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Impact of Neoadjuvant Chemotherapy on Postoperative Morbidity after Gastrectomy for Gastric Cancer

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Key Words
Gastric cancer · Neoadjuvant chemotherapy · Postoperative morbidity

Abstract
Background/Aims: Patients with locally advanced gastric cancer benefit from neoadjuvant chemotherapy. Potential disadvantages of neoadjuvant chemotherapy include increased surgical complications, leading to increased postoperative morbidity. ***Methods:*** We retrospectively studied medical records of 135 patients with resectable cancer of the stomach who underwent gastrectomy between 2002 and 2009. The impact of neoadjuvant chemotherapy on postoperative morbidity was investigated. We compared demographic, clinical and operative data, morbidity and mortality from 105 patients who received surgical treatment immediately after diagnosis (SURG group), versus 30 patients who first received neoadjuvant chemotherapy (CHEMO group). ***Results:*** Demographic, clinical and surgical procedure parameters did not differ significantly between both groups. Postoperative morbidity was 46.7% in CHEMO- and 41.9% in SURG-patients (p = 0.680). There were eight cases of death, 2/30 (6.7%) in CHEMO and 6/105 (5.7%) in the SURG group (p = 1). The overall complications according to Clavien-classification did not differ significantly (p = 0.455). The wound infection rate (23.3 vs. 3.8%; p = 0.002) and insufficiency of the duodenal stump (13.3 vs. 1.9%; p = 0.022) were significantly higher in the CHEMO group. ***Conclusion:*** This study showed no significant impact of neoadjuvant chemotherapy on postoperative morbidity after gastrectomy using the Clavien-classification. Only an increase in wound infections in CHEMO compared with the SURG group were noted. Therefore, neoadjuvant chemotherapy can be considered safe and feasible.

Introduction

Despite its declining incidence, gastric cancer is still ranked third among the world's leading cause of cancer deaths, affecting approximately 800,000 people annually [1]. Due to a standardized operative approach, surgical morbidity and mortality rates are constantly declining, but the overall prognosis of stomach cancer still remains poor. In the Western world, the five-year overall survival rate for all tumor stages is only between 20 and 25%, with a median survival time of 24 months. Nowadays, cancer of the stomach is treated with stage-adapted therapy [2]. In Europe multimodal treatment, including neoadjuvant chemotherapy and surgical resection with negative

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margins (R0-resection), is considered to be the standard treatment of gastric cancer [3, 4]. Several trials demonstrated a statistically significant increase in disease-free and overall survival in patients treated with perioperative chemotherapy [5, 6]. One question that still remains unanswered is whether the neoadjuvant use of chemotherapy has a negative influence on the postoperative course of the patients and therefore could increase the postoperative morbidity after gastrectomy [7–14]. In previous trials regarding the use of neoadjuvant chemotherapy in gastric cancer, the efficacy and feasibility of chemotherapy is described in particular. Most of the research conducted earlier focused on the adverse effects of chemotherapy before gastrectomy, and the effect in correlation with the following resection is often only generally [5, 6, 15]. Other studies providing this information have not included a comparative group of patients who solely underwent surgery [16–21].

The aim of this retrospective study was to investigate, in a retrospective parallel group, the influence of neoadjuvant chemotherapy on the postoperative morbidity after gastrectomy in patients with gastric cancer.

Patients and Methods

Patients' medical records and histological data during the period from June 2002 to December 2009 were retrospectively studied. The 135 patients included in this study had histologically proven gastric cancer and they received gastrectomy with curative intent, including D2 lymph node dissection at the Department of General and Visceral Surgery, Goethe University, Frankfurt. One hundred and five patients underwent surgical treatment immediately after diagnosis (SURG group) and 30 patients were treated with neoadjuvant chemotherapy first (CHEMO group). This treatment was decided by a multidisciplinary tumour conference. Information regarding postoperative morbidity and mortality were available for each patient studied. Postoperative complications were considered in addition to lethal outcomes that occurred during hospital stay. In addition to morbidity, all postoperative complications were graded according to the Clavien-classification [22].

Patients received total, remnant or distal gastrectomy, depending on the anatomic location of the tumour, to achieve R0-resection. Multivisceral resection was performed when necessary. All received a preoperative single-shot antibiotic prophylaxis. Reconstruction of the gastrointestinal passage was performed according to the local standard using a long Roux-en-Y loop. Esophagojejunostomy was performed with a 25 mm circular stapler, and gastrojejunostomy was hand sewn. A D2 lymphadenectomy was performed in all patients according to the guidelines of the Japanese Gastric Cancer Association. Pathological data was analysed by the Senckenberg Institute for Pathology of Goethe University, Frankfurt, according to the 6th TNM-classification from 2002 [23].

Demographic, clinical, operative and pathological characteristics as well as postoperative complications of the two groups were analysed. Statistical analysis was performed with SPSS 21.0 statistical software. The comparisons among the groups were performed with Fisher's test, t-test and Mann-Whitney U test. p values ≤0.05 were considered to be significant.

Results

Preoperative Staging and Neoadjuvant Chemotherapy Regimens

For staging, patients routinely underwent gastroscopy, endoscopic ultrasound (EUS), and chest and abdominal CT scan. Diagnostic staging laparoscopy was performed in 6 patients to exclude peritoneal carcinosis. All had negative results.

Patients within the CHEMO group received their neoadjuvant chemotherapy with different regimens, mainly ECF (Epirubicin, Cisplatin, Fluorouracil), ECX (Epirubicin, Cisplatin, Capecitabine), EOX (Epirubicin, Oxaliplatin, Capecitabine) and PLF (Cisplatin, Leucovorin®, Fluorouracil) courses, in standard doses [5, 24, 25]. Two (6.7%) could not be assigned to one of the four abovementioned courses and received their chemotherapy according to the FOLFOX and FOLFIRI regimens. None of them received radiation therapy. 68.7% received all planned courses. In four cases chemotherapy had to be discontinued, all involving the ECX course. Reasons were renal toxicity (Cisplatin), anaemia (5-FU), neutropenia (5-FU) and in one case unknown.

Patient Demographic and Pathological Characteristics

The average age for the entire group was 64.8. CHEMO patients tended to be slightly younger (61.7 vs. 65.6 years). The entire group included 83 men, with slightly more men within the CHEMO group (70.0 vs. 59.0%). The BMI value for the whole group was 24.9 kg/m^2 (15.6–35.6). The median ASA status (American Society of Anesthesiologists) was three in both groups (1–4). Within the two groups, 20.0% (CHEMO) versus 14.3% (SURG) of patients had diabetes mellitus. CHEMO and SURG groups did not differ significantly for one of the abovementioned parameters. Patient demographics are summarized in table 1.

Pathological characteristics are outlined in table 2. SURG patients were more likely to have proximal tumours, with 35.2% being located at the cardia compared to 30.0% in the CHEMO group (p = 0.667). Conversely, CHEMO patients were more likely to have lesions in the middle and distal part of the stomach (p = 0.361

Table 1. Patient demographics and clinical data

	CHEMO (%) (n = 30)	SURG (%) (n = 105)	p value
Age, years			0.123
Mean ± SD	61.7±9.7	65.6±12.8	
Range	37–75	22–92	
Gender			0.298
Male	21 (70.0)	62 (59.0)	
Female	9 (30.0)	43 (41.0)	
BMI, kg/m^2			0.689
Mean ± SD	24.6±3.8	24.9±4.0	
Range	15.6–35.6	17.5–33.0	
ASA status, median	3	3	0.917
1	2 (6.7)	8 (7.6)	1
2	9 (30.0)	30 (28.6)	
3	17 (56.7)	58 (55.2)	
4	1 (3.3)	3 (2.9)	
X	1 (3.3)	6 (5.7)	
Comorbidities			
Diabetes mellitus	6 (20.0)	15 (14.3)	0.568
Chronic infectious disease	1 (3.3)	6 (5.7)	1

X = Missing data; chronic infections = chronic viral hepatitis and HIV infections.

Table 2. Pathological findings

	CHEMO (%) (n = 30)	SURG (%) (n = 105)	p value
Type of tumour			
Adenocarcinoma	30 (100)	103 (98.2)	1
Other	0 (0)	2 (1.8)	1
Tumour location			
Proximal part	9 (30.0)	37 (35.2)	0.667
Middle part	11 (36.7)	28 (26.7)	0.361
Distal part	9 (30.0)	25 (23.8)	0.484
Entire stomach	1 (3.3)	5 (4.8)	1
Remnant cancer	0 (0)	10 (9.5)	0.118
UICC			
Stage 0	0 (0)	2 (1.9)	1
Stage IA	4 (13.3)	19 (18.1)	0.783
Stage IB	4 (13.3)	19 (18.1)	0.783
Stage II	8 (26.7)	18 (17.1)	0.294
Stage IIIA	4 (13.3)	15 (14.3)	1
Stage IIIB	5 (16.7)	16 (15.2)	0.783
Stage IV	5 (16.7)	16 (15.2)	0.783

UICC = Union for International Cancer Control.

and p = 0.484). Gastric remnant cancer occurred only within the SURG group (9.5%; p = 0.118). Two patients in the SURG group did not suffer from an adenocarcinoma of the stomach, but had a squamous cell and undifferentiated carcinoma. According to the postoperative UICC (Union for International Cancer Control) classification (6th TNM classification from 2002), the two groups did not differ significantly.

Operative Parameters

The mean total operating time was 236.0 min in CHEMO and 243.9 min in the SURG group (p = 0.589). The median blood loss was 400 ml in both groups. Perioperative transfusion was accomplished in 30.0% of CHEMO and 29.5% of SURG patients. CHEMO patients (90.0%) had more total gastrectomies than the SURG group (79.0%) (p = 0.285), and only in the SURG group was a resection of the gastric remnant was performed (p = 0.118). In total, 56 (41.5%) patients underwent transhiatal extended gastrectomy, 43.3 in the CHEMO and 40.9 in the SURG group. Complete resection (R0) was achieved in 90.0% of CHEMO and in 90.5% of SURG patients (p = 0.711). The median number of dissected lymph nodes did not differ significantly in both groups, 30 with chemotherapy (14–71) vs. 23 (8–56) with surgery alone, as well as positive lymph node ratio with 4.5% (0–70) and 11.0% (0–100) (p = 0.686). Multivisceral resection including splenectomy due to oncological or technical reasons, partial pancreatectomy, partial colectomy and partial liver resection was performed in 10.0% of CHEMO patients, compared to 10.5% of SURG patients (p = 1). Operative parameters are shown in table 3. Surgery was performed within the median of 37.5 days (10–79) after the last day of chemotherapy.

Postoperative Complications

Postoperative complications occurred in 58 (43.0%) of the 135 patients. Both groups did not differ significantly (46.7% in CHEMO and 41.9% in the SURG group; p = 0.680; table 4). The median postoperative hospital stay was 13.5 days in CHEMO and 15.0 days in the SURG group. For patients without complications and for those suffering from complications, the median of postoperative stay did not differ significantly in either group (p = 0.284 and p = 0.052).

A nosocomial infection was the most commonly observed postoperative complication, with an average rate of 29.6% (43.3% in CHEMO and 25.7% in the SURG group; p = 0.073). In declining order, urinary tract infections, pneumonia, wound infections and intra-abdominal infections occurred. Significantly more wound infections could be noted in the CHEMO group (23.3 vs. 3.8%; p = 0.002). A leakage of the esophagogojejunostomy was the second most commonly observed complication (11.1%), 3.3% in CHEMO and 13.3% in the SURG group

Table 3. Patient operative parameters

	CHEMO (%) (n = 30)	SURG (%) (n = 105)	p value
Total operative time, min			0.589
Mean ± SD	243.9±74.0	236.0±69.5	
Range	135–461	80–435	
Operative blood loss, ml			1
Median	400	400	
Range	100–2,000	100–2,800	
Patients with transfusion	9 (30.0)	31 (29.5)	1
Type of resection			0.198
Total	27 (90.0)	83 (79.0)	0.285
Partial distal	3 (10.0)	12 (11.4)	1
Gastric remnant resection	0 (0)	10 (9.5)	0.118
Extent of resection			
R0	27 (90.0)	95 (90.5)	0.711
R1/2	3 (10.0)	8 (7.6)	0.711
Missing	0 (0)	2 (1.9)	
Number of resected lymph nodes			0.638
Median	30	23	
Range	14–71	8–56	
Lymph node ratio, positive LN/total LN, % (range)	4.5 (0–70)	11.0 (0–100)	0.686
Patient with multivisceral resection	3 (10.0)	11 (10.5)	1
Spleen	2 (6.7)	9 (8.6)	1
Oncological	2 (6.7)	8 (8.6)	1
Technical	0 (0)	1 (1.0)	1
Pancreas	2 (6.7)	8 (7.6)	1
Colon	2 (6.7)	2 (1.9)	0.214
Liver	1 (3.3)	1 (1.0)	0.396
Reconstruction			
Y-Roux	29 (96.7)	100 (95.2)	1
Other	1 (3.3)	5 (4.8)	
Stapler	27 (90.0)	93 (88.6)	1
Hand sewn	3 (10.0)	12 (11.4)	

LN = Lymph node.

(p = 0.189). A leakage of the duodenal stump occurred less frequently, in 13.3% (CHEMO), and 1.9% (SURG). Only the rate of insufficiency of the duodenal stump differed significantly (p = 0.022). The one anastomotic leakage in CHEMO was treated conservatively. In the SURG group, the anastomotic dehiscence was treated in 6/14 (42.8%) cases by reoperation, in 4/14 (28.6%) cases conservatively, in 2/14 (14.3%) cases by interventional radiology, and in 2/14 (14.3%) cases by endoscopy. During the six reexplorations in 4/6 (66.7%) cases, the esophagojejunostomy was sutured, and in 2/6 (33.3%) cases, a new anostomosis was constructed. The four leakages of the duodenal stump in the CHEMO group were treated in 3/4 (75.0%) cases by reexploration with suture and could be managed in 1/4 (25.0%) cases conservatively. In the SURG group, the two patients were treated by reoperation (50.0%) and conservatively (50.0%). Other complications were internal hernias, one in each group, and a perforation of the jejunum simultaneously with the stomach (CHEMO group). All three cases were reexplored. A reexploration had to be performed in 14.1% of all patients. Neither group did differ significantly (16.7 vs. 13.3%; p = 0.766). The most common causes for reoperation were intra-abdominal bleeding, explorative laparotomy to rule out peritonitis, and anastomotic leakage.

Postoperative mortality was 6.7% in CHEMO and 5.7% in SURG patients (p = 1). Both cases of death in the CHEMO group were the result of multi-organ failure due to sepsis. In one case, an anastomotic leakage was the rea-

Table 4. Morbidity and mortality

	CHEMO (%) (n = 30)	SURG (%) (n = 105)	p value
Postoperative LOS, days			0.184
Median	13.5	15.0	
Range	8–90	7–91	
Postoperative morbidity (any complication)	14 (46.7)	44 (41.9)	0.680
Postoperative infection	13 (43.3)	27 (25.7)	0.073
Urinary tract infection	5 (16.7)	11 (10.5)	0.349
Pneumonia	3 (10.0)	10 (9.5)	1
Wound infection	7 (23.3)	4 (3.8)	0.002*
Intra-abdominal abscess	1 (3.3)	2 (1.9)	0.533
Anastomotic dehiscence (esophagojejunostomy)	1 (3.3)	14 (13.3)	0.189
Postoperative haemorrhage	3 (10.0)	7 (6.7)	0.692
Duodenal stump leakage	4 (13.3)	2 (1.9)	0.022*
Fascial dehiscence	1 (3.3)	2 (1.9)	0.533
Anastomotic dehiscence (jejunojejunostomy)	1 (3.3)	1 (1.0)	0.396
Other postoperative complication	2 (6.7)	1 (1.0)	0.124
Relaparotomy	5 (16.7)	14 (13.3)	0.766
Hospital mortality	2 (6.7)	6 (5.7)	1

LOS = Length of stay. * $p \leq 0.05$.

Table 5. Severity of complications according to Clavien-classification in the two groups

	CHEMO (%) (n = 30)	SURG (%) (n = 105)	p value
Clavien-classification (any complication)	22 (73.3)	84 (80.0)	0.455
Grade I	0 (0)	4 (3.8)	0.578
Grade II	10 (33.3)	41 (39.0)	0.815
Grade III	6 (20.0)	25 (23.8)	1
Grade IV	4 (13.3)	8 (7.6)	0.267
Grade V	2 (6.7)	6 (5.7)	0.670

son for sepsis, and in the second case, a cardiac arrest of a 75-year multimorbid old man, with myocardial re-infarction and preexisting renal failure. Three of six cases of death (50.0%) in the SURG group were caused by respiratory insufficiency caused by an anastomotic leakage. Two patients (33.3%) died due to diffuse bleeding that could not be stopped by operation. In one case (16.7%), multiorgan failure due to sepsis was caused by an anastomotic leakage. The median interval between operation and death was 19.0 days (17–21) in the CHEMO group and 18.0 days (8–36) in the SURG group (p = 0.867). Regarding the entire Clavien-classifcation, the two groups did not differ significantly, with 73.3% in the CHEMO group and 80.0% in the SURG group (p = 0.455; table 5).

Discussion

In the Western world, most gastric cancers are diagnosed in advanced stages because of unspecific symptoms [26]. The goal of surgery for gastric cancer is a curative resection, with the removal of all gross tumour and regional lymph nodes. Because of the improvements in staging and the increase of knowledge about the value of neoadjuvant strategies, multimodal therapy in the treatment of gastric cancer is gaining more and more importance. Two pioneering studies showed a significant increase of disease-free and overall survival rate in a direct randomised comparison of patients with locally advanced adenocarcinoma of the stomach or lower

esophagus treated with perioperative chemotherapy and surgery, compared to those who solely underwent surgery [5, 6]. Besides that, a possible theoretical advantage of neoadjuvant chemotherapy is that blood vessels, which may be important for the chemotherapy local drug delivery, are not altered by surgery. Thus, neoadjuvant chemotherapy offers the possibility of an in vivo testing of the therapy applied, and micrometastasis can be treated. Due to the better condition of patients in preoperative administration of chemotherapy compared to the postoperative approach, a higher concentration of chemotherapeutics can be administered, and compliance as well as tolerability are usually better in the preoperative neoadjuvant setting. Furthermore, in more advanced stages, a higher complete R0-resection rate could be achieved and therefore, a positive influence on overall survival [27–29]. Essential problems of neoadjuvant chemotherapy are the possible impact on wound healing and immunocompetence. In animal studies on Cisplatin, a negative influence on wound healing was demonstrated. In these rodent studies, a reduced proliferation of fibroblasts, a decline of tissue proliferation and an inhibition of neovascularisation occurred [12]. In addition, a reduction of bursting pressure resistance of intra-abdominal anastomosis was noted [7, 8]. In rats, the administration of a high perioperative dose of 5-FU led to a decrease in wound tensile strength. Animal experiments on 5-FU also showed a decline of the strength of visceral anastomosis, especially in the early postoperative phase [9–11, 13, 14]. As a result, a higher rate of postoperative complications could occur. In previous trials on the use of neoadjuvant chemotherapy in gastric cancer, the efficacy and feasibility of chemotherapy are described in detail. Most preceding research focused on the acute toxicity and adverse effects of chemotherapy before gastrectomy, and the effect in correlation with the following resection is often only generally measured [5, 6, 15]. Other studies providing this information have not included a comparative group of patients who solely underwent surgery [16–20].

Multimodal treatment in the therapy of gastric cancer gained consideration because of the pioneering results of the MAGIC trial, published in 2006 [5]. Patients included in our study were treated between June 2002 and December 2009. As mentioned above, the decision about treatment and allocation to the CHEMO or the SURG group, was decided by a multidisciplinary tumour conference. UICC stages were collected postoperatively on the resected specimens. 53.3% of patients within the CHEMO group had postoperative UICC stages I and II, and he proportion of ypT0/1/2 tumour-stage was 70.0%. Therefore, we assume that a downstaging due to neoadjuvant chemotherapy occurred. Based on the German S3-guideline 'Diagnosis and Treatment of Esophagogastric Cancer', published in 2011, from UICC stage IIIA and tumour stage uT3 (endoscopic ultrasound), neoadjuvant chemotherapy should be administered. For stages IB, II and uT2, a neoadjuvant therapy is 'possible' [2]. In conclusion, around the time of our study, guidelines incorporated the concept of neoadjuvant chemotherapy and thus, the decision to treat patients with neoadjuvant chemotherapy was made more broadly.

Age, BMI and gender are considered possible risk factors for postoperative complications [30–33]. The CHEMO and SURG groups did not differ significantly for one of these parameters (table 1). Likewise, the two groups also did not differ significantly in their UICC stages and operative parameters (tables 2 and 3). Therefore, despite the limits of a retrospective study, it seems justified to explore the influence of neoadjuvant chemotherapy on postoperative morbidity with this design. Our patients' demographics are comparable to other studies. In a study by Ychou et al. [6], the median age was 63, and 62 in a study of Cunningham et al. [5]. The average BMI was 23 kg/m^2 in a comparable study [34]. In contrast, our patients tended to be slightly older and their average BMI was a bit higher. In studies by Siewert et al. [35] and Ott et al. [25], 60.0% of all patients were male.

The most frequent complications following gastrectomy are surgical site infections, such as wound infections and intra-abdominal abscess, as well as a leakage of the esophagogojejunostomy [35–44]. Postoperative morbidity after gastric cancer resection ranges between 7.7% [35] and 57.9% [45], and mortality between 0.0% [25, 34, 46–48] up to 13.0% [49]. It should be noted that there is, in general, a problem in the comparability of postoperative morbidity of different studies: the criteria of postoperative morbidity either were not outlined [5, 6, 25, 49–54] or different criteria were included [15–20, 34, 35, 45, 46, 55–61]. For this reason, we used the Clavien-classification to compare the two groups. In our study, we could not observe a significant influence of neoadjuvant chemotherapy on postoperative complications using Clavien-classification (table 5). We abstained from dividing the groups in rank IIIa/b and IVa/b in Clavien-classification because of the small number of cases.

Postoperative morbidity was 46.7% in CHEMO and 41.9% in the SURG group, and postoperative mortality was 6.7 and 5.7%, respectively. Neither group differed

significantly (table 4). Our results are in accordance with the results of two big randomised controlled trials: that the use of neoadjuvant chemotherapy in treatment of gastric cancer has no significant negative influence on postoperative morbidity after gastrectomy [5, 6]. In the MAGIC trial, postoperative morbidity in the CHEMO and SURG groups was 45.7 and 45.3%, respectively, and mortality was 5.6 vs. 5.9%. In these two trials, a detailed analysis of the observed postoperative complications was missing, as emphasis was placed on the oncological outcome.

In our study, nosocomial infection (29.6%) was the most commonly observed postoperative complication (table 4). The wound infection rate differed significantly between the two groups, with 23.3% in CHEMO and 3.8% in the SURG group ($p = 0.002$). This difference may be caused by neoadjuvant chemotherapy. An anastomotic leakage (11.1%) was the second most commonly observed complication. A leakage of the duodenal stump occurred in 13.3% in the CHEMO group and in 1.9% in the SURG group. This incidence showed a significant difference ($p = 0.022$). According to the different results concerning the number of leakages of the anastomosis and the duodenal stump, no clear correlation to the neoadjuvant chemotherapy can be drawn in this patient cohort. The observed mismatch may be caused by technical differences or just by chance and the relatively low number of patients. Technical aspects of closing the duodenal stump were not possible to be considered in this retrospective analysis. The third most frequently observed complication was postoperative bleeding (8.1%) ($p = 0.692$). A reoperation was necessary in 14.1% of the patients and neither group differed significantly ($p = 0.766$). The most common indications for reoperation were intra-abdominal bleeding, explorative laparotomy to rule out peritonitis, and anastomotic leakage.

Conclusion

In conclusion, according to this study, the use of neoadjuvant chemotherapy in the operative therapy of gastric cancer does not significantly increase the rate of postoperative morbidity using the Clavien-classification. Only an increase of wound infections in the CHEMO group compared with the SURG group was noted. Therefore, neoadjuvant chemotherapy can be considered safe and feasible.

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