Current concepts in gastric cancer surgery

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ABSTRACT

Objectives: Current problems in gastric cancer surgery concern the extent of gastric resection, the need for abdominal evisceration, the degree of lymphadenectomy, and an optimal preoperative tumor staging procedure.

Methods: A retrospective clinical trial of 284 patients who underwent surgery at Ernst-Moritz-Arndt-University, Greifswald, Germany for gastric cancer between 1987 and 1996. Main outcome measures consist of epidemiological parameters, data on type of surgery, histopathology, postoperative complications, mortality and cancer survival. Statistical analysis between groups was performed using Chi square test (perioperative risk factors, tumor localization, and surgical treatment) and Mann Whitney U tests (Laurén classification). Survival was calculated according to the Kaplan Meier method.

Results: The results are in favor of subtotal gastrectomy performed for all T stages located in the distal or middle 3rd provided that a tumor-free margin of 5 cm in intestinal type and 10 cm in diffuse Lauren's type tumor can be achieved, since this operation carries the lowest postoperative risks and provides the best postoperative quality of life. Resection of adjacent organs are indicated only if they are invaded by the primary tumor (T4). They should not be resected as part of an extended lymphadenectomy procedure. The primary tumor site should guide the degree of lymph node removal. Multimodal therapeutic approaches and high postoperative morbidity and mortality after exploratory laparotomy justify the use of diagnostic laparoscopy in T3 and T4 stage tumors and if diagnostic scans suggest tumor spread.

Conclusion: Even though surgery for gastric cancer is well standardized, a tailored surgical approach to different extents of gastric cancer appears justified.

Keywords: Gastric cancer, gastrectomy, lymphadenectomy, staging procedure.

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The present review of gastric cancer surgery addresses the following aspects. Firstly, in spite of a decrease in gastric cancer incidence, proximal 3rd carcinomas have been steadily climbing along with associated problems. Secondly, controversial opinions with regards to the extent of gastric resection emerge from the desire to accomplish complete tumor control on the one hand, and to achieve low morbidity and mortality rates as well as to provide the best quality of life. Thirdly, studies from Japan have demonstrated improved survival and no increase of morbidity and mortality in patients who underwent extended lymphadenectomy. In Western countries, which are battling with higher postoperative complications, this procedure is fiercely debated. Fourthly, high morbidity and mortality rates after exploratory laparotomy requires alternative diagnostic measures.

Results. The analysis of epidemiological figures demonstrates a shift of the sex ratio towards female patients and a shift of the age of the patient population towards higher age groups (**Table 1**). The increase in patient age was accompanied by a significant rise in co-morbidity. From 1987 to 1991, only 1.6% of the patients had to be assigned to American Society of Anesthesiologists (ASA) grade IV.[1] In contrast, from 1992 to 1996 this ASA-subgroup rose to 11.2%. Localized lesions involving

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Table 1 - Gastric cancer surgery, patient population.

Period	N of patients	Male N (%)	Female N (%)	M/ F - Ratio	Age ± SD (years) M	F
1987 - 1991	137	113 (83)	24 (17)	4.7:1.0	57.7±10.09	60.7±9.56
1992 - 1996	147	107 (73)	40 (27)	2.7:1.0	61.8±11.17	67.3±9.32
Total	**284**	**220 (78)**	**64 (22)**	**3.5:1.0**	**59.8±10.63**	**64.0±9.44**
N - number; F - Female; M- Male; SD - standard deviation						

either the upper, middle, or lower 3rd of the stomach were found in 53.7% of the patients.[2] In 32.7%, the tumor involved more than one 3rd and in 6.3%, the entire stomach was cancerous. Gastric stump carcinoma was observed in 7.3% of the patients (**Table 2**). There has been a significant increase in the proportion of proximal lesions with a corresponding decrease in the proportion of tumors of the middle and lower 3rd. A hallmark of the study group is the high proportion of patients with advanced disease. At the time of surgery, 75% of the tumors had invaded the serosal layer and one 3rd had already infiltrated adjacent organs. In 75% of the lymphadenectomized patients, metastasis to regional lymph nodes was detected. Distant metastases were observed in 25% of the cases. An analysis of correlation shows a close relationship between depth of tumor invasion and extent of lymph node involvement as well as distant metastasis. A pN1 (metastasis in one to 6 regional lymph nodes)[3] grade of nodal involvement without occurrence of distant metastases was found exclusively in pT1 (tumor invades lamina propria or submucosa of the stomach) and pT2 (tumor invades muscularis propria or subserosa of the stomach) tumors, whereas pT3 (tumor penetrates serosa of the stomach and pT4 (tumor invades adjacent structures of the stomach) tumors were combined with a pN3 (metastasis in more than 15 regional lumph nodes) grade in 37% and with remote metastases in 20% and 48%. Evaluation of growth pattern according to Lauren's classification[4] demonstrates a diffuse type in 122 cases (43%), an intestinal type in 133 cases (46.8%), and a mixed type in 29 cases (10.2%). With regards to the Union Internationale Centre Le Cancer (UICC) staging system, 70% of the study population needed to be assigned to stage III and IV (**Table 3**).

Of the 284 patients evaluated, 218 patients (76.8%) had resective surgery. A comparison of the 2 5-year-periods in terms of resective surgery indicates a significant increase in the proportion of gastric resection from 68.6% to 84.3% ($p < 0.005$) 33.5% of these patients underwent subtotal gastrectomy (SG), 50% of these patients underwent total gastrectomy (TG), and 16.5% of these patients underwent extended gastrectomy (EG). The proportion of total and extended gastrectomies combined increased significantly from 1992 to 1996, while the proportion of subtotally gastrectomized patients decreased significantly during the same period of time (**Table 4**). Palliative gastroenterostomy (GE) was performed in 24 patients (8.4%) and 42 patients (14.8%) underwent exploratory laparotomy (EL). Principally, subtotal

Table 2 - Gastric cancer surgery, lesion location. The significance level ($p<0.05$) indicates the proximal shift of the gastric cancer lesions.

Location	1987 - 1991 N (%)	1992 - 1996 N (%)	p
Proximal 3rd	25 (18.3)	55 (37.4)	<0.001
Middle 3rd	48 (35)	37 (25.1)	ns
Lower 3rd	42 (30.7)	38 (25.9)	ns
Entire stomach	8 (5.8)	10 (6.8)	ns
Gastric stump	14 (10.2)	7 (4.8)	ns
Total	**137 (100)**	**147 (100)**	
N - number; ns - not significant			

Table 3 - Gastric cancer surgery, UICC stages.

UICC - stage	N (%)
IA	26 (9.2)
IB	22 (7.7)
II	37 (13)
IIIA	49 (17.3)
IIIB	17 (6)
IV	133 (46.8)
N - number; UICC - Union Internationale Centre Le Cancer	

Table 4 - Time trends in cancer treatment. The significance level ($p<0.05$) indicates an increase of total and extended gastrectomies within the 1992 - 1996 period.

Procedure	1987 - 1991 N (%)	1992 - 1996 N (%)	Total N (%)	p
Subtotal Gastrectomy	45 (32.8)	28 (19)	73 (25.7)	<0.010
Total Gastrectomy	43 (31.4)	66 (44.9)	109 (38.4)	<0.025
Extended Gastrectomy	6 (4.4)	30 (20.4)	36 (12.7)	<0.001
Gastrectomy	17 (12.4)	7 (4.8)	24 (8.4)	<0.025
Exploratory Laparotomy	26 (19)	16 (10.9)	42 (14.8)	ns
Total	**137 (100)**	**147 (100)**	**284 (100)**	

N - number; ns - not significant

Table 5 - pT stage, Lauren's classification, and median age of patients who underwent resective surgery (*$p<0.05$). The significance level ($p<0.05$) indicates performed subtotal gastrectomy regardless of the Lauren type in a high age patient group with T3 and T4 tumors and extent comorbidity.

Subtotal gastrectomy						Total and extended gastrectomy				
pT stage	N	Median age (year)	Lauren's classification diffuse	intestinal	mix.	N	Median age (year)	Lauren's classification diffuse	intestinal	mix.
pT1	15	67	2	13	0	15	66	7	5	3
pT2	16	70	0	13	0	27	69	19	6	2
pT3	36	80*	8	27	3	73	61*	36	27	10
pT4	6	75*	2	3	1	30	63*	21	5	4

pT1 -tumor invades lamina propria or submucosa of the stomach; pT2 - tumor invades muscularis propria or subserosa of the stomach; pT3 - tumor penetrates serosa of the stomach; pT4 - tumor invades adjacent structures of the stomach; N - number; mix. - mixture

Table 6 - Type of surgery and grade of residual disease according to UICC stage.

UICC	N	SG R0	R1	R2	TG R0	R1	R2	EG R0	R1	R2	GE R0	R1	R2	EL R0	R1	R2
IA	26	13			13											
IB	22	15			7											
II	37	3			23	11										
IIIA	49	21	5		15	7				1						
IIIB	17		2		8	1		6								
IV	133	6		8	12		12	22	3	4	24			42		
Total	**284**	**58**	**7**	**8**	**78**	**12**	**19**	**28**	**3**	**5**	**24**			**42**		
%		79	10	11	72	11	17	78	8	14	100			100		

UICC - Union Internationale Centre Le Cancer; R0 - No residual tumor; R1 - Microscopic residual tumor; R2 - Macroscopic residual tumor; SG- subtotal gastrectomy, TG - total gastrectomy; EG - extended gastrectomy; GE - palliative gastroenterostomy, EL - explorative laparotomy, N - number

Table 7 - Age-adjusted 5-year survival according to stage (*p<0.05). The significance level (p<0.05 indicates the decrease in the average 5-year survival from 87.5% for stage IA to 9.6% for stage IV.

UICC	N (%)	5-year survival rate (%)
IA	26 (9.2)	(87.5)
IB	22 (7.7)	(69.2)
II	37 (13)	(52.9)
IIIA	49 (17.3)	(32.1)
IIIB	17 (6)	(22.4)
IV	133 (46.8)	(9.6)

UICC - Union Internationale Centre Le Cancer; N - number

Table 8 - Five year survival rate of curatively resected patients (R0) shows no significant differences in comparison of subtotal and total/extended gastrectomy.

UICC stage	Subtotal gastrectomy N	Subtotal gastrectomy 5-yr survival rate	Total and extended gastrectomy N	Total and extended gastrectomy 5-yr survival rate
IA	13	(92.3)	13	(84.6)
IB	15	(66.7)	7	(71.4)
II	3	(66.7)	23	(69.6)
IIIA	21	(47.6)	15	(40)
IIIB	0	-	14	(28.6)
IV	6	(16.7)		(20.6)

UICC - Union Internationale Centre Le Cancer; N - number; yr - year

gastrectomy was performed in T1 and T2 tumors designated as intestinal according to Lauren's classification and located in the distal 3rd of the stomach. All other tumors were treated by total or extended gastrectomy. However, in a significantly older patient group with high comorbidity, T3 and T4 tumors of the distal and middle 3rd were subtotally resected regardless of the Lauren type (**Table 5**). The obtained results demonstrate that subtotal gastrectomy of middle and distal 3rd gastric cancer regardless of the T stage of the tumor serve a curative purpose (R0), provided that a tumor-free margin of 5 cm in intestinal type and of 10 cm in diffuse type could be achieved. In 75.2% of the cases treated by resection, a complete tumor clearance (R0) was obtained. The number of R1 (microscopic residual tumor) resections amounted to 10.1%. Macroscopic residual tumor (R2) resections made up 14.7%. The proportion of R0 (no residual tumor) resections did not depend on the extent of gastric removal. Gastric carcinoma UICC stage IA and IB were exceptionally amenable to curative resection. Microscopic residual tumor resections (R1) of UICC stage II – IV tumors due to involved proximal margins were reported in 45.5% and distal involvement was found in 27.3%. The 3rd space was infiltrated in 27.2%. Gross involvement (R2) was tolerated in gastric resections carried out for tumor complications, which could not be managed by bypass surgery (**Table 6**). The extent of lymphadenectomy depended on the location of the primary tumor. As a standard procedure, resection of primary tumor was combined with removal of perigastric lymph nodes (group one to 6 according to the Japanese Research Soceity for Gastric Cancer (JRSGC)).[5] In carcinomas of the upper 3rd of the stomach, a D2-dissection of lymph node groups 7 through 11 was added. Tumors in the middle 3rd were treated by D2 dissection omitting lymph node group 10. In distal 3rd carcinoma, lymph node groups 10 and 11 were spared, but lymph nodes in the hepatoduodenal ligament were included in the dissection procedure. Depending upon the type of gastric resection performed the ratio of involved lymph nodes varied from 27% and 32%. Following subtotal gastrectomy, intestinal continuity was re-established by Roux-en-Y gastrojejunostomy and following total gastrectomy by Roux-en-Y esophagojejunostomy without pouch procedure. In 128 cases, the latter was carried out by stapling device. Wound infection (9.2%), anastomotic dehiscence (4.6%), and intraabdominal abscess (4.6%) were the main complications observed after resective surgery. During the study period, the rate of leakage from esophagojejunostomy dropped from 8.2% to 2.1%. Leakage from gastrojejunostomy was evident only in 2 cases throughout the 10-year period. The proportion of septic complications decreased significantly (p<0.005) from 8.5% to 1.6% (intraabdominal abscess) and from 16% to 4% (wound infection) in the last 5 years. Twelve left-sided pancreatectomies were associated with 2 pancreatic fistulas. Non-surgical complications for example pneumonia, urologic tract infection and so on ranged from 4.3% to 20.2%. Palliative gastroenterostomies showed a complication rate of 19%. Explorative laparotomies caused complications at a rate of 24%. Thirty and 90-day-mortality were identical and amounted to 4.1% (SG), 4.6% (TG), and 5.6% (EG). In palliative bypass procedures and exploratory laparotomies death occurred in 12% and 19%. The median 5-year-survival was 34.2%, decreasing significantly from 87.5% for stage IA to 9.6% for stage IV (**Table 7**). Long term results after curative subtotal and curative total gastrectomy are shown in **Table 8**. A comparison of both methods does not demonstrate a significant difference in 5-year-survival rates.

Discussion. ***Shift in lesion location and associated increase in extended gastrectomy.*** Although there has been a continuous decrease in gastric cancer incidence in Western countries, proximal 3rd gastric cancer has been steadily climbing.[6,7] In the first 5-year period of the study, 18.3% of the patients suffered from lesions located in the upper 3rd of the stomach. This proportion had increased to 37.4% in the 2nd 5-year period. The problem of proximal 3rd tumor is due to anatomical, diagnostic, and therapeutic features distinctive of the upper portion of the stomach. About 30% of the proximal 3rd of the stomach are not covered by visceral peritoneum. This allows tumors located in this region to easily invade the pancreas and the spleen as well as lymphatic spread towards the left renal vein, the left adrenal gland, and the left renal hilum. Diagnostic difficulties result from the demanding endoscopic visualization of the cardia-fundus-region. Curative resections (R0) of these tumors require an extended gastrectomy in most cases, which might include the distal esophagus, the left-sided pancreas, the spleen, the liver and the above mentioned lymph node stations.[8] Because of this proximal shift of gastric cancer, the proportion of extended gastrectomy procedures ranges from 10% to 28.5% in the more recent literature.[9-12] In the German Gastric Cancer Study (GGCS 1992),[13] this proportion was 23.5%. In our study, the ratio of extended gastrectomy rose from 4.4% between 1987 and 1991 to 20.4% between 1992 and 1996. In about one 3rd of the cases, this procedure was combined with distal esophagectomy or left-sided pancreatectomy. Postoperative complications characteristic of these operations are leakage from esophagojejunostomy, pancreatic fistula, and abscess in the left subphrenic space. We had to deal with anastomotic insufficiency in one out of 13 transmediastinally-performed esophagojejunostomies (7.7%) and with pancreatic fistulas in 2 out of 12 left-sided pancreatectomies (16.7%). All pancreatic fistulas were followed by subphrenic abscesses, which in turn were handled by ultrasound (US) and computed tomography (CT) guided drainage procedures. Pancreatic fistulas are commonly observed after left-sided pancreatectomy and lymph node dissection of station numbers 10 and 11. These fistulas, lymphatic fistulas, and splenectomies trigger the onset of subphrenic abscesses. The GGCS 1992 reported an increase of abscesses from 4.9% in patients without pancreatectomy to 18% in left-sided pancreatectomized patients. A similar development of this complication from 2.7% to 7.1% was reported after splenectomy. Since left-sided pancreatectomy and splenectomy are performed not only for direct organ invasion but also in order to achieve complete lymph node removal, organ preserving lymph node dissection is still a hot topic in upper gastric cancer surgery.[14] A further problem in extended gastrectomy concerns the mortality rate, which ranges from 5.7% to 12% in the national literature.[13,15,16] In our study, 2 patients died after an extended gastrectomy equaling a mortality rate of 5.6%.

Subtotal or total gastrectomy. Controversial opinions with regard to the extent of gastric resection emerge from the desire to accomplish complete tumor control on the one hand and to achieve low morbidity and mortality as well as to provide the best quality of life. As a rule, subtotal gastrectomy was performed in T1- and T2-stage tumors designated as intestinal according to Lauren's classification and located in the distal 3rd of the stomach. The study demonstrates that an increasing portion of the patient population has been afflicted with concomitant diseases and consecutively bears higher postoperative risks. Those patients, 75 to 85-year-old women and men, most of them assigned to ASA grade III or IV were subtotally resected regardless of T stage and Lauren's classification. An analysis of the subtotally resected group showed that in case of an oral safety margin of 10 cm in diffuse type and of 5 cm in intestinal type even in T3 and T4 stage tumor a curative result was attainable. Furthermore, a comparison of subtotally with totally gastrectomized patients showed no statistically significant differences in 5-year-survival. Aiming at postoperative complications, mortality, and quality of life, total gastrectomy appears to be the operation that carried more risks. As far as anastomotic leakages are concerned, 5 insufficiencies (4.6%) occurred at the esophagojejunostomy, only 2 insufficiencies (2.7%) were observed at the gastrojejunostomy. The GGCS 1992 reported dehiscence in 7.2% and in 2.9% at the above mentioned anastomotic sites. Septic complications such as intraabdominal abscesses and severe wound infections occured in 2.7% and 9.6%, after subtotal gastrectomy and in 3.7% and 9.2%, after total gastrectomy. During the last 5 years of the study, septic complications have steadily decreased. Intraabdominal abscesses have dropped from 8.5% to 1.6% (GGCS 1992: 4%) and severe wound infections have declined from 16% to 4% (GGCS 1992: 4%). In this context, a substantial contribution came from the implementation of perioperative antibiotic prophylaxis utilizing 2nd generation cephalosporine and from the local application of gentamicin-containing collagen-implants (SulmycinR). In terms of postoperative quality of life, assessed by means of Gastrointestinal Quality of Life Index (GQLI),[17] the subtotally resected group showed significantly better long-term outcome.[18] The mortality rate after total gastrectomy (4.6%) was only slightly higher than the one after subtotal gastrectomy (4.1%). The corresponding figures in the GGCS 1992 were 4.4% and 6%. The GGCS 1992 emphasizes the large proportion of total gastrectomies in the German multicenter trial compared with other European trials and points out

that the decision for this type of operation should be well defined. We support these results, since total gastrectomy carries more risks without improving 5-year-survival.

D1 or D1 + D2 lymph node dissection. There is considerable debate about the value of D2-lymph node dissection in gastric cancer treatment. In Japan, this type of lymph node dissection is part of the standard operation for this tumor entity.[19] In Europe and in the United States of America (USA), D2-dissection rates of 27% and 4.7%, demonstrate skepticism towards extended lymph node removal.[12,20] According to retrospective studies conducted in Japan,[19] there was an improvement in 5-year-survival after D2-dissection in patients with tumor stage I to III provided that the removed lymph nodes were involved by cancer. Since the very low postoperative mortality in these studies (0.4%-1.7%) favorably affects overall outcome, only centers that report comparable postoperative results can expect similar 5-year-survival rates. In contrast, are the results obtained in the GGCS 1992. So benefited only patients without detectable metastases in the dissected D2 lymph node compartment from the extended procedure, namely patients with tumor stage II and IIIA.[21] In all other stages, a decrease in 5-year-survival rate was observed. With regards to the overall patient population, only one out of 20 patients had a prognostic benefit from the D2 lymph node dissection. All prospective randomized trials that were carried out to determine the value of D2 lymph node dissection reported higher postoperative complications and mortality rates and did not show any significant improvement in 5-year-survival.[22-25] A further analysis of the Medical Research Council of the United Kingdom (MRC) and Dutch trial results indicates that the higher morbidity in the D2 arm is due not to the extended lymphadenectomy but largely to left-sided pancreatic resection and splenectomy.[23,25] In this context, it has been stressed that additional organ resection should not be part of extended lymhadenectomy and is indicated only in cases of tumor invasion.[14] We performed the resection of the primary tumor en bloc with the perigastric lymph node stations (group one to 6 according to JRSGC.[5] D2 lymph node removal depends on the primary tumor site and, hence, includes lymph node stations most likely involved with tumor metastasis. As a result of this more selective lymphadenectomy procedure, we obtained a ratio of metastasized to involved lymph nodes, which amounted to 27% to 32%, thus, exceeding the 20% described as threshold for a favorable prognostic outcome.[26] Our survival rates did not differ from those reported in the GGCS 1992.

Preoperative tumor staging and significance of exploratory laparotomy. The proportion of exploratory laparotomy in gastric cancer ranges between 8% and 20%. That is of particular concern due to the high mortality rate quoted between 13% and 36% in the literature.[12,13,27,28] A high rate of exploratory laparotomy is indicative of an inadequate preoperative assessment of the M stage of the tumor in particular. In the last 10 years, the development of endoscopically and laparoscopically placeable ultrasound probes has enabled gathering of information not attainable by CT and MRI. Therefore, combined diagnostic effort seems advisable in order to obviate a procedure rich in complications on the one hand and exploit the advantages of multimodal therapeutic approaches on the other hand. In the present study, the combined application of endosonography and CT scan reduced the rate of exploratory laparotomy from 19% to 10.9%. This figure can be further cut if exploratory laparoscopy in combination with the aforementioned probes, abdominal tumor cell washout included, is being strictly applied especially in advanced T stages. In our opinion, detection of tumor cells in the peritoneal washout without apparent peritoneal or other remote metastasis is no contradiction to gastric resection but might trigger intraoperative or postoperative chemotherapy.

In conclusion, aiming at curative gastric cancer surgery, primary tumor and lymph node metastasis should be handled in the following manner. Carcinoma of the upper 3rd is to be treated by total gastrectomy. A more restricted, namely subtotal gastrectomy can be performed in tumors of the middle and distal 3rd regardless of T stage provided a tumor free safety margin of 5 cm in intestinal type and of 10 cm in diffuse Lauren's type can be accomplished. Gastrectomy extended to the spleen and left-sided pancreas is indicated only in cases of direct organ involvement. Organ resection should not be part of extended lymphadenectomy. The extent of D2 lymph node dissection should be guided by the primary tumor site but D1 lymph node removal is to be carried out en bloc with gastrectomy. High postoperative mortality after exploratory laparotomy requires exploratory laparoscopy in advanced T stages (T3 and T4) in order to detect remote metastasis and therefore avoid unnecessary surgery. It has to be pointed out that if metastases were ruled out laparoscopically, local resectability of the lesion has to be verified by laparotomy.

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