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ORIGINAL ARTICLE

#### **Retrospective Study**

# Prognostic factors and survival in patients with gastric stump cancer

Hua Huang, Wei Wang, Zhong Chen, Jie-Jie Jin, Zi-Wen Long, Hong Cai, Xiao-Wen Liu, Ye Zhou, Ya-Nong Wang

Hua Huang, Jie-Jie Jin, Zi-Wen Long, Hong Cai, Xiao-Wen Liu, Ye Zhou, Ya-Nong Wang, Department of Gastric Cancer and Soft Tissue Sarcoma, Fudan University Shanghai Cancer Center, Shanghai 200032, China

Hua Huang, Jie-Jie Jin, Zi-Wen Long, Hong Cai, Xiao-Wen Liu, Ye Zhou, Ya-Nong Wang, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China

Wei Wang, Zhong Chen, Department of Hepatobiliary Surgery, Affiliated Hospital of Nantong University, Nantong 226001, Jiangsu Province, China

Author contributions: Huang H and Wang W performed the research; Chen Z, Jin JJ, Long ZW, Cai H, Liu XW, Zhou Y and Wang YN analyzed the data and drafted the article.

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Correspondence to: Ya-Nong Wang, MD, PhD, Department of Gastric Cancer and Soft Tissue Sarcoma, Fudan University Shanghai Cancer Center, 270 Dong An Road, Shanghai 200032, China. wangyanongsh@gmail.com

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# Abstract

**AIM:** To elucidate the clinicopathological characteristics and prognostic factors of gastric stump cancer (GSC).

**METHODS:** The clinical data for 92 patients with GSC were collected at Fudan University Shanghai Cancer Center. The prognostic factors were analyzed with Cox proportional hazard models.

**RESULTS:** GSC tended to occur within 25 years following the primary surgery, when the initial disease is benign, whereas it primarily occurred within the first 15 years post-operation for gastric cancer. Patients with regular follow-up after primary surgery had a better survival rate. The multivariate Cox regression analysis revealed that Borrmann type I/II (HR = 3.165, 95%CI: 1.055-9.500, P = 0.040) and radical resection (HR = 1.780, 95%CI: 1.061-2.987, P = 0.029) were independent prognostic factors for GSC. The overall 1-, 3-, and 5-year survival rates of the 92 patients were 78.3%, 45.6% and 27.6%, respectively. The 1-, 3-, and 5-year survival rates of those undergoing radical resection were 79.3%, 52.2%, and 37.8%, respectively. The 5-year survival rates for stages I, II, III, and IV were 85.7%, 47.4%, 16.0%, and 13.3%, respectively (P = 0.005).

**CONCLUSION:** The appearance of GSC occurs sooner in patients with primary malignant cancer than in patients with a primary benign disease. Therefore, close follow-up is necessary. The overall survival of patients with GSC is poor, and curative resection can improve their prognosis.

Key words: Gastric stump cancer; Clinicopathological characteristics; Prognosis



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Core tip: We retrospectively analyzed 92 patients. This study indicated that gastric stump cancer (GSC) has unique clinicopathologic characteristics, early detection of GSC is indeed possible, close follow-up is necessary and the radical resection may significantly improve the survival.

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# INTRODUCTION

The concept of gastric stump cancer (GSC) was originally described in the  $1920s^{[1]}$ , and was defined as a carcinoma occurring in the gastric remnant at least 5 years post-surgery for benign peptic ulcer disease. Currently, the concept of GSC has been expanded to include recurrence after gastric cancer resection<sup>[2,3]</sup>.

Gastric stump as a precancerous condition remains a substantial clinical concern. The incidence of GSC accounts for 1%-7% of all gastric carcinomas following gastrectomy, and this frequency continues to increase<sup>[3-5]</sup>. Nevertheless, GSC is often described as a tumor with poor prognosis, and poor curative resection rates (38%-40%)<sup>[6,7]</sup>. The 5-year survival rate is only 7%-20% because GSC has unique biological features compared with conventional stomach cancer, and GSC is commonly diagnosed at an advanced stage<sup>[4,8,9]</sup>.

The present study aimed to clarify the clinicopathological characteristics and operative methods for patients with GSC in order to improve their long-term outcomes.

#### MATERIALS AND METHODS

#### Patients

We retrospectively analyzed 92 patients who had undergone stomach resection between January 2003 and December 2012 at the Gastric Surgery Department of Fudan University Shanghai Cancer Center, China. All the patients were diagnosed through barium meal, endoscopic, and pathological examinations. Patient information was obtained from the medical records of Fudan University Shanghai Cancer Center. The clinical symptoms included abdominal pain, emesis, dysphagia, weight loss, anemia, and weakness. The clinical variables included age, gender, initial gastric disease, interval from initial surgery, reconstruction type of the first operation, type of gastric resection, tumor location, and tumor stage.

#### Follow-up

All patients were regularly contacted by telephone, and all patients received a follow-up. The duration of the follow-up period was defined as the interval from treatment date to the date of death or the last follow-up. The last follow-up occurred on March 31, 2014. Sixty-seven patients died at the last followup.

#### Evaluation

Tumor-node-metastasis (TNM) classification of gastric carcinoma was based on the seventh edition of the American Joint Committee on Cancer staging system. The surgical and pathological findings were recorded according to the Japanese Classification of Gastric Carcinoma, and the histological types were classified as differentiated or undifferentiated. The differentiated type included papillary adenocarcinoma and well/moderately differentiated adenocarcinoma, while the undifferentiated type included poorly or undifferentiated adenocarcinoma, and mucinous carcinoma. To calculate the survival curves, only patients who underwent tumor resection were included because these were the only patients with complete histopathological data and staging data.

#### Statistical analysis

Statistical analyses were performed using the SPSS version 19.0 statistical software package (SPSS IBM, United States). All continuous variables are presented as the median (range). The cumulative cause-specific overall survival rates were calculated using the Kaplan-Meier method. The log-rank test was used to assess differences between clinical factors. Cox proportional hazard models were used to determine which clinicopathological variables were predictive of GSC. P < 0.05 was regarded as significant.

# RESULTS

The median age was 60.8 (range: 37-91) years, and the male:female ratio was 4.4:1. The median interval time from the initial operation to the development of GSC was 16.5 years (range: 1-40 years). The latency periods were different between benign disease and gastric cancer. GSC tended to occur within 25 years post-operation with a benign initial disease and within the first 15 years post-operation for gastric cancer (Table 1, Figure 1). Seventy-six (82.6%) patients had clinical symptoms, including abdominal pain, emesis, dysphagia, weight loss, anemia and weakness. Other patients were diagnosed *via* routine endoscopy.

The detailed clinicopathological characteristics of all the patients are listed in Table 1. Concerning the initial gastric disease, 38 (41%) patients had benign disease, and 54 (59%) patients had gastric cancer. In total, 26 (28%) patients underwent Billroth-I reconstruction, and 65 (71%) patients received Billroth-II



# Table 1 Clinicopathologic features of the 92 patients with gastric stump cancer n (%)

Characteristic	Value
Age (yr) <sup>1</sup>	$60.8 \pm 10.0$
Sex	00.0 ± 10.0
Male	75 (81)
Female	17 (19)
Initial gastric disease	17 (17)
Benign	38 (41)
Malignant	54 (59)
Interval time from initial surgery (yr) <sup>1</sup>	$16.5 \pm 13.0$
Regular follow-up after primary surgery	
Yes	76 (83)
No	16 (17)
Reconstruction of primary surgery	
Billroth- I	26 (28)
Billroth-II	65 (71)
Roux-en-Y	1 (1)
Location	
Anastomotic	59 (64)
Non-anastomotic	33 (36)
Tumor size (mm) <sup>1</sup>	$4.0 \pm 2.0$
Borrmann type	
I	3 (3)
II	13 (14)
Ш	69 (75)
IV	7 (8)
Depth of invasion	
T1	0 (0)
T2	6 (7)
T3	5 (5)
T4	81(88)
Lymph node involvement	
N0	35 (38)
$\ge$ N1	57 (62)
Presence of distant metastasis	
M0	63 (68)
$\ge$ M1	29 (32)
Stage	
Ι	8 (9)
П	25 (26)
Ш	30 (33)
IV	29 (32)
Histology	
Differentiated	18 (20)
Undifferentiated	74 (80)
Type of treatment	
Curative resection	58 (63)
Palliative resection	12 (13)
Chemotherapy/radiotherapy	16 (17)
No treatment	6 (7)

<sup>1</sup>Age, tumor size and disease-free time are mean  $\pm$  SD.

reconstruction. Most patients (59, 64%) had malignant lesions at the anastomotic site, and the median tumor size was 4.0 cm. Additionally, Borrmann III (69, 75%) was the most common type based on the gross appearance. Histology revealed that the most common type of cancer was undifferentiated (80%). The TNM classification was as follows: stage I in 8 patients (9%), stage II in 25 (26%), stage III in 30 (33%), and stage IV in 29 (32%). The lymph node metastasis rate in patients with GSC was 38% (35/92).

Seventy patients received surgical treatments, and 58 patients were qualified for radical surgery. The

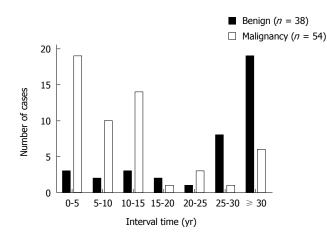


Figure 1 Time trend of stump carcinoma every 5 years for the primary gastric disease.

resectability rate was 59.8%, and 12 patients underwent palliative resection. Twenty-two patients declined surgery. Among them, 6 patients declined treatment, and 16 patients chose to receive chemotherapy/radiotherapy.

All 92 patients provided complete follow-up data. At the time of the last follow-up, 67 (72.8%) patients had died, and 25 (27.2%) patients were alive. The median survival duration was 29 mo, and the cumulative 1-, 3-, and 5-year overall survival rates were 78.3%, 45.6%, and 27.6%, respectively (Figure 2A). The survival curves also suggested that patients with regular follow-up after primary surgery had a better survival rate (Figure 2B and C). Their 1-, 3-, and 5-year survival rates were 93.8%, 75.0%, and 66.7%. However, the 1-, 3-, and 5-year survival rates were 87.5%, 47.7%, and 25.6%, respectively, for patients without regular follow-up after the primary surgery. Figure 2D demonstrates that patients with Borrmann type II cancer had the best survival rate (P = 0.0083). The 1-, 3-, and 5-year survival rates of the 58 patients who underwent radical resection were 79.3%, 52.2%, and 37.8%, respectively. Among them, 3 (3.3%) patients died during the peri-operative period. The perioperative mortality was similar to that of patients with conventional gastric cancer (2%-3%)<sup>[10]</sup>. The 1-, 3-, and 5-year survival rates of the 12 patients who received palliative resection were 66.7%, 25.0%, and 0%, respectively, and there were significant differences between the three groups (P = 0.0007) (Figure 2E). Table 2 shows the group characteristics according to the tumor stage. The 5-year survival rates for stages I, I, III, and IV were 85.7%, 47.4%, 16.0%, and 13.3%, respectively (P = 0.005).

# DISCUSSION

Despite a decline in the overall incidence of gastric cancer<sup>[11]</sup>, the incidence rate of GSC has increased during recent decades<sup>[3-5]</sup>. The incidence of GSC accounts for 1%-2% of all gastric cancers in Japan<sup>[2]</sup>.

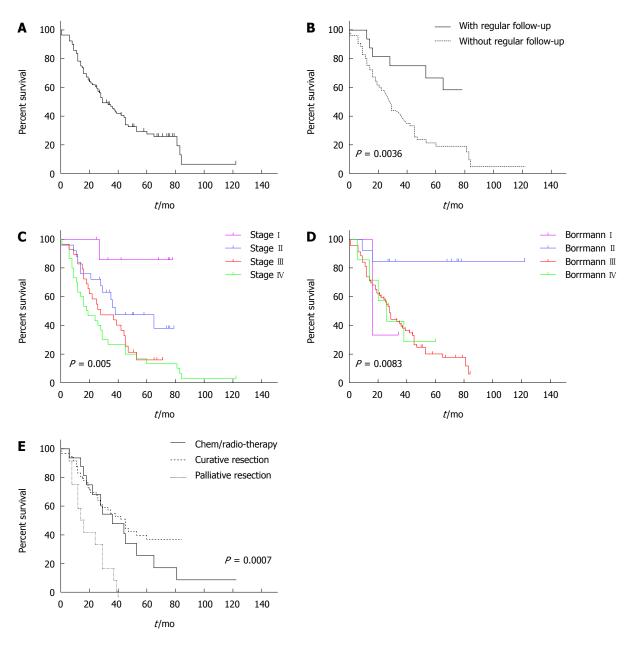


Figure 2 Overall survival proportions. A: Overall survival proportions of 92 patients with gastric stump cancer; B: Overall survival proportions between patients with and without regular follow-up after primary surgery are significantly different. The patients without regular follow-up after primary surgery had significantly porer overall survival; C: Overall survival proportions for patients with different stages; D: Overall survival proportions for patients with different Borrmann type; E: Overall survival proportions in gastric stump cancer according to type of treatments.

This increase indicates that we will face increasing challenges in the future.

To the best of our knowledge, the type of initial gastric disease has significant impact on the latency to GSC. The median interval for patients with benign disease is 30 years, and that for patients with gastric cancer is 12 years<sup>[12]</sup>. The incidence of GSC after gastric resection increases over time<sup>[13]</sup>. In the present study, the interval for benign disease was significantly longer than that for gastric cancer. Additionally, we observed different interval periods between benign disease and gastric cancer (Figure 1). The median interval time from initial operation to the development of GSC was 16.5 years (range: 1-40 years), which

is consistent with other studies<sup>[9]</sup>. Figure 1 indicates that GSC tends to occur within 25 years following the initial benign disease, and during the 15 years post-operation for patients who have gastric cancer.

The clinical symptoms of GSC have no obvious specificity, and GSC usually manifests as upper abdominal pain, loss of appetite, swallowing difficulty, vomiting, weight loss, and anemia. GSC is often diagnosed at an advanced stage due to the lack of early symptoms. It is easily misdiagnosed as an ulcer recurrence or anastomotic inflammation, which can lead to a delayed diagnosis and the loss of the best treatment opportunity. The remnant stomach is viewed as a precancerous lesion. The specific etiology of GSC is currently

Table 2 Comparison of baseline characteristics according to tumor stage $n$ (%)						
Variable		I ( <i>n</i> = 8)	II (n = 25)	III (n = 30)	IV ( <i>n</i> = 29)	
Histology	Differentiated	4 (4.3)	6 (6.5)	6 (6.5)	2 (2.2)	
	Undifferentiated	4 (4.3)	19 (20.6)	24 (26.1)	27 (29.3)	
Tumor Location	Anastomotic	4 (4.3)	17 (18.5)	21 (22.8)	17 (18.5)	
	Non-anastomotic	4 (4.3)	8 (8.7)	9 (9.8)	12 (13.0)	
Initial gastric disease	Benign disease	4 (4.3)	8 (8.7)	13 (14.1)	13 (14.1)	
	Gastric cancer	9 (9.8)	17 (18.5)	17 (18.5)	16 (17.4)	

Values in parentheses are percentages.

#### Table 3 Univariate and multivariate survival analyses in gastric stump cancer patients

Variable	<b>Univariate</b> <sup>1</sup>		<b>M</b> ultivariate <sup>2</sup>		
	P value	HR	95%CI	P value	
Age (yr) ( $\geq 65 vs < 65$ )	0.896				
Sex ratio (male vs female)	0.302				
Initial gastric disease (benign vs cancer)	0.443				
Interval time from initial surgery (yr) ( $\ge 15 vs < 15$ )	0.428				
Reconstruction of first operation (B-I vs B-II)	0.357				
Regular follow-up (yes vs no)	0.004	1.332	0.539-3.287	0.535	
Tumor size (mm) ( $\geq 40 vs < 40$ )	0.040	0.707	0.415-1.206	0.203	
Location (anastomotic vs non-anastomotic)	0.857				
Histology(differentiated vs undifferentiated)	0.005	0.470	0.212-1.038	0.062	
Borrmann type (I - II vs III-IV)	0.001	3.165	1.055-9.500	0.040	
Depth of invasion (T1-T2-T3 vs T4)	0.305				
Lymph node involvement (NO $vs \ge N1$ )	0.254				
Presence of distant metastasis (M0 vs M1)	0.004				
Stage (I - II vs III-IV)	0.002	0.603	0.323-1.124	0.111	
Type of treatment (curative vs other treatments)	0.001	1.780	1.061-2.987	0.029	

<sup>1</sup>The Kaplan-Meier method, and significance was determined by the log-rank test; <sup>2</sup>Multivariate survival analysis was performed using Cox proportional hazard models.

unclear. According to our data, 16 (17%) patients had no clinical symptoms, and the malignant lesions of the remnant stomach were identified through periodic endoscopies. Most of these patients had early-stage GSC, and their 5-year survival rate was 66.7%. The 5-year survival rate of patients who had clinical symptoms was 19.0%. The survival curves also suggested that patients who were followed had better survival rates (Figure 2B). Regular follow-up can facilitate early detection and early therapy, which improve the survival rate.

Previous studies report the unique clinicopathological characteristics for  $GSC^{[2,8,14]}$ . Our analysis demonstrated that the histological type was associated with prognosis (Table 3). The prognosis of patients with GSC was ultimately determined by the Borrmann lesion type and radical resection. Tumor location was also an important factor for predicting surgical outcomes<sup>[15-17]</sup>. The tumors commonly developed at the site of the gastrojejunal anastomosis. Some scholars thought that the type of reconstruction was associated with  $GSC^{[18-20]}$ . In our study the Billroth-II reconstruction and anastomotic groups were more likely to develop GSC, although there was no significant difference due to the small number of patients.

Some drugs have been used to treat GSC in Japan<sup>[21]</sup>.

However, in our study, surgery was still the most effective treatment. Although there were no significant differences in the histopathologic categories and tumor location of GSC compared with primary proximal gastric cancer<sup>[22-24]</sup>, GSC is the most frequently occurring tumor after the initial surgery and occurs in the remnant stomach due to an abnormal anatomy. Additionally, because surgery for GSC is the second surgery, there is an increased number of adhesions around the residual stomach. Therefore, radical surgery is more difficult than ordinary surgery. There were no severe complications during and after our operations, therefore, radical surgery is feasible. The survival rate in the radical resection group was significantly higher than those in the palliative resection group and the chemotherapy/ radiotherapy group. Our results demonstrated that chemotherapy/radiotherapy has a good short-term curative effect, but the long-term curative effect is still poor. Previous studies have reported higher incidences of postoperative complications in patients with GSC than in patients with primary gastric cancer<sup>[25]</sup>. Radical resection is still the best treatment option and may improve the survival outcomes of patients with GSC.

Admittedly, our study had a relatively small sample and was based on a retrospective analysis. However, even after acknowledging these limitations, we can

draw some meaningful conclusions regarding GSC.

In conclusion, the findings in the present study led us to draw the following conclusions. Borrmann type I /II and radical resection are independent prognostic factors for patients with GSC. Early detection of GSC is possible. Regular endoscopies and gastric biopsies for subtotal gastrectomy patients have significant impact on postoperative survival. Therefore, it is necessary and feasible to perform repeated endoscopic followups. If GSC is diagnosed, surgery should be performed. Additionally, radical resection may significantly improve the long-term survival of patients.

# COMMENTS

#### Background

Gastric stump as a precancerous condition remains a substantial clinical concern. However, few studies explored the clinicopathological characteristics and prognostic factors for gastric stump cancer (GSC).

#### **Research frontiers**

GSC is often described as a tumor with a poor prognosis because of the unique biological features and it is commonly found at an advantage stage. Therefore, it is necessary to explore the clinicopathological characteristics in a great number of clinical cases.

#### Innovations and breakthroughs

This is the first comprehensive clinical trial about GSC in China. We observed the unique clinicopathological characteristics and prognostic factors for GSC, and the radical resection may significantly improve the long-term survival.

#### Applications

The results of the present study suggest that regular follow-up by endoscopy and gastric biopsy is necessary for subtotal gastrectomy patients, and the radical resection may significantly improve the long-term survival.

#### Terminology

The incidence of GSC accounts for 1%-7% of all gastric carcinomas following gastrectomy, and this frequency continues to increase. Gastric stump as a precancerous condition remains a substantial clinical concern. GSC is often described as a tumor with poor prognosis.

#### Peer-review

The manuscript is a remarkable article regarding GSC, which remains a substantial clinical concern and has its unique clinicopathological characteristics, as the appearance of GSC is earlier in the primary malignant cases than in the primary benign cases. So it is necessary to follow patients closely.

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