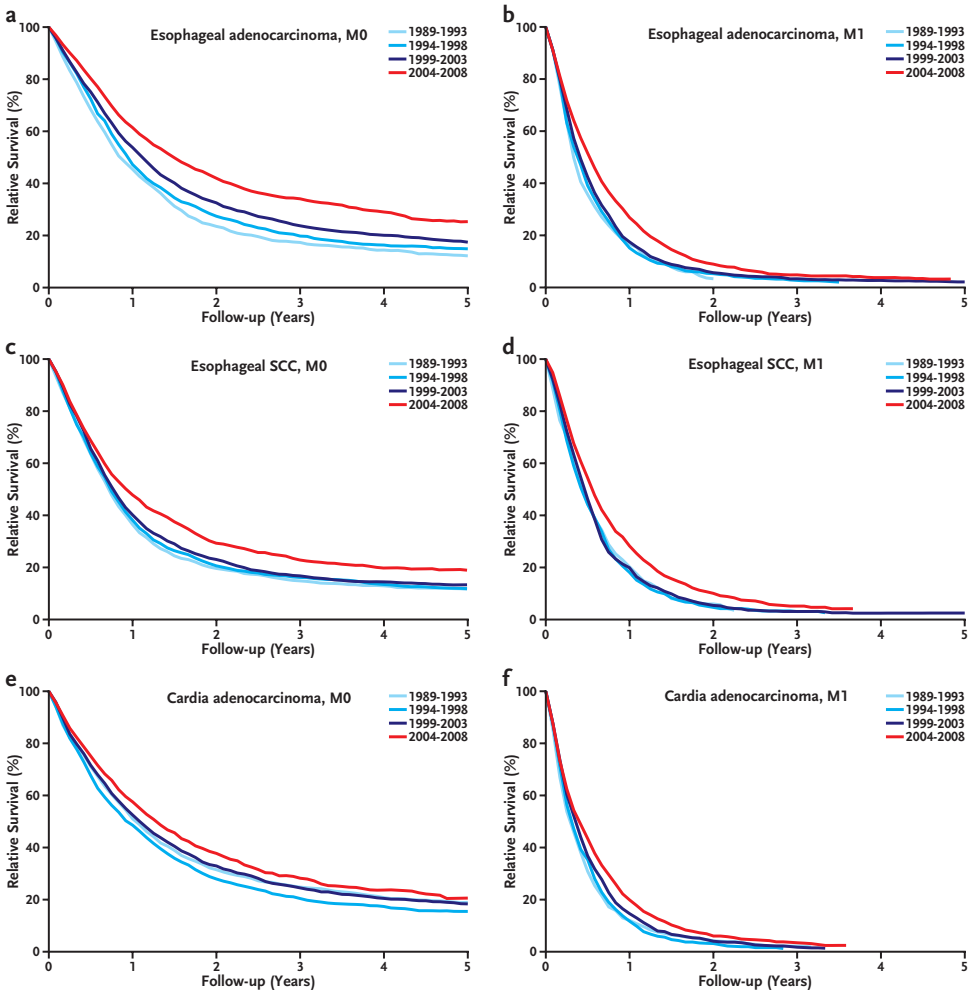
95% CI: 95% confidence interval, SCC: squamous cell carcinoma

All three studied cancers have their specific etiologic factors. Esophageal adenocarcinoma has been associated with obesity[28], smoking[21], reflux disease[29], Barrett's esophagus[30], high meat consumption[31], and a high fat consumption[31], whereas esophageal SCC has been associated with alcohol consumption[21], smoking[21], and low fruit intake[32]. For gastric cardia adenocarcinoma, risk factors are male sex and white race,[33] obesity[28], reflux disease[34], meat consumption[31], and fat consumption[31]. These risk factors show a significant overlap with the risk factors for esophageal adenocarcinoma, making it difficult to explain why incidence changes for esophageal and gastric cardia adenocarcinoma are discordant. It has been suggested that these tumors consist of two different histopathological entities but evidence for this is limited[35].

Others have favored the hypothesis that gastric cardia cancer consists of two distinct etiologies: one arising from *H. pylori* associated severe atrophic gastritis and being of intestinal or diffuse subtype similar to non-cardia cancer, and one related to reflux disease and intestinal in subtype, similar to esophageal adenocarcinoma.[34] With a decreasing incidence of *H.* pylori, the first subtype might be responsible for the decreasing incidence of cardia carcinoma.[9] Although this might be a plausible explanation, underlying mechanisms for the differences in incidence trends need further investigation before definite conclusions can be drawn.

For both M0 and M1 esophageal cancer, relative survival rates improved during the study period. For M0 tumors, this may be the result of centralization of esophageal cancer surgery in the Netherlands. Centralization improves patient selection, perioperative care, surgical experience, and decreases failure to rescue in case of complications. As of 2006, a yearly minimum of ten esophagectomies per hospital was enforced by the Dutch Health Care Inspectorate. In two regions of the Netherlands, the minimum volume was introduced earlier, significantly improving survival.[36] Secondly, the increased

Figure 4. Relative survival of patients with esophageal and gastric cardia carcinoma in the Netherlands, 1989-2008. Relative survival estimates and confidence intervals are shown in Table 2



use of neoadjuvant chemotherapy or chemoradiation might have contributed to the better survival rates for M0 esophageal cancer.[37,38] From 2004 to 2008, a large Dutch multicenter trial has explored the use of preoperative chemoradiation in esophageal cancer.[39] All patients in this trial were included in the current analysis. For M1 tumors, the increase in survival can be attributed to stage migration due to improved detection of distant metastases.

A very recent study shows that esophagectomies were centralized to a great extent over the past 20 years in the Netherlands, while most gastrectomies are performed in low volume centers. High volume esophagectomies were associated with lower postoperative mortality, while there were hardly any high volume gastrectomies to conduct a properly

powered volume-outcome analysis for gastrectomy.[40] Furthermore, in the study period multimodality therapy has been administered more frequently in esophageal as compared to cardia carcinoma (results not shown). This might explain why for gastric cardia cancer, relative survival did not significantly increase, corresponding with earlier results from one region in the Netherlands.[41] Because postoperative chemoradiotherapy and perioperative chemotherapy have emerged as adjuvant strategies that improve outcome in gastric cancer, it is expected that survival will increase over the coming decades.

In conclusion, the current manuscript reveals an increase in the incidence of esophageal adenocarcinoma both in males and females, and a decrease in the incidence of gastric cardia adenocarcinoma in males. These are most likely true changes in disease burden, rather than being caused by either improved diagnosis or reclassification. The question why incidence trends for esophageal and cardia adenocarcinoma are different remains to be elucidated, but the existence of two different types of gastric cardia cancer is a possible explanation.

The improved survival for M0 esophageal carcinoma reflects an increasing number of esophagectomies performed in high-volume centers and the increased use of modern multi-modality therapy. These two factors are poorly acknowledged in treating gastric cancer in the Netherlands, which might explain why no significant increase in survival was detected in this tumor type.

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PART III

Surgical quality assurance

CHAPTER 12

Gastric cancer: decreasing incidence but stable survival in the Netherlands

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ABSTRACT

BACKGROUND

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

PATIENTS AND METHODS

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

RESULTS

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

CONCLUSIONS

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

INTRODUCTION

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

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

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

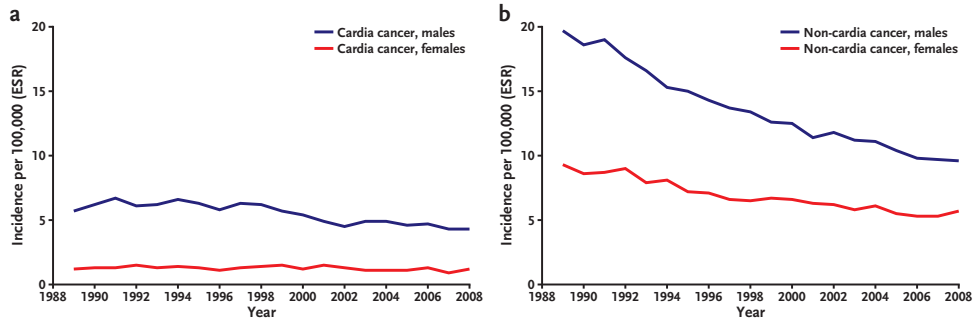
METHODS

DATA COLLECTION

Data were obtained from the nationwide Netherlands Cancer Registry (NCR). This registry serves the total Dutch population of 16.6 million inhabitants. The NCR is based on notification of all newly diagnosed malignancies in the Netherlands by the automated pathological archive (PALGA). Additional sources are the national registry of hospital discharge, hematology departments and radiotherapy institutions. Completeness is estimated to be at least 95%.[21] The information on vital status was initially obtained from municipal registries and from 1994 onwards from the nationwide population registries network. These registries provide complete coverage of all deceased Dutch citizens.

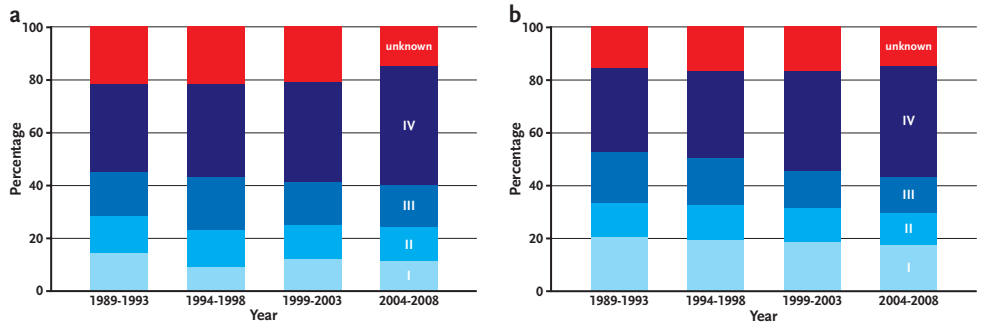
Patients diagnosed from 1989 to 2008 with a tumor of the stomach, classified as ICD-9 151 and ICD-10 C16 according to the International Classification of Diseases (ICD), were included. Tumors were staged according to the International Union Against Cancer TNM classification that was used at the date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

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



ESR: European Standardized Rate per 100.000 inhabitants

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



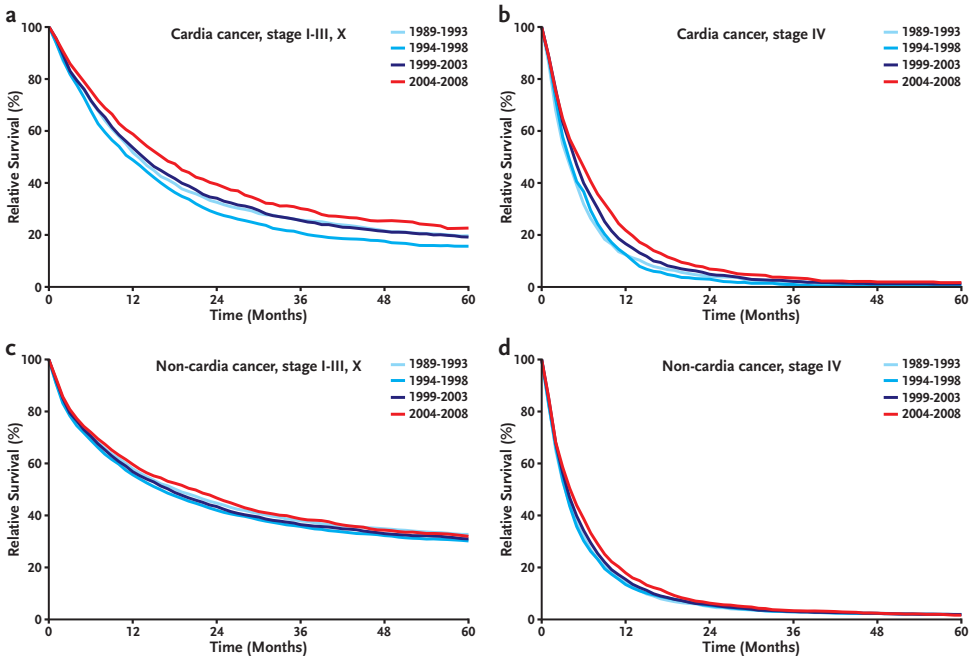
STATISTICAL ANALYSES

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

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

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

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



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

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

RESULTS

PATIENT CHARACTERISTICS AND INCIDENCE

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

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

TUMOR STAGE

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

SURVIVAL

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

DISCUSSION

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

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

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

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

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

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

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

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

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PART III

Surgical quality assurance

CHAPTER 13

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

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ABSTRACT

BACKGROUND

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

PATIENTS AND METHODS

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

RESULTS

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

CONCLUSIONS

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

INTRODUCTION

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

Over the past decades, many trials have been conducted to improve survival of patients with gastric cancer. In the Dutch D1-D2 trial, no benefit was found for a D2 resection after 5 years of follow-up, which was the result of a high postoperative mortality in the D2 group. However, after 15 years, cancer-specific mortality and the number of recurrences was lower in the D2 group.[5] In other trials the role of preoperative and postoperative therapy in gastric cancer treatment was investigated. In the MAGIC trial, a benefit was proven for patients receiving perioperative chemotherapy consisting of epirubicin, cisplatin and 5-FU (ECF), although it is suggested that the survival benefit was mainly achieved by neoadjuvant chemotherapy.[6] In the United States Intergroup 0116 study that was conducted in the nineties, a survival benefit for patients receiving postoperative chemoradiotherapy was found. However, 54% of the patients received a D0 lymphadenectomy. It is therefore suggested that postoperative chemoradiotherapy mainly improves survival in patients with inadequate lymph node dissection.[7] A retrospective study conducted in the Netherlands showed a decreased local recurrence rate and higher overall survival for patients who underwent a D1 resection followed by postoperative chemoradiotherapy, compared to D1 surgery alone. No difference was found for D2 surgery alone versus D2 surgery with postoperative chemoradiotherapy.[8,9]

In 2009, these studies led to the formation of the first official guideline for treatment of gastric cancer in the Netherlands. For stage II and III gastric cancer, it is recommended to offer neoadjuvant chemotherapy based on an ECF schedule. If a patient did not receive neoadjuvant chemotherapy and the resection margins were tumor-positive (R1), adjuvant chemoradiotherapy is recommended.[10]

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

PATIENTS AND METHODS

DATA COLLECTION

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

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

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

STATISTICAL ANALYSES

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

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

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

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

RESULTS

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

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

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

to patients with non-cardia cancer.

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

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

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

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

ref: reference category, OR: odds ratio

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

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

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

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

ref: reference category, OR: odds ratio

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

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

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

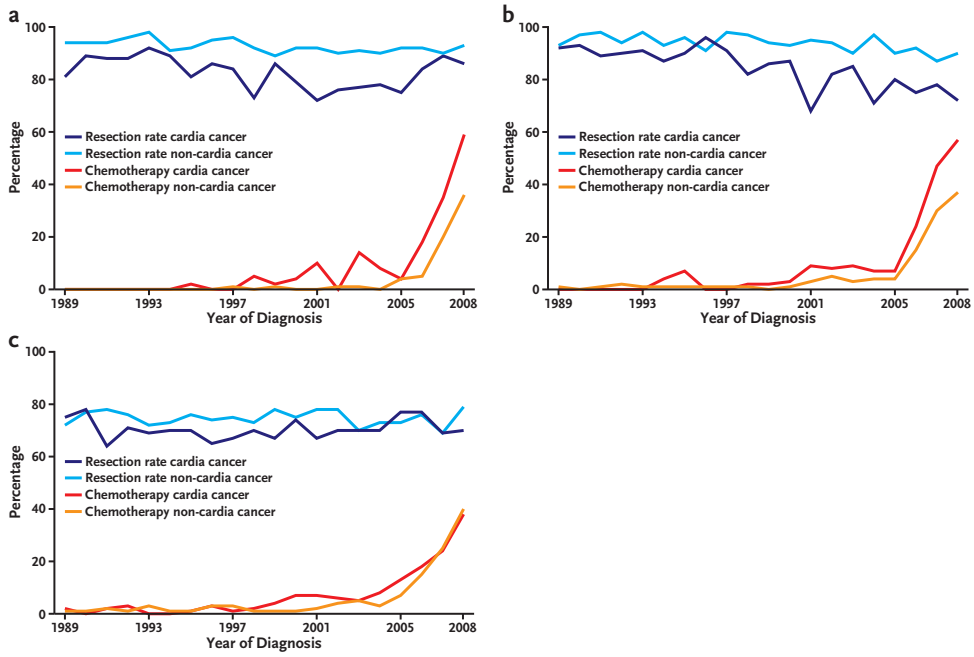
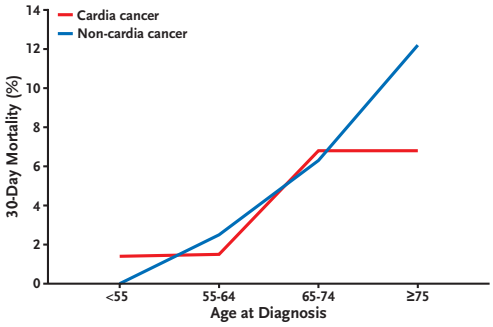


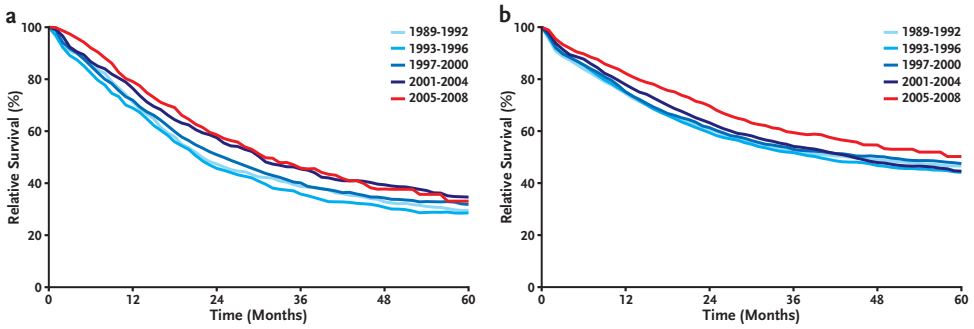
Figure 2. Thirty-day mortality after resection for gastric cancer in the Netherlands, 2005-2008



regional differences.

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

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



DISCUSSION

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

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

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

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

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

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

ref: reference category, OR: odds ratio

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

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

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

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

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

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

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

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

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

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PART III

Surgical quality assurance

CHAPTER 14

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, five-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.

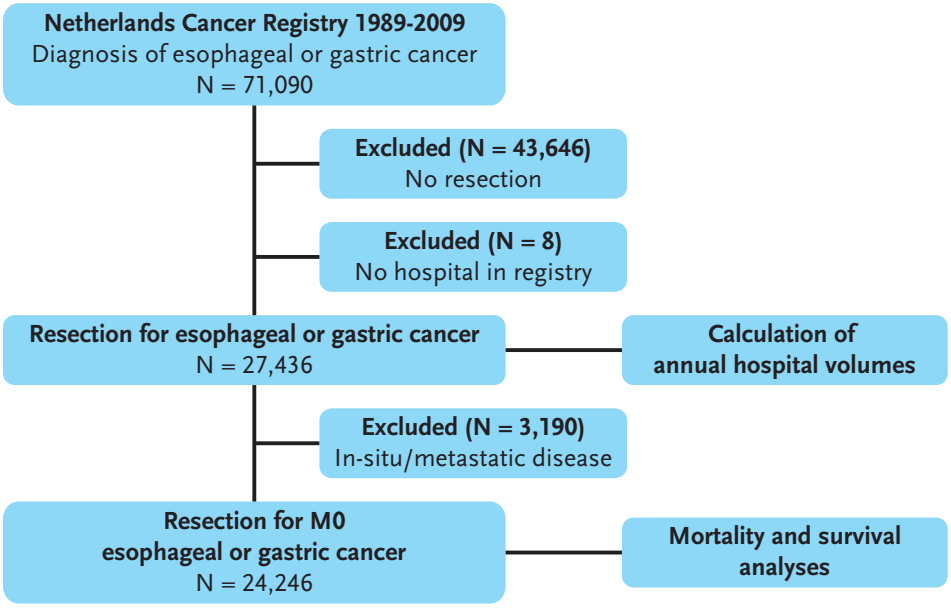
PATIENTS AND METHODS

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-

Figure 1. Study profile



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.

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 per year), low (6-10 per year), medium (11-20 per year), and high (≥21 per 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)

Annual hospital volume	1-5		6-10		11-20		≥21		
	N	%	N	%	N	%	N	%	*P*
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									
<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 group									
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[a]	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*	

SES: socio economic status, SCC: squamous cell carcinoma, preoperative/postoperative therapy: chemotherapy with/without radiotherapy
[a]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 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.

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)

Annual hospital volume	1-5		6-10		11-20		≥21		
	N	%	N	%	N	%	N	%	P
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									
<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 group									
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[a]	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*	

SES: socio economic status, preoperative/postoperative therapy: chemotherapy with/without radiotherapy
[a]T4N1-3M0 and T1-4N3M0 gastric cancers were assigned stage IV in the 6th edition TNM-classification

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 $P < 0.01$)

Figure 2. Number of (a) esophagectomies and (b) gastrectomies per hospital volume category

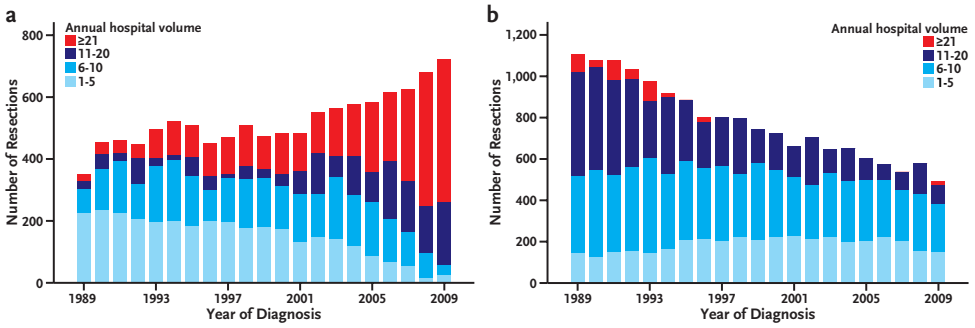
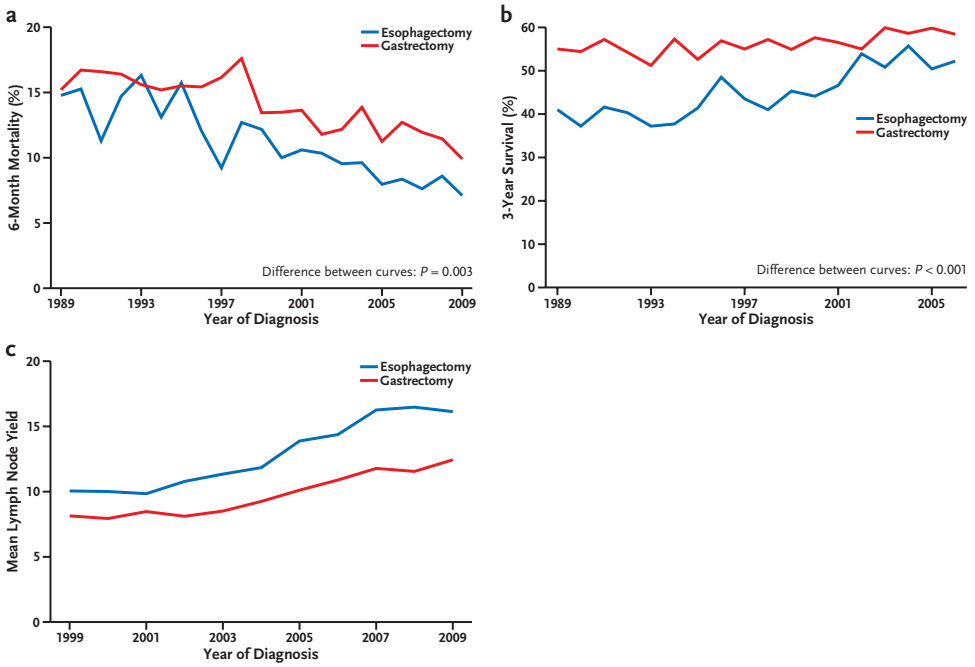


Figure 3. Adjusted (a) 6-month mortality , (b) 3-year conditional survival, and (c) median lymph node yield for esophagectomy and gastrectomy, 1989-2008

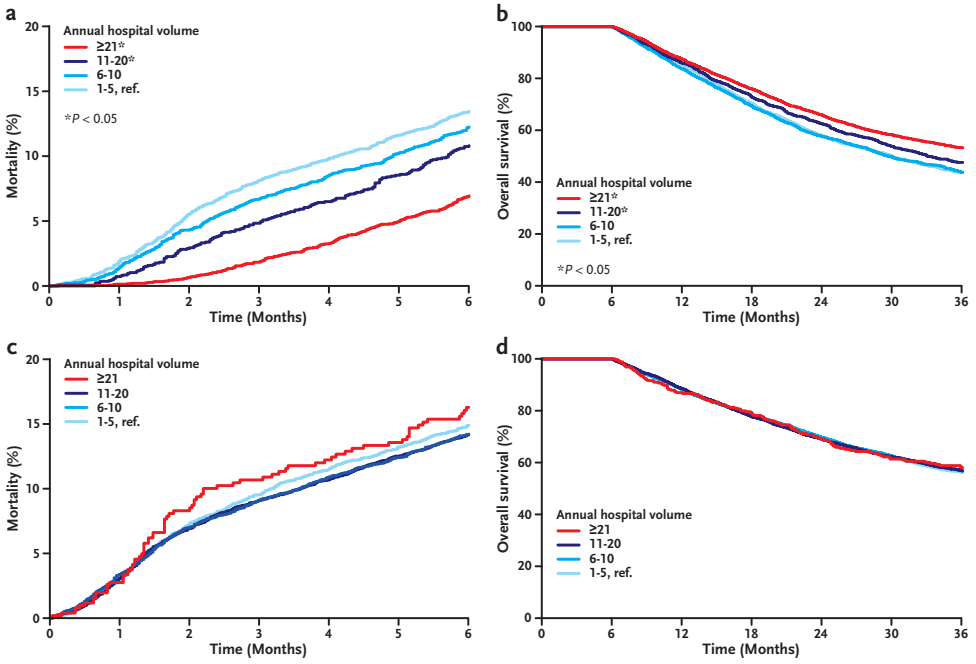


Mean lymph node yield after esophagectomy increased from 10.1 in 1999 to 16.2 in 2009 ($P < 0.001$), and mean lymph node yield after gastrectomy increased from 8.1 in 1999 to 12.4 in 2009 ($P < 0.001$) (Figure 3c).

VOLUME-OUTCOME RELATIONS

Results from the multivariable analyses on volume-outcome relations are shown in Table 3 and 4. After esophagectomy, medium and high volume hospitals were associated with lower six-month mortality and longer three-year conditional survival when compared

Figure 4. Adjusted relation between annual hospital volume and (a) 6-month mortality and (b) 3-year conditional survival after esophagectomy, and relation between annual hospital volume and (c) 6-month mortality and (d) 3-year conditional survival after gastrectomy



to very-low volume hospitals (Figures 4a, 4b). After gastrectomy, neither six-month mortality, or three-year conditional survival were associated with hospital volume category (Figures 4c, 4d). High hospital volume was associated with high lymph node yield both after esophagectomy and gastrectomy.

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).

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

Table 3. Volume-outcome relations for esophagectomy (1989-2009)

	6-month mortality		3-year survival[a]			LN yield[b]
	HR	95% CI	HR	95% CI	OR	95% CI
Annual hospital volume						
1-5	1.00		1.00		1.00	
6-10	0.90	0.78-1.03	1.01	0.94-1.10	1.00	0.91-1.09
11-20	**0.78**	**0.62-0.97**	**0.90**	**0.81-0.99**	1.10	1.00-1.22
≥21	**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						
<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 group						
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			
yes			1.07	0.94-1.21		

[a]conditional on surviving the first six months, [b]1999-2009
HR: hazard ratio, OR: odds ratio, SES: socio economic status, SCC: squamous cell carcinoma,
95% CI: 95% confidence interval, **Bold:** significant ($P < 0.05$)

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.[7,24,26,27]

Table 4. Volume-outcome relations for gastrectomy (1989-2009)

	6-month mortality		3-year survival[a]			LN yield[b]
	HR	95% CI	HR	95% CI	OR	95% CI
Annual hospital volume						
1-5	1.00		1.00		1.00	
6-10	0.95	0.84-1.07	0.99	0.91-1.07	1.02	0.96-1.08
11-20	0.95	0.83-1.08	0.99	0.90-1.08	0.99	0.90-1.10
≥21	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						
<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 group						
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	
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		

[a]conditional on surviving the first six months, [b]1999-2009
HR: hazard ratio, OR: odds ratio, SES: socio economic status, 95% CI: 95% confidence interval
Bold: significant ($P < 0.05$)

Over the past two decades, the number of esophagectomies in the Netherlands has increased, corresponding with an increasing incidence of esophageal cancer.[28] The decreasing incidence of gastric cancer explains the low number of gastrectomies currently performed in the Netherlands.[29] 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.[17,27]

The current study covers an extensive period of two decades of esophagogastric 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.[30] The absence of comorbidity in the current dataset was partly compensated by the use of SES, which can be considered a proxy for comorbidity.[31]

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.[7,27,32] 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.[33] 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,[3,34] and by educating surgeons participating in the trial.[35,36] 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.[11,27] 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.[37] 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.[38]

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.[39]

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.[40]

Combining centralization with auditing substantially adds to improvement of care.[41] 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,[38] 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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PART III

Surgical quality assurance

CHAPTER 15

The influence of hospital type on outcomes after esophageal and gastric cancer surgery

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ABSTRACT

BACKGROUND

Outcomes after esophagectomy and gastrectomy vary considerably between hospitals. Possible explanations include differences in case mix, hospital volume and hospital type. The present study examined the distribution of esophagectomies and gastrectomies between hospital types in the Netherlands, and the relationship between hospital type and outcome.

PATIENTS AND METHODS

Data were obtained from the nationwide Netherlands Cancer Registry. Hospitals were categorized as university hospitals (UH), teaching non-university hospitals (TNUH) and non-teaching hospitals (NTH). Hospital type-outcome relationships were analyzed by Cox regression, adjusting for case mix, hospital volume, year of diagnosis and use of multimodal therapies.

RESULTS

Between 1989 and 2009, 10,025 esophagectomies and 14,221 gastrectomies for cancer were performed in the Netherlands. The percentage of esophagectomies and gastrectomies performed in UH increased from 17.6% and 6.4% respectively in 1989 to 44.1% and 12.9% in 2009. After esophagectomy, the 3-month mortality rate was 2.5% in UH, 4.4% in TNUH and 4.1% in NTH ($P = 0.006$ for UH versus TNUH). After gastrectomy, the 3-month mortality rate was 4.9% in UH, 8.9% in TNUH and 8.7% in NTH ($P < 0.001$ for UH versus TNUH). Three-year survival was also higher in UH than in TNUH and NTH.

CONCLUSIONS

Esophagogastric resections performed in UH were associated with better outcomes but, owing to variation in outcomes within hospital types, centers of excellence cannot be designated solely on hospital type. Detailed information on case mix and outcomes is needed to identify centers of excellence.

INTRODUCTION

Long-term survival for patients with resectable esophageal and gastric cancer is low in the Western world. The 5-year overall survival rate is below 25% after esophagectomy and less than 40% after gastrectomy.[1,2] Both are high-risk operations with correspondingly high postoperative mortality rates.[3,4]

Both postoperative mortality and long-term survival after esophagogastric cancer surgery can be improved by performing these complex procedures in centers with sufficient experience and high annual volumes.[3,5] An exact cut-off value that defines high-volume surgery has not, however, been established. In a recent survey of all esophagectomies and gastrectomies performed in the Netherlands between 1989 and 2009, esophagectomies carried out in high-volume hospitals (more than 20 procedures per year) were associated with lower postoperative mortality and improved survival compared with those performed in low-volume hospitals. No such relationship was found after gastrectomy, but the number of high-volume hospitals was small.[6]

Although hospital volume can be used as a proxy for quality of care, another approach is to compare outcomes by type of hospital in which the surgery takes place.[7] University hospitals have been associated with better outcomes than non-university hospitals for a variety of procedures and diseases, including radical prostatectomy,[8] heart failure, myocardial infarction and stroke.[9,10] In a previous study, no difference was found in survival after gastrectomy between university teaching, non-university teaching and non-teaching hospitals, although the number of patients and hospitals was limited.[11] The effect of hospital type on outcomes after esophagogastric resections remains unclear.

The present study aimed to describe the distribution of esophagectomies and gastrectomies between hospital types in the Netherlands between 1989 and 2009, and to analyze the effect of hospital type on short- and long-term outcomes after these operations.

METHODS

NETHERLANDS CANCER REGISTRY

Data were obtained from the Netherlands Cancer Registry (NCR), in which information on all newly diagnosed malignancies in the Netherlands, a country of 16.5 million inhabitants, was collected. Patient, tumor and treatment characteristics were collected routinely by trained registrars from the hospital records 6-18 months after diagnosis. The quality and completeness of the data are known to be almost 100%.[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 (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 tumor node metastasis (TNM) classification in use

in the year of diagnosis. Vital status was obtained initially 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 31 December 2009. The study was approved by the NCR Review Board.
Esophagectomy and gastrectomy were analyzed separately. As the NCR is a topography-based registry, 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).
If the hospital of surgery was not registered, the hospital of diagnosis was assumed to be the hospital of surgery. Annual hospital volumes were defined as the number of esophagectomies or gastrectomies per hospital per year. Volume categories were defined as very low (1-5 per year), low (6-10 per year), medium (11-20 per year) and high (at least 21 per year). Hospital types were defined as university hospitals, teaching non-university hospitals and non-teaching hospitals. University hospitals are attached to one of the eight universities in the Netherlands, and these hospitals collaborate closely with the corresponding medical faculty. A hospital was considered a teaching hospital if it offered (part of) a surgical residency programme.

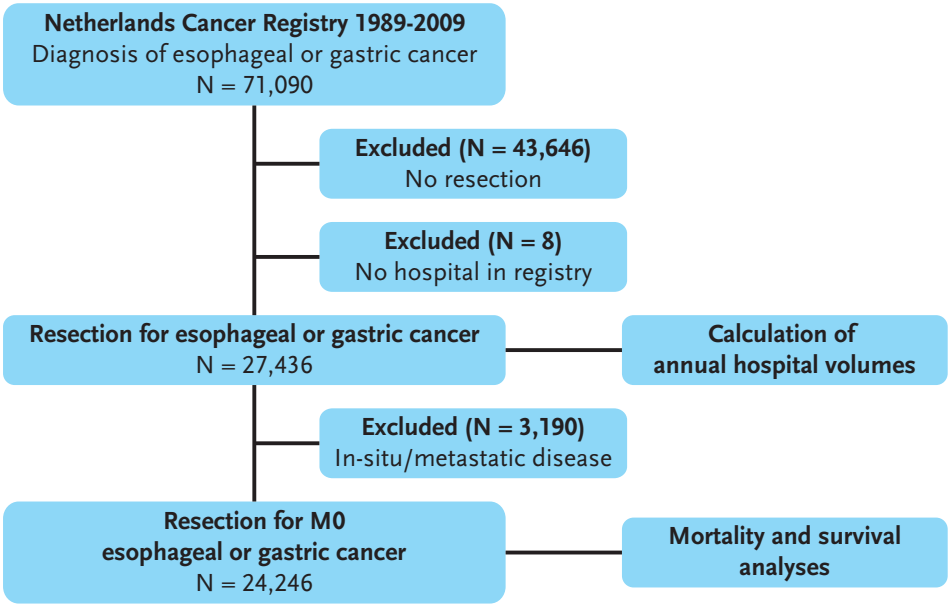
STATISTICAL ANALYSIS

Changes in the distribution of operations between hospital types over time and differences in patient characteristics between hospital types were analyzed by means of the χ^2 test. Overall survival was calculated from the day of the histological diagnosis until death, because the date of surgery was not available before 2005. Three-month overall survival was calculated unconditionally, whereas 3-year overall survival was calculated conditionally on surviving the first 3 months after diagnosis. Possible relationships between hospital type and outcomes were analyzed by stratified Cox regression, adjusted for annual hospital volume, year of diagnosis, sex, age, socioeconomic status,[14] tumor stage, morphology, preoperative therapy use, postoperative therapy use (only for 3-year survival) and for clustering of deaths within hospitals.[15] A separate analysis was performed including only patients diagnosed between 2005 and 2009. To assess potential referral bias, analyses were repeated for hospital of diagnosis instead of hospital of surgery. Analyses were performed with SPSS® version 17.0.2 (SPSS, Chicago, Illinois, USA) and R version 2.12.2 (R Project for Statistical Computing, Vienna, Austria).

RESULTS

Between January 1989 and December 2009, 71,090 patients with esophageal or gastric cancer were diagnosed (Figure 1). Some 43,646 patients who did not undergo surgical treatment and eight without information on the hospital of diagnosis or surgery were excluded, leaving 27,436 resections for analysis.
Before 2005, the hospital where the resection was performed was registered in 53.3%

Figure 1. Study flow chart



of cases, showing a match with the hospital of diagnosis in 79.8% of patients. For the remaining 46.7% of cases, the hospital of diagnosis was considered the hospital of surgery.

After analyzing hospital type distributions and their relation with annual hospital volume, 288 patients with carcinoma *in situ* and 2902 with distant metastases were excluded, leaving 24,246 patients with non-metastatic invasive carcinoma available for hospital type-outcome analyses.

HOSPITAL TYPES OVER TIME

There are eight university hospitals in the Netherlands and one specialized cancer center that was analyzed as a university hospital. The number of non-university hospitals where esophagectomies and gastrectomies were performed decreased, from 120 in 1989 to 82 in 2009.

The annual number of esophagectomies increased over the years, from 352 in 1989 to 723 in 2009 (Figure 2a). The percentage of esophagectomies performed in university hospitals increased from 17.6% (62/352) in 1989 to 44.1% (319/723) in 2009 ($P < 0.001$). The annual number of gastrectomies decreased from 1107 in 1989 to 495 in 2009 (Figure 2b). The percentage of gastrectomies performed in university hospitals increased from 6.4% (71/1107) in 1989 to 12.9% (64/495) in 2009 ($P < 0.001$). Most gastrectomies are currently performed in teaching non-university hospitals.

Table 1. Characteristics for all patients with resected non-metastatic esophageal cancer in the Netherlands between 1989 and 2009 (N = 10,025)

	University Hospital		Teaching Non-University Hospital		Non-Teaching Hospital		
	N	%	N	%	N	%	*P*
Total	3559	*100.0*	3905	*100.0*	2561	*100.0*	
Sex							
male	2694	*75.7*	3004	*76.9*	1952	*76.2*	0.454
female	865	*24.3*	901	*23.1*	609	*23.8*	
Age							
<60	1324	*37.2*	1330	*34.1*	785	*30.7*	<0.001
60-75	1947	*54.7*	2139	*54.8*	1446	*56.5*	
>75	288	*8.1*	436	*11.2*	330	*12.9*	
median age	63		64		65		
SES							
low	290	*8.1*	489	*12.5*	227	*8.9*	<0.001
medium	2633	*74.0*	3083	*79.0*	2162	*84.4*	
high	162	*4.6*	156	*4.0*	108	*4.2*	
unknown	474	*13.3*	177	*4.5*	64	*2.5*	
Morphology							
adenocarcinoma	2552	*71.7*	2997	*76.7*	1992	*77.8*	<0.001
SCC	928	*26.1*	818	*20.9*	509	*19.9*	
other	79	*2.2*	90	*2.3*	60	*2.3*	
TNM stage group							
I	624	*17.5*	810	*20.7*	507	*19.8*	<0.001
II	1305	*36.7*	1551	*39.7*	1042	*40.7*	
III	1388	*39.0*	1306	*33.4*	881	*34.4*	
IV	39	*1.1*	45	*1.2*	24	*0.9*	
unknown	203	*5.7*	193	*4.9*	107	*4.2*	
Preoperative therapy							
yes	907	*25.5*	634	*16.2*	163	*6.4*	<0.001
no	2652	*74.5*	3271	*83.8*	2398	*93.6*	
Postoperative therapy							
yes	194	*5.5*	233	*6.0*	104	*4.1*	0.003
no	3365	*94.5*	3672	*94.0*	2457	*95.9*	
Annual hospital volume							
1-5	144	*4.0*	1024	*26.2*	1746	*68.2*	<0.001
6-10	415	*11.7*	1623	*41.6*	657	*25.7*	
11-20	512	*14.4*	824	*21.1*	158	*6.2*	
≥21	2488	*69.9*	434	*11.1*	0	*0*	

SES: socio economic status, SCC: squamous cell carcinoma, preoperative/postoperative therapy: chemotherapy with/without radiotherapy

PATIENT, TUMOR AND TREATMENT CHARACTERISTICS

Between 1989 and 2009, 10,025 patients underwent esophagectomy and 14,221 underwent gastrectomy for cancer (Tables 1 and 2). The median age of patients who underwent esophagectomy in university hospitals was 63 years, compared with 64 and 65 in teaching non-university and non-teaching hospitals respectively. They were more likely to have a squamous cell carcinoma (26.1% in university hospitals *versus* 20.9% and 19.9% in teaching non-university and non-teaching hospitals respectively) and had higher tumor stages (stage III disease in 39.0% (1388/3559), 33.4% (1306/3905) and

Table 2. Characteristics for all patients with resected non-metastatic gastric cancer in the Netherlands between 1989 and 2009 (N = 14,221)

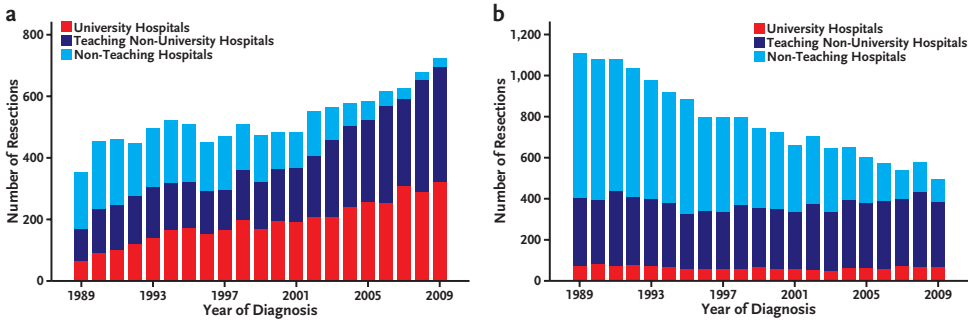
	University Hospital		Teaching Non-University Hospital		Non-Teaching Hospital		
	N	%	N	%	N	%	*P*
Total	1132	*100.0*	5702	*100.0*	7387	*100.0*	
Sex							
male	683	*60.3*	3458	*60.6*	4423	*59.9*	0.669
female	449	*39.7*	2244	*39.4*	2964	*40.1*	
Age							
<60	352	*31.1*	1151	*20.2*	1346	*18.2*	< 0.001
60-75	521	*46.0*	2711	*47.5*	3530	*47.8*	
>75	259	*22.9*	1840	*32.3*	2511	*34.0*	
median Age	67		71		71		
SES							
low	198	*17.5*	882	*15.5*	694	*9.4*	< 0.001
medium	789	*69.7*	4319	*75.5*	6256	*84.7*	
high	48	*4.2*	181	*3.2*	233	*3.2*	
unknown	97	*8.6*	320	*5.6*	204	*2.8*	
Morphology							
adenocarcinoma	1109	*98.0*	5602	*98.2*	7249	*98.1*	0.780
other	23	*2.0*	100	*1.8*	138	*1.9*	
TNM stage group							
I	436	*38.5*	2195	*38.5*	2781	*37.6*	<0.001
II	259	*22.9*	1569	*27.5*	2010	*27.2*	
III	329	*29.1*	1528	*26.8*	2112	*28.6*	
IV	72	*6.4*	258	*4.5*	264	*3.6*	
unknown	36	*3.2*	152	*2.7*	220	*3.0*	
Preoperative therapy							
yes	125	*11.0*	378	*6.6*	113	*1.5*	<0.001
no	1007	*89.0*	5324	*94.8*	7274	*98.5*	
Postoperative therapy							
yes	65	*5.7*	299	*5.2*	145	*2.0*	<0.001
no	1067	*94.3*	5403	*94.8*	7242	*98.0*	
Annual hospital volume							
1-5	235	*21.8*	893	*15.7*	2283	*30.9*	<0.001
6-10	511	*45.1*	2306	*40.4*	3282	*44.4*	
11-20	366	*32.3*	2284	*40.1*	1706	*23.1*	
≥21	20	*1.8*	219	*3.8*	116	*1.6*	
Type of resection[a]							
total gastrectomy	143	*51.1*	479	*32.6*	266	*37.7*	<0.001
subtotal gastrectomy	137	*48.9*	986	*67.3*	440	*62.3*	

SES: socio economic status, preoperative/postoperative therapy: chemotherapy with/without radiotherapy
[a]only available from 2005-2009

34.4% (881/2561) respectively). A higher proportion of patients in university hospitals received multimodal therapy. Annual hospital volumes were higher in university hospitals: 69.9% of esophagectomies (2488/3559) in such hospitals were performed in centers with an annual volume of at least 21, compared with 11.1% (434/3905) in teaching non-university hospitals and no esophagectomies in non-teaching hospitals.

Patients who underwent a gastrectomy in university hospitals had a median age of 67 years, compared with 71 years in both types of non-university hospital. Patients in university hospitals also received more preoperative and postoperative multimodal

Figure 2. Number of (a) esophagectomies and (b) gastrectomies performed in different hospital types, 1989-2009



therapy. Annual hospital volumes were highest in non-university teaching hospitals: 43.9% of gastrectomies (2503/5702) in teaching non-university hospitals were performed in centers with an annual volume of ≥11, compared with 34.1% (386/1132) in university hospitals and 24.7% (1822/7387) in non-teaching hospitals.

RELATIONSHIP BETWEEN HOSPITAL TYPE AND OUTCOMES

In multivariable regression analysis adjusting for case mix, annual hospital volume, year of diagnosis and use of multimodal therapy, both esophagectomies and gastrectomies in university hospitals were associated with lower 3-month mortality and higher 3-year survival (Table 3).

The adjusted 3-month mortality rate after esophagectomy was 2.5% (95% confidence interval 1.8-3.2%) in university hospitals, 4.4% (3.5-5.2%) in teaching non-university hospitals and 4.1% (3.2-5.0%) in non-teaching hospitals (Figure 3a). Corresponding 3-year survival rates were 46% (44-49%), 42% (40-44%) and 43% (40-59%) (Figure 3b). Adjusted 3-month mortality rates after gastrectomy were 4.9% (3.7-6.1%) in university hospitals, 8.9% (8.1-9.7%) in teaching non-university hospitals and 8.7% (8.0-9.4%) in non-teaching hospitals (Figure 3c). Respective 3-year survival rates were 58% (55-61%), 52% (51-54%) and 52% (51-54%) (Figure 3d).

Hospital type-outcome analyses including only patients diagnosed between 2005 and 2009 produced no major changes in the results, except that the difference in 3-year survival after gastrectomies between hospital types became non-significant (not shown). When analyses for 1989-2009 were repeated with the hospital of diagnosis instead of the hospital of surgery, again no major changes were found, although 3-month mortality after esophagectomy lost significance (not shown). When the analyses were repeated with university hospitals as the reference category, these hospitals were found to be associated with a significantly lower 3-month mortality rate after both esophagectomy and gastrectomy, and significantly better 3-year survival after gastrectomy, compared with non-teaching hospitals (not shown).

Figure 3. Relationship between hospital type and 3-month mortality and 3-year survival for (a, b) esophagectomy, and (c, d) gastrectomy

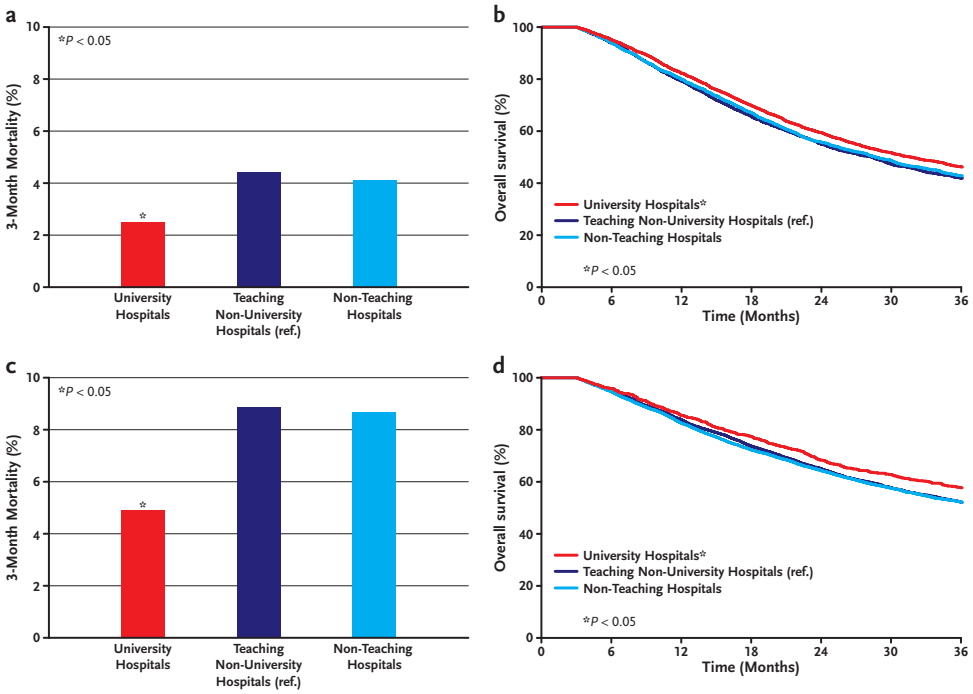
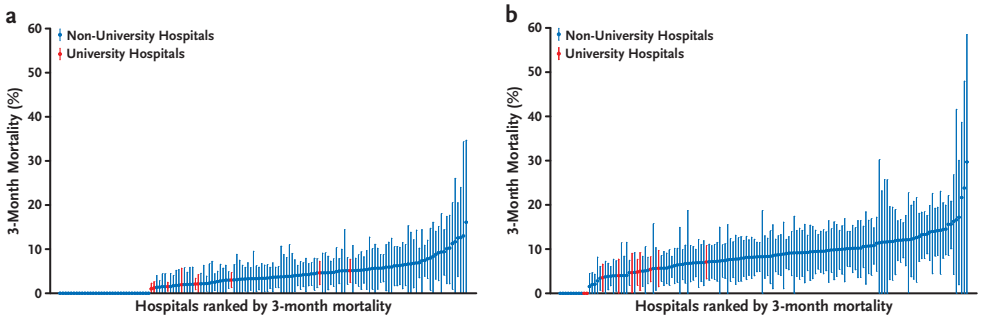


Figure 4. Three-month mortality rates after (a) esophagectomy and (b) gastrectomy analyzed at individual hospital level



PERFORMANCE OF INDIVIDUAL HOSPITALS

Analysis of 3-month mortality rates at the level of individual hospitals indicated that most university hospitals had good outcomes (Figure 4). There were, nevertheless, non-university hospitals with outcomes similar to, or better than those of all university hospitals. There were also university hospitals with average outcomes. The number of patients per hospital was too small for statistical assessment of differences in outcomes between hospitals.

DISCUSSION

The effect of hospital type on outcomes after esophagectomy or gastrectomy has been studied in a limited way before in the Netherlands.[11,16] In a large American study, postoperative mortality after esophagectomy and gastrectomy in National Cancer Institute (NCI)-designated hospitals was lower than in non-NCI hospitals, even after adjustment for hospital volume.[7] Most of these NCI centers are university hospitals.

In the present study, the increasing number of esophagectomies in the Netherlands reflects the increasing incidence of esophageal cancer. This increase has been taken up by university and teaching non-university hospitals. University hospitals have high annual volumes, whereas non-university hospitals operate in lower volumes.

In contrast, the incidence of gastric cancer is declining, leading to a smaller number of gastrectomies over the years.[17] Although the absolute number of gastrectomies in university hospitals (approximately 100 per year) and teaching non-university hospitals (about 300 per year) has remained stable, the number performed in non-teaching hospitals has decreased. Most centers, even university hospitals, performed fewer than 11 gastrectomies annually. In 2012, gastrectomy will be centralized in the Netherlands to hospitals with a minimum annual volume of 20 per year, mainly towards those centers currently performing esophagectomy.

In the present study, outcomes after esophagectomy and gastrectomy were better in university hospitals than in non-university hospitals, but there were no significant differences between teaching non-university hospitals and non-teaching hospitals. Despite differences of approximately 10% between university and non-university hospitals, 3-year survival rates after gastrectomy in the Netherlands remain low compared with Asian outcomes.[18] This difference might be explained by differences in tumor stage at presentation, stage migration owing to more extended lymph node retrieval, and intrinsic biological differences between Western and Asian patients with gastric cancer.[19]

Studies comparing outcomes between hospitals are vulnerable to various types of bias. The present methodology was chosen to limit some of these factors. Most esophagectomies performed in recent years were performed in university and teaching non-university hospitals. As quality of care in general is likely to have improved over the years, better outcomes for operations performed in university and teaching non-university hospitals might reflect improvements in perioperative care over the years, rather than a true difference between hospital types. Adjustment for year of diagnosis was used to eliminate this effect.

Adjustments were also made for annual hospital volume, reducing the effect of hospital volume on outcome when examining hospital types. Referral bias was assessed by repeating the analyses with the hospital of diagnosis instead of the hospital of surgery. No major differences in the results were found, indicating that the better outcomes in university hospitals were not the result of selective referral of healthier patients from non-university to university hospitals. A third of all esophagectomies were performed in

Table 3. Multivariate Cox regression analysis of the relationship between hospital type and outcomes after esophagectomy and gastrectomy, 1989-2009

	Esophagectomy				Gastrectomy			
	3-month mortality		3-year survival		3-month mortality		3-year survival	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Hospital type								
teaching non-university	1.00		1.00		1.00		1.00	
non-teaching	0.95	0.80-1.13	0.97	0.89-1.06	0.98	0.85-1.13	1.02	0.94-1.10
university	**0.56**	**0.37-0.85**	**0.87**	**0.78-0.99**	**0.53**	**0.42-0.66**	**0.85**	**0.78-0.93**
Annual hospital volume								
1-5	1.00		1.00		1.00		1.00	
6-10	0.88	0.74-1.05	1.02	0.94-1.10	0.95	0.83-1.09	0.99	0.92-1.06
11-20	0.83	0.63-1.09	0.94	0.84-1.05	0.95	0.82-1.10	1.00	0.91-1.09
≥21	**0.44**	**0.25-0.76**	0.86	0.73-1.01	1.08	0.81-1.44	1.01	0.91-1.13
Year of diagnosis								
1989-1993	1.00		1.00		1.00		1.00	
1994-1997	0.93	0.76-1.14	0.91	0.83-1.01	0.97	0.85-1.11	0.97	0.91-1.04
1998-2001	0.77	0.59-1.01	**0.88**	**0.80-0.96**	0.90	0.76-1.05	0.94	0.87-1.02
2002-2005	**0.58**	**0.43-0.80**	**0.69**	**0.63-0.76**	**0.76**	**0.64-0.91**	**0.86**	**0.79-0.94**
2006-2009	**0.42**	**0.29-0.63**	**0.74**	**0.66-0.83**	**0.64**	**0.51-0.81**	**0.80**	**0.73-0.87**
Sex								
male	1.00		1.00		1.00		1.00	
female	**0.68**	**0.57-0.81**	**0.84**	**0.78-0.89**	**0.67**	**0.61-0.74**	**0.92**	**0.87-0.98**
Age category								
<60	1.00		1.00		1.00		1.00	
60-75	**2.11**	**1.73-2.57**	**1.18**	**1.10-1.26**	**2.44**	**2.04-2.91**	**1.29**	**1.21-1.38**
>75	**3.66**	**2.82-4.74**	**1.52**	**1.36-1.70**	**5.65**	**4.70-6.79**	**1.61**	**1.49-1.74**
SES								
low	1.00		1.00		1.00		1.00	
medium	**0.77**	**0.62-0.97**	1.01	0.91-1.12	**0.85**	**0.73-0.98**	1.00	0.91-1.10
high	**0.44**	**0.26-0.73**	0.95	0.81-1.12	**0.56**	**0.39-0.81**	1.00	0.84-1.18
unknown	0.65	0.37-1.13	0.97	0.81-1.16	0.92	0.67-1.27	1.02	0.87-1.20
TNM stage group								
I	1.00		1.00		1.00		1.00	
II	1.12	0.90-1.40	**2.56**	**2.31-2.85**	**1.24**	**1.09-1.40**	**2.88**	**2.69-3.08**
III	**1.33**	**1.04-1.70**	**4.77**	**4.11-5.54**	**1.67**	**1.47-1.89**	**5.16**	**4.85-5.49**
IV	**2.74**	**1.43-5.24**	**9.31**	**7.24-11.97**	**2.65**	**2.17-3.23**	**8.24**	**7.36-9.21**
unknown	**1.51**	**1.01-2.27**	**2.45**	**2.08-2.87**	**1.96**	**1.42-2.71**	**2.28**	**1.92-2.70**
Morphology								
adenocarcinoma	1.00		1.00		1.00		1.00	
SCC	**1.37**	**1.15-1.64**	**1.10**	**1.01-1.21**				
other	0.82	0.46-1.45	1.17	0.96-1.44	1.17	0.79-1.74	**0.66**	**0.50-0.88**
Preoperative therapy								
No	1.00		1.00		1.00		1.00	
Yes	**0.06**	**0.02-0.15**	**0.80**	**0.74-0.88**	**0.08**	**0.03-0.25**	1.00	0.81-1.24
Postoperative therapy								
no			1.00				1.00	
yes			1.02	0.90-1.15			0.95	0.79-1.14

HR: hazard ratio, 95% CI: 95% confidence interval, SCC: squamous cell carcinoma, **Bold:** significant ($P < 0.05$)

university hospitals, but only 8.0% of gastrectomies. This tends to reduce the impact of the observation that university hospitals had better outcomes after gastrectomy.

The differences in outcomes between university and non-university hospitals may not be simply explained by type of hospital, regardless of any other factors. Rather, hospital

type might act as a proxy for differences in infrastructure and processes of care between different types of hospitals. In the Netherlands, university hospitals have higher staff-to-patient ratios, more financial resources per patient, more specialized treatments,[20] and have higher-level intensive care units than non-university hospitals.[21] Furthermore, individual hospitals may differ in quality of the diagnostic process, patient selection, administration of multimodal therapy, perioperative care, quality of surgery and ability to deal with complications. Excellent performance in all parts of this multidisciplinary care pathway contributes to a high standard of care and favorable outcome.[22] Identification of centers of excellence should be based on robust and case mix-adjusted data provided by high-quality clinical audits, where detailed information on the performance of individual hospitals is collected.

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PART III

Surgical quality assurance

CHAPTER 16

Differences in outcomes of esophageal and gastric cancer surgery across Europe

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ABSTRACT

BACKGROUND

In several European countries, centralization of esophagogastric cancer surgery has been realized and clinical audits have been initiated. Aims of the present study were to evaluate differences in resection rates, outcomes, and annual hospital volumes between these countries, and to analyze the relation between annual hospital volume and outcomes.

PATIENTS AND METHODS

National data were obtained from cancer registries or clinical audits in the Netherlands, Sweden, Denmark, and England. Differences in outcomes were analyzed between countries and between hospital volume categories, adjusting for available case-mix factors.

RESULTS

Between 2004 and 2009, 10,854 esophagectomies and 9,010 gastrectomies were registered. Resection rates in England were 18.2% and 21.6% for esophageal and gastric cancer, compared with 28.5-29.9% and 41.4-41.9% in the Netherlands and Denmark ($P < 0.001$). Adjusted 30-day mortality after esophagectomy was lowest in Sweden (1.9%). After gastrectomy, adjusted 30-day mortality was significantly higher in the Netherlands (6.9%) compared with Sweden (3.5%) and Denmark (4.3%) ($P < 0.05$). Increasing hospital volume was associated with lower 30-day mortality after esophagectomy (odds ratio 0.55 for ≥41/year versus 1-10/year, 95%CI 0.42-0.72) and gastrectomy (odds ratio 0.64 for ≥21/year versus 1-10/year, 95%CI 0.41-0.99)

CONCLUSIONS

The present results demonstrate a lower 30-day mortality in hospitals performing higher numbers of esophagogastric cancer resections. However, differences in outcomes between several European countries could not be explained by existing differences in hospital volumes. To understand these differences in outcomes and resection rates, and to provide more reliable case-mix adjustments, a uniform European Upper GI Cancer Audit recording standardized data is warranted.

INTRODUCTION

Quality assurance is increasingly acknowledged as a crucial factor for improvement of care for patients with esophageal and gastric cancer. In Europe, the average five-year survival rate is 11% for esophageal cancer, and 25% for gastric cancer, but variation between and within countries is considerable.[1] The reasons for these inter and intra country variations are difficult to assess. In some countries there are nationally sponsored cancer registries whereas others have established clinical audits. Furthermore the data recorded is variable and there are differences in data interpretation. Thus comparison of outcomes can be limited. One of the key elements to any comparison is the completeness of the recorded data in order to eliminate any bias as this would adversely affect any resultant change in service configuration and therefore outcome.

In the Netherlands, Sweden, Denmark, and England programs and processes have been established which are designed to achieve as comprehensive data collection as possible with the aim of quality assuring treatment of esophageal and gastric cancer.

The purposes of the current study are to evaluate differences in annual hospital volumes, resection rates and treatment outcomes in these four countries and to determine where improvements can be made to allow better inter country comparisons.

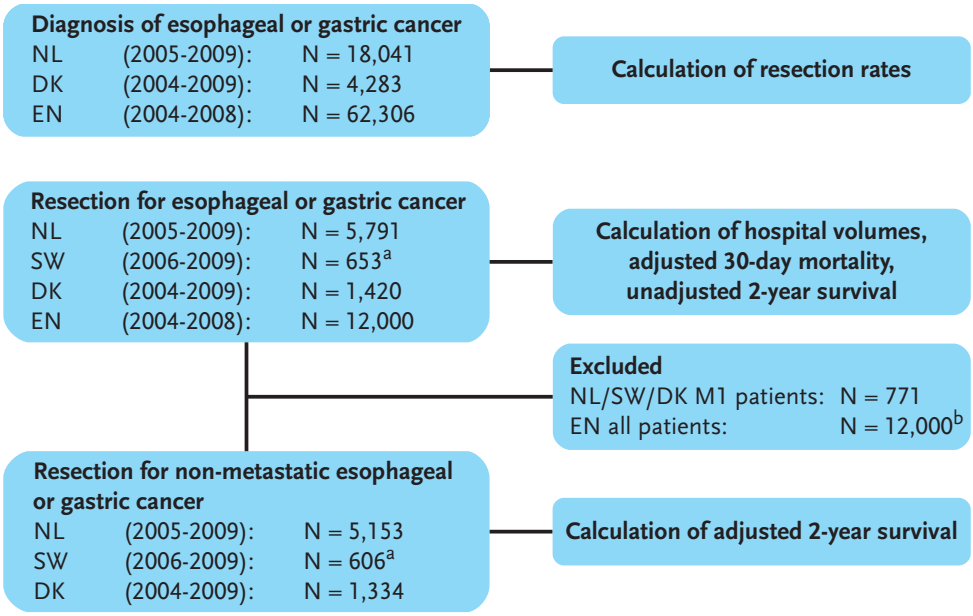
PATIENTS AND METHODS

National data were obtained from cancer registries in the Netherlands and England, and from clinical audits in Sweden and Denmark (Table 1). The Cancer Registries from the Netherlands and England, and the audit from Denmark, provide national coverage of all patients with a diagnosis of esophagogastric cancer. In the Swedish audit, only patients who underwent surgery were included, and therefore no resection rates could be calculated for Sweden. Furthermore, in several Swedish regions, not all patients who underwent surgical resection were registered. To reduce the chance of selection bias, only Swedish regions with a case ascertainment above 90% were included. These were Uppsala-Örebro (2006-2009), Norra (2006-2009), Sydöstra (2007-2009), and Stockholm-Gotland (2008-2009).

Detailed data from patients included in the UK National Esophago-Gastric Cancer Audit (NOGCA) have not been included as the case ascertainment at 71% is lower than the population based English Cancer Registry data, which partly reflects the voluntary nature of the NOGCA.[2]

Resection rates were calculated in the cohort of patients with a diagnosis of esophageal or gastric cancer between 2004 and 2009 (not all countries had data in each year, (Figure 1). Postoperative mortality, survival, and annual hospital volumes were calculated in the cohort of patients who underwent surgical resection between 2004 and 2009.

Figure 1. Study profile



NL: Netherlands, SW: Sweden, DK: Denmark, EN: England

DATA AVAILABILITY

Demographic data were available in all datasets, but comorbidity data were not uniformly registered and could therefore not be used for case-mix adjustments. Tumor location and histology based on the International Classification of Diseases for Oncology (ICD-O) were available in all datasets.[3] Tumor location was defined as esophagus (ICD-O C15.0-16.0), or stomach (ICD-O C16.1-16.9). Staging was performed according to the 6th edition of the International Union Against Cancer (UICC) TNM classification.[4] Information on TNM stage group was not available for the English data as stage was not routinely recorded during the study period by the English registries.

CALCULATION OF ANNUAL HOSPITAL VOLUMES

The hospital (in England: trusts, some of which manage several hospitals) where the operation was performed was available in all datasets. Annual hospital volume was defined separately for esophagectomy and gastrectomy as the number of resections per hospital in each calendar year. Volume categories were defined according to the distribution of resection numbers among hospitals (Figure 2).

STATISTICAL ANALYSES

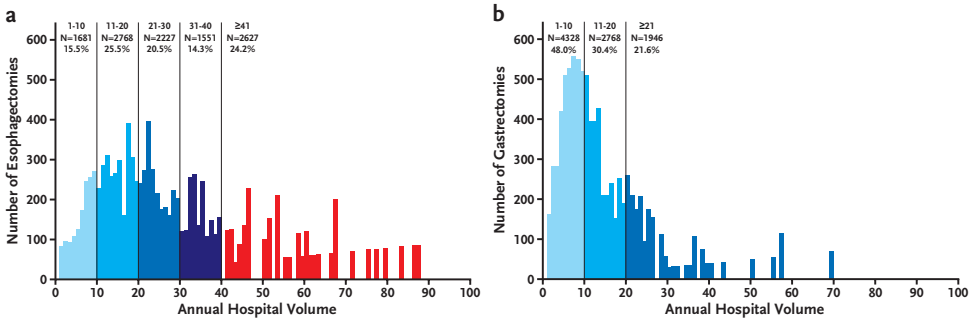
Data regarding esophagectomies and gastrectomies were analyzed separately. Differences in patient characteristics, resection rates, and annual hospital volumes between countries were analyzed with the Chi-square test.

Table 1. Characteristics of participating countries and available datasets

Country	Netherlands	Sweden	Denmark	England
inhabitants (x10^6)	16.7	9.4	5.5	52
incidence esophageal cancer (m/f)[a]	8.0 / 2.5	3.9 / 0.9	6.1 / 1.7	9.2 / 3.4
incidence gastric cancer (m/f)[a]	9.7 / 4.2	6.2 / 2.9	7.1 / 3.5	8.9 / 3.7
Centralization of surgery				
centralization of esophagectomy	2006: 10/year[b]	no	2003: 5 centres 2008: 4 centres	2001: 40/year[b]
centralization of gastrectomy	no	no	2003: 5 centres 2008: 4 centres	2001: 60/year[b]
Registry				
registry used	Netherlands Cancer Registry	National Quality Registry of Esophageal and Gastric Cancer	National Database of Esophagogastric Cancer; National Pathology Registry; National Registry of Patients; Danish Civil Registration System	English Cancer Registries
registry type	cancer registry	clinical audit	clinical audit	cancer registry
registry active since	1989	2006	2003	multiple years
data collection	trained registrars	trained doctors and nurses	surgeons treating the patients	multiple sources
years of diagnosis in dataset	2005-2009	2006-2009	2004-2009	2004-2008
follow-up until	January 2010	April 2011	January 2011	December 2009
case ascertainment	nationwide	partial[c]	nationwide	nationwide
Data availability				
patient age and sex	+	+	+	+
comorbidity (Charlson/ASA)	-/-	-/+	+/+	-
tumor location (E/EGJ/S)	+	+	+	+
tumor histology (AC/SCC/other)	+	+	+	+
TNM stage group	+	+	+	-
number of lymph nodes evaluated	+	+	+	-
surgery type	+	+	+	+
surgery hospital	+	+	+	+
(neo-)adjuvant therapy	+	+	-	-
30-day postoperative mortality	+	+	+	+
in-hospital mortality	-	-	+	-
2-year survival from surgery	+	+	+	+

[a]incidence per 100,000 world standard ratio, Karim-Kos et al.[39]
[b]minimal annual hospital volume
[c]in certain regions in Sweden, case ascertainment was incomplete. Therefore, regions with a case ascertainment below 90% were excluded
E: esophagus, EGJ: esophagogastric junction, S: stomach, AC: adenocarcinoma, SCC: squamous cell carcinoma,
+ yes, - no, ± sometimes

Figure 2. Distribution of (a) esophagectomy (N = 10,854), (b) gastrectomy (N = 9,010) over different hospital volume categories



Postoperative mortality was defined as death from any cause within 30 days after surgery. In-hospital mortality data was not available from all the four data sources. Differences in 30-day mortality between countries were analyzed with generalized estimating equations, adjusting for available case-mix factors (sex, age, morphology) and clustering of patients within hospitals using a random hospital effect model.[5] Two-year overall survival after surgery was chosen as the long term outcome because of the relatively short follow-up period due to the recent nature of the data, and was calculated from the day of surgery until death from any cause (event) or alive at last follow-up (censored). Detail of cause of death was not available. Unadjusted two-year overall survival for each country was calculated with Kaplan Meier analysis. Adjusted differences in two-year overall survival between countries were analyzed with Cox regression, adjusting for case-mix factors as categorical covariates (sex, age, morphology, stage group) and clustering of patients within hospitals. English patients were excluded from the adjusted two-year survival analyses as stage data were not available.

Differences in outcomes between hospital volume categories were evaluated in the same way as differences in outcomes between countries, including the adjustment for clustering of patients within hospitals. An interaction analysis was performed between country and annual hospital volume. Annual hospital volume was analyzed as a categorical variable and also as a linear variable. Statistical analyses were performed with SPSS (version 17.0.2) and R (version 2.12.2).

RESULTS

RESECTION RATES

Between January 2004 and December 2009, 84,630 patients with a diagnosis of esophageal or gastric cancer were registered in the Netherlands, Denmark, or England (Figure 1). Resection rates were similar in the Netherlands and Denmark, approximately 29% for esophageal cancer, and 41% for gastric cancer. Resection rates in England were significantly lower: 18% for esophageal cancer and 22% for gastric cancer (both $P < 0.001$).

PATIENT CHARACTERISTICS OF RESECTED PATIENTS

Between 2004 and 2009 19,864 patients underwent esophagectomy or gastrectomy for cancer (Table 2). Median age was 64 years for all patients who underwent esophagectomy and 71 for all patients who underwent gastrectomy. The percentage of patients undergoing resection with an age above 75 years was lowest in Denmark: 7.1% (63/892) for esophagectomy, and 22.7% (120/528) for gastrectomy, compared with 9.9-10.8% for esophagectomy and 32.4-38.4% for gastrectomy in the other countries. The highest proportion of stage I patients (esophagectomy: 15.8%, [446/2819] and gastrectomy 34.2%, [1015/2972]) and the highest proportion of stage IV patients (oesophagectomy: 12.0% [339/2819] and gastrectomy 17.1% [508/2972]) were recorded in the Netherlands.

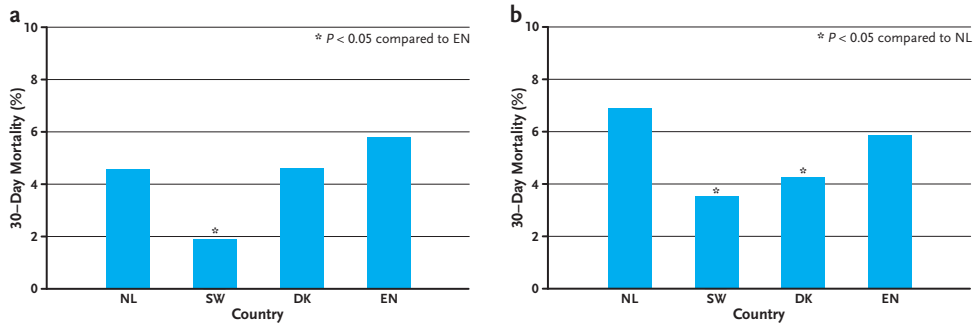
Table 2. Patient characteristics for patients who underwent esophagectomy (N = 10,854) or gastrectomy (N = 9010) for cancer

Country	Netherlands		Sweden		Denmark		England		
	N	%	N	%	N	%	N	%	*P*
Esophagectomy	2819	*100.0*	231	*100.0*	892	*100.0*	6912	*100.0*	
Sex									
male	2179	*77.3*	185	*80.1*	699	*78.4*	5295	*76.6*	0.4
female	640	*22.7*	46	*19.9*	193	*21.6*	1617	*23.4*	
Age									
<60	973	*33.5*	73	*31.6*	299	*33.5*	2171	*31.4*	0.003
60-75	1567	*55.6*	133	*57.6*	530	*59.4*	4001	*57.9*	
>75	279	*9.9*	25	*10.8*	63	*7.1*	740	*10.7*	
mean age	63		64		63		64		
median age	63		64		63		64		
Histology									
adenocarcinoma	2141	*76.0*	162	*70.1*	637	*71.4*	5483	*79.3*	<0.001
SCC	615	*21.8*	42	*18.2*	201	*22.5*	1190	*17.2*	
other carcinoma	63	*2.2*	27	*11.7*	54	*6.1*	239	*3.5*	
TNM stage group									
0	10	*0.4*	15	*6.5*	20	*2.2*			<0.001[b]
I	446	*15.8*	18	*7.8*	67	*7.5*			
II	977	*34.7*	101	*43.7*	381	*42.7*			
III	912	*32.4*	71	*30.7*	334	*37.4*			
IV[a]	339	*12.0*	12	*5.2*	37	*4.1*			
unknown	135	*4.8*	14	*6.1*	53	*5.9*	6912	*100.0*	
mean stage[c]	2.43		2.38		2.42				
median stage[c]	II		II		II				

Country	Netherlands		Sweden		Denmark		England		
	N	%	N	%	N	%	N	%	*P*
Gastrectomy	2972	*100.0*	422	*100.0*	528	*100.0*	5088	*100.0*	
Sex									
male	1838	*61.8*	241	*57.1*	305	*57.8*	3304	*64.9*	<0.001
female	1134	*38.2*	181	*42.9*	223	*42.2*	1784	*35.1*	
Age									
<60	599	20.2	67	15.9	141	26.7	820	16.1	<0.001
60-75	1409	47.4	193	45.7	267	50.6	2585	50.8	
>75	964	32.4	162	38.4	120	22.7	1683	33.1	
mean age	69		71		66		70		
median age	71		72		67		72		
Histology									
adenocarcinoma	2929	98.6	396	93.8	502	95.1	4879	95.9	<0.001
other carcinoma	43	1.4	26	6.2	26	4.9	209	4.1	
TNM stage group									
0	15	0.5	13	3.1	6	1.1			<0.001[b]
I	1015	34.2	110	26.1	83	15.7			
II	695	23.4	105	24.9	109	20.6			
III	666	22.4	111	26.3	159	30.1			
IV[a]	508	17.1	54	12.8	40	7.6			
unknown	73	2.5	29	6.9	131	24.8	5088	100.0	
mean stage[c]	2.23		2.29		2.4				
median stage[c]	II		II		III				

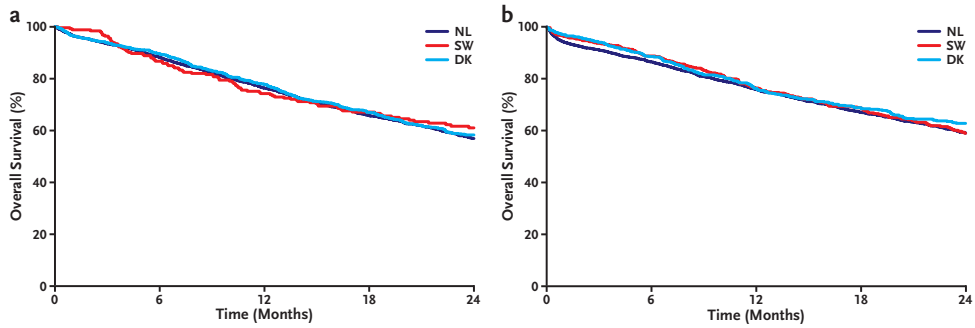
[a] Majority of this group: in the 6th edition TNM classification for gastric cancer, T4N+M0 and T1-3N3 cancers were assigned stage IV. A smaller part of this group are palliative resections for gastric cancers.
[b]Chi square test: England excluded
[c]Calculated by excluding unknown stage and considering stage group as continuous variable
SCC: squamous cell carcinoma

Figure 3. Postoperative 30-day mortality after (a) esophagectomy and (b) gastrectomy, adjusted for sex, age, and histology



NL: Netherlands, SW: Sweden, DK: Denmark, EN: England

Figure 4. Two-year survival after (a) esophagectomy and (b) gastrectomy, adjusted for sex, age, histology, and stage group



NL: Netherlands, SW: Sweden, DK: Denmark

DIFFERENCES IN OUTCOMES BETWEEN COUNTRIES

Median follow-up for all patients was 37 months. In all countries, postoperative 30-day mortality was lower after esophagectomy (4.6%) than after gastrectomy (6.7%), but variation between countries was considerable. Adjusted 30-day mortality after esophagectomy was lowest in Sweden (1.9%), and highest in England (5.8%), (P = 0.028) (Figure 3a, Table 3). Differences between other countries were not significant. After gastrectomy, adjusted 30-day mortality in the Netherlands (6.9%) was significantly higher when compared to Sweden (3.5%, P = 0.017), and Denmark (4.3%, P = 0.029), (Figure 3b). Unadjusted 2-year overall survival estimates were not significantly different between countries, except for 2-year survival after gastrectomies between the Netherlands and England (51.9% versus 56.3%, $P < 0.001$) (Table 3). Adjusted two-year survival rates were not significantly different between the Netherlands, Sweden, and Denmark, in either resection group (Figure 4, Table 3).

Table 3. Differences in postoperative 30-day mortality and two-year survival between countries

	Esophagectomy				Gastrectomy			
	30-day mortality (NL, SW, DK, EN)		two-year survival (NL, SW, DK)		30-day mortality (NL, SW, DK, EN)		two-year survival (NL, SW, DK)	
Absolute adjusted	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Country								
Netherlands	4.6	3.3-5.9	56.8	54.5-59.3	6.9	5.1-8.8	59.0	56.8-61.3
Sweden	1.9	0.0-3.8	61.0	54.6-68.0	3.5	1.5-5.6	59.0	54.2-64.3
Denmark	4.6	2.4-6.8	58.2	54.8-61.9	4.3	2.4-6.2	62.8	58.5-67.5
England	5.8	4.7-6.9			5.9	4.3-7.4		
Absolute unadjusted			%	95% CI			%	95% CI
Country								
Netherlands			52.4	50.2-54.6			51.9	49.9-53.9
Sweden			56.7	50.0-63.4			51.7	46.8-56.6
Denmark			53.3	50.0-56.6			53.7	49.4-58.0
England			54.4	53.2-55.6			56.3	54.9-57.7
Adjusted Odds Ratio's	OR	95% CI	HR	95% CI	OR	95% CI	HR	95% CI
Country								
Netherlands (ref.)	1.00		1.00		1.00		1.00	
Sweden	0.40	0.14-1.16	0.93	0.75-1.15	**0.50**	**0.28-0.88**	0.97	0.85-1.11
Denmark	1.00	0.60-1.69	0.96	0.80-1.15	**0.60**	**0.38-0.95**	0.89	0.80-1.00
England	1.28	0.96-1.72			0.84	0.65-1.07		
Sex								
male (ref.)	1.00		1.00		1.00		1.00	
female	**0.75**	**0.61-0.93**	**0.78**	**0.69-0.89**	0.81	0.68-0.96	0.93	0.83-1.03
Age								
<60 (ref.)	1.00		1.00		1.00		1.00	
60-75	**1.80**	**1.44-2.25**	**1.40**	**1.27-1.55**	**2.58**	**1.79-3.73**	**1.29**	**1.08-1.54**
>75	**3.88**	**2.96-5.05**	**1.89**	**1.60-2.24**	**5.98**	**1.09-8.75**	**1.94**	**1.65-2.29**
Histology								
adenocarcinoma (ref.)	1.00		1.00		1.00		1.00	
SCC	**1.44**	**1.16-1.79**	**1.27**	**1.14-1.41**				
other carcinoma	1.33	0.84-2.11	**1.46**	**1.02-2.09**	**1.57**	**1.01-2.45**	0.97	0.66-1.43
TNM stage group								
I (ref.)			1.00				1.00	
II			**1.95**	**1.46-2.60**			**2.10**	**1.81-2.42**
III			**3.68**	**2.73-4.95**			**3.81**	**3.29-4.41**
IV			**8.21**	**4.42-15.3**			**6.40**	**5.37-7.62**
unknown			1.73	0.99-3.02			**2.06**	**1.60-2.64**
0			0.58	0.29-1.15			0.52	0.20-1.37

NL: Netherlands, SW: Sweden, DK: Denmark, EN: England, 95%CI: 95% confidence interval, OR: odds ratio, HR: hazard ratio, ref.: reference category, SCC: squamous cell carcinoma, **Bold:** significant ($P < 0.05$)

DIFFERENCES IN OUTCOMES IN RELATION TO HOSPITAL VOLUME

Overall, annual hospital volumes for esophagectomies were higher than for gastrectomies (Figure 2). Variation between countries is shown in Figure 5. In Denmark, 65.6% of esophagectomies were performed in hospitals with an annual volume above 30 per year, while a similar proportion (63.6%) was performed in Sweden in hospitals with an annual volume of less than 11 per year. Fifty nine per cent of all gastrectomies for cancer were performed in Denmark in hospitals with an annual volume above 20 per year, whereas over 75% of gastric resections were performed in the Netherlands and in Sweden in

hospitals with an annual volume of less than 11 per year, and 68.9% of gastrectomies in England were performed in annual hospital volumes of less than 21 per year.

Increasing hospital volume was significantly associated with lower postoperative mortality, both after esophagectomy and gastrectomy (Figure 6, Table 4). Adjusted 30-day mortality after esophagectomy in hospitals with an annual volume of at least 41 per year was lower than in hospitals with an annual volume of less than 11 per year (4.3% versus 7.2%; $P < 0.001$). Adjusted 30-day mortality after gastrectomy in hospitals with an annual volume of at least 21 per year was also lower at 4.4% than in hospitals with an annual volume of less than 11 per year (6.7%, $P = 0.047$). Testing for interaction between country and hospital volume category revealed a significant interaction regarding postoperative 30-day mortality after esophagectomy, which was the result of a stronger volume-outcome relation in Denmark than in the other countries (not shown). No such interaction was found for gastrectomy.

High hospital volume was also significantly associated with better two-year survival after esophagectomy, with a hazard ratio of 0.79 (95%CI 0.66-0.96) for the highest volume group (≥41 per year) compared with the lowest volume group (1-10 per year). There was no statistically significant association between hospital volume and two-year survival after gastrectomy (Table 4, Figure 7). No interaction was found between country and hospital volume category regarding two-year survival.

DISCUSSION

This study has shown variations in annual hospital volumes for esophagectomy and gastrectomy with highest volumes in Denmark. Resection rates were similar in the Netherlands and Denmark but considerably lower in England. Postoperative 30-day mortality was lowest in Sweden, both after esophagectomy and gastrectomy, and 30-day mortality after gastrectomy in the Netherlands was significantly higher compared with Sweden and Denmark. Higher numbers of stage I and stage IV esophageal and gastric cancers were resected in the Netherlands than in the other countries. Increasing hospital volume was associated with lower postoperative mortality after both esophagectomy and gastrectomy. Two year adjusted survival after surgery was similar in each country, with longer overall survival after esophagectomy.

SOURCES OF DATA

Studies on outcomes after cancer surgery are commonly based on data from clinical trials or on patient series from specialized surgical centers. Due to selection of patients, such series do not reflect the general practice and cannot be used to compare outcomes between countries. Population-based studies, as performed by EUROCARE, provide insight in differences in mortality and survival patterns between countries.[1] In the EUROCARE framework, however, for some countries only part of the national cancer registries is covered, and no data from recent years are available. Furthermore, it is

intended for incidence and survival trend analyses, and not to monitor clinical practice or to provide feedback to individual health care providers. Nationwide clinical audits, as currently performed in the UK, Sweden, Denmark, and the Netherlands, provide detailed information on patient, tumor, treatment, and hospital characteristics, and data are quickly available for comparative analyses. However, a disadvantage of clinical audits is that data are reported by the health care provider and are therefore not always complete. In contrast, cancer registries mostly include all available patients, but the captured information is less detailed. For example, patient comorbidity was missing in the Dutch and English dataset, and tumor stage in the English dataset. The lack of this information may bias the outcome data and may even partly explain some of the differences.

RESECTION RATES

In the current study, resection rates for both esophageal and gastric cancer were lower in England than in the Netherlands and Denmark (and not available in Sweden). The UK NOGCA has confirmed a steady reduction in resection rates over the past decade describing rates of curative resection for esophageal junctional and gastric cancer respectively of 33% and 31% in 1998 decreasing to 24% and 23% in 2005,[6] which has been attributed to improved preoperative staging and multidisciplinary management, thereby better selecting patients for surgery.[7] Comparison of resection rates is also confounded by differences in clinical practice, but with the current datasets no conclusions can be drawn on which country has the optimal resection rate. This should be addressed in future studies with adequate information on preoperative staging.

DIFFERENCES IN CENTRALIZATION OF SURGERY

A Dutch study published in 2001 showed lower postoperative mortality after esophagectomies in high volume hospitals, and as of 2006 esophagectomies in the Netherlands were centralized with a minimum annual volume of 10/year.[8] As of 2011, this was increased to 20/year. Over the study period, there was no minimum volume standard for gastrectomy, but gastrectomies will be centralized as of 2012. In addition in 2011, a national esophagogastric cancer audit has started.[9] This may answer why the resection rate in stage IV disease is higher than elsewhere as it may reflect clinical practice in peripheral hospitals where preoperative assessment is less robust.

In Sweden, a national esophagogastric cancer audit was initiated in 2006. Both esophagectomies and gastrectomies were performed in low volumes, but very recently, also Sweden has started centralization of upper GI surgery. In Denmark, a nationwide esophagogastric cancer registry has been initiated, and upper GI surgery was restricted to five centers in 2003, and further to four centers in 2008.[10] This was accompanied by a strongly reduced postoperative mortality after gastrectomy and an increase in the number of evaluated lymph nodes, which is often used as a quality indicator in gastric cancer surgery.[11] In the current study, hospital volumes in Denmark were higher than

Table 4. Multivariate analysis on the effect of annual hospital volume on 30-day mortality and two-year survival

	Esophagectomy				Gastrectomy			
	30-day mortality (NL, SW, DK, EN)		two-year survival (NL, SW, DK)		30-day mortality (NL, SW, DK, EN)		two-year survival (NL, SW, DK)	
	OR	95% CI	HR	95% CI	OR	95% CI	HR	95% CI
Annual hospital volume								
1-10 (ref.)	1.00		1.00		1.00		1.00	
11-20	0.82	0.61-1.11	0.92	0.78-1.08	0.84	0.67-1.05	1.04	0.93-1.15
21-30[a] / ≥21[b]	**0.68**	**0.50-0.93**	0.84	0.63-1.11	**0.64**	**0.41-0.99**	1.01	0.84-1.22
31-40	**0.58**	**0.39-0.85**	**0.77**	**0.63-0.94**				
≥41	**0.55**	**0.42-0.72**	**0.79**	**0.66-0.96**				
P-value for trend	<0.001		0.004		0.03		0.56	
Sex								
male (ref.)	1.00		1.00		1.00		1.00	
female	**0.77**	**0.62-0.95**	**0.78**	**0.69-0.90**	**0.80**	**0.67-0.95**	0.92	0.83-1.02
Age								
<60 (ref.)	1.00		1.00		1.00		1.00	
60-75	**1.82**	**1.45-2.28**	**1.40**	**1.27-1.55**	**2.58**	**1.78-3.72**	**1.30**	**1.09-1.55**
>75	**3.99**	**3.06-5.21**	**1.87**	**1.58-2.23**	**5.88**	**4.04-8.58**	**1.96**	**1.67-2.30**
Histology								
adenocarcinoma (ref.)	1.00		1.00		1.00		1.00	
SCC	**1.44**	**1.15-1.79**	**1.29**	**1.15-1.44**				
other carcinoma	1.28	0.81-2.04	**1.45**	**1.03-2.05**	1.50	0.96-2.33	0.97	0.65-1.43
TNM stage group								
I (ref.)			1.00				1.00	
II			**1.96**	**1.46-2.62**			**2.08**	**1.80-2.40**
III			**3.71**	**2.74-5.04**			**3.75**	**3.24-4.35**
IV			**8.13**	**4.39-15.1**			**6.38**	**5.34-7.62**
unknown			**1.77**	**1.01-3.11**			**1.94**	**1.51-2.48**
0			0.57	0.29-1.14			0.52	0.20-1.35

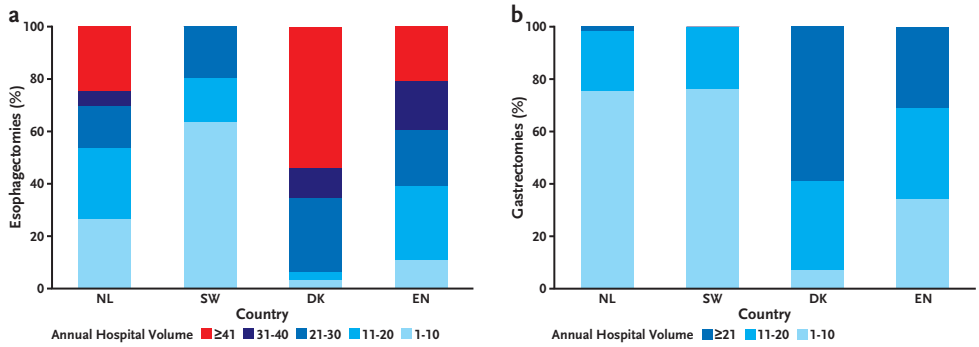
[a]esophagectomy, [b]gastrectomy
NL: Netherlands, SW: Sweden, DK: Denmark, EN: England, OR: odds ratio, HR: hazard ratio, ref.: reference category, SCC: squamous cell carcinoma, **Bold:** significant ($P < 0.05$)

in any other country, with the majority of esophagectomies being performed in hospital volumes of over 40/year. In the UK, a National Health Services (NHS) Cancer Plan became effective in 2001.[12] In this plan, recommendations were made to centralize esophagogastric cancer surgery, to establish specialist treatment teams, and to audit all steps in esophagogastric cancer care.[13] Over the last 10 years, centralization of esophagogastric cancer surgery has occurred. In 2008 and 2009, 82% of esophageal and gastric cancer resections were done in 41 designated centers with 63% of esophagectomies and 65% of gastrectomies being performed in high-volume centers (at least 50 resections per year).[14] Centralization of surgery is not unique to Europe. A recent US study describes centralization of several surgical procedures including esophagectomy for cancer, resulting in a decrease in postoperative mortality over the past decade.[15]

DIFFERENCES IN OUTCOMES BETWEEN COUNTRIES

Due to its population-based nature, the present study provides an accurate comparison of postoperative mortality and long-term survival after esophagectomy and gastrectomy

Figure 5. Annual hospital volumes for (a) esophagectomy and (b) gastrectomy



NL: Netherlands, SW: Sweden, DK: Denmark, EN: England

Figure 6. Postoperative 30-day mortality after (a) esophagectomy and (b) gastrectomy, adjusted for sex, age, and histology, by annual hospital volume category

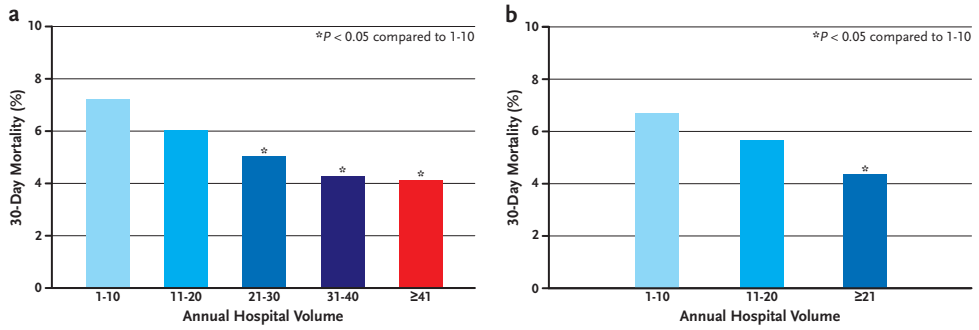
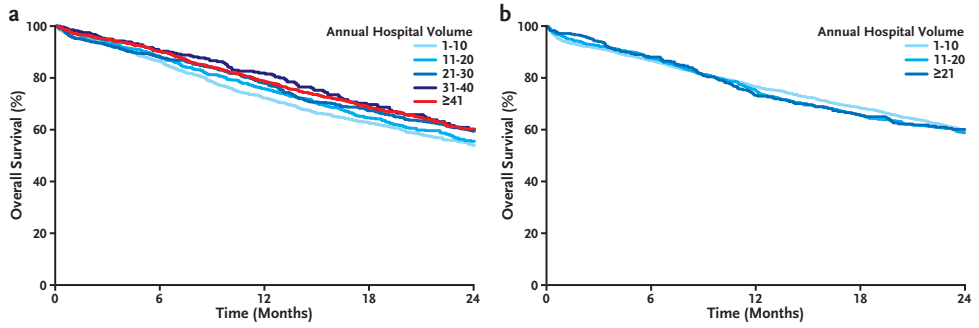


Figure 7. Two-year survival after (a) esophagectomy and (b) gastrectomy, adjusted for sex, age, histology, and stage group, by annual hospital volume category.



between several countries in Europe. However, the variability in the recorded data and missing information on patient comorbidities, multimodality therapy, and cause-specific survival do not justify explaining the differences between countries simply on annual hospital volumes. Sweden has superior postoperative mortality rates when compared to

the other participating countries, even after adjustment for case-mix, without performing surgery in high annual volumes. It is known that Sweden in general has a high quality health care with nationwide quality assurance programs, which might have contributed to the current results.[16] A second, hypothetical explanation might be differences in selecting patients for surgery between Sweden and the other countries. Furthermore the inclusion of only regions in Sweden with high case ascertainment may have excluded patients who did less well and hence bias the findings. Completeness of the data requires dedication of the surgical team to report all cases, which might be correlated to a high standard of care in these regions. On the contrary, postoperative mortality after gastrectomies in the Netherlands is high. This might be explained by the absence of a quality assurance program during the studied period for gastric cancer surgery in the Netherlands. A centralization program for gastrectomies has been initiated as of 2012. It should be noted that differences in unadjusted two-year survival rates between countries should be interpreted with care, as tumor stage distributions in the group of patients who underwent surgical resection might differ between countries.

DIFFERENCES IN OUTCOMES IN RELATION TO HOSPITAL VOLUME

The relationship between annual hospital volume and postoperative mortality after esophagectomy and gastrectomy has been investigated extensively.[15,17] In the majority of studies on esophagectomy, a benefit for high volume surgery was found.[18] Results from studies on hospital volumes for gastrectomies are less uniform. In a significant number of studies, no effect of hospital volume on postoperative mortality was found.[19-22] However, patient numbers in these studies were relatively small (below 5,000) when compared to studies in which a benefit for high volume gastrectomies was found (up to 56,000).[23-26] The available evidence on hospital volume in relation to long term survival is more limited: two out of four available studies for esophagectomy were positive,[27-30] and five out of seven available studies on gastrectomy were positive.[26,31-35] In the current study, a significant relation between annual hospital volume and postoperative mortality was found both for esophagectomy and gastrectomy. Furthermore, increasing hospital volume for esophagectomy was associated with improved long term survival. No such relation for gastrectomy was found, which might be explained by the low threshold of what was considered 'high volume surgery' (≥21/year).

It could be argued that in the current study, individual surgeon volumes should be analyzed as well as hospital volume. Quality of care and outcomes, however, are the result of collaboration between different professionals, including surgeons, anesthesiologists, ICU staff and nursing staff. All these disciplines contribute to outcomes.[36] The role of the individual surgeon is one, yet important factor.

Using hospital volume as the only basis for determining outcome quality has been criticized.[23] There can be low volume hospitals with excellent outcomes and vice versa. Outcome-based referral avoids this problem, by selecting centers of excellence based on

case-mix adjusted outcomes. It has been used to centralize esophagectomy in one part of the Netherlands, which led to a reduction in postoperative mortality from 12% to 3% over a ten-year period.[37]

CONCLUSIONS

In the current study, considerable differences between European countries were documented regarding resection rates, postoperative 30-day mortality, and annual hospital volumes in esophagogastric cancer surgery. Increasing hospital volume was associated with better outcomes, but differences in outcomes between countries could not be explained by existing differences in annual hospital volumes. Nationwide clinical audits aim to identify centers of excellence based on case-mix adjusted outcomes. On an international level, these audits can be used to understand differences in outcomes between countries. This, however, requires uniform definitions and registration of data, which is currently not the case. The current study provides a first step towards recording standard clinical data for each country to facilitate intercountry comparisons, analogous to the EURECCA initiative for colorectal cancer.[38] It is proposed to develop a European esophageal and Gastric Cancer Audit to provide further insight into differences between countries with the ultimate aim of improving quality of care for esophageal and gastric cancer patients throughout Europe.

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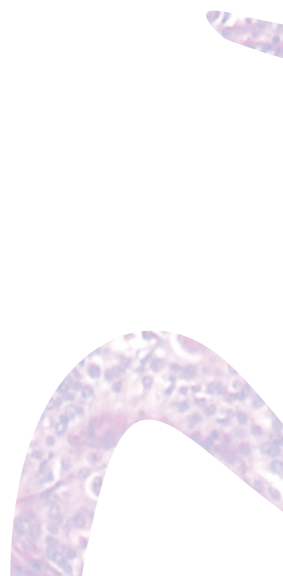

CHAPTER 17

General discussion and summary

GENERAL DISCUSSION

Gastric cancer is the second leading cause of cancer death worldwide, affecting approximately one million new individuals per year.[1] Highest incidence rates are described in Northeast Asia, Eastern Europe, and much of the east part of South America, while Europe and North America are low incidence areas.[2] Survival in the Western world is dismal, with five-year survival rates for all patients with gastric cancer of approximately 25%, both in Europe and the United States.[3,4] In the Netherlands, approximately 1,800 patients are diagnosed with gastric cancer each year, and five-year survival is 22%.[5]

STAGING

Cancer staging is one of the fundamental activities in oncology.[6,7] For over 50 years, the TNM classification has been a standard in classifying the anatomic extent of disease.[8] In order to maintain the staging system relevant, the International Union Against Cancer and the American Joint Committee on Cancer (AJCC) have collaborated on periodic revisions of this staging system, leading to the 7th edition in 2010.[9] With each staging system revision, there is a tension between improving prognostic value of the staging system by adding subdivisions of existing stage groupings and introducing new predictive parameters, and the desire to keep the staging system simple. With an increasing number of categories for the 7th edition gastric cancer staging system, it has become more complex, while predictive accuracy has not improved. Increasing the number of categories of the staging system is not unique to gastric cancer.[9] With the growing availability of pathologic and molecular data, there is a trend towards incorporating more and more information into newer staging systems. Although these new categories might better reflect the natural history and prognosis of these diseases, there is a limit to the improvement of prognostic accuracy achievable with a categorical anatomic-based staging system like the TNM-classification.[10,11] At the same time, the goal of creating an intuitive, easy to use staging system disappears, and in daily clinical practice, cancer staging consists of using complex tables.

Meanwhile, tools for individual patient prognostication have been developed that significantly outperform the TNM-classification in prognostic accuracy. For gastric cancer, a nomogram has been developed based on a single US-institution database,[12,13] and has been validated in several international patient cohorts.[14-16] The question is if the TNM-classification should aspire to the same goal of highly accurate individual patient prognostication as these nomograms. Prognostication is only one of the five goals of the TNM-classification, and all other goals are directed towards a simple intuitive international language: to aid the clinician in planning and evaluating treatment, to facilitate the exchange of consistent information, and to contribute to research.[6]

SURGERY

Shortly after finishing accrual of the Dutch Gastric Cancer Group trial comparing D1 (limited) with D2 (extended) lymphadenectomy, morbidity and mortality results were published indicating a significantly higher mortality after a D2 dissection (10% versus 4%),[17] similar to the Medical Research Council Gastric Cancer trial.[18] The number of splenectomies and pancreatic tail resections, which have shown to increase postoperative mortality, was also higher in the D2 group. Analyses performed after 11 and 15 years of follow-up revealed no significant differences in overall survival.[19,20] However, gastric-cancer related death at 15 years was significantly lower after a D2 (37%) when compared to a D1 (48%) dissection ($P = 0.01$),[20] suggesting that when postoperative mortality can be avoided, a D2 lymphadenectomy improves survival compared to a D1 lymph node dissection. In a more recent, Italian study, a D1 versus D2 lymphadenectomy was analyzed in 267 patients treated in five centers.[21] Although long-term survival results have to be awaited, and the study population might be too small to detect differences in overall survival, postoperative mortality after a D2 dissection was only 2.2%. This taken together with the currently performed spleen-preserving gastrectomy indicates that a D2 lymph node dissection in experienced centers should be the recommended type of surgery in advanced gastric cancer, not only in Asia, but also in Europe and the United States.[22,23] A routine pancreatic tail and spleen resection should be avoided.[24]

Although laparoscopic surgery has been applied for gastric cancer for over two decades, only a limited number of randomized controlled trials on this subject have been reported.[25-29] A recent review on these randomized studies indicates that laparoscopic gastrectomy is safe and feasible, and that short term outcomes are better than those of open gastrectomy in patients with early gastric cancer.[30] Large multicenter randomized controlled trials are necessary to establish the role of laparoscopy in the treatment of gastric cancer. As the learning curve for laparoscopic gastrectomy takes at least 60 operations, laparoscopic gastrectomy should not be performed in low-volume hospitals.[31]

SURGICAL QUALITY ASSURANCE

Improving quality of care for patients with resectable gastric cancer is a major challenge, especially when performed in lower volume centers like in many European countries. Whereas Japan has established national screening programs for gastric cancer, and has a two to seven-fold higher incidence rate as compared to European countries, in Europe incidence rates are relatively low leading to lower exposure of hospitals to patients with resectable gastric cancer.

Although randomized controlled trials provide important information on the optimal treatment strategy for gastric cancer, and trials in general can improve outcomes on a national level, the majority of patients are treated outside the framework of clinical trials. Especially improvements in the structure and process of care on a nationwide level will bring benefit to this group of patients. National quality assurance programs aim to

reduce variations between providers of care and to improve outcomes after gastric cancer surgery. The most frequently used quality assurance programs include centralization of care to high-volume or high-quality hospitals and clinical auditing.

Luft et al. were the first to publish on the relation between hospital volume and outcomes.[32] More than 20 years later, Birkmeyer et al. published another landmark study showing a relation between increasing hospital volume and lower postoperative mortality for several surgical procedures.[33] Ever since, a large number of studies on the effect of hospital volume on both short term and long term outcomes after gastrectomy has been published, and in the majority of these studies, a significant relation between high hospital volume and better outcomes was found.[33-48]

In Denmark, the available evidence on a volume-outcome relationship has led to enforced centralization of gastric cancer surgery from 37 to 5 hospitals as of 2003, which has resulted in a significant decrease in postoperative mortality (8.2% in 2003 to 2.4% in 2008, $P < 0.05$), and an increase in the number of patients with at least 15 lymph nodes examined (19% - 67%).[37] Centralization of gastric cancer surgery is currently implemented in the United Kingdom, Sweden, Finland, and as of 2012 in the Netherlands. As esophagectomies have already been centralized in the Netherlands, esophagogastric cancer surgery will be centralized towards centers currently performing esophagectomies, resulting in upper GI centers. This enables the formation of dedicated upper GI surgical and multidisciplinary teams, and eliminates the possibility that patients with incorrectly staged junctional tumors need to be transferred from an esophageal to a gastric cancer center or vice versa after first surgical inspection of the tumor.

Meanwhile, using hospital volume as the sole basis for referral to improve outcomes is criticized.[33] Although hospital volume can be used to identify groups of hospitals with better outcomes 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 region, 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.[49] Others have advocated the identification of processes associated with excellent outcomes, and to implement these in low volume hospitals, rather than to refer patients to centers of excellence. However, identification of these processes and determination of their impact on quality of care remains challenging.[50]

It has been suggested that centralization combined with auditing is more effective when compared to centralization alone.[51] With auditing, providers of care are monitored and their performance is benchmarked against their peers. Data is usually entered by the providers of care and is centrally collected. A disadvantage of auditing is the effort needed to collect the data. Information technology solutions incorporated in electronic

medical record systems are needed to solve this problem. In the United Kingdom, a national esophagogastric cancer audit was initiated in 2002 by the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland.[52] In the United States, the National Surgical Quality Improvement Program is used to audit many different surgical procedures, and several studies have shown a decrease in postoperative morbidity and mortality for vascular and general surgical procedures after introduction of this audit.[53-55] Sweden also has a long tradition of clinical auditing, which started with the Swedish Rectal Cancer Registry, but is now extended to upper-GI surgery.[56] In the Netherlands, as of 2011, the Dutch Upper-GI Cancer Audit has started, with the aim of capturing all esophageal and gastric cancer resections in the Netherlands, and to provide weekly feedback to participating surgeons. Surgeons from several European countries are currently collaborating on the development of a European Upper GI Cancer Audit (EURECCA Upper GI).

MULTIMODALITY TREATMENT

Whereas Asian patients mainly receive postoperative chemotherapy with S-1, in the Western world postoperative chemoradiotherapy or perioperative chemotherapy are administered. Due to differences in patient selection, it is not possible to compare results from the Intergroup 0116 study on postoperative chemoradiotherapy with results from the MAGIC study on perioperative chemotherapy.[57,58] However, it becomes clear that the toxicity profile of the multimodality regimen is crucial for both the patient to complete therapy, and for the trial to finish accrual. As preoperative therapy is generally associated with improved compliance without compromising resectability,[59] this should be the recommended therapy for patients with advanced, resectable gastric cancer. After radical surgery, postoperative therapy should be administered when tolerated by the patient, but no standard regimen for this has been established. In case of contaminated resection margins (R1 resection), locoregional disease is left behind and postoperative chemoradiotherapy should be the recommended therapy.[60] Patients with distant micrometastases will benefit from postoperative chemotherapy, but no diagnostic modality can identify these metastases so far, and therefore, the regimen of choice remains unclear. To address this issue, the Dutch CRITICS study was initiated in 2008.[61] In this study, all patients receive three cycles of preoperative ECC, followed by gastrectomy with D1+ surgery (i.e. an extended lymphadenectomy without the lymph nodes in the splenic hilus and without a spleen and pancreatic tail resection). Then patients in arm A receive another three cycles of ECC, while patients in arm B receive postoperative CRT with cisplatin, capecitabine, and 45 Gy radiotherapy. An estimated 788 patients are required for this study; currently over 400 patients from the Netherlands, Sweden, and Denmark are included.

Another, recent development is the use of the monoclonal antibody trastuzumab for HER2 positive gastric cancers, which account for approximately 30% of all gastric

cancers.[62] In the large, international ToGA trial, a significant benefit in overall survival was found for patients with inoperable locally advanced or recurrent HER2 positive gastric cancer receiving trastuzumab versus conventional chemotherapy. Currently, in many trials the use of trastuzumab in HER2 positive resectable gastric cancer is investigated, but no results have been published so far. However, there is debate on the currently accepted diagnostic methods to detect HER2 positive tumors.[63,64] In contrast to breast cancers, gastric cancers are highly heterogeneous, and HER2 expression is different throughout the tumor. Furthermore, a considerable number of tumors in the ToGA trial were negative by immunohistochemistry, which is the diagnostic modality used in daily clinical practice, but showed HER2 gene amplification with FISH, which is the gold standard. Therefore, more research is needed on the diagnosis of HER2 expression in gastric cancer in order to accurately interpret data from currently accruing clinical trials.

CONCLUSIONS AND FUTURE PERSPECTIVES

Cancer staging represents a compromise in accounting for the most prognostically relevant factors to aim at a simple, intuitive, useful, common language to describe the natural history of a tumor. It should not be confused with more complex, multivariable prognostication models, which may be useful in defining groups of patients at homogenous risk of recurrence, regardless of anatomic TNM characteristics. Future TNM classifications for gastric cancer should aspire more simplicity and should aim for a clinically more useful staging system.

Surgery is the only potentially curative treatment for gastric cancer, and despite recent developments in multimodality therapy it remains the cornerstone of treatment. A gastrectomy with D2 lymphadenectomy without routine spleen and distal pancreatic resection is the recommended type of surgery for advanced, resectable gastric cancer. The current debate focuses on the question which multimodality treatment schedule should be administered to patients with resectable gastric cancer. Because of the higher compliance of preoperative therapy when compared to postoperative therapy, preoperative chemotherapy should be recommended for all patients with advanced gastric cancer, followed by either postoperative chemotherapy or chemoradiotherapy, an issue currently addressed in the international CRITICS trial.

Further tailoring of treatment based on a patient's genetic profile has been pursued. However, HER2, which is the most promising genetic marker so far, has been subject to critique due to the intratumoral heterogeneity of HER2 expression in gastric cancers and discrepancies between IHC and FISH results for HER2 testing, thereby impeding an accurate assessment of HER2 status. Truly clinically useful genetic markers for gastric cancer remain to be awaited.

Another approach to tailor made treatment is practiced in Japan. Due to the high caseload of patients, Japanese surgeons and gastroenterologists have the opportunity to differentiate treatment based on clinical tumor stage. More experience with endoscopic

techniques, including endoscopic (sub)mucosal dissection, high volume and laparoscopic surgery, and the use of a preoperative sentinel node procedure provide a level of care for gastric cancer patients far beyond that in most Western centers.

Because gastric cancer surgery in the Western world is associated with high postoperative mortality, and patients presenting with gastric cancer become older and have an increasing number of comorbidities, gastric cancer resections should be performed in centers with sufficient experience. Although in the Netherlands, several regional initiatives were started to centralize gastric cancer care, nationwide programs are needed to improve care for all gastric cancer patients. The proposed minimal hospital volume standards of 10 per year in 2012 and 20 per year as of 2013 for gastric cancer resections are a first step towards this improvement. With this centralization of surgery, it is expected that postoperative 30-day mortality for the annual 500 gastric cancer resections in the Netherlands will decrease from the current 8% to below 5%, saving the lives of approximately 15 patients annually in the perioperative period. But the available evidence also confirms that long-term survival will improve with referral of gastrectomies towards high volume centers.

However, surgical excellence in the treatment of gastric cancer not only requires expertise in gastrectomies, but also in other upper gastrointestinal surgery, including esophagectomies. Only with the formation of 'upper GI centers' it is possible to adequately treat patients with junctional tumors and patients with complex gastric cancers. Furthermore, expertise should not be limited to the surgical treatment of these cancers. Rather, experience should be present in the whole multidisciplinary chain involved in treating gastric cancer, including diagnostic imaging, upper GI endoscopy and endoscopic ultrasound, surgery, perioperative care, intensive care, nutritional support, chemotherapy, and radiotherapy. Therefore, it should be encouraged that the Dutch Upper GI Cancer Audit (DUCA), which is currently a monodisciplinary surgical audit, will expand to all disciplines involved in esophagogastric cancer care, thus also capturing patients who are never considered for surgery. As the DUCA has started in 2011, and only 60% of all gastrectomies in the Netherlands were registered in the first registration year, comparing quality of care between participating hospitals is not yet possible. But when case ascertainment will increase over the years and centralization of gastrectomies will take place, in the near future the DUCA will be an instrument to identify centers of excellence which can share their best practice with other hospitals in the Netherlands. Collaboration with other upper GI audits in Europe, which is currently under way in the EURECCA Upper GI consortium, will provide the opportunity to share knowledge with other countries and define best practice throughout Europe. Bringing together this international high quality data will also enable the development of refined treatment algorithms for specific subgroups of patients, for example the elderly. Ultimately this will lead to the optimal choice of treatment for every gastric cancer patient in Europe.

SUMMARY

Research described in this thesis focuses on several aspects of gastric cancer care: staging and prognostication, multimodality treatment, and surgical quality assurance.

PART I - STAGING AND PROGNOSTICATION

Cancer staging is one of the fundamental activities in oncology.[6,7] For over 50 years, the TNM classification has been a standard in classifying the anatomic extent of disease.[8] In order to maintain the staging system relevant, the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) have collaborated on periodic revisions of this staging system, leading to the 7th edition in 2010.[65] In **Chapter 2**, differences between the 6th and 7th edition TNM classification for gastric cancer are described, and both staging systems are compared with regards to complexity and predictive accuracy. In the 7th edition TNM classification, nodal status cut-off values were changed, leading to a more even distribution for the redefined nodal classification groups. This increased the predictive accuracy of N-classification. Overall, the TNM staging system became more complex, with an increase in the number of TNM groupings from 56 to 80, which did not result in an increased predictive accuracy. Future refinements of the TNM-classification should consider whether increased complexity is balanced by improved prognostic accuracy.

Another change that was incorporated in the 7th edition TNM classification was the addition of tumor grade as an independent determinant of stage grouping in early stage tumors. With the significantly lower prognosis of poorly differentiated early stage adenocarcinomas, these tumors might become candidate for neoadjuvant therapy, given an accurate identification of these tumors with preoperative staging. In **Chapter 3**, the accuracy of preoperative histopathologic grading in adenocarcinomas of the gastroesophageal junction (GEJ) was evaluated. The overall accuracy of tumor grade assessment was 73%. However, in early stage tumors the sensitivity to detect a poorly differentiated tumor was only 43%, and 21% of patients with an early stage GEJ tumor were assigned to an incorrect stage/prognostic group based on preoperative tumor grading. Caution should therefore be exhibited in staging patients with esophageal adenocarcinoma based on preoperative biopsy data.

Although the TNM classification can be used to assess a patient's prognosis, tools for individual patient prognostication have been developed that significantly outperform the TNM-classification in prognostic accuracy. For gastric cancer, a nomogram has been developed based on a single US-institution database,[12,13] and has been validated in several international patient cohorts.[14-16] **Chapter 4** describes the development of a new gastric cancer nomogram that not only can predict survival for patients directly after an R0 gastrectomy, but also for patients alive at time points after surgery. This conditional probability of survival nomogram was highly discriminating (concordance index: 0.772), and surviving one, two, or three years from surgery showed a median improvement of

5-year disease-specific survival of 7.2%, 19.1%, and 31.6%, as compared to the baseline prediction directly after surgery. This nomogram was based on variables available directly after surgery, while variables available with follow-up (such as weight loss and performance status) did not further improve the predictive accuracy of this nomogram.
In **Chapter 5**, the performance of the original gastric cancer nomogram, which was based on patients who underwent surgery without multimodality therapy, was assessed in a group of patients who received postoperative chemoradiotherapy after an R0 resection for gastric cancer. The nomogram significantly underpredicted 5-year survival for patients who received postoperative chemoradiotherapy, indicating a benefit in survival for patients who receive postoperative chemoradiation after an R0 resection for gastric cancer. Furthermore, this study stresses the need for updating nomograms that incorporate multimodality therapy use.

PART II - MULTIMODALITY TREATMENT

Over the past decade, many trials have been performed in which the effect of multimodality treatment on survival for resectable gastric cancer was evaluated. In **Chapter 6**, an overview of the literature on the treatment of gastric cancer is presented, and the available multimodality strategies are discussed. Currently accepted regimens include postoperative monochemotherapy with S-1 in Asia,[66] and perioperative chemotherapy and postoperative chemoradiotherapy in the Western world.[57,58]
In **Chapter 7**, patterns of recurrence and survival of patients who received postoperative chemoradiotherapy were compared to recurrence and survival patterns of patients who only underwent surgery. The local recurrence rate was significantly lower in the chemoradiotherapy group (5% versus 17%, $P = 0.0015$). Subgroup analysis revealed that this difference was even stronger in patients who underwent a gastrectomy with a limited (D1) lymph node dissection (2% versus 18%, $P = 0.001$), while no difference was found for patients who underwent an extended (D2) lymph node dissection. Additional analysis with prolonged follow-up showed a higher 2-year overall survival for patients who received postoperative chemoradiotherapy after a D1 lymphadenectomy compared to surgery alone, and no difference in overall survival for patients who received a D2 dissection. Postoperative chemoradiotherapy was also significantly associated with higher two-year overall survival for patients who underwent a microscopically irradical (R1) resection (66% versus 29%, $P = 0.02$). Results from this study indicate that, especially after a gastrectomy with a limited lymph node dissection, postoperative chemoradiotherapy has a major impact on local recurrence and overall survival. Postoperative chemoradiotherapy should be offered to patients who undergo a microscopically irradical (R1) resection.
In **Chapter 8**, the results of a study on lymph node yield after gastric cancer resections are described. While it is suggested that more than 15 lymph nodes (LNs) should be evaluated for accurate staging of gastric cancer, LN yield in Western countries is generally low. The effect of preoperative chemotherapy on LN yield in gastric cancer is unknown. In this

study, LN yields of patients who received preoperative chemotherapy and patients who only underwent surgery were compared. Preoperative chemotherapy was not associated with a decrease in LN yield, indicating that evaluating more than 15 LNs after gastrectomy is feasible, also after administration of preoperative chemotherapy.

In **Chapter 9**, the final chapter of part II of this thesis, the study protocol of the currently accruing Dutch-Swedish-Danish CRITICS trial is described. This trial was initiated to determine which of the two currently used standard regimens for the multimodality treatment of gastric cancer in the Western world, postoperative chemoradiotherapy, or perioperative chemotherapy, should be preferred. In this trial, all patients receive three cycles of preoperative ECC (epirubicin, cisplatin, and capecitabine), followed by D1+ surgery (D2 dissection without splenectomy or pancreatectomy). Postoperative therapy consists of another three cycles of ECC, or chemoradiotherapy with capecitabine and cisplatin without epirubicine. Results of this study will play a key role in the future management of patients with resectable gastric cancer.

PART III - SURGICAL QUALITY ASSURANCE

As an introduction to part III of this thesis, in **Chapter 10**, the results of a systematic review of the literature on quality of care indicators for gastric cancer surgery are described. The availability of specific literature on quality of care indicators was limited, but several indicators could be identified in more general literature on gastric cancer surgery. High hospital volume was found to be strongly related to lower postoperative mortality and higher long-term survival. Several quality indicators regarding operative technique were identified, including the performance of an extended lymphadenectomy, avoiding a routine spleen and pancreatic tail resection, and the use of a pouch reconstruction. Free resection margins were also associated with improved long-term survival.

In **Chapter 11** and **Chapter 12**, incidence and survival patterns for tumors of the esophagus, GEJ, and stomach in the Netherlands over the past 20 years are described. While the incidence of esophageal adenocarcinoma has doubled, the incidence of both tumors of the GEJ and stomach has decreased. These findings most likely reflect true changes in disease burden, rather than being the result of changes in diagnosis or reclassification. The increasing incidence of esophageal adenocarcinoma can be attributed to the increasing incidence of obesity and gastroesophageal reflux disease.[67,68] Over the study period, five-year survival for non-metastatic esophageal cancer strongly improved (12% to 25% for adenocarcinoma, 12% to 19% for squamous cell carcinoma), while five-year survival for non-metastatic GEJ cancer (20%) and stomach cancer (32%) remained stable.

In **Chapter 13**, patterns of care for gastric cancer in the Netherlands over the past 20 years are described. Whereas resection rates for stage I-III gastric cancer have remained stable at about 85%, the use of preoperative and/or postoperative chemotherapy has strongly increased since 2005. In 2008, nearly 40% of the patients with stage I-III gastric cancer received preoperative or postoperative chemotherapy with curative intent, and it is likely

that since then, this percentage has further increased.

In **Chapter 14**, the results of a study on hospital volumes, mortality, and long-term survival for esophagogastric cancer surgery in the Netherlands between 1989 and 2009 are described. In the Netherlands, a minimum hospital volume standard of at least 10 esophagectomies per year was introduced in 2006, while during the study period, no such standard was present for gastrectomies. During the study period, esophagectomy was effectively centralized in the Netherlands, and in 2009, 64% of all esophagectomies were performed in annual volumes of ≥21/year. Gastrectomy has not been centralized, and in 2009 only 5% of all gastrectomies were performed in annual volumes of ≥21/year. Whereas short-term and long-term survival after esophagectomy and gastrectomy improved over the years, this improvement was significantly stronger for esophagectomy. 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. However, for gastrectomy, the number of high volume resections in the current study was too low to detect a statistical significant difference in outcomes when compared with low volume resections. This study indicates an urgent need for improvement in the treatment of resectable gastric cancer in the Netherlands.

Chapter 15 describes the results of a study on the effect of hospital type on outcomes after esophagectomy and gastrectomy in the Netherlands. Hospitals were categorized into university hospitals, teaching non-university hospitals, and non-teaching hospitals. Three-month mortality after esophagectomy in university hospitals was 2.5%, compared to above 4% in non-university hospitals ($P = 0.006$). After gastrectomy, three-month mortality was 4.9% in university hospitals, and 8.7% in non-university hospitals ($P < 0.001$). Both after esophagectomy and gastrectomy, three-year survival was higher in university hospitals compared to non-university hospitals. No differences in mortality or survival were found between teaching and non-teaching non-university hospitals. However, when analyzing differences between individual hospitals, there were non-university hospitals with excellent outcomes. Therefore, it can be concluded that centers of excellence can not be designated solely by hospital type, and that detailed information on case-mix and outcomes is needed to identify centers of excellence.

In **Chapter 16**, the results of an international study on esophagogastric cancer surgery between 2004 and 2009 in several European countries are described. Differences in resection rates, postoperative mortality, survival and hospital volumes were compared between the Netherlands, Sweden, Denmark, and England. In the Netherlands, postoperative mortality was average after esophagectomy (4.6%), but significantly higher after gastrectomy (6.9%) when compared to the other countries. Although increasing hospital volume was associated with lower 30-day mortality both after esophagectomy and gastrectomy, differences in outcomes between countries could not just be explained by existing differences in hospital volumes. To further investigate the differences in outcomes, a European upper GI audit is currently initiated.

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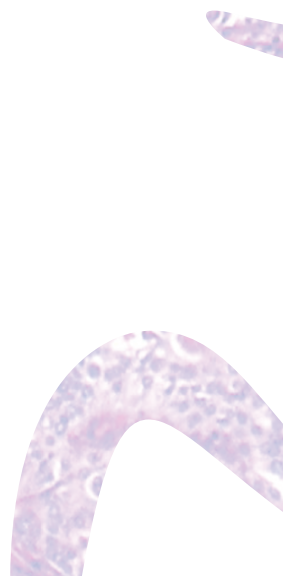

APPENDICES

SUMMARY IN DUTCH (NEDERLANDSE SAMENVATTING)

Het onderzoek in dit proefschrift richt zich op verschillende aspecten van de behandeling van het maagcarcinoom: de stagering en het voorspellen van de prognose, de behandeling met chemotherapie en radiotherapie (bestraling) en de kwaliteit van de chirurgie.

DEEL I - STAGERING EN HET VOORSPELLEN VAN PROGNOSE

Stageren (het classificeren van tumoren) is een van de basisactiviteiten binnen de oncologie. Al meer dan 50 jaar is de TNM classificatie de standaard voor het anatomisch classificeren van maligne tumoren. In 2010 werd door de *International Union Against Cancer (UICC)* en de *American Joint Committee on Cancer (AJCC)* de 7e editie van de TNM classificatie gepubliceerd. **Hoofdstuk 2** beschrijft de verschillen tussen de 6e en 7e editie van de TNM classificatie van het maagcarcinoom en vergelijkt de complexiteit en voorspellende nauwkeurigheid van beide systemen. In de 7e editie zijn de afkapwaarden voor de N-classificatie (aantal tumorpositieve lymfeklieren) gewijzigd, waardoor een meer gelijke verdeling van patiënten over de N-categoriën ontstaat. Hierdoor is de voorspellende nauwkeurigheid van de N-classificatie verbeterd. In zijn geheel is de TNM classificatie van het maagcarcinoom complexer geworden, met een toename van het aantal TNM groepen van 56 naar 80. Dit heeft echter niet geleid tot een verbeterde voorspellende nauwkeurigheid. In verband met gebruikersgemak moet hier in de toekomst rekening mee gehouden worden.

Een andere vernieuwing in de 7e editie van de TNM classificatie is het gebruik van de differentiatiegraad voor de bepaling van het tumorstadium bij vroege stadium slokdarmcarcinomen. Slecht gedifferentieerde vroege stadium slokdarmcarcinomen hebben een slechte prognose, en kunnen daarmee in aanmerking komen voor preoperatieve chemotherapie. Maar dan moeten deze tumoren wel bij de preoperatieve diagnostiek geïdentificeerd kunnen worden. In **Hoofdstuk 3** wordt de nauwkeurigheid van het preoperatief bepalen van de differentiatiegraad van adenocarcinomen van de slokdarm-maagovergang onderzocht. De nauwkeurigheid voor het bepalen van de differentiatiegraad is 73%, maar bij vroege stadium adenocarcinomen is de sensitiviteit voor het detecteren van een slecht gedifferentieerde tumor slechts 43%. Hierdoor wordt 21% van de patiënten met een vroege stadium tumor van de slokdarm-maagovergang in een verkeerd tumorstadium ingedeeld. Het stageren van patiënten met een adenocarcinoom van de slokdarm op basis van gegevens van een preoperatieve biopsie moet daarom met terughoudendheid worden uitgevoerd.

Hoewel de TNM classificatie kan worden gebruikt om de prognose van een patiënt te bepalen, zijn er hulpmiddelen voor het bepalen van de prognose van individuele patiënten ontwikkeld die een significant betere voorspellende nauwkeurigheid hebben dan de TNM classificatie. Voor het maagcarcinoom is een nomogram (statistisch model) ontwikkeld dat gebaseerd is op een database uit één Amerikaans ziekenhuis en dat gevalideerd is in verschillende internationale datasets. **Hoofdstuk 4** beschrijft de ontwikkeling van een

nieuw nomogram voor maagkanker dat niet alleen een voorspelling doet voor patiënten direct na een maagresectie, maar ook voor patiënten die al een periode overleefd hebben na een maagresectie. Dit nomogram heeft een hoge voorspellende nauwkeurigheid. Het overleven van één, twee of drie jaar na een maagresectie geeft een verbetering van de 5-jaars overleving van respectievelijk 7,2%, 19,1% en 31,6% in vergelijking met de voorspelling direct na de operatie. Dit nomogram baseert zijn voorspelling op gegevens die bekend zijn bij de operatie, terwijl gegevens verkregen bij controle afspraken na de operatie (zoals gewichtsverlies en conditie van de patiënt tijdens de controle afspraak) de voorspellende nauwkeurigheid van dit nomogram niet verder verbeteren.
In **Hoofdstuk 5** wordt de voorspellende waarde van het al eerder gepubliceerde nomogram, dat gebaseerd is op patiënten die chirurgie ondergingen zonder chemotherapie of radiotherapie, onderzocht in een groep patiënten die postoperatieve chemoradiotherapie ondergingen na maagresectie. De door het nomogram voorspelde 5-jaars overleving voor deze patiënten was significant te laag, hetgeen wijst op een overlevingsvoordeel voor patiënten die chemoradiotherapie ondergaan ten opzichte van patiënten die alleen chirurgie ondergaan. Daarnaast wijst deze studie op de noodzaak van het ontwikkelen van nomogrammen die ook kijken naar het gebruik van chemotherapie en radiotherapie.

DEEL II - CHEMOTHERAPIE EN RADIOTHERAPIE

Gedurende de laatste tien jaar zijn veel studies uitgevoerd waarin het effect van chemotherapie en radiotherapie op de overleving bij het resectabel maagcarcinoom wordt onderzocht. **Hoofdstuk 6** geeft een overzicht van de literatuur naar de behandeling van het maagcarcinoom, waarbij de verschillende soorten behandelingen aan de orde komen. Geaccepteerde behandelschema's zijn onder andere postoperatieve monochemotherapie met S-1 in Azië en perioperatieve chemotherapie en postoperatieve chemoradiotherapie in Europa en de Verenigde Staten.
In **Hoofdstuk 7** worden recidief- en overlevingspatronen van patiënten die postoperatieve chemoradiotherapie kregen vergeleken met recidief- en overlevingspatronen van patiënten die alleen geopereerd werden. Het lokale recidiefpercentage (een recidief tumor op de plaats waar de maag zat) was significant lager in de chemoradiotherapie groep (5% versus 17%). Een subgroepanalyse liet zien dat dit verschil zelfs nog groter was bij patiënten die een maagresectie met een beperkte (D1) lymfeklierdissectie ondergingen (2% versus 18%), terwijl geen verschil werd gevonden bij patiënten die een uitgebreide (D2) lymfeklierdissectie ondergingen. Aanvullende analyses waarbij patiënten langer in de tijd gevolgd werden toonden een hogere 2-jaars overleving voor patiënten die na een D1 lymfeklierdissectie postoperatieve chemoradiotherapie kregen in vergelijking met patiënten die alleen geopereerd werden. Bij patiënten die D2 lymfeklierdissectie kregen werd dit verschil niet gevonden. Postoperatieve chemoradiotherapie was ook geassocieerd met een significant hogere 2-jaars overleving bij patiënten die een microscopisch irradicale (R1) resectie ondergingen (66% versus 29%). Resultaten van

deze studie laten zien dat, vooral na een beperkte (D1) lymfeklierdissectie, postoperatieve chemoradiotherapie een grote invloed heeft op het aantal lokale recidieven en de algehele overleving. Postoperatieve chemoradiotherapie zou gegeven moeten worden aan patiënten die een microscopisch irradicale (R1) resectie ondergaan.
In **Hoofdstuk 8** worden de resultaten van een studie naar het aantal gevonden lymfeklieren na maagresecties beschreven. Terwijl wordt geadviseerd om ten minste vijftien lymfeklieren te verwijderen en te onderzoeken om een maagcarcinoom accuraat te kunnen stageren, is het aantal klieren dat wordt gevonden in Europa en Amerika laag. Het effect van preoperatieve chemotherapie op de lymfeklieropbrengst is onbekend. Deze studie vergelijkt de lymfeklieropbrengsten van patiënten die preoperatieve chemotherapie kregen met patiënten die alleen chirurgie kregen. Preoperatieve chemotherapie is niet geassocieerd met een daling in het aantal gevonden lymfeklieren, hetgeen erop wijst dat het evalueren van meer dan vijftien klieren na een maagresectie haalbaar is, ook na preoperatieve chemotherapie.
Hoofdstuk 9 beschrijft het studieprotocol van de internationale CRITICS studie. Deze studie vergelijkt de huidige twee standaardbehandelingen van het maagcarcinoom in de Westerse wereld: postoperatieve chemoradiotherapie en perioperatieve chemotherapie. Alle patiënten krijgen drie kuren ECC (epirubicine, cisplatine en capecitabine), gevolgd door D1+ chirurgie (D2 maagresectie zonder milt- en pancreasstaartresectie). Postoperatief volgen nog drie kuren met ECC, of wordt chemoradiotherapie met cisplatine en capecitabine gegeven. De resultaten van deze studie worden rond 2015 verwacht.

DEEL III - KWALITEIT VAN CHIRURGIE

Als introductie op deel III van dit proefschrift beschrijft **Hoofdstuk 10** de resultaten van een systematisch onderzoek naar de literatuur over kwaliteitsindicatoren bij maagkankerchirurgie. Een hoog ziekenhuisvolume (het aantal operaties dat een ziekenhuis per jaar uitvoert) is sterk gerelateerd aan een lagere postoperatieve sterfte en een betere langetermijnoverleving. Er worden verschillende kwaliteitsindicatoren over de operatietechniek gevonden, waaronder het uitvoeren van een uitgebreide lymfeklierdissectie, het niet routinematig verwijderen van de milt en de pancreasstaart, en het gebruik van een reservoir gemaakt van een stuk darm (pouch). Ook zijn tumorvrije snijvlakken sterk geassocieerd met een betere langetermijnoverleving.
In **Hoofdstuk 11** en **Hoofstuk 12** wordt de incidentie (het aantal nieuwe gevallen per jaar) en overleving van tumoren van de slokdarm, de slokdarm-maagovergang en de maag gedurende de afgelopen twintig jaar in Nederland beschreven. Terwijl de incidentie van het adenocarcinoom van de slokdarm is verdubbeld, daalde de incidentie van tumoren van de slokdarm-maagovergang en de maag. Deze bevindingen zijn niet het resultaat van veranderingen in diagnose of een andere indeling, maar geven zeer waarschijnlijk echte verschillen in incidentie weer. De toenemende incidentie van slokdarmkanker kan toegewezen worden aan de toenemende incidentie van overgewicht en zuurbranden.

Gedurende de studieperiode verbeterde de vijfjaarsoverleving voor niet-uitgezaaide slokdarmcarcinoom sterk (van 12% naar 25% voor adenocarcinomen, van 12% naar 19% voor plaveiselcelcarcinomen), terwijl de vijfjaarsoverleving voor niet-uitgezaaide tumoren van de slokdarm-maagovergang (20%) en de maag (32%) gelijk bleef. **Hoofstuk 13** beschrijft de behandeling van het maagcarcinoom in Nederland gedurende de afgelopen 20 jaar. Terwijl het percentage patiënten dat geopereerd wordt stabiel blijft rond de 85%, is het gebruik van preoperatieve en/of postoperatieve chemotherapie sterk gestegen sinds 2005. In 2008 werd bijna 40% van de patiënten met een stadium I-III maagcarcinoom behandeld met chemotherapie en waarschijnlijk is dit percentage de laatste jaren alleen maar verder gestegen.

Hoofdstuk 14 beschrijft de resultaten van een studie naar ziekenhuisvolumes (het aantal operaties dat een ziekenhuis per jaar doet), sterfte, en langetermijnoverleving voor slokdarm- en maagkankerchirurgie in Nederland tussen 1989 en 2009. In Nederland werd een minimale volumestandaard van tien slokdarmresecties per jaar geïntroduceerd in 2006, terwijl er tijdens de studieperiode geen minimale volumestandaard voor maagkankerchirurgie was. Tijdens de afgelopen twintig jaar zijn slokdarmresecties in Nederland sterk gecentraliseerd en in 2009 werd 64% van deze operaties uitgevoerd in volumes van meer dan twintig per jaar. Maagresecties werden niet gecentraliseerd en in 2009 werd slechts 5% van alle maagresecties uitgevoerd in volumes van meer dan twintig per jaar. Terwijl de postoperatieve sterfte en de langetermijnoverleving zowel na slokdarm- als maagresecties verbeterde, was deze verbetering significant groter voor slokdarmresecties. Een hoog ziekenhuisvolume werd geassocieerd met een lagere 6-maanden sterfte en een langere 3-jaars overleving na slokdarmresecties, maar niet na maagresecties. Echter, het aantal hoogvolume maagresecties in de huidige studie was te beperkt om een statistisch significant verschil in overleving aan te tonen tussen laag- en hoogvolume resecties. Deze studie laat wel zien dat er een dringende noodzaak is voor de verbetering van maagkankerchirurgie in Nederland.

Hoofdstuk 15 geeft de resultaten weer van een studie naar het effect van het type ziekenhuis op de overleving na slokdarm- en maagkankerresecties in Nederland. Ziekenhuizen werden geclassificeerd als universitaire ziekenhuizen en perifere opleidings- en niet-opleidingsziekenhuizen. De 3-maanden sterfte na slokdarmresecties in universitaire ziekenhuizen was 2,5%, vergeleken met meer dan 4% voor perifere ziekenhuizen. De 3-maanden sterfte na maagresecties was 4,9% in universitaire ziekenhuizen en 8,7% in perifere ziekenhuizen. Zowel na slokdarm- als maagresecties was de 3-jaarsoverleving hoger in universitaire ziekenhuizen vergeleken met perifere ziekenhuizen. Tussen perifere opleidings- en niet-opleidingsziekenhuizen werden geen verschillen gevonden. Bij het analyseren van verschillen tussen individuele ziekenhuizen presteerden enkele perifere ziekenhuizen bovengemiddeld goed. Hieruit kan geconcludeerd worden dat de beste ziekenhuizen niet alleen op basis van het type ziekenhuis geselecteerd kunnen worden.

In **Hoofdstuk 16** worden de resultaten van een internationale studie naar slokdarm- en maagkankerchirurgie van 2004 tot 2009 in verschillende Europese landen beschreven. Verschillen in het percentage geopereerde patiënten, de postoperatieve sterfte, de langetermijnoverleving en ziekenhuisvolumes werden vergeleken tussen Nederland, Zweden, Denemarken en Engeland. In Nederland was de postoperatieve sterfte in vergelijking met de andere landen gemiddeld na slokdarmresecties (4,6%), maar het hoogst na maagresecties (6,9%). Hoewel een toenemend ziekenhuisvolume geassocieerd was met een lagere 30-dagen sterfte zowel na slokdarm- als maagresecties konden verschillen in uitkomsten tussen landen niet alleen verklaard worden door verschillen in ziekenhuisvolumes. Om deze verschillen verder te onderzoeken wordt gewerkt aan een grote Europese slokdarm- en maag registratie.

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Dikken JL, Jansen EPM, Cats A, Bakker B, Hartgrink HH, Kranenbarg EM, Boot H, Putter H, Peeters KC, van de Velde CJH, Verheij M. Impact of the extent of surgery and postoperative chemoradiotherapy on recurrence patterns in gastric cancer.
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CURRICULUM VITAE

Johan Dikken was born on July 23rd of 1983 in Apeldoorn, the Netherlands. He graduated from the Greijdanus College (gymnasium) in Zwolle in 2001. In the same year, he started to study Pharmacy at Utrecht University, but switched to study Medicine at the University of Amsterdam as of 2003. While attending medical school, he was an active member of Student Society VGSU in Utrecht, and served as president of the board in the years 2004-2005. In 2007, he received a bachelor's degree in Pharmacy and a master's degree in Medicine. During his internships at the Leiden University Medical Center (LUMC) in 2009 he became interested in surgical oncology and started working as a research student at the department of surgical oncology. In 2010, he received his Doctor of Medicine degree in Leiden.

From February to August 2010, he worked as a research fellow at Memorial Sloan-Kettering Cancer Center (MSKCC) in New York, under supervision of dr. D.G. Coit and dr. M.F. Brennan. His research at MSKCC focused on staging and prognostication in gastric cancer, and was awarded with the American Society of Clinical Oncology Merit Award in San Francisco, 2011.

From September 2010 to February 2012 Johan Dikken worked as a PhD student at the department of surgical oncology of the LUMC and the department of radiotherapy of the Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital in Amsterdam under supervision of prof. dr. C.J.H. van de Velde and prof. dr. M. Verheij. Here, he performed several studies on quality of care for esophageal and gastric cancer in the Netherlands, and he worked on a project instrumental for the development of a European upper GI cancer audit. His research was funded by the Dutch Cancer Society (KWF Kankerbestrijding). In 2011, he received the Young Investigators Award from the European Cancer Organisation.

Currently he works as a resident not in training at the department of surgery at Medisch Centrum Haaglanden.

He lives in The Hague with his wife Javotte and their daughter Norah.

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