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WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

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ORIGINAL ARTICLE

Observational Study

Does gastric stump cancer really differ from primary proximal gastric cancer? A multicentre, propensity score matching-used, retrospective cohort study

Shuan-Hu Wang, Jing-Cheng Zhang, Liang Zhu, He Li, Kong-Wang Hu

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Abstract

BACKGROUND

Although the location of proximal cancer of the remnant stomach is the same as that of primary proximal cancer of the stomach, its clinical characteristics and prognosis are still controversial.

AIM

To evaluate the clinicopathological features and prognosis factors of gastric stump cancer (GSC) and primary proximal gastric cancer (PGC).

METHODS

From January, 2005 to December, 2016, 178 patients with GSC and 957 cases with PGC who received surgical treatment were enrolled. Patients in both groups underwent 1:1 propensity score matching analysis, and both clinical and pathological data were systematically collected for statistical purposes. Quality of

life was evaluated by the C30 and STO22 scale between GSC-malignant (GSC following gastric cancer) and GSC-benign (GSC following benign lesions of the stomach).

RESULTS

One hundred and fifty-two pairs were successfully matched after propensity score matching analysis. Of the 15 demographic and pathological variables collected, the analysis further revealed that the number of lymph nodes and positive lymph nodes were different prognostic and clinicopathological factors between PGC and GSC. Univariate and multivariate analyses showed that gender, differentiation degree and tumor-node-metastasis stage were independent risk factors for patients with GSC. Gender, vascular invasion, differentiation degree, depth of infiltration, positive lymph nodes, and tumor-node-metastasis stage were independent risk factors for patients with PGC. The 5-year overall survival and cancer-specific survival of patients with GSC were significantly lower than those in the PGC group, the scores for overall quality of life in the GSC-malignant group were lower than the GSC-benign, and the differences were statistically significant.

CONCLUSION

The differences in clinicopathological characteristics between GSC and PGC were clarified, and PGC had a better prognosis than GSC.

Key Words: Gastric stump cancer; Primary gastric cancer; Clinicopathological risk factors; Quality of life; Propensity score matching

Core Tip: Although the location of gastric stump cancer (GSC) is the same as that of primary proximal gastric cancer (PGC) , its clinical characteristics and prognosis are still controversial. In our research, 152 pairs of patients were successfully matched after propensity score matching analysis. The differences in clinicopathological characteristics between GSC and PGC were clarified, and PGC had a better prognosis than GSC. The scores for overall quality of life in the GSC-malignant group were lower than the GSC-benign group, and the differences were statistically significant.

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INTRODUCTION

Gastric cancer is one of the most common malignant tumours of the digestive tract worldwide. According to the latest statistics, there were approximately 1.034 million new cases of gastric cancer worldwide in 2018, resulting in a total of approximately 783000 deaths[1-3]. The 5-year survival rate of early gastric cancer patients exceeds 90%. However, the diagnostic rate of early gastric cancer is < 10%[4], and the 5-year survival rate of advanced gastric cancer is still < 50%[5, 6]. In recent years, gastric stump cancer (GSC), which accounts for only approximately 1%-7% of gastric cancers, has attracted more attention from scholars[7-10].

The concept of GSC was first proposed as the occurrence of residual cancer after surgery for benign lesions in 1922 by Balfour[11]. The current definition of GSC is, regardless of the method of first surgical resection or type of reconstruction, cancer found in the stump stomach 5 years after primary surgery for benign diseases or 10 years after primary surgery for malignant diseases. Although the detection rate of early gastric cancer continues to increase, due to the lack of typical symptoms and longer postoperative time leading to a decrease in patients' willingness to undergo gastroscopy, GSC is often still in the late stage when detected, which seriously reduces the survival time of patients. Although radical surgery is still the only treatment method for GSC, this complex surgery still has a high incidence of postoperative complications and mortality. Anatomical changes, intra-abdominal adhesions, and frequent combined resection of other organs make the surgery of GSC difficult. Currently, most studies on this surgical treatment have only registered a few patients and provided a brief descriptive analysis of their complications.

It is worth noting that although GSC originates from the same region after distal gastrectomy for gastric cancer and proximal gastric cancer (PGC), the lymphatic drainage direction of GSC patients and PGC patients is different due to the influence of first-time surgical lymph node dissection. Moreover, intra-abdominal adhesions in GSC patients may affect the quality of lymph node dissection. Although the clinical and pathological characteristics of GSC and PGC have been compared in the past, clinical studies on GSC are very rare, especially high-quality, large-scale randomised controlled studies. In recent years, there has been continuous literature exploring the prognosis of GSC and PGC, there is still controversy in this regard, partly due to the limited number of GSC patients. In addition, the scope of lymph node dissection and how these patients should be staged are still unresolved issues. It is necessary to understand the character-

istics of GSC to determine its prognosis and appropriate treatment strategies.

This study aims to evaluate the differences in clinical pathological characteristics and prognosis between PGC and GSC. Moreover, for patients with GSC caused by benign or malignant lesions, we evaluated their postoperative quality of life (QoL) to explore the impact of disease duration and psychological factors.

MATERIALS AND METHODS

This article is in line with the STROCSS criteria[12].

Patients and Follow-up

One hundred and seventy-eight patients with GSC and 957 patients with PGC were enrolled as the control group from January, 2005 to December, 2016. None of the patients received neoadjuvant therapy. The clinical and pathological data of the patients were collected, including age, gender, tumor-node-metastasis (TNM) stage (T and N stages were classified according to the criteria described in the American Joint Committee on Cancer Staging Manual, 8th edition), number of lymph nodes obtained, nerve invasion, vascular invasion, surgical methods, blood transfusion, length of hospital stay, American Society of Anaesthesiologists (ASA) grade, and bypass type. Variables that were initially recorded as continuous variables were also included in the current analysis.

In this study, the survival time ranged from the day of surgery to the day of death *via* telephone and outpatient visits, which included enhanced computed tomography every 6 mo, routine blood tests, and biochemical and tumour indicators, and terminated when the patients died. In the first year after surgery, all GSC patients who were still alive during the follow-up period were followed up to assess QoL, and the scoring scale was used to record the patient's general living conditions.

QoL

QoL was evaluated using the Chinese version of the EORTC QLQ-C30 and QLQ-STO22[13,14]. After the patients were introduced, they completed the questionnaire. Based on the EORTC QLQ-C30 and QLQ-STO22 scoring manuals, the original data of each scale were converted into 0-100. Statistical processing was performed using the EORTC QLQ-C30 questionnaire survey. For the QLQ-STO22 questionnaire survey, the higher the score, the worse the QoL. The *t*-test was used to compare the QoL.

Propensity score matching

In this propensity score matching (PSM) analysis, the following variables were considered potential confounders between the groups and were adjusted: Gender (female *vs* male), age (> 55 *vs* ≤ 55 years), and ASA score (ASA I/II *vs* III/IV). Propensity scores were calculated by bivariate logistic regression, using a 1:1 case-control match with a caliper value of 0.1 (one-to-one nearest-neighbor matching). The standardized difference (10% or 0.1) was used to compare the distribution of all paired.

Statistical analysis

The Cox proportional hazards regression model with backward variable selection was used to determine the factors independently related to survival time. It has also been reported that the 95% confidence interval (CI) of the hazard ratio (HR) has a significant effect. In this study, a P value of < 0.05 was used to define statistical significance, and all analyses were performed using SPSS 19.0.

RESULTS

Results of the PSM analysis

In this cohort, a total of 178 patients with GSC underwent surgical treatment in the general surgery department of the three hospitals (Figure 1). The mean age was 63 years. According to the American Joint Committee on Cancer Staging Manual, there were 15, 43 and 94 cases of stage I, II and III GSC, respectively. Nine hundred and fifty-seven patients with PGC underwent surgical treatment in the three hospitals. There were 736 male patients and 221 female patients. The mean age was 67 years. According to the American Joint Committee on Cancer Staging Manual, there were 132, 168, and 657 cases of stage I, II and III PGC, respectively.

Before PSM, there were significant differences in the number of lymph nodes, blood transfusion, TNM stage and differentiation degree between the PGC and GSC group. After PSM, there were 152 cases in these two groups, the statistical results showed that there were significant differences in the number of lymph nodes, positive lymph nodes, and differentiation degree between two groups (Table 1).

Risk factors

Table 2 shows that gender, degree of differentiation, and TNM stage were found to be risk factors for GSC. The prognostic factors in PGC determined by the univariate analysis were as follows: Gender, vascular invasion, degree of differentiation, depth of infiltration, number of positive lymph nodes, and TNM stage were found to be risk factors for

Table 1 Clinicopathologic characteristics of included patients before and after propensity score matching

Variables	Before PSM				After PSM			
	GSC (*n* = 178)	PGC (*n* = 957)	χ^2/Z	*P* value	GSC (*n* = 152)	PGC (*n* = 152)	χ^2/Z	*P* value
Gender			0.222	0.638			0.017	0.895
Female	44	221			38	39		
Male	134	736			114	113		
Age (yr)			0.452	0.502			0.020	0.0889
> 55	127	706			120	119		
≤ 55	51	251			32	33		
Tumor size			2.300	0.129			2.608	0.106
> 3.5 cm	103	611			91	77		
≤ 3.5 cm	75	346			61	75		
ASA grade			2.590	0.108			0.058	0.809
I/II	112	540			99	101		
III/IV	66	417			53	51		
Hospital stay after surgery (d)	12.65 ± 5.13	12.77 ± 4.42	1.023	0.133	11.13 ± 4.71	11.45 ± 5.90	1.156	0.232
Blood transfusion			10.705	0.001			2.114	0.156
Yes	42	127			34	57		
No	126	780			108	85		
Vascular invasion			0.405	0.525			0.920	0.337
Positive	36	339			32	70		
Negative	51	415			49	82		
Missing	91	203			71	-		
Nerve invasion			0.475	0.491			0.280	0.596
Positive	49	389			40	63		
Negative	55	378			49	89		
Missing	74	190			63	-		
Differentiation degree			18.537	0.000			1.452	0.028
High/median	38	100			27	21		
Low	128	824			115	131		
Missing	12	33			10	-		
Depth of infiltration			0.310	0.578			0.838	0.360
T1/T2	40	198			36	43		
T3/T4	138	762			116	109		
Number of lymph nodes			3.859	0.049			6.752	0.009
≥ 7	101	617			94	115		
< 7	77	340			58	37		
Positive lymph nodes			0.570	0.450			19.667	0.000
≥ 3	86	433			71	109		
< 3	92	524			81	43		
TNM stage			10.367	0.006			0.062	0.969
I	15	132			17	18		
II	43	168			38	39		

III	94	657	97	95

PSM: Propensity score matching; GSC: Gastric stump cancer; PGC: Proximal gastric cancer; TNM: Tumor-node-metastasis; ASA: American Society of Anaesthesiologists.

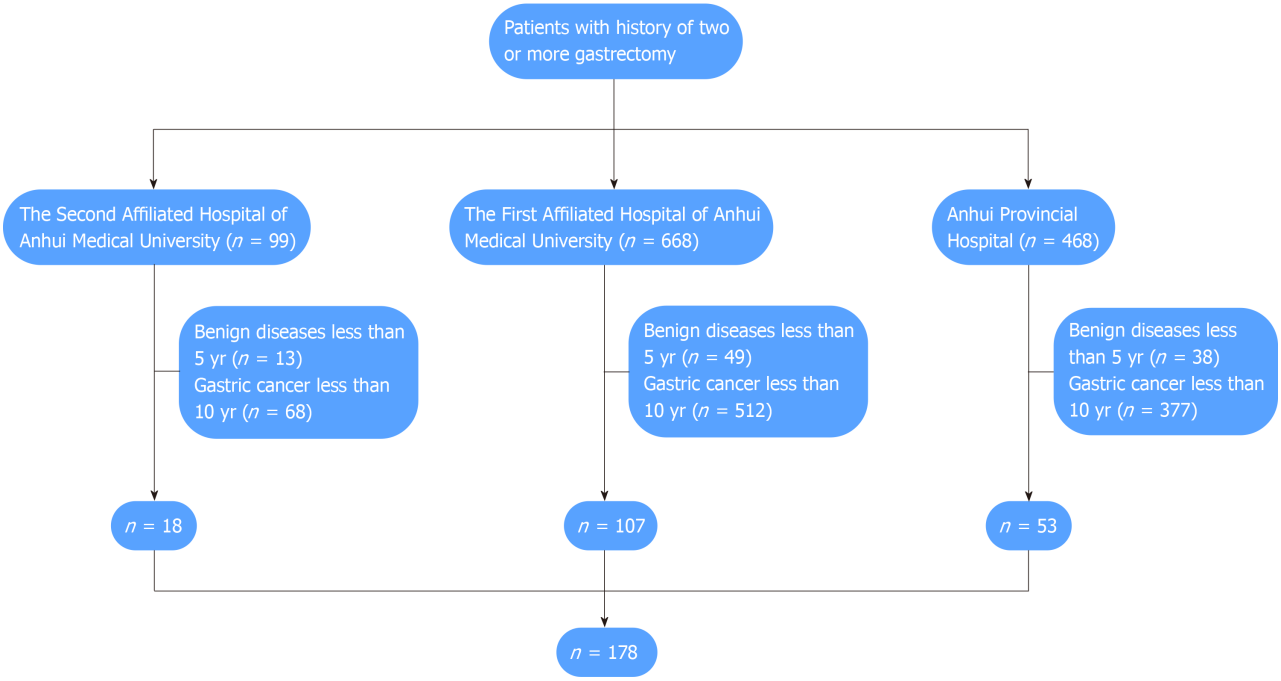

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Figure 1 Flow chart of gastric stump cancer patient selection.

PGC. Multivariate analyses were conducted to identify the independent prognostic factors, and the results are shown in Table 3. The degree of differentiation, and TNM stage were independent prognostic factors for patients with GSC and differentiation degree, depth of infiltration, positive lymph nodes and TNM stage were independent prognostic factors for PGC patients.

Actual survival

The median follow-up time in the PGC group was 83 mo. At the last follow-up in June 2022, 72.2% of patients had died. The median follow-up time in the GSC group was 80 mo, and 82.1% of patients had died. The overall median survival in the PGC group was 34 mo and was 24 mo in the GSC group. The risk of death after GSC radical surgery was not constant. Most patients with GSC experienced overall-cause death or cancer-specific death in the first 3 years after surgery. After a period of evaluation, the probability of all-cause death and cancer-specific death peaked at 12 mo after surgery and then gradually decreased. We also evaluated the probability of survival for patients with GSC over a period and showed that the probability of cancer-specific survival increased with prolongation of postoperative survival. Correspondingly, with the prolongation of survival time, the recurrence rate in patients with GSC decreased. In the GSC control group, the overall survival during the follow-up period was significantly lower than that in the PGC group (HR = 0.7290, 95%CI: 0.5578-0.9529, P = 0.0207, Figure 2A), the cancer specific survival in the PGC group was also significantly higher than that in the GSC group (HR = 0.7504; 95%CI: 0.5686-0.9902, P = 0.0424, Figure 2B).

QoL

According to the QLQ-C30 questionnaire, the overall health status scores of patients with GSC-benign (GSC-B) and those with GSC-malignant (GSC-M) were 67.15 ± 20.1 and 56.2 ± 18.5, respectively. There was a significant difference between the two groups by statistical analysis, which showed that the overall health status of the GSC-M group was worse than that of the GSC-B group. In terms of function scale, the scores for physical, emotional and cognitive function in patients on the symptom scale, and the scores for fatigue, pain, diarrhea, economic difficulties, and reflux in the two groups were not different.

Table 2 Univariate analysis of cancer-specific survival in gastric stump cancer and proximal gastric cancer

Variables	GSC				PGC			
	n = 152	HR	95%CI	*P* value	*n* = 152	HR	95%CI	*P* value
Gender		1.991	0.937-3.422	0.038[a]		1.991	0.937-3.422	0.038[a]
Female	38				38			
Male	114				114			
Age (yr)		1.117	0.681-1.833	0.900		1.111	0.690-1.804	0.893
> 55	120				119			
≤ 55	32				33			
Tumor size		1.012	0.622-1.646	0.961		1.405	0.598-1.837	0.902
> 3.5 cm	91				77			
≤ 3.5 cm	61				75			
ASA grade		1.338	0.792-2.260	0.276		1.257	0.777-2.900	0.331
I/II	99				101			
III/IV	53				51			
Hospital stay after surgery (d)	11.13 ± 4.71	0.635	0.308-1.307	0.218	12.45 ± 5.90	0.873	0.299-1.780	0.412
Blood transfusion		1.114	0.655-1.896	0.690		1.296	0.588-2.001	0.255
Yes	44				67			
No	108				85			
Vascular invasion		1.662	0.210-2.138	0.630		1.603	1.000-9.568	0.049[a]
Positive	32				70			
Negative	49				82			
Missing	71				-			
Nerve invasion		1.710	0.971-3.012	0.063		4.660	0.981-22.134	0.053
Positive	40				63			
Negative	49				89			
Missing	63				-			
Differentiation degree		2.714	1.603-4.596	0.000[a]		3.503	1.734-11.385	0.000[a]
High/median	27				21			
Low	115				131			
Missing	10				-			
Depth of infiltration		3.614	2.290-4.289	0.080		2.332	0.074-4.498	0.041[a]
T1/T2	36				43			
T3/T4	116				109			
Number of lymph nodes		0.792	0.336-1.869	0.595		3.432	0.874-12.441	0.077
≥ 7	94				115			
< 7	58				37			
Positive lymph nodes		0.223	0.110-0.881	0.124		0.485	0.260-0.906	0.023[a]
≥ 3	71				109			
< 3	81				43			
TNM stage		5.727	2.579- 12.715	0.000[a]		5.446	2.555-11.992	0.000[a]
I	17				18			
II	38				39			

III	97	95

[a]*P* < 0.05.

HR: Hazard ratio; CI: Confidence interval; GSC: Gastric stump cancer; PGC: Proximal gastric cancer; TNM: Tumor-node-metastasis; ASA: American Society of Anaesthesiologists.

Table 3 Multivariate analysis of factors affecting cancer-specific survival

	GSC			PGC		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Gender	1.552	0.129-3.428	0.058	1.847	0.135-2.990	0.043
Differentiation degree	1.430	1.055-1.938	0.021[a]	1.999	0.636-3.004	0.027[a]
Depth of infiltration				2.929	1.383-4.691	0.000[a]
Positive lymph nodes				2.452	1.085-3.942	0.012[a]
TNM stage	1.426	1.040-1.955	0.027[a]	2.771	1.448-4.662	0.000[a]
Vascular invasion				1.269	0.680-3.998	0.070

[a]*P* < 0.05.

HR: Hazard ratio; CI: Confidence interval; GSC: Gastric stump cancer; PGC: Proximal gastric cancer.

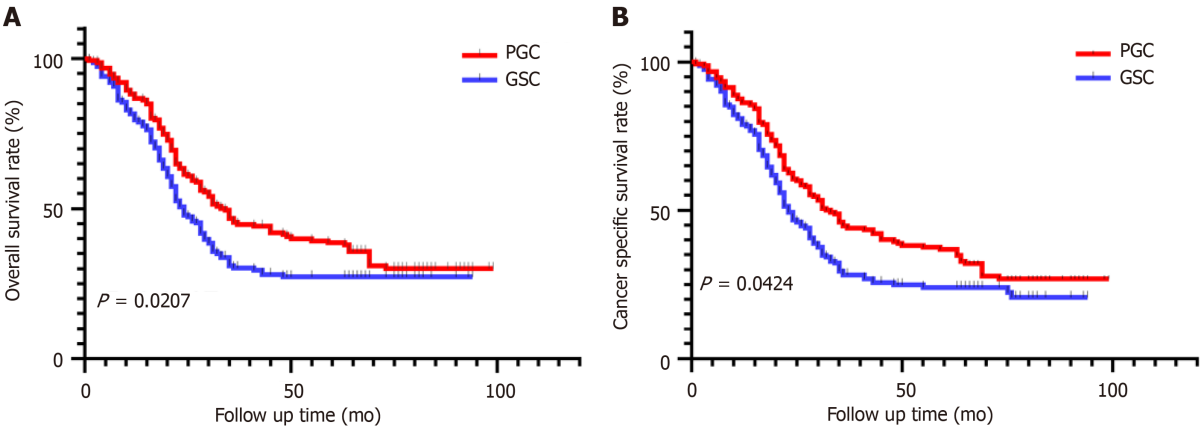

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Figure 2 Differences in survival between proximal gastric cancer patients and gastric stump cancer patients. A: Overall survival in proximal gastric cancer (PGC) and gastric stump cancer (GSC) patients; B: Cancer-specific survival in PGC and GSC patients. PGC: Proximal gastric cancer; GSC: Gastric stump cancer.

DISCUSSION

There has been no large-scale high-quality study in the field of GSC. Previous studies on GSC are few, especially clinical trials with more than 100 cases. A study by Japanese scholars included 156 GSC patients and 755 PGC patients and the authors believed that the prognosis of GSC patients was worse than that of PGC patients, moreover, GSC secondary to malignant lesions occurred earlier than that of benign lesions after surgery[15]. Wang *et al*[16] focused on cardiac cancer, and included 48 GSC patients and 96 primary cardiac cancer patients. The results confirmed that the survival rate of patients with residual gastric cardia cancer after radical resection was lower than that of primary cardiac cancer patients, but the survival rate of patients without serous infiltration or lymph node metastasis was similar to that of primary cardiac cancer patients. Ramos *et al*[17] also obtained similar results, indicating that there is still a lot of controversy regarding the prognosis of GSC and PGC patients, and further clarification is needed in large-scale clinical trials, especially high-quality randomised controlled trials.

At present, the definition of GSC is still controversial. These disputes easily make researchers focus on the time interval and the nature of the primary disease, and often ignore the nature of GSC, its cause. The incidence of GSC has been increasing in recent years, and the reason for this is unclear. However, some scholars believe that damage to the epithelial cells of the gastric mucosa and weakening of the gastric mucosal barrier by alkaline reflux after the previous surgery are important factors in the occurrence of GSC. Healed anastomoses or suture ulcers are important factors in stress

stimulation; the occurrence and development of some GSCs may be related to Epstein-Barr virus infection; the occurrence of GSCs is also related to the previous surgical method[18,19]. After partial resection, Billroth II (B-II) surgery is associated with a higher incidence of GSC due to its higher reflux rate. In this study, more than half of patients in the GSC group underwent B-II anastomosis during their first surgery, while the proportion of Roux-en-Y (R-Y) anastomosis was less than 11%. It can be seen that the proportion of GSC in patients with B-II anastomosis was higher. Undeniably, R-Y anastomosis performs better in resisting digestive reflux.

R-Y anastomosis can reduce reflux, the occurrence of residual gastritis, and the incidence of GSC[20-22]. Cutting the vagus nerve during distal gastrectomy also causes cancer. After cutting, the gastric defence factors are reduced, and the blood circulation, secretion, and regeneration of the gastric mucosa are affected, resulting in cell DNA mutations during the proliferation process. This is carcinogenic[23], and its occurrence is related to factors such as age, heredity, and sex. Research shows that in patients diagnosed with GSC, the median age is between 67 and 71 years and male patients are at greater (4-9 times) risk of developing GSC than female patients[24]. In this study, the number of male patients with GSC was more than three times that of female patients, with a mean age of 63 (range, 39-76) years.

It is worth noting that in this study, only 36.2% of patients who underwent surgical treatment for benign diseases developed GSC, while the proportion of patients with GSC-M was 63.8%. Due to the fact that the biological behavior of tumor cells, especially their metastatic ability, may vary depending on the location of the tumor, in order to avoid this bias, we only selected one-third of primary PGC patients as the control group. Overall, the GSC group exhibited similar characteristics to PGC patients. In addition, survival data processed by statistical methods showed a difference in survival time between the GSC group and the PGC group, which is contrary to the previous research results of Ramos *et al*[17]. As expected, among the patients we included, the number of lymph nodes after GSC surgery was significantly lower than that in the PGC group. Some studies have shown that the characteristics of lymph node metastasis in GSC are different due to the interruption of lymphatic pathways during the first operation, which may lead to more involvement of the splenic artery, splenic hilum, lower mediastinum and jejunum mesentery lymph nodes[25-27]. However, the standard extension for lymph node resection has not yet been determined. It is well known that an enlarged lymph node resection in this area can seriously affect the QoL after surgery. Therefore, the scope of mesentery lymph node resection should be determined according to the extent of lymph node involvement, taking into account the risks and benefits[28].

In recent years, the application of neoadjuvant therapy in the perioperative period of gastric cancer has become a consensus. However, the application of this conclusion in GSC still needs more evidence. Patients with neoadjuvant therapy were not included in this study as the number of patients with GSC receiving neoadjuvant therapy was small, and the inclusion of too many patients with neoadjuvant therapy in the PGC group may have a significant impact on the results. There is no denying that neoadjuvant therapy has several potential advantages, including improving R0 removal rates, testing tumour response to a specific treatment regimen, and not only that, it provides a time window to evaluate tumour biology. Despite local control, an important risk of neoadjuvant therapy is that it may introduce a greater probability of distant metastasis if treatment fails to control tumour progression. The best approach, however, is unclear. In conclusion, selective addition of neoadjuvant chemotherapy and/or radiotherapy is beneficial in specific anatomical and histopathological subtypes.

The clinical symptoms of GSC lack specificity, the resection rate is low after diagnosis, and the prognosis is poor. It causes damage to the patients' physical, psychological, and social functions and affects their health-related QoL (HRQOL). However, few studies have evaluated the postoperative QoL in patients with GSC. In this study, the HRQOL in two groups of GSC patients caused by benign (GSC-B) and malignant (GSC-M) lesions was comprehensively evaluated using the QLQ-C30 and gastric cancer-specific scale QLQ-STO22. The results of this study show that the scores for overall QoL in the GSC-B group were higher than those in the GSC-M group and there was no significant statistical difference in other aspects. We speculate that this may be related to the postoperative chemotherapy received by patients in the GSC-M group, as the proportion of postoperative chemotherapy in the GSC-M group was significantly higher. On the other hand, we found that the differentiation level of patients in the GSC-M group was worse than that in the GSC-B group, and the proportion of poorly differentiated patients was higher, which may also be a reason for the decline in their QoL. Early clinical diagnosis, appropriate treatment, timely control of disease progression, and reduction of physical symptoms are conducive to improving patients' HRQOL. While improving their physiological function, patients should recognise the positive role of psychological and spiritual factors in the course of cancer, carry out necessary psychological treatment and intervention, alleviate psychological obstacles, and eliminate the negative impact of bad emotions on HRQOL as far as possible.

CONCLUSION

The differences in clinicopathological characteristics between GSC and PGC were clarified, and PGC had a better prognosis than GSC.

ARTICLE HIGHLIGHTS

Research background

The clinicopathological characteristics of gastric stump cancer (GSC) and proximal gastric cancer (PGC) have not yet been confirmed. There has always been controversy regarding the differences in treatment and prognosis prediction.

Research motivation
Evaluation of the differences between GSC and primary PGC using a larger sample size.

Research objectives
The object of this study was to evaluate the clinicopathological features, and prognostic factors of GSC and primary PGC.

Research methods
After detailed data statistics and data collection, 178 GSC patients and 957 PGC patients underwent surgical treatment at multiple centers. A 1:1 propensity score matching analysis was conducted on the two groups of patients, with 152 patients in each group entering the final analysis. Single factor and multivariate analysis were used to study the risk factors in gastric cancer patients. The survival curve was plotted to compare the differences in survival time between the two groups. The quality of life (QoL) of GSC-malignant (GSC-M) (post cancer GSC) and GSC-benign (GSC-B) (post benign gastric lesion GSC) patients was evaluated using the C30 and STO22 scales.

Research results
The number of lymph nodes and positive lymph nodes were different prognostic and clinicopathological factors between PGC and GSC. The 5-year overall survival and cancer-specific survival of patients with GSC were significantly lower than the PGC group, the scores for overall QoL in the GSC-M group were lower than the GSC-B group, and the differences were statistically significant.

Research conclusions
The differences in clinicopathological characteristics between GSC and PGC were significant, and compared to GSC patients, PGC patients had a better prognosis, and the overall health status of the GSC-M group was worse than that of the GSC-B group.

Research perspectives
More large-scale randomised controlled trial studies are needed to provide higher-level evidence regarding the comparison between PGC and GSC.

FOOTNOTES

Co-corresponding authors: He Li and Kong-Wang Hu.

Author contributions: Wang SH and Zhang JC contributed to the data statistics and writing; Wang SH, Zhang JC, and Zhu L collected the data; Li H and Hu KW were involved in the design of ideas and quality control; Wang SH and Zhang JC contributed equally to this work. KW Hu and Li H contributed equally to this work as co-corresponding authors. There are several reasons for this decision. First of all, although the two authors have slight differences in their contributions to the research, they have maintained close communication and effective discussion throughout the whole process of the project, which has made the project move forward in the right direction and finally improved the quality of the paper. In terms of project design, our original plan was not the research idea presented now, but with deepening of the research, the two authors timely revised the direction of the article, and finally achieved successful publication of the manuscript. We believe that the designation of co-authors accurately reflects the degree of contribution to the research and reflects the collaborative spirit of the team.

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