

Long Term Outcome Following Surgical Treatment for Distal Gastric Cancer

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ABSTRACT

Background. At the current time, the belief that total gastrectomy (TG) offers a better survival benefit compared with distal gastrectomy (DG) in distal gastric cancer still persists among many surgeons. The aim of the study was to determine whether TG in patients with distal stomach cancer offers a benefit in long term survival compared with DG.

Methods. Data on 180 consecutive patients with adenocarcinoma of the distal stomach that underwent surgery during the period 2000-2003 were analyzed. Distal gastrectomy was performed on 91 patients (50.5%), and 89 patients (49.5%) underwent TG.

Results. The postoperative morbidity (anastomotic leakage, intraperitoneal hemorrhage and pulmonary complications) was significantly higher in the TG group than in the DG group. The TG group had a significantly higher rate of 30-day postoperative mortality than DG group, and a longer mean postoperative hospital stay. The 5-year survival rate was significantly higher for the DG group than for the TG group. The number of lymph node metastases and TNM stages are significant predictors of poor survival.

Conclusions. Compared with patients undergoing TG, a better long-term survival time, lower postoperative morbidity and mortality rates and a lower hospitalization stay was obtained in patients that underwent DG for distal gastric cancer. This observation justifies the use of this procedure for the surgical therapy of the cancer of distal stomach.

Key words: total gastrectomy – distal gastrectomy – gastric cancer – survival – surgical treatment – postoperative morbidity – prognosis.

BACKGROUND

Gastric cancer represents one of the leading death causes all over the world [1]. Moreover, at the current time, almost 10% of newly identified cancer cases and over 12% of cancer-related deaths are attributed to gastric cancer [2-4].

The consensus exists that resection represents the sole up-to-date treatment option for gastric cancer. However, the optimal choice for surgical technique in middle and distal stomach is still controversial. Arguments exist in favor of total gastrectomy (TG). Initially

performed by Billroth over a century ago, the procedure has the advantage of offering an improved loco-regional control [5]. By contrast, distal gastrectomy (DG), as proposed by Schlatter, is considered to provide lower postoperative mortality and morbidity rates [6]. Improved quality of life has also been attributed to the DG technique. Importantly, no significant difference in oncological outcome after TG could be demonstrated as compared to the DG procedure.

The main purpose of this study was to evaluate the impact of the surgical procedure (DG or TG, respectively) in the long term outcome (perioperative morbidity and mortality, median hospital stay, long-term survival) of patients with distal gastric cancer.

MATERIAL AND METHODS

Patients

Between January 2002 and December 2005, 215 consecutive patients admitted at the 3rd Surgical Clinic, Regional Institute of

Gastroenterology and Hepatology, Cluj Napoca, Romania were surgically treated with curative intent for adenocarcinoma of the distal half of the stomach. Their medical records were reviewed. All the interventions were performed by experienced surgeons with more than 200 gastrectomies using a standard protocol issued by the Japanese Gastric Cancer Association.

Patients presenting a previous history of cancer, gastric resection or cytotoxic chemotherapy, those presenting a lower than 6 cm distance between the proximal edge of the tumor and cardia, liver and/or intraperitoneal tumor dissemination or unresectable infiltration into contiguous organs were excluded. The final number of patients enrolled was 180. Enrolled patients were divided into two groups depending on the performed procedure: DG (n=91) and TG (n=89).

In all patients, the entire macroscopic tumor was removed. For a part of cases, the procedure involved additional organ resection, as to assure optimal conditions for R0 resection. The choice of lymphadenectomy was based on intraoperative local conditions :D1 or D 1.5/2 lymph node dissection, according to the Japanese Classification for Gastric Cancer and Treatment Guidelines (JCGA). No D3 lymphadenectomy was performed. All tumor specimens underwent a histopathological evaluation and were classified according to the recent Union Internationale Contre le Cancer (UICC)[7].

Distal gastrectomy was followed by Billroth I gastroduodenostomy or by Billroth II gastrojejunostomy. In the TG patients, Roux-en-Y esophagojejunostomy or omega esophagojejunostomy were performed following the initial surgical resection.

Every 3 months, patients have been investigated by means of a follow-up protocol including: physical examination, routine blood chemistry, tumor markers, abdominal ultrasonography, chest X-ray. Additionally, the patients received CT examinations every 6 months. Computed tomography and gastroduodenal endoscopy were performed only on suspicion of recurrence.

The study protocol received the approval of the institutional Ethics Committee.

Statistical analysis

Survival curves were constructed by means of the Kaplan-Meier model. Log Rank (Mantel-Cox) test was used to compare the survival curves. Survival time was calculated from the date of surgery to the date of death due to any cause. Comparative analyses were performed using chi square or Fisher Exact test in case of dichotomous data. The *t*- test or Mann-Whitney U test were used to assess between-group differences in continuous data, according to the normality of distribution, as detected by the Kolmogorov-Smirnov test. Statistical significance was considered whenever P was less than 5%. Survival predictors were assessed using the Cox's proportional hazards multivariate regression model. All statistical analyses were performed using the SPSS 17 software package.

RESULTS

Clinical and pathological characteristics

The 180 enrolled patients had a mean age of 63.5 ± 8.1 years, with a male/female ratio of 1.46. Out of 180 surgical interventions for adenocarcinoma of the distal half of the

stomach, DG was performed on 91 patients (50.5%) and TG was performed on the rest of 89 patients (49.5%). Detailed demographical data and clinical and pathological characteristics of both study groups are presented in Table I. No significant between-group difference was recorded for age, gender, site, size or histological type of the tumor.

Similar distribution was recorded for the tumor invasion into the gastric wall (T) as well as for lymph node status and the number of involved lymph nodes (N) was also similar in the two groups (Table II). Higher early stages (stage 0, I and II) were recorded in DG group as compared to TG group. However, the difference did not reach statistical significance ($p=0.102$).

Table III shows the extension of the surgery and the type of lymphadenectomy performed for both DG and TG groups. Splenectomy was an optional procedure at the choice of the attending surgeon. There was a higher splenectomy rate in the TG group (4.8%) than in the DG group (1.1%). This difference was not statistically significant ($p=0.162$).

Digestive continuity after distal gastrectomy was restored by a Billroth I gastroduodenostomy in 80 patients (88.9%) and by a Billroth II gastrojejunostomy in the rest of the 11 patients (11.1%). Total gastrectomy was followed by a Roux-en-Y esophagojejunostomy in 82 patients (92.1%) and by an omega esophagojejunostomy in 7 patients (7.9%) (Table IV).

Perioperative morbidity and mortality

Although the two study groups were similar regarding several baseline complications (Table IV), the statistical analysis of the postoperative outcome revealed that the incidence of the

Table I. Demographic data of the patients who underwent DG or TG and clinicopathological characteristics of the tumor.

	Distal gastrectomy Group n=91	Total gastrectomy Group n=89	P
Age (n, %)			
<65 years	50 (54.9%)	53 (59.5%)	0.55
>65 years	41 (45.1%)	36 (40.4%)	
Gender (n, %)			
Female	42 (46.2%)	31 (34.8%)	0.13
Male	49 (53.8%)	58 (65.1%)	
Tumor location (n, %)			
Antrum	18 (19.8%)	24 (27.0%)	0.39
Body	35 (38.4%)	34 (38.2%)	
Body and Antrum	22 (24.2%)	15 (16.9%)	
Multiple lesions	5 (5.5%)	9 (10.1%)	
Undetermined	11 (12.1%)	7 (7.8%)	
Tumor size (n, %)			
< 2 cm	42 (46.2%)	36 (40.5%)	0.36
2-5 cm	18 (19.8%)	22 (24.7%)	
>5 cm	12 (13.1%)	18 (20.2%)	
Undetermined	19 (20.9%)	13 (14.6%)	
Histopathological type (n, %)			
Intestinal	58 (63.7%)	44 (49.4%)	0.15
Diffuse	10 (11.0%)	13 (14.6%)	
Mixed	23 (25.8%)	32 (36.0%)	

anastomotic leakage was significantly higher for the TG group (n=8; 8.9%) than for the DG group (n=1; 1.1%) (p=0.037). It also evidenced that intraperitoneal hemorrhage appeared more frequently in the TG group (n=9; 10.1%) than in the DG group (n=1; 1.1%) (p= 0.02). In terms of systemic complications, the incidence of pulmonary complications was more common in the TG group (n=8; 8.9%) compared with the DG group (n=1; 1.1%) (p= 0.04).

Overall 30-day postoperative mortality was 5.0% (n=9), significantly higher for the TG group (n=8; 8.9%) than for the DG group (n=1; 1.1%), (p=0.02). The median postoperative stay was 7.58 days in the DG group and 13.14 days in the TG group, significantly longer for the TG group (p=0.03).

Table II. TNM staging of the tumors in patients that underwent distal gastrectomy or total gastrectomy.

	Distal gastrectomy Group n=91	Total gastrectomy Group n=89	P
Wall invasion (pathologic stage) (n, %)			
Mucosa (pT1)	8 (8.8%)	9 (10.1%)	0.24
Submucosa (pT1)	22 (24.2%)	15 (16.9%)	
Muscularis (pT2)	16 (17.6%)	24 (27%)	
Serosa (pT3)	38 (41.8%)	29 (32.6%)	
Serosa and other structures (pT4)	7 (7.6%)	12 (13.4%)	
Nodal status (n, %)			
Negative	38 (41.7%)	44 (49.4%)	0.07
Positive	53 (58.2%)	45 (50.6%)	
Number of metastatic lymph nodes (n, %)			
1-6 (N1)	29 (54.7%)	25 (55.6%)	0.66
7-15 (N2)	17 (32.0%)	15 (33.4%)	
>16 (N3)	7 (13.2%)	4 (8.8%)	
Undetermined	0 (0%)	1 (2.2%)	
Stage Grouping (n, %)			
0, IA	14 (15.4%)	6 (6.8%)	0.25
IB	21 (23.1%)	19 (21.3%)	
II	18 (19.8%)	15 (16.9%)	
IIIA	33 (36.3%)	38 (42.7%)	
IIB	5 (5.4%)	10 (11.2%)	
Undetermined	0 (0%)	1 (1.1%)	

Table III. Univariate analysis of the intraoperative procedures in the analyzed patients.

	Distal gastrectomy Group n=91	Total gastrectomy Group n=89	P
Extension of surgery (n, %)			
None (standard procedure)	8 (8.8%)	9 (10.1%)	0.24
To spleen	22 (24.2%)	15 (16.9%)	
To spleen and neighboring organs or structures	16 (17.6%)	24 (27%)	
To neighboring organs or structures but not to spleen	38 (41.8%)	29 (32.6%)	
Lymphadenectomy (n, %)			
D1	42 (46.1%)	25 (28.1%)	0.009
D1.5/D2	49 (53.9%)	64 (71.9%)	

Long-term survival

The overall 5-year survival rate for the entire group was 43%. The estimated 5-year survival rate (Fig. 1) was significantly higher for the DG group than for the TG group (58% vs 37%, p=0.04). While analyzing the survival rate within each stage (IA, IB, II, IIIA, IIIB), we encountered a significant difference in the two groups between the survival rates for patients in stage IB of the disease according to TNM classification (Fig. 2). In these patients, the 5-year survival rate was significantly poorer for the TG group compared with DG group (50% vs 82%, p=0.02).

Univariate analysis identified the number of involved/metastatic lymph nodes (p=0.014) and TNM stage (p=0.024) as significant predictors of poor survival. Non-significant variables found by the univariate analysis included age, gender, size and number of tumors. The multivariate analysis model composed of the two factors confirmed both the number of metastatic lymph nodes (OR: 3.7; 95% CI: 1.1-10.6, p=0.027) and TNM stages (HR: 3.4; 95% CI: 1.2-10.1, p=0.036) as independent predictors of survival.

DISCUSSION

From a surgical point of view, the R0 resection is the only therapy with curative intent in patients with distal gastric cancer. In such cases, the optimal surgical procedure is still a matter of debate [8]. Tumor extension is the first criterion when choosing the extent of gastric resection. However, when limited resections are feasible from a curative point of view, perioperative morbidity and mortality, long-term survival rate and quality of life are also equally important criteria [9-11].

Worldwide, a general consensus regarding the optimal surgical procedure in distal gastric cancer is not well established. Thus, USA surgeons usually perform a TG for cancer of the distal stomach [12], while in most European centers DG is the treatment of choice [13, 14]. The rationale behind the use of TG as a routine procedure in these cases is to avoid the tumor locoregional recurrence and to eliminate both the multicentric tumors and the risk of recurrence in

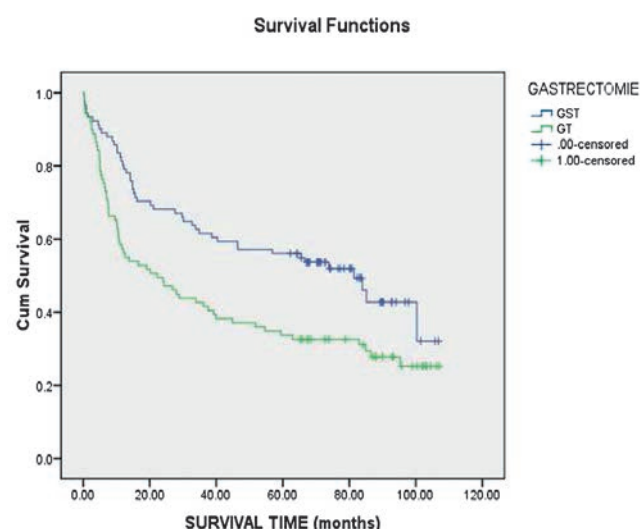


Fig. 1. Overall survival curves of patients treated by DG (blue) and TG (green) (p=0.04).

Table IV. Postoperative morbidity, 30-day mortality and mean hospital stay of the patients enrolled in the study.

	Distal gastrectomy			Total gastrectomy			P value
	Type of anastomosis		Total n=91	Type of anastomosis		Total n=89	
	Billroth I n=80	Billroth II n=80		Roux en Y n=82	Omega n=7		
Postoperative outcome (n, %)							
Anastomotic leakage	1 (1.25%)	0 (0%)	1 (1.1%)	6 (7.31%)	2 (28.57%)	8 (8.98%)	0.04
Abscesses	2 (2.5%)	0 (0%)	2 (2.2%)	5 (5.5%)	2 (28.57%)	7 (7.8%)	0.16
Wound infection	3 (3.75%)	1 (9.09%)	4 (4.4%)	8 (9.8%)	2 (28.57%)	10 (11.23%)	0.15
Intraperitoneal hemorrhage	1 (1.25%)	0 (0%)	1 (1.1%)	9 (10.9%)	0 (0%)	9 (10.1%)	0.02
Systemic complications (n, %)							
Cardiovascular	2 (2.5%)	0 (0%)	2 (2.2%)	7 (8.54%)	2 (28.57%)	9 (10.11%)	0.06
Pulmonary	1 (1.25%)	0 (0%)	1 (1.1%)	8 (9.7%)	0 (0%)	8 (8.98%)	0.04
Other	2 (2.5%)	2 (18.18%)	4 (4.4%)	8 (9.8%)	1 (14.28%)	9 (10.11%)	0.23
Post-operative 30 day mortality	1 (1.25%)	0 (0%)	1 (1.1%)	9 (10.97%)	0 (0%)	9 (10.11%)	0.02
Hospitalization (median)	7.45	8.56	7.58	13.23	12.11	13.14	0.03

the remaining stomach [15, 16]. On the other hand, it is well known that TG is responsible for several complications such as long-term digestive symptoms, postoperative weight loss, diarrhea, anorexia and metabolic changes [17]. Based on these evidences, correlated with similarly long survival rates, DG has become routinely used and widely accepted for distal

cancer in Europe. Another matter of controversy in such cases is represented by the extent of the lymphadenectomy. Because neither large studies nor randomized trials have shown any benefits, we did not perform extended lymphadenectomy (D3 lymphadenectomy - Japanese classification) on any patient [18-20].

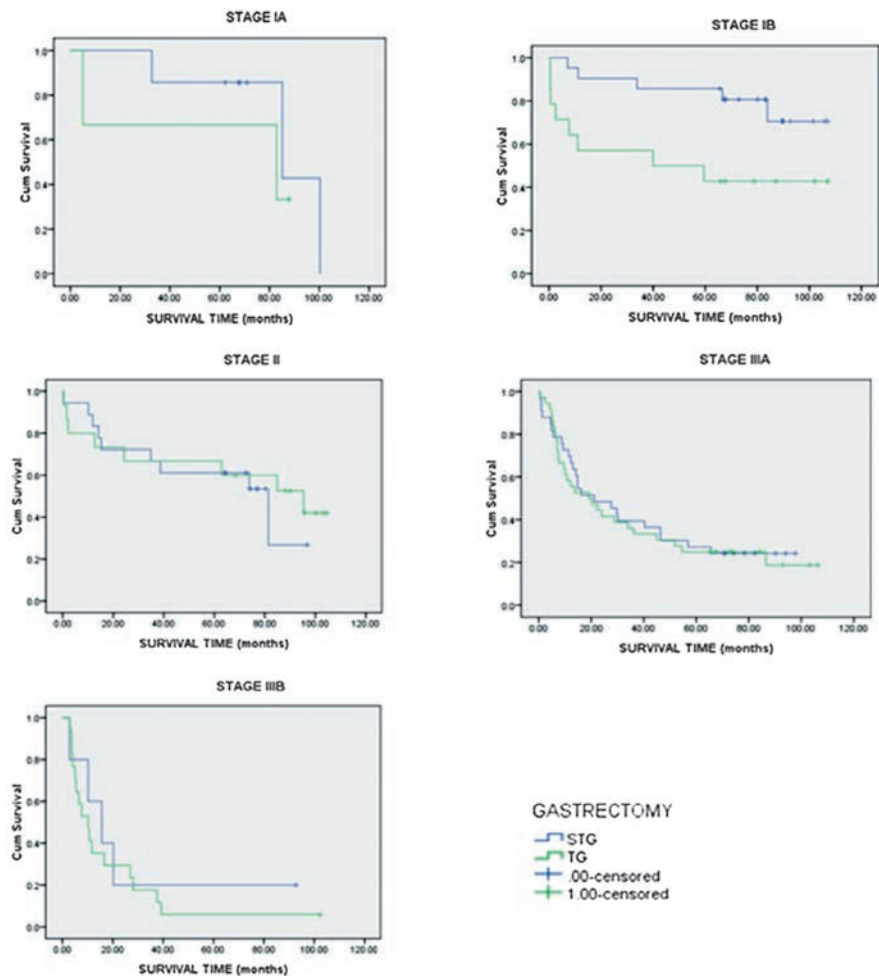


Fig. 2. Cumulative survival of patient treated by DG (blue) and TG (green) according to UICC classification: stage IA (p=0.27); stage IB (p=0.02); stage II (p=0.38); stage IIIA (p=0.79); stage IIIB (p=0.17).

At the current time, there is a lack of published controlled randomized trials comparing these procedures. Several retrospective studies [21] have demonstrated a significant decrease in perioperative mortality in the TG group compared with the DG group at stable morbidity rates, while other authors have reported similar postoperative morbidity and mortality rates between these two surgical attitudes [16, 17, 22-24].

There are several lines of evidence showing that TG is at least two times more risky than distal gastrectomy, with a higher morbidity and mortality rate [25-27]. In contrast with our findings, a study that included 338 consecutive patients who underwent surgery for adenocarcinoma of the stomach [28] reported similar morbidity and mortality rates in DG compared with TG ($p=0.928$).

In accordance with these results, our study revealed an increased postoperative morbidity, systemic complications and an increased 30-day postoperative mortality in the TG group compared with the outcome of DG group. The main cause of perioperative death was anastomotic leakage and that was in accordance with the results reported by other authors [28-30].

The postoperative hospital stay in our study was similar to data reported by other authors for each type of surgical resection that was performed [28, 31, 32]. According to our study, the mean postoperative hospital stay of the TG group was significantly higher than that of the DG group. This finding may be explained by the fact that the postoperative morbidity was higher in the TG group, and those patients who developed complications required a longer hospitalization.

Although previous reports concerning an overall 5-year survival rate showed superior survival rates in patients who underwent DG, the difference was not statistically significant [22, 28, 33, 34]. Our study found a significantly lower survival rate in the TG group compared to the DG group. Moreover, while analyzing the survival rates within each stage (IA, IB, II, IIIA, and IIIB), we found a significant difference between the two groups regarding the 5-year survival rate for stage IB, the DG group being favoured.

In the study published by Gockel et al, a 39% 5-year survival rate was reported in the TG group, and 43% in the DG group. Better long term survival results were reported by Bozzetti et al [22]: 65.3% 5-year survival rate for the DG group, and 62.4% for the TG group. A large database analysis, published by the National Cancer Center in Tokyo [35], reported a 75% 5-year survival rate after TG. These more favorable results may be due to the high prevalence of T1 carcinomas in their patients (49% of the entire series was represented by early gastric cancer).

Both univariate and multivariate analysis confirmed the number of involved/metastatic lymph nodes and TNM stages as significant predictors of poor survival. The univariate analysis of the results obtained by Gockel et al [28] pointed out the number of lymph nodes, the lymph node ratio, the transfused blood volume, the general complications, the TNM stage and tumor grading as significant predictors of poor survival. In the next step, their multivariate analysis detected the last four factors and the postoperative hospital stay as independent predictors of survival. Bozzetti et al suggested in a

multivariate analysis that the extension of the surgery towards the spleen and the neighboring organs, tumor penetration through the gastric wall and lymph nodes metastasis had a negative prognostic impact on survival [22].

There are major advantages of performing a more conservative surgery, i.e. DG, in patients with cancer of the lower/middle stomach: lower postoperative morbidity and mortality rates and higher survival rates. In addition, TG is a surgical procedure which is technically more demanding than DG and it is more often associated with splenectomy. Furthermore, TG involves a longer postoperative hospital stay and higher costs. In addition, many authors have proved a better quality of life and a better nutritional status after DG than after TG [28, 35-37].

CONCLUSIONS

Better long-term survival rates, lower postoperative morbidity (anastomotic leakage, intraperitoneal hemorrhage and pulmonary complications) and mortality rates, shorter length of hospital stay yielded by distal gastrectomy make us assert that the modern surgical strategy for cancer of the lower/middle stomach should include this conservative procedure provided that it is performed according to the oncological protocol.

Competing interests. The authors declare that they have no competing interests.

Authors' contributions. LM, TM, FZ and CI planned and designed this research; TM and DM analyzed the data; LM wrote the first draft and CT, AB, ZF, and CI revised the paper. All authors read and approved the final manuscript.

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