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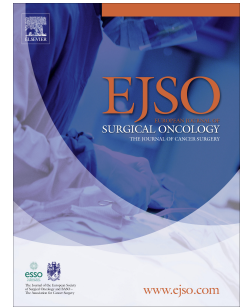


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# **Effect of hospital characteristics on outcome of patients with gastric cancer: A population based study in North-East**

## **Netherlands**

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## Abstract

**Background:** Surgical resection is an important factor in the curative treatment of gastric cancer. However a variety of aspects of surgical treatment that potentially influence outcome are still not well defined. This study aims to assess the influence of hospital type, referral pattern and proximal or distal location of the tumour on the ultimate survival.

**Methods:** From January 1994 to January 2007, a total of 5245 patients were diagnosed with gastric adenocarcinoma in the region of the Comprehensive Cancer Centre North-East Netherlands. Hospitals in this region were categorized into three types: teaching university (TU), teaching non-university (TNU), and non-teaching hospitals (NT). The influence of hospital type, referral for surgery and location of the tumour on the relative survival of operated patients was studied.

**Results:** Of the 5245 patients, 2334 patients underwent surgery. For operated patients, the 5-year relative survival was 42.5% for the TU versus 34.0% and 35.5% for respectively TNU and NT hospitals ( $p=0.064$ ), with no difference ( $p=0.38$ ) in relative survival (25.6-31.9%) in the proximal tumours. A significant difference was found between the hospitals in the 5-year relative survival in the distal tumours; 59.7% in the TU versus 36.4% in the TNU and 36% in the NT ( $p=0.03$  univariate), however this was not confirmed in the multivariate analysis ( $p=0.184$ ). High referral centres did not perform better as far as survival is concerned than low referral hospitals.

In conclusion the hospital type in our region did not significantly influence outcome of surgery for gastric cancer.

## Introduction

Although decreasing in incidence, gastric cancer still is diagnosed in more than 2000 patients per year in the Netherlands. In the past decades half of them died of their disease within 5 years after diagnosis. Currently, gastric cancer ranks as the fourth cause of cancer death in the western world [1].

It is widely recognised that prognosis depends on factors related to tumour and patient. The stage of the tumour is of paramount importance, and the patient age and especially co-morbidity are highly relevant factors in predicting outcome [2].

More recently however, other variables, related to surgeon and even hospital characteristics have been recognised to be potentially important for the ultimate fate of the patient. *These hospital related factors might be important, as the overall survival in Japan, where patients undergo more extensive curatively intended resection methods, is higher[2].*

*Data demonstrating the importance of various structural characteristics including the hospital volume, surgeon volume and hospital type where the surgical intervention is performed as well as the experience and expertise of the surgical team itself, remain equivocal [3-6].*

In the population based study described here, we analysed some of these aspects in relation to the *patient survival*. Data were provided in a group of gastric cancer patients treated in all hospitals in the North-East region of the Netherlands regarding the hospital type and the location of the tumour, whether proximal or distal in the stomach. *The outcome of this study is important in the discussion on centralization of surgical cancer care.*

## Patients and Methods

### *Patients*

All patients diagnosed with primary invasive gastric cancer from January 1994, until January 2007 were selected for entry in the study by the regional cancer registry of the Comprehensive Cancer Centre North-East Netherlands.

### *Comprehensive Cancer Centre North-East Netherlands*

This regional cancer registry is a population based registry which covers the north-eastern part of the Netherlands, a mainly rural area with a population of about 3.3 million. The area is served by 22 community hospitals, among which 8 teaching hospitals, and one university hospital, five radiotherapy departments and nine pathology laboratories. Reports of all new, cytological or histological proven cancer cases are submitted to the regional cancer registry regularly through these pathology laboratories. The national hospital discharge databank, to which hospitals in the region provide the discharge diagnosis of all admitted patients on a yearly basis, further completes case ascertainment.

### *Data collection.*

After notification, trained registry clerks abstract all relevant data directly from patient records, including pathology and surgery reports, within the hospitals. Data collection occurs at a minimum of 6 months after cytological or histological diagnosis in order to document all aspects of the primary therapy. All patients are staged according to the TNM system [7;8].

In the Netherlands the municipal population registries contain information on the vital status of their inhabitants. Since October 1994 population data from all Dutch municipalities are collected in a national database. Vital status was established through linkage of cancer registry data with the national automated population registry.

### *Variable definitions and Statistics*

*The referral rate was calculated as the proportion of all operated patients, within the population of patients diagnosed in a given hospital, which were operated in another hospital.*

*Survival time was calculated from the date of diagnosis and ended at the date of death or the date of most recent linkage with the national automated populated registry, whichever came first. The 5-year overall survival rates were estimated using the actuarial method and survival was compared with the log rank test. Besides overall survival, relative survival rates were estimated. The relative survival is an estimate for the disease-specific survival and is calculated by dividing the absolute overall survival in our cohort by the expected survival based on age, sex and period matched mortality rates from the general population. The main advantage of using the relative survival is that it does not rely on cause of death information and captures both direct and indirect mortality due to gastric cancer and its treatment. Multivariate analysis of relative survival was performed according to the method described by Dickman et al [9].*

## Results

### *Patients*

In the period January 1994 until January 2007, 5245 patients were diagnosed with gastric adenocarcinoma of which 3440 were male. The median age was 72.3 (range: 18.5-98.3) years. Patient characteristics are described in Table 1. A large proportion of the patients was diagnosed at an advanced stage, 2714 patients were in stage IIIA or higher. A further 954 patients were insufficiently staged. One hundred ninety-four patients were diagnosed in the university hospital, 2869 in the non-university teaching hospitals and the remaining 2182 patients were diagnosed in community hospitals.

As table 1 shows, 2334 patients underwent surgery. Older age ( $p<0.001$ ), advanced or unknown stage ( $p<0.001$ ) and proximal tumour location ( $p<0.001$ ) resulted in a lower probability of tumour resection. A tumour with intermediate or poor differentiation was also associated with less surgery, but this was highly correlated with stage. In all, 40.2% of the patients diagnosed in non-teaching hospitals were operated on, compared to 45.6% and 43.5% for non-university teaching and university hospitals, respectively ( $p=0.162$ ). Only a minority of the operated patients received (neo)adjuvant chemotherapy, respectively 57 out of 2334 patients.

### *Hospitals characteristics*

A total of twenty-three hospitals participated with fourteen non-teaching hospitals, eight teaching hospitals and one university hospital. For proximal gastric cancers a difference in stage distribution was observed ( $p=0.039$ ) due to a higher frequency of patients with stage III and a lower frequency of stage IV cancers among patients operated in the university hospital. For the non-proximal tumours there were no meaningful differences in stage and sub-site distribution between the three hospital types. There was some imbalance in the distribution



over the age-groups ( $p<0.001$ ), with slightly younger patients operated in the university hospital although overall the age distribution did not appear to differ that much when analysed categorical (Table 2).

### *Referral characteristics*

Of all operated patients 6 % were referred for surgery. Referral differed markedly by tumour sub-site, however. Of the operated patients with a tumour located in the proximal part of the stomach 18.0% were referred for surgery, while only 2.6% of the operated patients with a non-proximal tumour (body or distal part of the stomach) were referred for surgery. The non-teaching hospitals referred 10.9% of the operated patients diagnosed in their hospitals, 35.2% of the patients with proximal and 4.6% of the patients with non-proximal tumours. Of the fourteen non-teaching hospitals, seven had a high propensity to refer (referral rates 50-83%) patients with proximal gastric cancers for surgery and three hospitals rarely (0.0%-10.0%) referred patients. The eight non-university teaching hospitals referred 2.8% of the patients diagnosed in their hospitals, 8.2% of the patients with proximal and 1.2% of the patients with non-proximal tumours (Table 3).

### *Survival in relation to patient, tumour and hospital characteristics*

The 5-year relative survival rate in the period of 1994-2006 for men with gastric cancer was 34.0% versus 37.4% for women. Age over 70 had a detrimental effect on survival compared to age  $<60$  years with an excess mortality risk of 1.17 (1.01-1.34;  $p=0.022$ ). The 5-year relative survival markedly decreased with more advanced stage, respectively 85.0% in stage IA, 62.0% in stage IB, 32.5% in stage II, 13.5% in stage III, 6.3% in stage IV ( $p<0.001$ ). Assessing all operated gastric cancers combined; 5-year relative survival did not significantly differ by hospital type, referral pattern or volume of the centres. *Although relative survival*

*appeared to be somewhat better in the TU, as the 5-year relative survival was 42.5% for the TU versus 34.0% and 35.5% for respectively TNU and NT hospitals (p=0.064 univariate).*

Survival was also analysed separately for patients with proximal and non-proximal tumour.

For proximal tumours outcome was strongly associated with stage, but neither hospital volume, nor teaching characteristics were significant factors. However in univariate analysis 5-year relative survival of the non-proximal tumours was significantly better in the TU compared to TNU and non-teaching hospitals (p=0.033 univariate) (Table 4). After adjusting for sex, age, period, stage, volume, referral and time since diagnosis this differences no longer reached statistical significance. *Survival with respect to age, stage, volume (< 5, 5-9 and  $\geq$  10 patients/year) and referral rate (<5%, 5-15% and >15%) was not different between the hospital types (Table 4).*

Survival before and after the year 2000, for all types of gastric cancer combined did differ.

For proximal cancer the results were similar between the two periods. However survival for non-proximal cancer was better in the later period. This improvement was not related to any of the hospital factors (volume teaching academic).

## Discussion

In this population based study patient characteristics such as gender and age distribution are comparable to other European countries [10]. Age, subsite and histology type are known factors in explaining survival variability [11]. In our study older age, advanced or unknown stage, poorly differentiated tumours and proximal location resulted in lower probability of resection. Moreover in gastric cancer both tumour (T) and nodal (N) status are important elements in determining treatment plans and independent prognostic factors of long-term survival [12-14].

However factors that are neither patient nor tumour related have been reported to influence the outcome of curative intended surgery in cancer patients. Some of them are related to the experience and expertise of the surgical team and the case volume. Others stem from non-oncological surgical experience, such as expertise in extensive transplantations. Several studies demonstrated hospital and surgeon volume to have an important impact on short and long term survival in patients with potentially curative resection in different cancer types. Better outcome was also found in specialised centres [15-18]. Verhoef et al. described significantly better outcome in oesophageal cancer surgery in the university hospital compared with other, non-university teaching and non teaching, hospitals in our region [19]. As shown in oesophageal cancer, some studies also support the impact of hospital and surgeon related factors on short and long-term results in gastric cancer [20-22].

The 5-year overall survival rate in our study reflects reported stage-specific 5-year survival rates of 10-64% [23]. *Patients treated in high referral hospitals did not have a better long term survival than those treated in low referral hospitals. Survival also seemed independent of hospital type for the whole group of surgical patients. Although relative survival appeared to be somewhat better in the TU compared to TNU and NT hospitals (42.5% versus 34.0% and 35.5% of TNU and NT ( $p=0.064$ )). This could partly be explained by an imbalance in*

tumour and patient characteristics between the hospital types. On average less patients, with lower stages of proximal gastric cancer and slightly younger of age were operated in the TU hospital (Table 2). With regard to survival and tumour location, there were no hospital related differences in outcome in proximal gastric cancer. However overall outcome in that location was worse compared to that in the distal stomach, an observation also found in the work of others [24-27]. For distal gastric cancer the univariate analysis showed a significant difference in the 5 year relative survival regarding hospital type, in favour of the university hospital (57.7 % versus 36.4% TNU and 36% NT). This difference could not be confirmed in multivariate analysis and to some extent might be explained by patient selection; the TU hospital operated on average, younger patients. Therefore, hypothetically maybe the high volume more experienced non-university hospitals (TNU and TU) have balanced the more academic approach of the TU resulting in no significant difference in survival. With regard to long-term survival we also did not observe hospital volume to play an important role. Of note, all surgeons in our region are low volume surgeons and the subdivision of centres based on volume of  $<5$ ,  $5-9$ ,  $\geq 10$  patients operated/ year served as a suitable separator between its 23 centres. Within this small window no striking differences were found in relation to survival. Controversy on the role of surgical volume still remains, as is also discussed by other authors [3;5;6;28]. This observation suggests that other factors than sheer number of procedures are important for outcome. As in our case, the university hospital is a low volume hospital for gastric cancer, it becomes evident that other factors than the caseload prevail. The better outcome for oesophageal cancer surgery that Verhoef et al. described in our region might therefore not be attributed to the university hospital on basis of the highest volume but other hospital related qualities [19]. This might also be the case for the benefit described by Bachmann et al., based on the difficulty to distinguish this volume aspect from other hospital related qualities [22]. Quality of initial surgical care, for example extended

*lymphadenectomy*, not fully reflected by operative mortality rates might play a role next to patient care in the follow up period after surgery. Enzinger et al. suggested delay in time of recurrence because of their observation that survival based on volume differences appear during the first 3 years after surgery [28].

It is interesting that comparison of the two observation periods showed an improvement in survival during the later period limited to distal cancer. The most likely cause of such differences is stage migration due to better diagnostics. However this would not readily explain the lack of improvement in proximal cancers.

*In conclusion the hospital type in our region did not significantly influence outcome of surgery for gastric cancer. For future consideration however, gastric cancer surgery will require the guaranteed availability of multidisciplinary oncological teams experienced in multimodality treatments.*

### **Conflicts of interest statement**

There are no conflicts of interest.

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**Table 1. Characteristics of patients diagnosed with gastric adenocarcinoma between 1994-2006, all patients combined, operated and non-operated patients**

		Total N	operated N	Not-operated N	*p-value
Gender	Men	3440	1555	1885	0.157
	Women	1805	779	1026	
Age at diagnosis	<50	364	189	175	<0.001
	50-59	672	332	340	
	60-69	1207	627	580	
	70-79	1751	835	916	
	80+	1251	351	900	
Histology	Adenocarcinoma, nos	4,051	1773	2278	<0.001
	Mucinous	282	158	124	
	Signet ring cell	767	403	364	
	No microscopic confirmation	145	0	145	
Tumour location	Cardia&fundus	1509	517	992	<0.001
	Body&curvature, nos	886	464	422	
	Antrum&pylorus	1430	888	542	
	Overlapping & unspecified	1420	465	955	
Differentiation	Good	144	99	45	<0.001
	Intermediate	1031	633	398	
	Poor	2238	1231	1007	
	Unknown	1832	371	1461	
Stage	Stage 1A	317	264	53	<0.001
	Stage 1B	562	464	98	
	Stage 2	698	603	95	
	Stage 3	807	598	209	
	Stage 4	1907	386	1521	
	Unknown/not applicable	954	19	935	
Therapy	Surgery	2277	2277	0	<0.001
	Surgery&CT	37	37	0	
	Neoadjuvant CT&surgery	20	20	0	
	CT	259	0	259	
	CT&RT	15	0	15	
	Other/none	2637	0	2637	
Total		5245	2334	2911	

\* p-value based on Chi-square or Fisher's exact test where applicable

**Table 2 Stage and age distribution for operated patients according to hospital type where surgery was performed 1994-2006, stratified by tumour subsite**

		Total	Teaching, university	Teaching, non- university	Non- teaching	p-value
<i>Stomach: cardia&amp;fundus</i>		N	N	N	N	
Stage	Stage 1A	41	9	23	9	0.039*
	Stage 1B	89	13	46	30	
	Stage 2	171	22	100	49	
	Stage 3	152	35	92	25	
	Stage 4	61	7	38	16	
	Unknown	3	2	0	1	
Age	<60	163	34	99	30	0.101
	60-69	174	23	100	51	
	70+	180	31	100	49	
	Median	65.4	64.4	64.8	66.8	
	(IQR#)	(57.9-72.5)	(55.8-72.1)	(57.5-72.5)	(61.5-73.0)	
Total		517	88	299	130	100.0
<i>Stomach: other</i>						
Stage	Stage 1A	223	14	121	88	0.409*
	Stage 1B	375	22	192	161	
	Stage 2	432	17	248	167	
	Stage 3	446	14	254	178	
	Stage 4	325	13	181	131	
	Unknown	16	2	6	8	
Age	<60	358	23	198	137	0.391
	60-69	453	18	251	184	
	70+	1,006	41	553	412	
	Median	71.7	70.1	71.8	71.8	
	(IQR#)	(63.0-78.0)	(58.1-77.6)	(62.7-77.8)	(63.8-78.3)	
Tumour location	Body&curvature, nos	464	20	252	192	0.359
	Antrum&pylorus	888	38	478	372	
	Overlapping & unspecified	465	24	272	169	
Total		1817	82	1,002	733	

\* Excluding stage unknown; # IQR=Inter Quartile Range

**Table 3. Hospital type, volume and referral pattern for gastric cancer-surgery for hospitals in the North-East Netherlands between 1994 and 2006**

Hospital type	Number of operated patients			
Hospital of diagnosis (n=number of hospitals; Operated number of patients/year)	Cardia/fundus tumours		Body/distal tumours	
	Operated in hospital of diagnosis N	Referral for surgery N	Operated in hospital of diagnosis N	Referral for surgery N
Hospitals (n=7; <5 year)	42	39	278	18
Hospitals (n=7; 5-9 year)	83	29	443	17
<b>Non-teaching</b>	<b>125</b>	<b>68</b>	<b>721</b>	<b>35</b>
Hospitals (n=1; 5-9 year)	23	1	88	1
Hospitals (n=7; ≥10 year)	256	24	903	11
<b>Teaching non-university</b>	<b>279</b>	<b>25</b>	<b>991</b>	<b>12</b>
Hospital (n=1; 5-9 year)	20	0	58	0
<b>Teaching university</b>	<b>20</b>	<b>0</b>	<b>58</b>	<b>0</b>
Total	424	93	1,770	47

**Table 4 Overall and relative 5-year survival and estimated excess risk of death with 95% confidence intervals (95% CI) for operated patients with gastric cancer, diagnosed between 1994-2006**

	All gastric cancers					Proximal gastric cancer					Distal gastric cancer				
	Univariate		Multivariate			Univariate		Multivariate			Univariate		Multivariate		
	5-year OS	5-year RS	EMR	95% CI	*p-value	5-year OS	5-year RS	EMR	95% CI	*p-value	5-year OS	5-year RS	EMR	95% CI	*p-value
<b>Sex</b>					0.075					0.519					0.224
male	27.1	34.0	1.00			24.7	28.6	1.00			28.0	36.0	1.00		
female	30.9	37.4	0.90	0.79-1.02		21.4	24.3	0.91	0.68-1.22		32.1	39.1	0.92	0.80-1.06	
<b>Age</b>					0.055					0.206					0.050
< 60 (ref)	32.0	32.8	1.00			23.8	24.4	1.00			35.7	36.5	1.00		
60-69	31.5	35.0	1.03	0.89-1.21		28.8	31.9	0.85	0.64-1.12		32.6	36.1	1.13	0.94-1.37	
70+	25.1	36.8	1.17	1.01-1.34		20.3	27.6	1.09	0.83-1.44		25.9	38.4	1.23	1.04-1.45	
<b>Period</b>					0.001					0.092					0.014
1994-1999	26.7	33.8	1.00			21.3	25.2	1.00			28.1	36.1	1.00		
2000-2006	30.0	36.3	0.83	0.74-0.94		27.5	30.9	0.83	0.65-1.04		30.9	38.1	0.84	0.73-0.96	
<b>Stage</b>					<0.001					<0.001					<0.001
stage 1 (ref)	55.6	70.5	1.00			46.1	54.2	1.00			57.6	73.8	1.00		
stage 2	26.5	32.5	2.96	2.44-3.60		24.5	28.3	2.12	1.49-2.99		27.2	34.1	3.25	2.57-4.13	
stage 3	11.2	13.5	5.20	4.31-6.27		14.0	15.9	3.49	2.43-4.99		10.3	12.7	5.99	4.78-7.51	
stage 4	5.3	6.3	8.05	6.61-9.80		2.0	2.3	4.93	3.29-7.38		5.9	7.1	9.37	7.43-11.83	
<b>Hospital type\$</b>					0.112					0.433					0.184

Non-teaching (ref)	28.6	35.5	1.00		27.1	31.9	1.00		28.9	36.0	1.00	
Teaching non-university	27.4	34.0	0.96	0.74-1.25	22.6	25.6	0.99	0.62-1.56	28.7	36.4	0.92	0.66-1.29
Teaching university	34.7	42.5	0.76	0.56-1.03	24.5	29.2	0.80	0.51-1.26	47.5	59.7	0.66	0.40-1.07
<b>Volume hospital#</b>				0.880				0.778				0.814
< 5 patients operated/yr	28.5	34.6	1.00		30.5	35.0	1.00		27.8	34.5	1.00	
5-9 patients operated/yr	28.2	35.5	1.00	0.81-1.22	23.4	28.1	1.15	0.75-1.76	29.1	37.1	0.98	0.77-1.25
≥ 10 patients operated/yr	28.4	35.2	1.06	0.80-1.40	22.5	25.9	1.14	0.73-1.78	30.1	38.3	1.08	0.74-1.55
<b>Referral rate hospital^</b>				0.377				0.627				0.498
Low (< 5.0%)	28.7	34.5	1.00		24.7	28.4	1.00		29.8	37.8	1.00	
Intermediate (5.0-15.0%)	28.0	35.3	0.95	0.77-1.17	20.7	25.2	1.10	0.74-1.63	29.7	37.8	0.91	0.71-1.17
High (> 15.0%)	26.0	32.2	1.12	0.91-1.39	23.6	27.4	1.19	0.82-1.72	26.7	33.7	1.08	0.83-1.40

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OS=Overall survival, RS=relative survival, EMR=Excess Mortality Risk, 95% CI=95% Confidence Interval, n.a.=not applicable

\* *p-values apply to the multivariate model, adjusted for time since diagnosis*

\$ *teaching status based on surgical subspecialisation*

# *subdivision based on <5 versus 5-9 or ≥ 10 patients operated/ year based on all gastric cancers combined*

^ *subdivision based on <5%, 5-15% and >15% referral of patients for surgery based on all gastric cancers combined*