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Editorial Board Member of *World Journal of Gastrointestinal Oncology*, Hiroshi Doi, MD, PhD, Assistant Professor, Lecturer, Department of Radiation Oncology, Kindai University Faculty of Medicine, Osaka 589-8511, Japan

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Retrospective Study

Surgical resection of gastric stump cancer following proximal gastrectomy for adenocarcinoma of the esophagogastric junction

Fu-Hai Ma, Li-Yan Xue, Ying-Tai Chen, Wei-Kun Li, Yang Li, Wen-Zhe Kang, Yi-Bin Xie, Yu-Xin Zhong, Quan Xu, Yan-Tao Tian

ORCID number: Fu-Hai Ma (0000-0003-2437-6881); Li-Yan Xue (0000-0001-5185-0126); Ying-Tai Chen (0000-0003-4980-6315); Wei-Kun Li (0000-0002-3883-1497); Yang Li (0000-0002-4549-7087); Wen-Zhe Kang (0000-0001-9965-8109); Yi-Bin Xie (0000-0002-7887-1389); Yu-Xin Zhong (0000-0002-8865-3297); Quan Xu (0000-0001-9246-3253); Yan-Tao Tian (0000-0001-6479-7547).

Author contributions: Tian YT and Xue LY designed the research; Ma FH, Li WK and Chen YT analyzed the data and wrote the paper; Li Y, Kang WZ, Xie YB, Zhong YX and Xu Q collected the patient's clinical data.

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Fu-Hai Ma, Ying-Tai Chen, Wei-Kun Li, Yang Li, Wen-Zhe Kang, Yi-Bin Xie, Yu-Xin Zhong, Quan Xu, Yan-Tao Tian, Department of Pancreatic and Gastric Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

Li-Yan Xue, Department of Pathology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

Corresponding author: Yan-Tao Tian, MD, Professor, Department of Pancreatic and Gastric Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 17 Panjiayuan Nanli, Beijing 100021, China. tyt67@163.com

Telephone: +86-10-87787120

Fax: +86-10-87787120

Abstract**BACKGROUND**

Proximal gastrectomy (PG) is performed widely as a function-preserving operation for early gastric cancer located in the upper third of the stomach and is an important function-preserving approach for esophagogastric junction (EGJ) adenocarcinoma. The incidence of gastric stump cancer (GSC) after PG is increasing. However, little is known about the GSC following PG because very few studies have been conducted on the disease.

AIM

To clarify clinicopathologic features, perioperative complications, and long-term survival rates after the resection of GSC following PG.

METHODS

Data for patients with GSC following PG for adenocarcinoma of the EGJ diagnosed between January 1998 and December 2016 were retrospectively reviewed. Multivariate analysis was performed to identify factors associated with overall survival (OS). GSC was defined in accordance with the Japanese Gastric Cancer Association.

RESULTS

A total of 35 patients were identified. The median interval between the initial PG

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and resection of GSC was 4.9 (range 0.7-12) years. In 21 of the 35 patients, the tumor was located in a nonanastomotic site of the gastric stump. Total gastrectomy was performed in 27 patients; the other 8 underwent partial gastrectomy. Postoperative complications occurred in 6 patients (17.1%). The tumor stage according to the depth of tumor invasion was T1 in 6 patients, T2 in 3 patients, T3 in 9 patients, and T4 in 17 patients. Lymph node metastasis was observed in 18 patients. Calculated 1-, 3-, and 5-year OS rates were 86.5%, 62.3%, and 54.2%, respectively. Multivariate analysis showed advanced T stage to be associated with OS.

CONCLUSION

This study reveals the characteristics of GSC following PG for adenocarcinoma of the EGJ and suggests that a surgical approach can lead to a satisfactory outcome.

Key words: Gastric stump cancer; Proximal gastrectomy; Esophagogastric junction; Distal gastrectomy

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Core tip: The clinicopathological characteristics, treatment, and prognosis of gastric stump cancer (GSC) after distal gastrectomy have been well investigated, however, there is limited information on GSC after proximal gastrectomy (PG). We revealed characteristics of GSC in detail using the largest number of patients to date. Our results suggest that surgical approaches can achieve satisfactory outcomes in GSC following PG. The factor associated with OS based on multivariate analysis was advanced T stage and GSC is more likely to be diagnosed at an advanced stage. Thus, endoscopic follow-up of the gastric stump should be conducted to detect GSC at an early stage.

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INTRODUCTION

Although the prevalence of gastric cancer is decreasing, the incidence of esophagogastric junction (EGJ) adenocarcinoma is increasing^[1]. The choice of surgical techniques for EGJ adenocarcinoma is controversial, yet proximal gastrectomy (PG) remains an important surgical option^[2,3]. PG is also widely used as a function-preserving approach for early-stage proximal stomach cancer^[4]. The incidence of gastric stump cancer (GSC) after PG is growing^[5-8], and GSC following PG may thus be increasingly encountered by surgeons in the coming years.

The clinicopathological characteristics, treatment, and prognosis of GSC after distal gastrectomy (DG) have been well investigated^[9-11]; however, there is limited information on GSC after PG. To our knowledge, there are only few studies have been published on GSC following PG^[8,12,13]. As such, we conducted a single-center retrospective study to understand the associated clinicopathological features, surgical results and long-term outcomes of GSC following PG.

MATERIALS AND METHODS

This retrospective study was approved by the Institutional Review Board of Cancer Hospital of the Chinese Academy of Medical Sciences and was based on demographic and pathological data retrieved from a computerized database of all patients with gastric cancer treated at this facility between January 1998 and December 2016. The need for informed consent was waived due to the retrospective nature of the study, and the data were anonymously analyzed.

PG or PG plus esophagectomy followed by esophagogastrostomy reconstruction

are usually indicated for EGJ adenocarcinoma and gastric cancer located in the upper third of the stomach. We defined GSC according to the Japanese Classification and Treatment Guidelines for Gastric Cancer (14th edition), in which GSC is defined as a cancer arising in the gastric stump after gastrectomy, regardless of the histology of the previous lesion (benign or malignant), risk of recurrence, extent of initial resection, or method of reconstruction^[14]. Thirty-five patients who had undergone resection of the gastric stump for GSC following PG at Cancer Hospital of the Chinese Academy of Medical Sciences were eligible for inclusion in the study.

To investigate whether the time interval significantly influenced survival, we divided the patients into 2 groups: Interval < 5 years ($n = 21$) and ≥ 5 years ($n = 14$). We also divided the patients into 2 groups to investigate whether the tumor location significantly impacted survival: Tumors located in anastomotic sites ($n = 14$) and tumors located in nonanastomotic sites ($n = 20$). Medical records were reviewed with regard to preoperative medical conditions, perioperative complications, histopathological results and follow-up data.

Statistical analysis

Cumulative survival rates were obtained using the Kaplan–Meier method and compared using the log-rank test to evaluate statistically significant differences. Cox proportional hazards regression analysis was used to evaluate factors affecting overall survival (OS). $P < 0.05$ was considered significant. The statistical analysis was performed with SPSS for Windows version 22.0.

RESULTS

Patients and clinical characteristics

The demographic and clinical characteristics of 35 patients with GSC following PG are shown in [Table 1](#). The mean age was 60 ± 11 years, and the male-to-female ratio was 7.75 to 1. Of the 35 patients, the mean interval between primary PG and the development of GSC was 4.9 (range 0.7–12) years. The time to treatment of GSC was within 5 years in 21 patients, within 5–10 years in 10 patients, and longer than 10 years in 4 patients. Regarding the initial EGJ adenocarcinoma, 2 patients had type I, 29 had type II, and 4 had type III disease according to Siewert Classification. All of the patients underwent PG with esophagogastromy. With regard to the site of tumors in the gastric stump, 14 and 21 were in anastomotic and nonanastomotic sites, respectively.

Surgical characteristics and short-term outcomes

Total gastrectomy as the primary procedure for GSC was performed in 27 patients (77.1%) of all patients; partial resection of the gastric remnant was performed in 8 patients (22.9%). In 5 patients, resection of one or more adjacent organs was performed together with gastrectomy. The mean operation time was 343 ± 132 min. The mean intraoperative blood loss volume was 513 ± 383 ml. Postoperative complications were detected in 6 patients (17.1%): 4 patients developed leakage from the anastomotic site, 1 developed wound infection, 1 developed hemorrhage, and 1 developed postoperative ileus. However, none of these patients died ([Table 2](#)).

Histopathological characteristics

Histological analysis revealed 26 adenocarcinomas and 9 adenocarcinomas with signet ring cells. Analysis of histological differentiation revealed 3 well-differentiated tumor types, 11 moderately differentiated tumor types, and 21 poorly differentiated tumor types. The disease stage according to the depth of tumor invasion was T1 in 6 patients, T2 in 3 patients, T3 in 9 patients, T4a in 11 patients, and T4b in 6 patients. The median number of dissected lymph nodes was 11.1 ± 7.4 , and the median number of lymph node metastases was 2.9 ± 4.2 . Lymph node metastasis was observed in 18 patients ([Table 3](#)).

Long-term outcomes and factors affecting survival

The 1-, 3-, and 5-year OS rates were 86.5%, 62.3%, and 54.2%, respectively. The results of the Cox proportional hazards model demonstrated T stage to be a significant independent prognostic factor for survival ([Table 4](#)). The 5-year survival rates for patients with T1/T2, T3 and T4 disease were 85.7%, 72.0% and 30.6%, respectively.

DISCUSSION

GSC was originally defined as gastric cancer occurring at least five years after after

Table 1 Clinical characteristics of patients

Characteristics		Number of patients (%)
Sex	Male	31 (88.6)
	Female	4 (11.4)
Age (yr)		60 ± 11 (33-83)
ASA	I-II	25 (71.4)
	III-IV	10 (28.6)
Comorbidity	Any comorbidity	7 (20)
	Hypertension	2 (5.7)
	Diabetes	1 (2.9)
	COPD	1 (2.9)
	Coronary artery disease	2 (5.7)
	Cerebral vascular disease	1 (2.9)
Family history of gastric cancer		4 (11.8)
Siewert type of initial EGJ adenocarcinoma	Siewert I	2 (5.7)
	Siewert II	29 (82.9)
	Siewert III	4 (11.4)
Adjuvant therapy after initial operation	Received	17 (48.6)
	Not received	4 (11.4)
	Unknown	14 (40)
Tumor location	Anastomotic site	14 (40)
	Nonanastomotic site	21 (60)
Interval (yr)		4.9 ± 3.2 (0.7-12)
Interval	< 5 yr	21 (60)
	≥ 5 yr, < 10 yr	10 (28.6)
	≥ 10 yr	4 (11.4)

COPD: Chronic obstructive pulmonary disease; EGJ: Esophagogastric junction.

DG for benign disease^[15,16]. Recently, GSC has been used to refer to all cancers detected in the gastric stump, irrespective of the primary disease or initial operation^[17]. The incidence of GSC following PG is increasing, and that of GSC is reportedly higher after PG (3.6%–9.1%) than after DG (0.4%–2.5%)^[18]. Moreover, Nozaki *et al*^[19] found that PG is an independent risk factor for GSC. Compared to DG, PG may result in an additional risk for GSC^[11]. Surgery, pathogenesis, and prognosis of GSC after DG are well investigated; however, little is known about GSC following PG because very few studies have been conducted on the disease. To the best of our knowledge, this is the first study investigating GSC following PG for EGJ adenocarcinoma.

Resection of GSC is associated with intra-abdominal adhesion after the initial procedure. Surgeons sometimes encounter technical difficulties during resection, which leads to prolonged operation time and excessive blood loss. Furthermore, intraoperative surgical complications, such as intestinal injury, may occur. Previous studies have reported an overall surgical complication rate of 19%–47% for GSC, with operation-related mortality rates of 2%–13%^[20]. However, little is known about the complication rate of GSC following PG. In our study, the overall complication rate was 17.1%, which is relatively low. Additionally, 5 of 35 patients (14.3%) required additional organ resection; this rate is also lower than that reported for GSC after DG^[21]. The need for additional organ resection may complicate surgery in patients with GSC.

Ohyama *et al*^[12] identified almost the same numbers of differentiated and undifferentiated tumors in GSC. However, in our study, 21 of 35 tumors were poorly differentiated. Because only a few studies have been published on the pathological type of GSC, the characteristics of this disease remain unclear. In the present study, early GSC was diagnosed in 6 (17%) of 35 patients, whereas T4 disease was identified in 17 (48.6%). As GSC is more likely to be diagnosed at an advanced stage, endoscopic follow-up of the gastric stump is necessary to detect GSC at an early stage. The incidence of metastasis to lymph nodes was 54.3% (19/35) in the present study, which is higher than that of GSC after DG^[11].

Although the number of patients in our study was small, the results showed a 5-

Table 2 Surgical characteristics and short-term outcomes

Surgical characteristics		Number of patients (%)
Operation type	Total gastrectomy	27 (77.1)
	Partial gastrectomy	8 (22.9)
Additional organ resection	Yes	5 (14.3)
	Yes	5 (14.3)
Estimated blood loss (mL)		513 ± 383
Operation time (min)		343 ± 132
Blood transfusion	No	9 (25.7)
	Yes	26 (74.3)
Postoperative complications	Any complication	6 (17.1)
	Leakage	4 (11.4)
	Hemorrhage	1 (2.9)
	Ileus	1 (2.9)
	Wound infection	1 (2.9)
Postoperative hospital stay (d)		18.4 ± 12.1

year OS rate of 54.2%. In addition, the results of the Cox proportional hazards model showed only T stage to be a significantly independent prognostic factor for survival. In contrast, the time interval or location did not affect survival, which may partly justify the definition of GSC, whereby time interval, tumor location and method of reconstruction are not considered.

Nevertheless, this study has several limitations. First, because not all patients in our study underwent PG at Cancer Hospital of the Chinese Academy of Medical Sciences, some important information on the initial operation was missing, such as the extent of lymphadenectomy, histology type, and pathologic stage. Second, the number of patients enrolled was small, mostly because of the rarity of the disease. Third, there is no standardized definition of GSC, which make our study not able to be accurately compared with previous studies on GSC.

Here, we reveal characteristics of GSC following PG in detail with the largest number of patients to date. Our results suggest that surgical approaches can achieve satisfactory outcomes in GSC following PG, similar to those in patients with typical gastric cancer. GSC is more likely to be diagnosed at an advanced stage, and thus, endoscopic follow-up of the gastric stump should be conducted to detect GSC at an early stage. Further larger-scale studies are necessary to clarify the characteristics of the disease.

Table 3 Histopathological characteristics

Pathological characteristics		Number of patients (%)
Histology	Adenocarcinoma	26 (74.3)
	Adenocarcinoma with signet ring cell	9 (25.7)
Pathologic grade	Poor	21 (60.0)
	Moderate	11 (31.4)
	Well	3 (8.6)
T stage	T1a-1b	6(17.1)
	T2	3 (8.6)
	T3	9 (25.7)
	T4a	11 (31.5)
	T4b	6 (17.1)
Number of dissected lymph nodes		11.1 ± 7.4
Number of lymph node metastasis		2.9 ± 4.2
N stage	N0	16 (45.7)
	N1/N2/N3	19 (54.3)

Table 4 Univariate and Multivariate analyses of clinicopathologic factors associated with overall survival

	5-yr OS (%)	Univariate		Multivariate	
		Hazard ratio	P value	Hazard ratio	P value
Sex: Male <i>vs</i> female	49.4 <i>vs</i> 66.7	3.352 (0.420-26.755)	0.229	-	-
Age: < 65 yr <i>vs</i> ≥ 65 yr	63.5 <i>vs</i> 44.7	0.597 (0.199-1.796)	0.354	-	-
Tumor location: Anastomotic <i>vs</i> nonanastomotic	57.7 <i>vs</i> 56.2	0.868 (0.265-2.846)	0.816	-	-
Interval: < 5 yr <i>vs</i> ≥ 5 yr	56.8 <i>vs</i> 55.4	0.665 (0.213-2.074)	0.479	-	-
Operation type: Completion gastrectomy <i>vs</i> segmental resection	56.2 <i>vs</i> 68.6	2.112 (0.464-9.614)	0.323	-	-
Histology: Adenocarcinoma <i>vs</i> adenocarcinoma with signet ring cell	65.6 <i>vs</i> 0	0.368 (0.104-1.306)	0.108	0.376 (0.098-1.44)	0.154
Pathologic grade: Poor <i>vs</i> moderate/well	49.7 <i>vs</i> 65.3	1.232 (0.401-3.786)	0.715	-	-
T stage: T1-3 <i>vs</i> T4	77.0 <i>vs</i> 30.6	0.144 (0.039-0.534)	0.001	0.166 (0.041-0.672)	0.012
N stage: N0 <i>vs</i> N+	73.8 <i>vs</i> 39.2	0.216 (0.058-0.807)	0.013	0.432 (0.103-1.822)	0.253

OS: Overall survival.

ARTICLE HIGHLIGHTS

Research background

Proximal gastrectomy (PG) is performed widely as a function-preserving operation for early gastric cancer located in the upper third of the stomach and is an important function-preserving approach for esophagogastric junction (EGJ) adenocarcinoma. The incidence of gastric stump cancer (GSC) after PG is increasing. However, little is known about the GSC following PG because very few studies have been conducted on the disease. To our knowledge, there are only few studies have been published on GSC following PG.

Research motivation

The clinicopathological characteristics, treatment, and prognosis of GSC after distal gastrectomy have been well investigated; however, there is limited information on GSC after PG. As such, we conducted a single-center retrospective study to understand the associated clinicopathological features, surgical results and long-term outcomes of GSC following PG.

Research objectives

The aim of this study is to clarify clinicopathologic features, perioperative complications, and long-term survival rates after resection of GSC following PG. We revealed characteristics of GSC following PG in detail with the largest number of patients to date.

Research methods

This is a retrospective study. Thirty-five patients who had undergone resection of the gastric stump for GSC following PG at Cancer Hospital of the Chinese Academy of Medical Sciences were eligible for inclusion in the study. Medical records were reviewed with regard to

preoperative medical conditions, perioperative complications, histopathological results and follow-up data. Cumulative survival rates were obtained using the Kaplan–Meier method and compared using the log-rank test to evaluate statistically significant differences. Cox proportional hazards regression analysis was used to evaluate factors affecting overall survival (OS).

Research results

This study reveals the characteristics of GSC following PG for adenocarcinoma of the EGJ and suggests that a surgical approach can lead to a satisfactory outcome. GSC is more likely to be diagnosed at an advanced stage, and thus, endoscopic follow-up of the gastric stump should be conducted to detect GSC at an early stage. Further larger-scale studies are necessary to clarify the characteristics of the disease.

Research conclusions

We revealed the characteristics of GSC following PG for adenocarcinoma of the EGJ and suggests that a surgical approach can lead to a satisfactory outcome. GSC is more likely to be diagnosed at an advanced stage, and thus, endoscopic follow-up of the gastric stump should be conducted to detect GSC at an early stage. The incidence of GSC after PG is increasing. Surgical approach can lead to a satisfactory outcome. This is the first study investigating GSC following PG for EGJ adenocarcinoma. GSC following PG should be compared with initial distal gastric cancer. We defined GSC according to the Japanese Classification and Treatment Guidelines for Gastric Cancer (14th edition). Our results suggest that surgical approaches can achieve satisfactory outcomes in GSC following PG, similar to those in patients with typical gastric cancer. There are only few studies have been published on GSC following PG. This study reveals the characteristics of GSC following PG for adenocarcinoma of the EGJ. Endoscopic follow-up of the gastric stump should be conducted to detect GSC at an early stage. Surgical approach should be performed for patients with GSC following PG.

Research perspectives

The factor associated with OS based on multivariate analysis was advanced T stage and GSC is more likely to be diagnosed at an advanced stage. Thus, endoscopic follow-up of the gastric stump should be conducted to detect GSC at an early stage.

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