Research Article

Is the Proximal Subtotal Gastrectomy a Better Choice in Selected Patients than Radical Gastrectomy: A Comparison of Morbidity, Mortality and Survival after Surgical Treatment of Proximal Third Gastric Adenocarcinoma

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Abstract

Background/Aim: The theoretical functional advantages of proximal resection with jejunal interposition could outweigh the higher risk of recurrence in the unfit elderly population. The aim of our study was to evaluate proximal resection as an alternative in selected patients.

Methods: Between 1993 and 2009, 161 patients were operated on in our centre for adenocarcinoma of the proximal third of the stomach. They were divided into three groups: PG: proximal resection with jejunal interposition; TH: transhiatal extended total gastrectomy; GT: total gastrectomy. We analysed the postoperative morbidity, 30-day mortality, survival, and quality of life with a questionnaire.

Results: The patients in the PG group were significantly older and in worse general condition. The number of harvested lymph nodes was significantly smaller than in the GT and TH groups. There were no significant differences in the distribution of TNM stages between groups. There were no differences in the morbidity and 5-year survival rates between groups. No differences were found in the total scores of the GIQLI questionnaire.

Conclusion: Proximal resection should be reserved only for high-risk elderly population with proximal gastric cancer. These resections carry acceptable morbidity and mortality; however, the reconstruction with jejunal interposition does not bring the desired functional benefits.

Keywords: Gastric Adenocarcinoma; Proximal Resection; Jejunal Interposition; Quality of Life

Introduction

The therapy of choice for carcinomas of the proximal third of the stomach is total gastrectomy and D2 lymphadenectomy [1-3] and the transhiatal extended total gastrectomy with resection of distal oesophagus and D2 lymphadenectomy for AEG (adenocarcinoma of esophagogastric junction) carcinomas Siewert II and III [3,4]. Numerous new types of resections and reconstructions have been evaluated in recent years, with the endeavor of preserving as much as possible of the organ and its function, and thus preventing or decreasing the number of complications that affect quality

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of life, and at the same time satisfying modern oncologic principles [3,5]. However, because limited resections are accompanied with less aggressive lymphadenectomies there is still much controversy surrounding their use in proximal gastric cancer. Theoretically, in early-stage adenocarcinomas of the esophagogastric junction Siewert II and III and polymorbid elderly population, proximal resection and modified D2 lymphadenectomy could serve as an alternative to total gastrectomy. Because the life expectancy of this patient population is short and they are less likely to tolerate the extensive resections with their consequent functional deficits, limited resections could outweigh the higher risk of local recurrence accompanying modified lymphadenectomies.

The surgical technique of proximal resection was abandoned because reconstruction with esophagogastrostomy led to severe alkaline reflux esophagitis and a poorer quality of life. Therefore, reconstructions with jejunal- or colon- interposition between the oesophageal stump and stomach appeared in medical practice. These reconstructions were reported to have better functional results on one hand and were marked by less morbidity and mortality than total gastrectomies [3,5].

Proximal resection with jejunal interposition has been practiced in our centre for early stage carcinomas of the AEG type II, and III in older patients or in patients in poorer general condition. In order to justify its use, we compared the results of total gastrectomies and total gastrectomies with resections of distal esophagus with proximal resections of the stomach with jejunal interposition in patients with cancer of the proximal third of the stomach treated at out hospital. The functional results were analyzed by means of GIQLI (Gastro intestinal quality of life index) questionnaires.

Methods
Patients

From November 1993 to May 2009, 161 patients with a carcinoma of the proximal third of the stomach and gastroesophageal junction of Siewert type II and III were operated on at our centre. The patients were divided into three groups according to the type of procedure performed: i) PG: proximal subtotal resection with jejunal interposition and limited D2 lymphadenectomy (19.3%, 31 patients); ii) the TH group: transhiatal extended total gastrectomy with resection of the distal esophagus and D2 lymphadenectomy

(23.6%, 38 patients); and iii) and the GT group: total gastrectomy with D2 lymphadenectomy (57.1%, 92 patients).

All patients were prospectively recorded in our database. We noted the patients' demographics, types of operations performed, their duration, as well as the clinical-pathological characteristics of tumor, postoperative recovery, along with complications, divided into surgical and general, and the 30-day postoperative morbidity and mortality.

The quality of life was evaluated with the GIQLI (gastro-intestinal quality of life index) questionnaire described by Eypash [6-8]. The questionnaire was sent to patients on average 1,560 days after surgery. Thirty-one patients participated in the survey.

All patients gave their informed consent previous to the inclusion in the study. The study was confirmed by the national ethnics committee (University Clinical Centre Maribor, Slovenia).

Surgical technique of proximal subtotal gastrectomy with jejunal interposition

Proximal resection with jejunal interposition was performed as described in the literature [1-3,5,13,14]. A 20 to 30 cm long jejunal limb was interposed between the esophageal stump and residual distal stomach. The anvil of the circular stapler was introduced into the esophagus and a stapled end-to-side esophagojejuno anastomosis was fashioned. Resected samples were examined according to established pathohistological procedures. Patients regularly followed up at the OPC.

Statistical analysis

Categorical variables were compared with the χ^2 test; continuous variables with t-test and a one-way ANOVA test was used where appropriate. A univariate survival analysis of survival was performed with a Kaplan-Meier model and the differences between groups were defined by using the Log-rank and Breslow test. P values below 0.05 were considered as the limit of significance. Statistical analysis was performed with SPSS 15.0 for Windows XP.

Frequently used methods for comparing survival distributions are the log-rank test [15,18] and the generalized Wilcoxon test [16,17,19]. Another frequently used method is the Kolmogorov–Smirnov test statistic [20], which may have greater power than the

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log-rank and Wilcoxon tests to detect the differences when the survival curves cross or differ in other, more general, ways. However, there is no guarantee that the Kolmogorov–Smirnov test is always better, even when the survival curves cross [21,22]. In our analysis we deal with three main problems: i) The selected treatment groups are small and differ in size considerably (Table 1); ii) Survival curves are close in the beginning but then separate (Figure 1); iii) An important part of the sample is right censored.

Group	Total	Failed	Censored	Percent censored
1	31	23	8	25.81
2	92	59	33	35.87
Sum	123	82	41	33.33

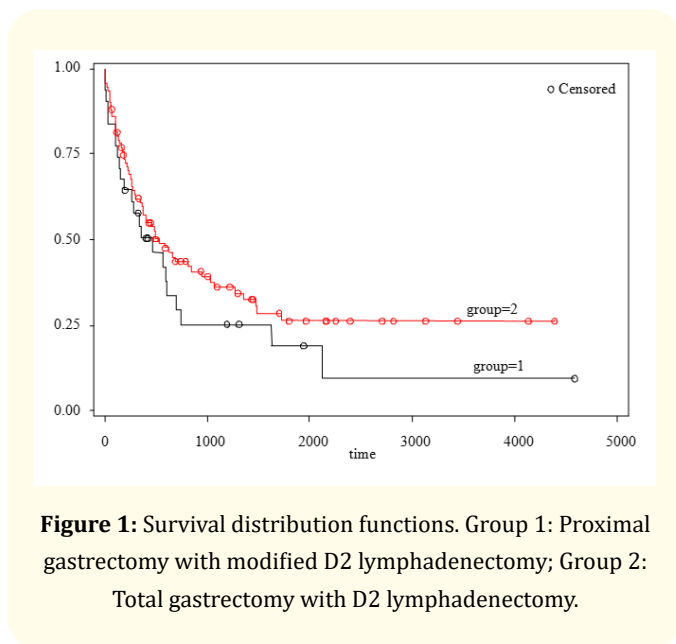**Table 1:** Summary of the number of censored and uncensored values.

Figure 1: Survival distribution functions. Group 1: Proximal gastrectomy with modified D2 lymphadenectomy; Group 2: Total gastrectomy with D2 lymphadenectomy.

In such circumstances, the standard methods for comparing survival distributions lose power. Therefore, in addition to the above-mentioned methods, we used a method proposed by Xun and Qiang [23] that is robust when compared to the overall homogeneity of the survival curves. The new method is based on the absolute difference of the area under the survival curves using normal approximation by Greenwood's formula. Xun and Qiang [23] demonstrate that the proposed method performs better in terms of statistical power than the log-rank, Wilcoxon, and Kolmogorov–Smirnov tests in a variety of situations (including such as in our case) on the basis of the Monte Carlo simulation.

Definitions

Survival is defined the as the time form the initial surgery to death from any cause. In this study median and five-year survivals are determined.

Functional results are defined as the cumulative score of five different sets of complaints patients experience after gastric cancer surgery and include abdominal complaints, physical condition, social interactions, emotional complaints and food tolerance as determined by the GIQLI (gastro-intestinal quality of life index) questionnaire described by Eypash [6-8].

Complications are defined as any postoperative complications of grade I or more according to Dindo-Claviene [25].

Perioperative therapy

We started to use the perioperative treatment in 2003. Patients were treated with one of the following protocols: i) Chemoradiotherapy with 5FU-LV (5-Fluorouracil-Leucovorin); ii) Chemotherapy with EOX (Epirubicin, Oxaliplatin, Capecitabine); iii) Chemotherapy with XELOX (Capecitabine, Oxaliplatin) or iv) Chemoradiotherapy with Xeloda (Capecitabine).

Results
Patients

The gender distribution between groups was not significantly different (p = 0.137) (Table 2). A significant difference was noticed in age distribution (p < 0.0001). The average age of patients in the PG group was 70.4 ± 9 years, which was significantly older than in the other two groups (GT: 63.9 ± 11 years; TH: 60.1 ± 12 years). There were also differences in the patients' general condition which is evident from the ASA scores (p = 0.015). Patients from the PG group were in the worst general condition, with the majority of patients in the groups ASA II (48.4%) and ASA III (38.7%). The patients in the TH group were in the best physical condition with 52.6% of patients in the ASA I group (Table 2).

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	PG	TH	GT	P
Male	21 (67.7%)	25 (65.8%)	72 (78.3%)	NS[1]
Female	10 (32.3%)	13 (34.2%)	20 (21.7%)	
Age	70.39 ± 9.13	60.13 ± 12.53	63.87 ± 10.61	p = 0.001[2]
ASA I	4 (12.9%)	20 (52.6%)	32 (35.2%)	
II	15 (48.4%)	15 (39.5%)	33 (36.3%)	p = 0.015[1]
III	12 (38.7%)	3 (7.9%)	26 (28.6%)	
Lauren's Intestinal type	16 (57.1%)	15 (42.9%)	39 (44.8%)	
Diffuse type	9 (32.1%)	16 (45.7%)	27 (31%)	NS[1]
Mixed type	3 (10.7%)	4 (11.4%)	21 (24.1%)	
R0	26 (83.9%)	33 (86.8%)	71 (77.2%)	NS[1]
T 1	4 (12.9%)	2 (5.3%)	9 (9.8%)	
2	10 (32.3%)	12 (31.6%)	25 (27.2%)	
3	14 (45.2%)	22 (57.9%)	49 (53.3%)	NS[1]
4	3 (9.7%)	2 (5.3%)	9 (9.8%)	
N 0	11 (52.4%)	6 (18.8%)	15 (19.2%)	
1	3 (14.3%)	10 (31.3%)	19 (24.4%)	
2	4 (19%)	11 (34.4%)	12 (15.4%)	NS[1]
3	3 (14.3%)	5 (15.6%)	32 (41%)	
M 0	26 (83.9%)	36 (94.7%)	76 (82.6%)	NS[1]
1	5 (16.1%)	2 (5.3%)	16 (17.4%)	
UICC stage Ia	4 (19%)	2 (6.3%)	7 (8.8%)	
Ib	4 (19%)	2 (6.3%)	5 (6.3%)	
II	2 (9.5%)	7 (21.9%)	10 (12.5%)	
IIIa	3 (14.3%)	8 (25%)	14 (17.5%)	NS[1]
IIIb	2 (9.5%)	6 (18.8%)	7 (8.8%)	
IV	6 (28.6%)	7 (21.9%)	37 (46.3%)	
OP duration (min)	203.1 ± 55	230.3 ± 37	191.4 ± 58	NS[2]
Tumour size (mm)	63 ± 37	81.5 ± 37	72.8 ± 38	NS[2]
Number of resected LN	17.24 ± 11.4	26.28 ± 12.8	24.47 ± 12.9	p = 0.011[2]
Proportion of positive LN to resected LN	29.9 ± 24.9	27.9 ± 26.8%	42.2 ± 35.4%	NS[2]
Splenectomy	13 (43.3%)	30 (78.9%)	45 (48.9%)	p = 0.002[2]
Surg. complications	3 (9.7%)	5 (13.2%)	20 (21.7%)	NS[1]
Gen. complications	3 (9.7%)	6 (15.8%)	7 (7.6%)	NS[1]

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Perioperative treatment				
None	30 (96.8%)	26 (68.4%)	86 (93.5%)	
Chemoradiotherapy-Xeloda	1 (3.2%)	7 (18.4%)	4 (4.3%)	
Chemotherapy-Xelox	0 (0%)	0 (0%)	1 (1.1%)	p < 0.0001
Chemotherapy-EOX	0 (0%)	1 (2.6%)	1 (1.1%)	
Chemoradiotherapy-5FU/LV	0 (0%)	4 (10.5%)	0 (0%)	
1 Hi^2 test				
2 One-way ANOVA				

Table 2: Patient and tumour characteristics.

Surgery and perioperative treatment

The duration of surgeries among groups were significantly different (p = 0.003). The fastest procedure was total gastrectomy with D2 lymphadenectomy (191 ± 58 minutes). Proximal resection with jejunal interposition and modified D2 lymphadenectomy (203 ± 55 minutes) was only insignificantly longer. The longest procedure was the transhiatal extended gastrectomy with D2 lymphadenectomy, lasting on average 230 ± 37 minutes. Because the proximal resection allowed only a modified D2 lymphadenectomy, an expected significant difference between the numbers of harvested lymph nodes was noted between the groups (GT: 24.5 ± 13 lymph nodes; TH: 26.3 ± 13 lymph nodes; PG: 17.2 ± 11 lymph nodes) (p = 0.011).

There were no significant differences in the histological type distributions (p = 0.443), in lymphocyte infiltration, vascular invasion, lymphangial invasion, perineural invasion, and extranodal invasion among the groups. An R0 resection was accomplished in 77.2% to 86.8% cases with no significant differences between groups (p = 0.096). Also, no differences were noted in the TNM stages among groups (Table 2). There were no significant differences in the perioperative treatment between patients in the PG and GT group. In both groups most of the patients received no perioperative treatment (96.8% in PG and 93.5% in GT; p = 0.335). Patients in TH group received perioperative therapy in 31.6% (p < 0.0001). The most common protocol was chemoradiotherapy with Xeloda (18.4%), followed by chemoradiotherapy with 5FU and LV (10.5%), while only 2.6% of patients received chemotherapy with EOX (Table 2).

Postoperative recovery

30-day mortality was 6.5% in the GT group, 9.7% in the PG group and 5.3% in the TH group. Despite the relatively high mortality in the PG group, a significant difference in the number of surgical complications among groups was not noted (p = 0.223). Surprisingly, the PG group had the lowest complication rate with 9.7%, as opposed to the GT group where 21.7% of patients had surgical complications. General complications were the most common in the TH group (15.8%) and less common in the PG group (9.7%) and GT group (7.6%). All differences were insignificant (p = 0.158).

Survival

There were no significant differences in median survival among groups (GT: 536 days, TH: 657 days, PG: 474 days; p = 0.451). Five-year survival was 26.3% in GT group, 28.9% in the TH group, and 25.3% in the PG group. The survival curves are shown in figure 2.

Figure 1 shows the survival curves in the two treatment groups. If we had to decide whether the curves are different by examining the figure, we could reject the null hypothesis. But in order to check if the observed differences are statistically significant, or if they are just the result of a sample selection process, we performed statistical tests (See table 3). The log-rank test yields a p-value of 0.22, the Wilcoxon test has a p-value of 0.31, and the Kolmogorov–Smirnov test has a p-value of 0.26. None of the log-rank, Wilcoxon, or Kolmogorov–Smirnov tests were able to detect a significant difference between the two procedures in the distributions of the times to terminal event.
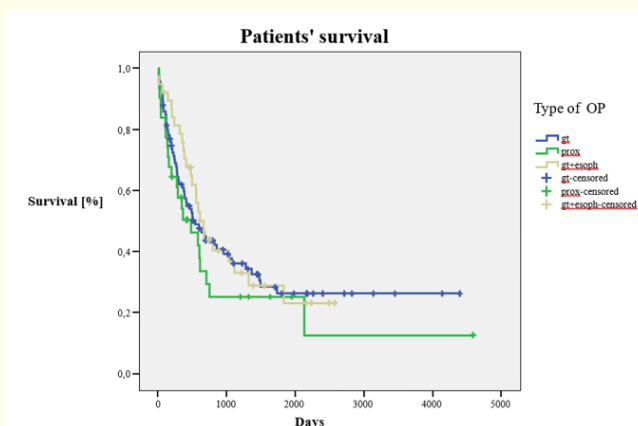
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Figure 2: Survival curves. PG: proximal gastrectomy with modified D2 lymphadenectomy; TH: transhiatal extended total gastrectomy with D2 lymphadenectomy; GT: total gastrectomy with D2 lymphadenectomy.

Test	Test statistic	Pr >
Log-Rank	1.4736	0.2248
Wilcoxon	1.0475	0.3061
Kolmogorov-Smirnov	1.2789	0.2580
New test	1.0994	0.1358

Table 3: Results.

Due to the fact that selected treatment groups are small and differ in size considerably, survival curves are close in the beginning but then separate, and an important part of the sample is right censored, the standard tests may fail in recognizing the difference between the observed curves. Therefore, we also calculated a test statistic based on a new method [23] designed to capture the differences over the entire time interval for which the survival information for both groups is available. In this real data example, the new testing method seems to be more appropriate to detect the overall differences than the log-rank, Wilcoxon, or Kolmogorov–Smirnov tests.

The proposed new testing method yields a test statistic value of 1.0994 with a p-value of 0.14. Hence, at a 5% significance level, the new test concludes that it is not possible to reject the null hypothesis significance of no difference between the two survival curves.

Quality of life

The functional results of operations were evaluated in 31 patients (GT: 13; TH 10; PG 8 patients). No significant differences in total scores were observed among groups (p = 0.893), however, values in GT (102.4 points) and PG (102.4 points) were the highest, followed by TH patients with 97.9 points. A comparison of GT and PG groups showed that despite somewhat decreased physical functions and poorer emotional states, GT patients achieved insignificantly better results in all fields as opposed to PG patients. Especially surprising are the differences in nutritional functions. Patients in the PG group complained of symptoms such as difficult swallowing, poor appetite and heartburn. A comparison of GT and PG shows better values in all areas for patients from the GT group. Patients from the GT group scored higher values than patients from the TH group in all fields. Intriguingly, a comparison between TH and PG groups showed worse results in the TH group than in most fields, but better results in nutritional functions, whereas PG group patients were plagued with more digestive problems (PG: 14.5 (72.5%); TH: 15.9 (79.5%). The total scores are shown in table 4.

	PG	TH	GT	P
Abdominal symptoms	45.6 ± 11	45.3 ± 12	46.6 ± 9	NS
Social interactions	10.1 ± 4	8.9 ± 4	11.2 ± 3	NS
Physical condition	8.6 ± 4	6.2 ± 4	7.3 ± 4	NS
Emotional status	23.5 ± 5	21.6 ± 7	21.2 ± 6	NS
Nutrition	14.5 ± 6	15.9 ± 3	16 ± 3	NS
Sum	102.4 ± 29	97.9 ± 25	102.4 ± 20	NS
One-way ANOVA				

Table 4: GIQLI questionnaire scores.

Discussion and Conclusion

In the therapy of gastroesophageal junction adenocarcinoma, proximal resection still remains the subject of heated debates.

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There are doubts concerning the sufficient extent of resection, related survival rates, and the possible functional benefits for patients after such surgery. Therefore, the aim of our study was to compare the clinical and functional results after proximal resection with jejunal interposition, total gastrectomy, and transhiatal extended gastrectomy with resection of the distal esophagus.

The patients selected for proximal resection with jejunal interposition were older and in worse general condition than in the other two groups. Similar indications for this procedure were pointed out in numerous studies [4,9,10,11]. The duration of the surgery was shorter in the PG than in the TH group, however, comparable to the GT group, which was the fastest procedure. The extent of lymphadenectomy was significantly smaller than in the GT and TH group, which together with the relatively short duration of surgery lowered the extent of resection and supposedly the burden of surgery on the patient. This was confirmed by the insignificantly lower general and surgical complication rates in PG compared to TH group. Even so, the analysis showed the highest postoperative mortality in the PG group. The most plausible causes for this were the older age and accompanying diseases of patients in the PG group, which was mirrored in the more common general complications in PG as opposed to the GT group. We can therefore assume that a more radical procedure would have probably caused even higher mortality rates.

A comparison of survival rates did not show any significant differences. Five-year survival rates ranged from 25.3% in the PG group to 28.9% in the TH group. These results support the fact that extended lymphadenectomy and resection did not provide a survival advantage in our patient cohort. Similar results were reported by numerous authors, confirming that in patients with carcinoma limited to *muscularis propria*, nodal stations of the lower part of the stomach were not affected, and extensive lymphadenectomy is not required [2,12,13]. Although we firmly believe that the therapy of choice in locally advanced gastric cancer is still total gastrectomy with D2 lymphadenectomy, our series shows that for physically unfit patients with more favorable stages, such as T1 and T2, and location in the upper third of the stomach, proximal resection with modified D2 lymphadenectomy is a sufficient procedure.

The analysis of the quality of life did not show any significant differences. However, a closer look at the total scores from the GIQLI questionnaires showed that patients in the GT group scored higher in digestive functions and complained less of symptoms like fullness, regurgitation, and heartburn than patients after proximal gastrectomy. This raises questions about the advantages of proximal resection with jejunal interposition. On one hand, we have similar survival rates with less extensive resections to radical resections, but on the hand, no significant overall functional improvement. Many other authors have published disappointing functional results of proximal resection with jejunal interposition [1,3,12,14]. But because patients often complain of poor tolerance for food, reflux problems, postprandial symptoms, and lower performance status after total gastrectomy, different centers are still searching for the best type of reconstruction.

Although our results question the functional benefits of reconstruction with jejunal interposition, they still need to be considered with some reservation. Small number of patients included in the analysis does not allow clear conclusions, but provides only a small insight into the functional results after surgery. In addition, because of the retrospective nature of this study a certain selection bias was present. Furthermore, the study was designed to select patients with the worst performance status for proximal resection with jejunal interposition, while thranshiatal extended total gastrectomy was performed only in generally fit patients, hence, it was impossible to avoid this selection bias. Nevertheless, the main objective of this paper was the comparison functional results where the general condition does not have a major impact. It is important to mention that the analysis also included patients who received adjuvant chemo-radio therapy. The regiments for adjuvant therapy of gastric cancer were capecitabine, EOX (Epirubicin, Oxaliplatin, Capecitabine), XELOX (Capecitabine, Oxaliplatin). These regiments are frequently accompanied by gastrointestinal and addition problems like chronic fatigue and depression that result from cytostatic treatment [24]. All the previously mentioned symptoms are impossible to distinguish from symptoms resulting from surgical reconstruction, therefore the interpretations of the GIQLI scores are to be taken with some reservation. Other studies excluded such patients from the analysis [1-3,5].

To conclude, our results indicate that proximal gastrectomy with jejunal interposition should not be performed in all proximal gastric cancers and even its use in early-stage gastric cancer is

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questionable. Not only is the extent of lymphadenectomy smaller, it also does not bring the desired functional results together with a lower mortality rate. We therefore think that this type of resection should be reserved only for the elderly population with proximal gastric cancer, in favorable stages and accompanying comorbidities, as their survival is expected to be shorter due to older age and would not benefit from extended resections. In this population, one can use a lesser resection without compromising long-term survival with a less radical lymphadenectomy and achieve a sufficient procedure with acceptable mortality and morbidity. The reconstruction with jejunal interposition did not provide the desired functional advantages. In future studies, it might be beneficial to supplement the positive results of the proximal resection with better reconstruction, such as the formation of a »pouch« reservoir or the so-called "tube" reconstruction. In this manner, an obligatory harmful operation could be supplemented with the best functional results and patients relieved from a procedure beset with a heavy physical and emotional scar.

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