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ORIGINAL ARTICLE

Outcomes of Proximal Versus Total Gastrectomy for Proximal Gastric Cancer: A Propensity Score-Matched Analysis of a Western Center Experience

Tevfik Kıvılcım Uprak[1] · Muhammer Ergenç[1] · Ahmet Akmercan[1] · Cumhur Yeğen[1]

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Abstract

Purpose In this western study, we aimed to compare perioperative outcomes, postoperative complications, and overall survival in patients who underwent total gastrectomy (TG) or proximal gastrectomy (PG) for proximal gastric cancer (GC).

Methods Patients who underwent GC surgery at Marmara University Hospital between January 2014 and December 2021 were evaluated retrospectively. Propensity score matching (PSM) was performed to balance the baseline characteristics of patients undergoing PG and TG. Data on patients' demographics, clinicopathological features of tumors, complications, and survival rates were analyzed. Perioperative outcomes and overall survival of the patients were compared between PG and TG groups.

Results A total of 212 patients were included in this study, with 53 patients in the PG and 159 in the TG group. After 1:1 matching according to PSM, 46 patients in the PG group were matched to 46 in the TG group. After PSM, there were no differences in clinicopathological outcomes except retrieved lymph nodes. In terms of short-term outcomes, overall perioperative morbidity (Clavien Dindo $\geq$ 3a) was significantly higher in the PG group ($p = 0.01$). However, there was no significant difference when the complications were considered separately. In the long-term follow-up, reflux esophagitis was associated with the PG group (p=0.04). In multivariate analysis, positive surgical margin and lymphovascular invasion were significant factors related to overall survival. Overall, 5-year survival was 55% in matched patients. The difference in survival was not statistically significant (57 vs. 69 months, $p = 0.3$) between the two groups.

Conclusions Proximal gastrectomy is applicable to patients up to stage 3 disease, with no difference in overall survival, with caution in early complications and reflux esophagitis. Among all demographic and oncological factors, lymphovascular invasion and resection margin were significantly associated with worse survival.

Keywords Carcinoma stomach · Gastrectomy · Proximal gastrectomy · Proximal gastric cancer · Total gastrectomy

Introduction

Gastric cancer is the fourth leading cause of cancer death worldwide and the fifth most common type of cancer diagnosed.[1] Cancer located in the gastric cardia and upper third of the stomach is defined as proximal gastric cancer (PGC). The incidence of cancer-related death of proximal gastric cancer is higher than other cancer sites of the stomach, and its incidence has been increasing in recent years.[2,3]

Surgical resection stays the most effective treatment for potentially curable proximal gastric cancer, despite advances in multimodal treatment strategies such as chemotherapy, radiotherapy, targeted therapy, and immunotherapy. Optimal surgical selection for PGC is a topic of interest and remains controversial.[2–4] There are two different types of gastric resection for proximal GC: total gastrectomy (TG) and proximal gastrectomy (PG). The type of resection is selected according to the tumor size, stage, and volume of the remaining stomach.[2]

Many studies comparing PG and TG in early gastric cancer have shown equivalent oncological results. However, the two methods differ in terms of postoperative

✉ Muhammer Ergenç
muhammerergenc@gmail.com

[1] Department of General Surgery, Marmara University School of Medicine, Başıbüyük Campus Başıbüyük Mah. Maltepe Başıbüyük Yolu Sok. No:9/1 Maltepe, 34854 İstanbul, Turkey

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nutritional outcomes and the incidence of post-gastrectomy syndrome.[2–8]

In this western study, we aimed to compare perioperative outcomes, postoperative complications, and overall survival in patients who underwent total or proximal gastrectomy for proximal gastric cancer.

Methods

The data obtained from prospectively collected medical records of patients who underwent surgery for gastric cancer in the Marmara University Hospital General Surgery Clinic between January 2014 and December 2021 were evaluated retrospectively.

This study was approved by the Marmara University Faculty of Medicine Clinical Research Ethics Committee (Number: 22.07.2022.1082).

Patients who underwent total and proximal gastrectomy for carcinoma of the upper third of the stomach were included in the study. Patients with distant metastases, previous neoplastic diseases or remnant gastric cancer, urgency procedures, non-adenocancer tumors, those who underwent neoadjuvant treatments, and those with missing data for estimation of propensity match analysis were excluded from the study.

Demographic characteristics, American Society of Anesthesiologists (ASA) scores, comorbidities, type of surgery, clinicopathological features of the tumor, complications developed during hospitalization, intensive care duration, and discharge dates were examined.

According to the American Joint Committee on Cancer (AJCC) 7th edition, the tumor stages were classified.[9] The Clavien–Dindo classification was used to evaluate postoperative complications.[10] Anastomotic stricture and esophagitis were confirmed according to endoscopic examinations. Los Angeles (LA) classification, grades C and D esophagitis were defined as severe reflux esophagitis. The time from the patient's operation to death was evaluated in terms of overall survival.

The location of the primary tumor was described with an upper endoscopy. Upper-third located gastric cancer was defined as adenocarcinoma of the upper one-third of the stomach according to the classification of the Japanese gastric cancer association.[11]

All surgical procedures were performed by experienced general surgeons with a standardized open surgical technique. Proximal gastrectomy procedure included resection of the upper two-thirds of the stomach and distal esophagus with D1+ lymphadenectomy followed by handsewn esophagogastrostomy. Vagal preservation was not used in any patient. All proximal gastrectomy patients underwent pyloromyotomy. Roux-en-Y reconstruction (using handsewn or stapled esophagojejunostomy) was performed after total gastrectomy with D1+ and D2 lymphadenectomy.[11,12]

The patients were divided into two groups: PG and TG. Clinicopathologic features, postoperative outcomes, and survival rates compared between TG and PG.

The primary outcome of this study was to determine whether there was a difference between the two groups in terms of overall survival. Secondary outcomes included the comparison of postoperative complications and mortality.

Statistical Analysis

Descriptive statistics were used to summarize patient demographics, clinicopathological features, and postoperative outcomes. Categorical variables were expressed as the frequency with percentage [n (%)], and the continuous variables were expressed as mean ± SD and median (interquartile ratio, IQR). Categorical variables were compared using the Pearson Chi-Square (χ^2) test or Fisher's exact test, and continuous variables using the Student's *t*-test (normal distribution) or the Mann–Whitney U test (not normally distributed). The Kaplan–Meier method was used to calculate the cumulative survival rates, and the log-rank test was used to compare the survival curves between the treatment groups. Multivariate analysis was performed using the Cox proportional hazards model to evaluate various factors simultaneously. A *p*-value less than 0.05 was considered statistically significant. Statistical analysis was performed using the SPSS software pack (Statistical Package for Social Sciences for Windows, version 22.0; Chicago, IL, USA) and the R program (version 2.15.2 for Windows).

Propensity Score-Matched Analysis

Propensity score-matched (PSM) analysis was conducted with eight variables to obtain comparable groups (TG and PG) and reduce the selection bias.[2,13] These variables were listed as age, gender, TNM stage, lymph node positivity, Lauren classification, degree of differentiation, lymphovascular invasion, and surgical margin. Propensity scores were estimated for all patients. After the propensity score estimation, patients were matched using a simple 1:1 nearest neighbor matching method without replacement. We imposed a caliper of 0.2 of the standard deviation of the propensity score logit to obtain a similar group with respect to the set of covariates. Standardized differences were examined to compare patients' features before and after matching, with imbalance being defined as an absolute value greater than 0.2.

Results

Between January 2014 and December 2021, 741 patients underwent elective surgery for gastric cancer in our center. Three hundred patients who underwent proximal or total gastrectomy for proximal tumors were evaluated, and 88 patients were excluded from the study (Fig. 1).

A total of 212 patients were included in the study. The unmatched cohort's median age was 65 (58–72), and 151 (71.2%) were male patients. A total of 159 (75%) of the patients underwent total gastrectomy (TG), while 53 (25%) underwent proximal gastrectomy (PG).

By matching the two techniques for demographics and clinicopathologic features, 92 patients (46 in each group) were included in the outcome assessment. After matching, we examined the overall balance to test the adequacy of our matching. The overall balance test was insignificant (p = 0.977), confirming that our groups were appropriately distributed. A second indication that our matching achieved an improved balance between cohort groups, the relative multivariate imbalance L1 measure was appropriately larger in the unmatched sample (0.937) than in the matched sample (0.826). The comparisons of baseline characteristics of the TG and PG groups before and after matching are given in Table 1.

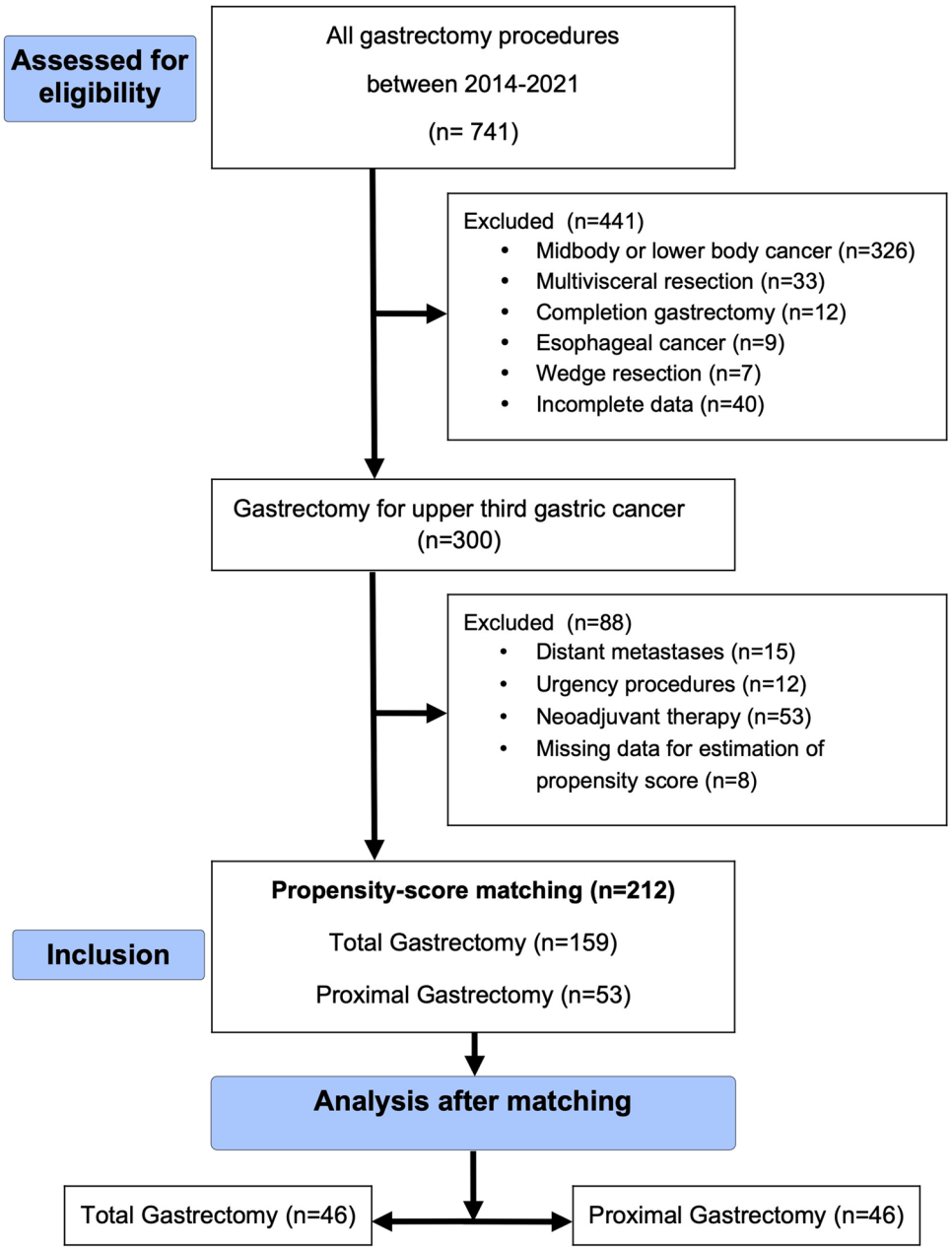

Fig. 1 Flowchart of patient selection

Table 1 Clinicopathological features of patients

Parameters	All patient (*n*=212)	Before PSM			After PSM		
		TG (*n*=159)	PG (*n*=53)	*p*-value	TG (*n*=46)	PG (*n*=46)	*p*-value
Age (years)	65.5 (58–72)	64 (57–71)	68 (61–75)	**0.01**	64.9 ± 9.6	66 ± 9.7	0.6
Sex							
Male	151 (71.2%)	112 (70.4%)	39 (73.6%)	0.6	33 (71.7%)	33 (71.7%)	1
Female	61 (28.8%)	47 (29.6%)	14 (26.4%)		13 (28.3%)	13 (28.3%)	
ASA score							
I	63 (29.7%)	50 (31.4%)	13 (24.5%)	0.5	14 (28.3%)	12 (26.1%)	0.7
II	133 (67.2%)	98 (61.6%)	35 (66%)		28 (60.9%)	31 (67.4%)	
III	16 (7.5%)	11 (6.9%)	5 (9.4%)		4 (8.7%)	3 (6.5%)	
Lauren classification							
Intestinal	126 (59.4%)	85 (53.5%)*	41 (77.4%)*	**0.01**	32 (69.6%)	34 (73.9%)	0.7
Diffuse	30 (14.2%)	27 (17%)*	3 (5.7%)*		5 (10.9%)	3 (6.5%)	
Mixed	51 (24.1%)	42 (26.4%)	9 (17%)		9 (19.6%)	9 (19.6%)	
Indeterminate	5 (2.4%)	5 (3.1%)	0		0	0	
TNM stage							
I	30 (14.2%)	19 (11.9%)	11 (20.8%)	**0.02**	8 (17.4%)	8 (17.4%)	0.9
II	50 (23.6%)	34 (21.4%)	16 (30.2%)		12 (26.1%)	13 (28.3%)	
III	132 (62.3%)	106 (66.7%)*	26 (49.1%)*		26 (56.5%)	25 (54.3%)	
Lymph nodes retrieved	23.5 (17–32)	25 (18–33)	19 (12–25)	**0.0001**	25.7 ± 9.8	19.8 ± 10.1	**0.006**
Positive lymph nodes	3 (0–9)	4 (0–11)	2 (0–7)	0.1	2 (0–9)	3.5 (0–9)	0.8
Tumor size (cm)	5.2 (3.6–7)	6 (4–8)	4 (2.5–5.4)	**0.0001**	4.2 ± 2.4	4.6 ± 1.9	0.4
Resection margin							
Negative	187 (88.2%)	139 (87.4%)	48 (90.6%)	0.5	43 (93.5%)	42 (91.3%)	0.6
Positive	25 (11.8%)	20 (12.6%)	5 (9.4%)		3 (6.5%)	4 (8.7%)	
Differentiation							
Well-differentiated	72 (34%)	49 (30.8%)	23 (43.4%)	0.09	27 (58.7%)	28 (60.9%)	0.8
Poorly differentiated	140 (66%)	110 (69.2%)	30 (56.6%)		19 (41.3%)	18 (39.1%)	
Lymphovascular invasion							
Absent	94 (44.3%)	66 (41.5%)	28 (52.8%)	0.1	24 (52.2%)	22 (47.8%)	0.6
Present	118 (55.7%)	93 (58.5%)	25 (47.2%)		22 (47.8%)	24 (52.2%)	
Follow-up (months)	25 (11–51)	23 (11–50)	30 (10–65)	0.6	25 (16–60)	30.5 (10–65)	0.6
5-year overall survival (%)	45	42	53	0.4	59	52	0.3

Categorical data are expressed as *n* (%), and the continuous data are expressed as mean ± standard deviation and median (interquartile ratio, IQR)

PSM, propensity score matching; *TG*, total gastrectomy; *PG*, proximal gastrectomy; ASA, American Society of Anesthesiology

Before matching, age was considerably higher in the PG group than in the TG group (68 and 64, respectively, $p = 0.01$). Tumor size and TNM stage were more advanced in the total gastrectomy group. The total retrieved lymph node count was significantly higher in the TG group ($p = 0.0001$). Intestinal and diffuse cancers were detected significantly more frequently in the total gastrectomy group (Table 1).

After propensity score matching analysis, hospital mortality (TG vs. PG, 0% vs. 6.5%, $p = 0.07$) and overall perioperative Clavien-Dindo ≥ 3a complications were significantly higher in the PG group (TG vs. PG, 2.2% vs. 17.4%, $p = 0.01$). However, there was no significant difference between the two groups when the complications were considered separately. In the long-term follow-up, severe reflux esophagitis was significantly higher in the proximal gastrectomy group ($p = 0.04$) (Table 2).

In univariate analysis, higher age, lymph node involvement, higher T stage, poor differentiation, lymphovascular invasion, and positive resection margin were independent factors in predicting worse surgical overall survival. However, multivariate analysis showed that lymphovascular invasion and positive resection margin were independent factors for worse overall survival. Surgical type (TG or PG) was not a predictive factor in univariate and multivariate analysis (Table 3).

The median follow-up periods of patients before and after matching were 25 (IQR = 11–51) and 27 (IQR = 12–63)

Table 2 Perioperative morbidity and mortality in proximal and total gastrectomy procedure

Parameters	All patients (n=212)	Before PSM			After PSM		
		TG (n=159)	PG (n=53)	p-value	TG (n=46)	PG (n=46)	p-value
Perioperative mortality	5 (2.4%)	2 (1.3%)	3 (5.7%)	0.06	0	3 (6.5%)	0.07
Morbidity (Clavien Dindo ≥ 3a)							
Absent	189 (89.2%)	144 (90.6%)	45 (84.9%)	0.2	45 (97.8%)	38 (82.6%)	**0.01**
Present	23 (10.8%)	15 (9.4%)	8 (15.3%)		1 (2.2%)	8 (17.4%)	
Anastomotic leak	14 (6.6%)	9 (5.7%)	5 (9.4%)	0.3	1 (2.2%)	5 (10.9%)	0.09
Bleeding	6 (2.8%)	4 (2.5%)	2 (3.8%)	0.6	1 (2.2%)	2 (4.3%)	0.5
Delayed GIS motility	10 (4.7%)	9 (5.7%)	1 (1.9%)	0.2	1 (2.2%)	1 (2.2%)	1.0
Pulmonary*	12 (5.7%)	9 (5.7%)	3 (5.7%)	1.0	0	2 (4.3%)	0.1
Cardiovascular	5 (2.4%)	4 (2.5%)	1 (1.9%)	0.7	1 (2.2%)	1 (2.2%)	1.0
Anastomotic stricture	8 (3.8%)	5 (3.1%)	3 (5.7%)	0.4	1 (2.2%)	2 (4.3%)	0.5
Severe reflux esophagitis	9 (4.2%)	2 (1.3%)	7 (13.2%)	**0.0001**	1 (2.2%)	6 (13%)	**0.04**
Length of hospital stay (days)	5 (4–7)	5 (4–7)	5 (4–7)	0.5	5 (4–6)	5 (4–7)	0.9

Categorical data are expressed as n (%), and the continuous data are expressed as median (interquartile ratio, IQR) *TG*, total gastrectomy; *PG*, proximal gastrectomy; *GIS*, gastrointestinal system

*Pneumonia, pleural effusion, pulmonary embolism

months, respectively. The overall 5-year survival of patients before and after matching was 45% and 55%, respectively. Before matching, patients with TG demonstrated a lower 5-year overall survival rate (42%, estimated mean survival was 55.5 ± 3.7 months) compared to PG (53%, estimated mean survival was 58.5 ± 5.6 months) (Table 1). After matching, patients with TG demonstrated a higher 5-year overall survival rate (59%, estimated mean survival was 69.2 ± 6.8 months) compared to PG (52%, estimated mean survival was 57.4 ± 6 months). However, the differences in survivals were not statistically significant ($p = 0.4$ and $p = 0.3$, respectively) (Fig. 2).

Discussion

Proximal and total gastrectomy methods for tumors located in the upper part of the stomach were compared in this study. Statistical analysis was performed using PSM to reduce the selection bias between the PG and TG groups. While proximal gastrectomy is recommended to be performed in early gastric cancer, in our study, we had the opportunity to compare up to stage 3 patients, and no difference was observed in terms of overall survival in the two groups. Also, surgery type was not found to be a significant factor affecting overall survival in multivariate analysis.

If a sufficient distal resection margin can be maintained, proximal gastrectomy is a substantial resection technique for early-stage proximal GC. Most surgeons have generally agreed with this concept. However, it still has not reached in terms of advanced diseases.[2] When treating locally advanced GC in the upper third of the stomach, many surgeons in Eastern prefer TG as the conventional treatment to conduct a more radical resection. With the TG procedure, all the perigastric lymph nodes can be removed while also preventing recurrent disease at the gastric border. However, some surgeons believe the two are equal in terms of the extent of resection since given that numerous published studies, including ours, found no significant difference in the survival rate between PG and TG.[14,15]

Table 3 Univariate and multivariate analysis of overall survival after propensity score matching

Variables	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
Age (> 65 vs. ≤ 65)	1.5	0.7–2.9	0.2	1.6	0.8–3.3	0.1
Lymph node involvement (absent vs. present)	3.4	1.2–9	**0.01**	1.8	0.6–5	0.2
T stage (>T2 vs. ≤T2)	4.4	1.06–18.5	**0.04**	1.8	0.3–8.6	0.4
Differentiation (poor vs. well)	2.1	1.02–4.7	**0.04**	1.7	0.8–3.8	0.1
Lymphovascular invasion (absent vs. present)	4.2	1.9–9.2	**0.0001**	2.8	1.2–6.4	**0.01**
Resection margin (positive vs. negative)	6.3	2–19.5	**0.001**	5.2	1.6–16.7	**0.005**
Surgery type (PG vs. TG)	0.7	0.3–1.4	0.7	0.7	0.3–1.4	0.3

HR, hazard ratio; *CI*, confidence interval; *TG*, total gastrectomy; *PG*, proximal gastrectomy

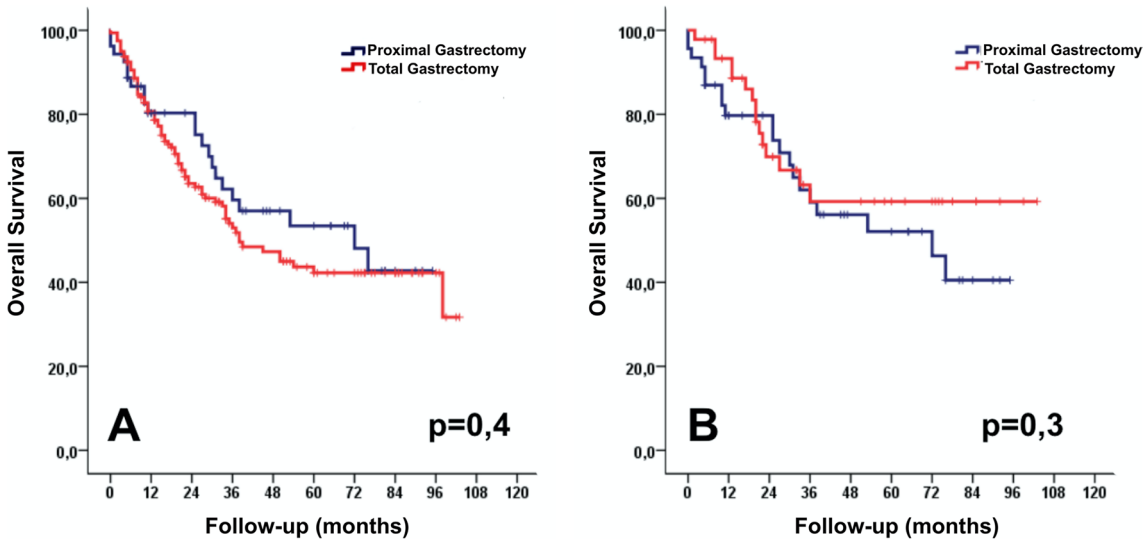

Fig. 2 Overall survival rates of total gastrectomy (TG) and proximal gastrectomy (PG) patients. **A** Before PSM, **B** after PSM

Various techniques are used for reconstruction after proximal gastrectomy.[6,16,17] Proximal gastrectomy was considered to reduce postoperative weight loss and improve patient performance by preserving half of the stomach. In addition, PG was thought to be effective in terms of both radicality and safety.[18,19] According to western-based studies, the extent of resection for proximal GC does not affect the long-term outcome.[2,19] Different results have been reported when PG and TG are compared in terms of perioperative complications. PG seems to be more advantageous in the early postoperative period.[13,20] However, long-term complications such as reflux esophagitis and anastomotic stricture were evaluated, and PG has a higher risk of complication than TG.[5] In our patient group, we found a significant difference between the two matched groups regarding early complications. But, when examined separately, complications related to surgery, such as anastomotic leakage, bleeding, and ileus, no difference was detected between the PG and TG, similar to other studies.[6,21]

Any difference between the two groups in terms of anastomotic stenosis, which is one of the late complications, was not found. However, similar to other studies, reflux esophagitis was significantly higher in the PG group. While our perioperative mortality was consistent with western studies, it was higher than in the east.[2,6,13,21,22]

Studies have shown that PG has good outcomes in terms of perioperative performance and has similar oncologic outcomes to TG. PG has been recognized as an effective surgical treatment for proximal early gastric cancer.[13,23] Although our study had advanced-stage patients, we did not detect a significant difference in survival between the two groups. Therefore, we consider PG as a preferable option for advanced-stage patients. Disease-free survival was not included in the study, so this result should be evaluated cautiously. Studies indicate that tumor stage, node stage, tumor differentiation, tumor size, and age are independent prognostic factors in patients with proximal gastric cancer.[2,24,25] In this study, lymphovascular invasion and resection margin were negatively associated with oncologic outcomes in the multivariate analysis.

Our study has certain limitations. It is a single-center and low-volume study. Due to the retrospective design, we could not include the following data in our research: Siewert classification of tumors, follow-up of patients' nutritional status and proportional weight loss, and an assessment of how surgery affects patients' quality of life (QoL).

Conclusions

Proximal gastrectomy is applicable to patients up to stage 3 disease, with no difference in overall survival, with caution in early complications and reflux esophagitis. Among all demographic and oncological factors, lymphovascular invasion and resection margin were significantly associated with worse survival.

Part of the data included in this manuscript has been presented as an oral presentation at the 33rd World Congress of International Association of Surgeons, Gastroenterologists and Oncologists (IASGO), 28 September–01 October 2022, Istanbul, Turkey, and published at Congress Abstract Book (33rd World Congress of IASGO).

Author Contribution All listed authors meet the ICMJE criteria. We attest that all authors contributed significantly to the creation of this manuscript, each having fulfilled the criteria as established by the ICMJE. We confirm that all named authors have read and approved the manuscript. Conceptualization: TKU, ME, CY; Methodology:

TKU, ME, AA, CY; Formal analysis and investigation: TKU, ME, AA, CY; Writing - original draft preparation: TKU, ME, AA, CY; Writing - review and editing: TKU, ME, AA, CY; Funding acquisition: TKU, ME, AA, CY; Resources: TKU, ME, AA, CY; Supervision: TKU, ME, CY.

Data Availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code Availability Not applicable.

Declarations

Ethics Approval This study was performed in line with the principles of the Declaration of Helsinki. This study was approved by the Marmara University Faculty of Medicine Clinical Research Ethics Committee (Number: 22.07.2022.1082).

Conflict of Interest The authors declare no competing interests.

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