

Prognostic relevance of demographics and surgical practice for patients with gastric cancer in two centers: in Poland versus Germany

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Abstract

Background Although studies comparing the surgical treatment of gastric carcinoma in Japan and Western industrialized countries have revealed differing survival rates, no studies to date have been performed comparing Western and Eastern Europe. This study aimed to compare demographics and surgical practice as well as the related prognostic impact on gastric cancer patients treated in Poland and Germany.

Methods This retrospective study included gastric cancer patients treated between 1999 and 2004 by surgical departments in Gdansk (Poland) and Cologne (Germany). Univariate and multivariate analyses of demographic, histopathological, surgical, and prognostic data were performed.

Results Included were 117 patients from Gdansk and 130 patients from Cologne. The Cologne patients showed higher incidence rates of serious comorbidity, pT1 cancer, and distant metastasis than those from Gdansk. Indications for and frequency of selected surgical procedures differed significantly. D2-lymphadenectomy was performed in 89% of the Cologne patients, while D1-lymphadenectomy was done for 85% of the Gdansk patients. Univariate analysis yielded a 5-year survival rate of 28.3% for the Gdansk patients, and 40.3% for the Cologne patients ($p = 0.056$).

Independent prognostic factors were pT category ($p = 0.002$), pN category ($p < 0.001$), pM category ($p = 0.027$), residual tumor (R) category ($p = 0.004$), age ($p = 0.012$), and number of resected lymph nodes ($p = 0.005$).

Conclusions Significant differences of clinical and surgical parameters exist between gastric cancer patients treated in Poland and Germany. In addition to established independent prognostic factors, we found that survival improved with each additionally resected lymph node.

Keywords Gastric cancer · Germany · Lymphadenectomy · Poland · Prognosis · Surgical procedures

Introduction

Gastric cancer is one of the most common malignancies worldwide [1]. Despite decreasing incidence rates in Western industrialized countries, gastric carcinoma remains in the top ten causes of tumor-related death in Germany [2]. The incidence rate of stomach cancer in Poland, also decreasing, is similar to that of Germany, with 16.9 cases per 100,000 population (1993–1997) [3]. Although surgery remains the only curative treatment, the type of operative treatment used for gastric cancer varies geographically [4]. Increased survival may depend on early detection made possible with endoscopy, surgical resection including appropriate lymph node dissection, and improvements in perioperative care. Differing survival rates have been reported for patients receiving surgical intervention in Japan versus those in Western industrialized countries [5, 6]. However, for patients with gastric cancer, there exists no published prognostic comparison between Eastern and Western Europe.

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The purpose of this study was to compare the characteristics of gastric cancer patients and the prognostic impact between two surgical departments: one in Gdansk (Poland), and the other in Cologne (Germany).

Patients and methods

Patients

The period of the study was 1 January 1999 until 31 December 2004. Patients underwent surgery with curative intent for primary gastric cancer. There were 117 patients (90% of all patients with gastric cancer) in Gdansk (Department of Surgical Oncology, Medical University of Gdansk [Poland]), and 130 patients (85% of all patients with gastric cancer) in Cologne (Department of General, Visceral and Cancer Surgery, University of Cologne [Germany]). Inclusion criteria were: histopathologically confirmed gastric cancer (from gastroscopy), no signs of metastases in preoperative assessment, and operable tumor. In all patients, the preoperative assessment of gastric cancer included not only gastroscopy but also standard laboratory tests, chest X-ray, and thoracic and abdominal computed tomography (CT) scans. Besides, in case of doubt the patients underwent laparoscopy (in Cologne), and a few patients had peritoneal cytology assessment performed. The comorbidity of a patient was classified according to the American Society of Anesthesiologists' Physical Status: ASA classification [7, 8]. For both centers the ASA grade assessment was reevaluated by one doctor according to the patient's medical history. Cardiac evaluation was mostly based on reviewing the patient's medical history and assessing the coexistence of coronary disease, arterial hypertension, diabetes mellitus, and the New York Heart Association (NYHA) score. All patients had electrocardiograms performed. Respiratory system evaluation included analysis of the patient's medical history, medical examination of the patient, and chest X-ray. Patients who had a prior history of a respiratory disorder had spirometry performed and its result had an impact on the final ASA score.

Surgical procedures

In Cologne, the guidelines of the German Society of Surgery were used to evaluate indications for therapy and the selection of the surgical procedure [9, 10]. Summarized, these guidelines are as follows: endoscopic mucosal resection and submucosal dissection are indicated in superficial cancer confined to the mucosa with special characteristics (T1a/no ulcer/G1,2/Laurén intestinal/L0/V0/tumor size <2 cm). In all other cases total gastrectomy or distal subtotal gastric resection are indicated, the latter in cases of tumors

located in the distal two-thirds of the stomach. Standard lymphadenectomy (LAD) is the D2-LAD without distal pancreatectomy or splenectomy. Carcinoma in the cardia or upper third of the stomach, classified according to Siewert et al. [11] as type II or III tumors, can be treated by an extended total gastrectomy with a transhiatal resection of the distal esophagus and LAD of the lower mediastinum and the abdominal D2 compartment. Extended organ resections are only indicated in cases where R0 resection is possible. In Gdansk, the main goal of surgical intervention was the complete removal of tumor. Indications for performing either subtotal gastrectomy, total gastrectomy, or extended total gastrectomy were based on tumor location, histological type, and trial for achieving surgical tumor-free margins. Splenectomy was carried out after iatrogenic stimulus or when there was apparent direct infiltration of tumor. Reconstruction of the digestive tract was performed with either Billroth II reconstruction (after subtotal gastrectomy), or with the Roux-en-Y reconstruction technique.

Histopathology

Resected specimens were routinely fixed in 5% phosphate-buffered formalin and embedded in paraffin. Histopathological examination of all resected specimens consisted of a thorough and standardized evaluation of tumor stage, residual tumor (R) category, grading, and number of resected and infiltrated lymph nodes. Postoperative staging was done according to the 6th edition of the International Union Against Cancer (UICC)-TNM classification of malignant tumors [12]. Gastric lymph nodes were documented according to the classification of the Japanese Research Society of Gastric Cancer (JRS GC), with lymph node groups 1–13. Tumor localization was defined according to the International Classification of Diseases for Oncology. Lesions were further classified and graded in accordance with the WHO recommendations, the Laurén classification, and tumor differentiation (G1–G4) [13].

Statistical analysis

Data were collected and analyzed retrospectively. Descriptive analysis included the frequency of nominal parameters, the median with the lower quartile (LQ) and upper quartile (UQ) for numeric variables (ordinal or asymmetric distribution), and the mean for numeric variables with normal distribution. Univariate analysis was calculated for tables using χ^2 statistics with the Yates correction or Fisher's exact test if necessary. The Mann-Whitney *U*-test was used to compare continuous variables.

More than 90% of the patients had a follow-up duration longer than four years. There was no difference of follow-up between the two centers. Univariate survival analysis was

conducted according to Kaplan–Meier, and survival curves were compared with the log rank test [14]. In addition, the hazard ratio with the 95% confidence interval (95% CI) was calculated. Multivariate analysis was performed by the Cox regression method, using the backward option, meaning: first enter all variables into the model and then remove nonsignificant variables sequentially. Assuming that the hazard function for Gdansk was different from that for Cologne over time, we stratified according to center [15].

Statistical significance was set at $p < 0.05$. For statistical analysis, the SPSS for Windows (version 17.0) application (SPSS, Chicago IL, USA) was used. For graphical presentation of the survival curve, the statistical program MedCalc for Windows Version 11.4 (MedCalc Software, Mariakerke, Belgium) was used.

Results

Demographics

There were 117 gastric cancer patients from Gdansk and 130 from Cologne. The proportion of females was significantly ($p = 0.019$) higher in the Polish group (41.9%) compared to the German group (27.7%). Patients from Gdansk were younger, with a median age of 63.9 years compared to those from Germany (median 66.8 years); however, the difference was not statistically significant ($p = 0.212$). Cologne patients had significantly ($p < 0.001$) more severe comorbidities (ASA III and IV) than patients in Gdansk. The demographic characteristics are shown in Table 1.

Table 1 Demographic and histopathological data from patients treated surgically for gastric carcinoma from Gdansk (Poland) and Cologne (Germany)

Feature	Gdansk, Poland ($n = 117$)	Cologne, Germany ($n = 130$)	p value
<i>Demographics</i>			
<i>Gender</i>			
Males	68 (58.1%)	94 (72.3%)	0.019
Females	49 (41.9%)	36 (27.7%)	
<i>Median age (min–max)</i>			
All patients	63.9 years (26–88 years)	66.8 years (31–87 years)	0.212
Males	63.3 years	66.7 years	0.063
Females	67.8 years	67.0 years	0.972
<i>Comorbidities</i>			
ASA I and II	77 (65.5%)	51 (39.0%)	<0.001
ASA III and IV	40 (34.5%)	79 (61.0%)	
<i>Histopathology</i>			
<i>Tumor localization</i>			
Upper third	43 (36.8%)	59 (45.4%)	0.356
Middle third	41 (35.0%)	37 (28.5%)	
Lower third	33 (28.2%)	34 (26.2%)	
<i>Type of histopathology (WHO)</i>			
Adenocarcinoma	100 (85.3%)	82 (63.2%)	<0.001
Signet-ring cell carcinoma	16 (13.7%)	45 (34.4%)	
Other histology	1 (1.0%)	3 (2.4%)	
<i>pT category</i>			
pT1	6 (4.8%)	29 (22.3%)	<0.001
pT2	22 (19.0%)	28 (21.5%)	
pT3	72 (61.9%)	37 (28.5%)	
pT4	17 (14.3%)	36 (27.7%)	
<i>pN category</i>			
pN0	37 (31.3%)	44 (33.8%)	0.339
pN1	42 (35.7%)	41 (31.5%)	
pN2	29 (25.0%)	26 (20.0%)	
pN3	9 (8.0%)	19 (14.6%)	
<i>pM category</i>			
pM0	100 (85.6%)	93 (71.5%)	0.009
pM1	17 (14.4%)	37 (28.5%)	

ASA anesthesia risk according to American Society of Anesthesiologists [7, 8], pT tumor infiltration depth into gastric wall, pN lymph node status, $pM0$ no distant metastases, $pM1$ distant metastases

Histopathology

The tumor was located in the upper third of the stomach for nearly half of the patients in both clinics. There was no significant difference in tumor localization. Signet-ring cell carcinoma histology was diagnosed significantly ($p < 0.001$) more often in patients from Cologne (34.4%) versus those from Gdansk (13.7%). In contrast, the Polish patients showed significantly ($p < 0.001$) more advanced pT categories than the German patients. At a rate of only 5%, early cancer was a rare diagnosis in Gdansk, in contrast to the Cologne group, where the frequency was 22% ($p < 0.001$). More details are provided in Table 1.

Surgical treatment

The details of surgical practice are listed in Table 2. Procedure frequency and indications for the various interventions differed between the two clinics. The 30- and 90-day mortality rates did not differ between the clinics, at 0.9 and 5.9% in Gdansk versus 2.3 and 4.6% in Cologne.

Prognosis

Univariate analysis identified no significant difference in prognosis between the two surgical departments (Table 3). The estimated 5-year overall survival rate for patients from Gdansk was 28.3% and that for patients from Cologne was 40.3% ($p = 0.056$), with a hazard ratio of 0.71 (95% CI 0.54–1.01) (Fig. 1). In the univariate analysis performed

separately for each center, the following prognostic factors were identified as significant for both centers: clear surgical resection margin (R0 category), pT, pN, and pM category ($p < 0.001$ for each). In Cologne, there was improved survival in younger (<60 years) versus older patients (≥ 60 years) ($p = 0.021$). For patients from Gdansk, tumor localization ($p = 0.012$), histological tumor type ($p = 0.001$), and type of lymphadenectomy performed ($p = 0.031$) had prognostic relevance. The following parameters did not influence survival in either clinic: gender, comorbidity (ASA I and II vs. III and IV), type of gastric resection, and splenectomy.

On comparison of the clinics, parameters responsible for the better prognosis in Cologne were healthy baseline status (ASA I or II), signet-ring cell carcinoma histology, and absence of distant metastasis (Table 3).

The most relevant prognostic factors from the univariate survival analysis were used for multivariate analysis: pT, pN, pM, and R category. In addition, the parameters age (continuous variable), gender, comorbidity, tumor localization, histology, and the number of resected lymph nodes (continuous variable) were included. Cox regression analysis was stratified according to surgical department. Table 4 shows the independent prognostic factors. The established independent prognostic factors, pT, pN, pM, and R category, were confirmed with our analysis. Patient age was an independent prognostic factor, with a hazard ratio of 1.022 for each subsequent year. As well, each additional resected lymph node improved the prognosis.

Table 2 Surgical treatment of patients with gastric cancer from Gdansk (Poland) and Cologne (Germany)

Feature	Gdansk, Poland ($n = 117$)	Cologne, Germany ($n = 130$)	p value
Type of resection			
Subtotal gastrectomy	14 (11.8%)	17 (13.4%)	<0.001
Total gastrectomy	82 (70.0%)	40 (30.7%)	
Extended gastrectomy	20 (17.3%)	36 (27.6%)	
Transhiatal extended gastrectomy	0 (0%)	36 (27.6%)	
Others	1 (0.9%)	1 (0.8%)	
Splenectomy			
Splenectomy during gastrectomy	67 (57.1%)	26 (19.8%)	<0.001
R0 resection			
R0	103 (87.7%)	119 (91.5%)	0.389
R1/R2	14 (12.3%)	11 (8.5%)	
Lymphadenectomy			
D1	99 (84.8%)	14 (10.6%)	<0.001
D2	18 (15.2%)	116 (89.4%)	
Number of resected lymph nodes			
Median (min–max)	13.0 (0–47)	33.5 (3–82)	<0.001
Number of metastatic lymph nodes			
Median (min–max)	3.0 (0–41)	3.0 (0–43)	0.948

R0 no residual tumor resection, R1 microscopic residual tumor resection, R2 macroscopic residual tumor resection, D1 limited lymph node dissection group, D2 extended lymph node dissection group

Table 3 Univariate survival analysis comparing the impact of demographic and histopathological factors between 117 patients with gastric cancer from Gdansk (Poland) and 130 patients from Cologne (Germany)

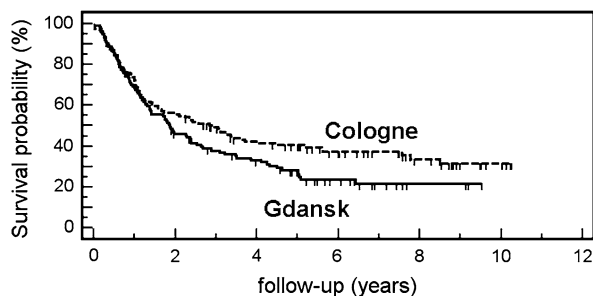
Univariate survival analysis:	Gdansk, Poland (<i>n</i> = 117) (%)	<i>p</i> value	Cologne, Germany (<i>n</i> = 130) (%)	<i>p</i> value	<i>p</i> value between the two centers
5 year survival rate					
Gender					
Male	30.1	0.388	42.3	0.962	0.168
Female	20.4		35.2		0.336
Comorbidities					
ASA I and II	26.5	0.691	47.3	0.102	0.017
ASA III and IV	30.7		36.1		0.781
Tumor localization					
Upper third	32.9	0.012	42.1	0.524	0.325
Middle third	14.6		32.1		0.202
Lower third	40.1		47.1		0.529
Histopathological classification (WHO)					
Adenocarcinoma (except for signet-ring cell cancer)	32.2	0.001	39.9	0.524	0.237
Signet-ring cell cancer	0.0		39.9		0.007
pT category					
pT1	–	<0.001	64.4	<0.001	–
pT2	45.2		46.7		0.928
pT3	18.7		35.8		0.271
pT4	0.0		18.7		0.201
pN category					
pN0	59.5	<0.001	63.1	<0.001	0.592
pN1	20.4		44.4		0.079
pN2	0.0		13.4		0.079
pN3	0.0		13.0		0.916
pM category					
pM0	32.0	<0.001	53.9	<0.001	0.013
pM1	0.0		8.5		0.175
R category					
R0	31.6	<0.001	41.8	<0.001	0.179
R1/R2	0		0		0.107
Type of gastric resection					
Subtotal resection	44.0	0.116	50.4	0.829	0.752
Total gastrectomy	29.9		34.1		0.437
Extended gastrectomy	15.8		24.0		0.314
Transhiatal extended gastrectomy	–		52.2		–
Lymphadenectomy					
D1	25.1	0.031	19.2	0.165	0.804
D2	47.1		42.8		0.521

ASA anesthesia risk according to American Society of Anesthesiologists [7, 8], *pT* tumor infiltration depth into gastric wall, *pN* lymph node status, *pM0* no distant metastases, *pM1* distant metastases, *R* category: *R0* no residual tumor resection, *R1* microscopic residual tumor resection, *R2* macroscopic residual tumor resection, *D1* limited lymph node dissection group, *D2* extended lymph node dissection group

Discussion

The patient populations from the two clinics studied here were clearly quite different. Not only did demographic and tumor characteristics vary, but also the indications for choice of therapy and the radicality of surgical intervention

performed varied. Despite these differences, established independent prognostic factors for gastric carcinoma, such as depth of tumor infiltration, extent of lymph node metastasis, and presence of distant metastasis, as well as *R0* resection, were reconfirmed by our results. The importance of these prognostic factors for the comparison between



Number at risk							
Gdansk	117	52	34	14	3	0	0
Cologne	130	72	47	31	17	4	1

Fig. 1 Comparison of survival curves of gastric cancer patients from Gdansk (Poland) and from Cologne (Germany) [$p = 0.056$; hazard ratio 0.71 (95% confidence interval [CI] 0.54–1.01)]

Table 4 Multivariate survival analysis of independent prognostic factors for patients with surgically treated gastric carcinoma

Feature	Hazard ratio	95% CI	p value
Age			
Each year	1.022	1.005	0.012
pT category			
pT1–pT2	1.45	0.64–3.30	0.379
pT1–pT3	2.83	1.34–5.93	0.006
pT1–pT4	3.19	1.43–7.13	0.005
pN category			
pN0–pN1	2.36	1.37–4.08	0.002
pN0–pN2	3.08	1.73–5.49	<0.001
pN0–pN3	8.82	4.10–18.98	<0.001
Number of resected LNs			
Each LN	0.979	0.97–0.99	0.005
pM category			
pM0–pM1	1.81	1.07–3.06	0.027
R category			
R0–R1/R2	2.42	1.32–4.45	0.004

CI confidence interval, pT tumor infiltration depth into gastric wall, pN lymph node status, $pM0$ no distant metastases, $pM1$ distant metastases, LN lymph node, R category: $R0$ no residual tumor resection, $R1$ microscopic residual tumor resection, $R2$ macroscopic residual tumor resection (according to the 6th edition of the International Union Against Cancer (UICC)-TNM classification of malignant tumors [12])

nations has already been reported in studies comparing Japan and Western industrialized nations [5, 6]. Depth of tumor infiltration and the extent of metastasis, as well as the possibility for an $R0$ resection selected from suitable surgical procedures, are clinical features that patients possess before entering a clinic. This applies also for the age of the patient. In contrast are the frequency of successful $R0$

resections and the extent of lymphadenectomies performed, which are determined at least partially by the operating surgeon.

In terms of patient-related factors, there were more women in Gdansk than in Cologne who were subjected to surgery for gastric carcinoma. It is possible that this represents a selection bias, because the incidence of gastric carcinoma in women in the two countries does not differ. Age and comorbidity also affect prognosis [16]. Although the age distribution at the two clinics did not differ, presentation of the illness later in life does decrease life expectancy. Age also correlates with the severity of comorbidities, a fact that could explain why more severe comorbidity appears to have no prognostic relevance [17]. Furthermore, the parameter chosen here, the ASA classification, is a nonspecific measure to estimate prognosis [18].

The main difference in clinicopathological features was seen in the depth of tumor invasion into the gastric wall. Early gastric cancer was more prevalent in Cologne than in Gdansk. This correlates with data published by the Polish Gastric Cancer Study Group and the “German Gastric Cancer Study, for Gdansk and Cologne, respectively [19–21]. We believe that the observed differences in tumor stage frequency are secondary to varying schools of thought in German society and Polish society, as well as differences in national health policies. There is probably less access to gastroscopy in Poland than in Germany, and perhaps Polish patients do not immediately visit general practitioners with the first symptoms of gastric disease. Although there were differences between the clinics in the tumor stage assessed at time of operation, the tumor stage distribution among our patients was nothing like that observed in Japan, where 56–65% of all gastric cancers are stage I [22]. This suggests that all European Union countries must take more care to achieve earlier diagnosis.

Surgeon-dependent factors include the selection of surgical therapy and the radicality of the tumor resection performed. In Germany, clear guidelines for the therapeutic approach to gastric cancer exist [10]. As a consequence, different indications were used by the two clinics to determine the types of resection and lymphadenectomy performed and the need for splenectomy, as well as the number of resected lymph nodes.

One of the most important prognostic factors was the number of resected lymph nodes. Each additional resected lymph node improved the probability of survival. These results correspond to other reports in the literature [22]. Peyre et al. [23] found similar results for patients with adenocarcinoma of the esophagus or gastric cardia in an international study assessing the impact of the extent of surgical resection.

Controversy regarding the optimal extent of lymph node dissection continues worldwide [24]. An extended lymph

node dissection is thought to provide more appropriate pathological staging and better regional disease control, as well as possible survival advantages compared to limited lymph node dissection [25]. Two recent prospective, randomized European trials (in The Netherlands and the United Kingdom) were designed to evaluate whether extended lymphadenectomy improves overall survival. Neither study identified a difference in survival rates. However, the results of both studies were influenced by increased postoperative morbidity/mortality rates associated with increased rates of splenectomy and pancreatectomy in patients undergoing D2-dissection [26–29]. In a review study, McCulloch et al. concluded that the question of extended versus limited lymph node dissection has not yet been decided [30].

The fact that 57% of Gdansk patients had splenectomy performed during gastrectomy came out as an unanticipated observation. It was related to the conviction that removal of the lymph nodes located in the splenic hilum may be a prognostic marker. Several studies have concluded that the disadvantages of splenectomy outweigh the prognostic benefits for patients with gastric cancer [22, 31, 32]. The results of our analysis convinced the Gdansk surgical team to change the strategy of management and to improve the surgical quality [33]. Currently, the rate of splenectomies in Gdansk does not exceed 20%.

Conclusions

Despite differences in the frequencies of various prognostic factors between Polish and German gastric carcinoma patients, established prognostic factors such as the depth of tumor infiltration, the existence of lymph node or distant metastasis, and complete removal of the tumor were verified by our results. Of interest is the simultaneous emergence, at the two study centers, of the number of removed lymph nodes as an independent prognostic factor.

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