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ABOUT COVER

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WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, etc.

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Retrospective Study

Subtotal gastrectomy combined with chemotherapy: An effective therapy for patients with circumscribed Borrmann type IV gastric cancer

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Author contributions: Huang HB and Li K designed the research; Gao ZM and Li K treated the patients and collected the material and clinical data from the patients; Huang HB and Sun AQ performed the assays; Liang WT and Huang HB analyzed the data; Huang HB wrote the paper.

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Abstract

BACKGROUND

Although Borrmann type IV (B-4) gastric cancer has a higher mortality rate and presents distant metastasis easily, especially peritoneal metastasis, when diagnosed, some B-4 patients were found to have no distant metastasis by preoperative detection and underwent curative surgery, which was defined as circumscribed B-4 in our study. In this study, we focused on the circumscribed B-4 patients without distant metastasis during surgery to identify factors related to prognosis and postoperative peritoneal cavity metastasis (PPCM), which is important for selecting an appropriate therapeutic strategy.

AIM

To identify factors related to the prognosis and PPCM of B-4 patients.

METHODS

A total of 117 B-4 patients who underwent gastrectomy between January 2005 and December 2012 were included in this study. Survival analysis was performed using Kaplan-Meier analysis and Cox multivariate models. Pearson correlation analyses were performed to identify the factors related to PPCM. All statistical analyses were performed using SPSS 20.0.

RESULTS

Lymph node status, gastrectomy type, and postoperative chemotherapy were independent prognostic factors in 117 circumscribed B-4 patients. Subtotal gastrectomy combined with chemotherapy could significantly improve the long-term survival time. Six patients who were diagnosed with pN0 and received the

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combination therapy had a 3-year survival rate of 100% and a median survival of 77.7 mo. Even for patients with metastatic lymph nodes ($n = 13$), the combination therapy also increased the 3-year overall survival rate to 57.1%. In addition, positive lymph node status was the only factor ($P = 0.005$) correlated with PPCM in certain B-4 patients, and chemotherapy was useful for suppressing PPCM in patients with subtotal gastrectomy but not in those with total gastrectomy.

CONCLUSION

Lymph node status is an independent prognostic factor for circumscribed B-4 patients. In addition, subtotal gastrectomy and postoperative chemotherapy could effectively improve prognosis and even suppress PPCM.

Key Words: Gastric cancer; Circumscribed; Borrmann type IV; Prognosis; Subtotal gastrectomy; Chemotherapy

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Core Tip: This is a retrospective study to evaluate the factors related to prognosis and prognostic postoperative peritoneal cavity metastasis for circumscribed Borrmann type IV (B-4) patients. We reported that lymph node metastatic status, gastrectomy type, and postoperative chemotherapy were the independent prognostic factors. Subtotal gastrectomy combined with chemotherapy could significantly improve the long-term survival time of circumscribed B-4 patients. And chemotherapy was also useful for suppressing postoperative peritoneal cavity metastasis in patients with subtotal gastrectomy. We believe that our study makes a significant contribution to the literature because it recommended reasonable treatment schedules for the B-4 patients, which can increase survival time to a certain extent.

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INTRODUCTION

Gastric cancer (GC) is the fourth most common malignancy and the second most frequent cause of cancer-related death worldwide, with approximately 951600 new cases and 723100 deaths every year^[1-3]. Borrmann type IV (B-4) GC, as an aggressive type of GC, accounts for approximately 10% of all GC cases in Asia^[4,5]. B-4 lesions are characterized as lesions that diffusely infiltrate the gastric wall without ulceration or elevation. Compared with other types of GC, the occurrence rates of serosal invasion, positive lymph nodes, and distant metastasis in B-4 patients are higher.

Currently, surgery with chemotherapy is the major treatment method for advanced GC, which significantly improves the rate of long-term overall survival (OS). However, many B-4 patients are not suitable for surgical treatment at the time of diagnosis, and the 3-year OS rate of B-4 patients is only approximately 15%-20%^[6-8]. Studies on the clinicopathology and prognosis of B-4 patients have had controversial findings^[4,8-12]. Some B-4 patients were found to have no distant metastasis by preoperative detection and underwent curative surgery, which was defined as circumscribed B-4 in our study. Circumscribed B-4 accounts for relatively fewer cases of B-4 patients, and the clinicopathological characteristics and prognostic analysis of these patients would help us to understand the recurrence and metastasis of GC. There is no related research, especially for circumscribed B-4 patients.

In this study, we aimed to identify the factors related to prognosis and postoperative peritoneal cavity metastasis (PPCM) for circumscribed B-4 patients and to further explore the appropriate therapeutic strategies.

MATERIALS AND METHODS

Patient selection

A total of 1803 patients were diagnosed with GC and underwent gastrectomy at the First Affiliated Hospital of China Medical University from January 2005 to December 2012. Among them, 117 circumscribed B-4 patients were included in our analysis. The inclusion criteria for the patients were as follows: (1) B-4 gastric lesions and no distant metastasis were confirmed by preoperative detection and histopathology postoperatively; (2) Gastrectomy, including subtotal or total, was performed without neoadjuvant therapy; and (3) Detailed clinicopathological and follow-up data could be obtained for each patient. This study was approved by the Ethics Committee of China Medical University, and informed consent was obtained from the patients.

Data collection

The following data were collected: Age, gender, tumor size, tumor location, radical degree (R0/R1), histological type (well/poor), tumor invasion depth (pT), lymph node status (pN), lymphatic vessel infiltration, subtotal/total gastrectomy, postoperative chemotherapy, PPCM, and overall survival time. Of these, highly or moderately differentiated adenocarcinoma was classified as the well differentiated histological type, while others were classified as the poorly differentiated histological type. Selection indication of chemotherapy for GC patients was based on the National Comprehensive Cancer Network (NCCN) Guidelines. The adjuvant chemotherapy regimen was FOLFOX6 in postoperative 6 mo, including 5-fluorouracil and platinum. Completion degree of chemotherapy was heterogeneous, with eight or less cycles. Follow-up was completed by December 2017, and stage was classified according to the 8th edition of the American Joint Committee on Cancer (AJCC) classification system.

Statistical analysis

Continuous variables are expressed as the mean \pm standard deviation (SD), and categorical variables are expressed as frequencies. We performed multivariate analyses with the Cox proportional hazards model to identify independent prognostic factors. In addition, Kaplan-Meier analysis and the log-rank test were also used to evaluate the prognostic difference between groups. Pearson correlation analyses were performed for related factors of PPCM. The above statistical analyses were performed using SPSS 20.0, and $P < 0.01$ was considered statistically significant.

RESULTS

Baseline clinicopathological characteristics

A total of 117 patients were diagnosed with circumscribed B-4 GC and finally included in our analyses. As shown in Table 1, the mean age of the patients was 57.55 years, and the mean diameter of tumors was 7.81 cm. According to TNM stage, there were 27 cases of stage II and 90 cases of stage III. Of these, 81 (69.2%) patients had stage pT4, and 65 (55.6%) had stage pN3. A total of 116 patients received D2 lymphadenectomy, and the other one underwent D2+ lymphadenectomy. None of the 117 patients had distant metastasis, and cytology result of peritoneal lavage fluid was negative in our study.

Results of univariate and multivariate prognostic analyses

According to the Cox analysis, gastrectomy type ($P = 0.003$), pN stage ($P = 0.000$), and postoperative chemotherapy ($P = 0.007$) were crucial for predicting the prognosis of these circumscribed B-4 patients (Table 2). As shown in Figure 1A, the prognosis of patients who underwent subtotal gastrectomy was better than that of patients who underwent total gastrectomy ($P = 0.000$). After screening out patients with lower-middle lesions, the prognostic superiority of subtotal gastrectomy was consistent (Figure 1B). Notably, patients with a higher pN stage always had a worse prognosis (Figure 1C), but the prognostic value of pT stage was not significant (Figure 1D). In addition, as shown in Figure 1E, postoperative chemotherapy improved the long-term survival rate of circumscribed B-4 patients ($P = 0.000$).

Role of postoperative chemotherapy in the circumscribed B-4 patient cohort

The survival curves of chemotherapy for subtotal or total gastrectomy are shown in Figure 2A-B. We revealed that circumscribed B-4 patients who underwent subtotal

Table 1 Main clinicopathological characteristics of patients with circumscribed Borrmann type IV gastric cancer

Variable	B-4 patients (n = 117)
Age (yr)	57.55 ± 10.69
Gender	
Male	75
Female	42
Diameter (cm)	7.81 ± 3.07
Tumor location	
Upper 1/3–1/2 (U or MU)	22
Lower 1/3–1/2 (M or L or ML)	59
Total (LAU or LMU)	36
Radical degree	
R0	45
R1+	72
Histological type	
Well	8
Poor	109
pT stage	
pT3	36
pT4	81
pN stage	
pN0	22
pN1	15
pN2	15
pN3	65
Venous/lymphatic infiltration	
Yes	74
No	43
Gastrectomy type	
Subtotal gastrectomy	26
Total gastrectomy	91
Adjuvant chemotherapy	
Yes	74
No	43

U: Upper; M: Middle; L: Lower; pT: Tumor invasion depth; pN: Lymph node status.

gastrectomy gained more benefit from postoperative chemotherapy ($P = 0.003$) than those who underwent total gastrectomy ($P = 0.04$). But therapeutic duration of chemotherapy was not the prognostic factor for circumscribed B-4. In addition, the efficacy of chemotherapy also seemed to be associated with patient age, and patients younger than 65 years had a better prognosis than the others (Figure 2C).

Survival results of the 117 B-4 patients according to therapeutic strategy

The prognostic results, including the median survival (MS) and 3-year OS rate, are shown in Figure 2. There was an obvious prognostic tendency of the different groups. For circumscribed B-4 patients with gastrectomy, postoperative chemotherapy could

Table 2 Cox univariate and multivariate analyses of circumscribed Borrmann type IV patients

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Age (yr)	1.012 (0.992-1.033)	0.226		
Gender	0.969 (0.638-1.470)	0.881		
Diameter (cm)	1.086 (1.013-1.164)	0.02		
Tumor location	1.206 (0.879-1.655)	0.246		
Radical degree	1.575 (0.687-3.612)	0.283		
Histological type	0.708 (0.310-1.620)	0.414		
pT stage	1.422 (1.021-1.982)	0.037		
pN stage	1.482 (1.224-1.794)	0.000	1.433 (1.179-1.742)	0.000
Venous/lymphatic infiltration	0.934 (0.615-1.418)	0.748		
Gastrectomy type	0.330 (0.182-0.595)	0.000	0.400 (0.219-0.728)	0.003
Postoperative chemotherapy	0.482 (0.320-0.727)	0.001	0.564 (0.373-0.853)	0.007

HR: Hazard ratio; CI: Confidence interval; pT: Tumor invasion depth; pN: Lymph node status.

significantly increase the MS time, regardless of lymph node metastasis. Notably, we revealed that circumscribed B-4 patients ($n = 6$) who were diagnosed with pN0 and finally underwent subtotal gastrectomy and chemotherapy had a 3-year OS rate of 100% and a median survival of 77.7 mo. Even for patients with metastatic lymph nodes ($n = 13$), combination therapy also increased the 3-year OS rate to 57.1% and the MS to 51.0 mo.

Analysis of circumscribed B-4 patients with PPCM

Peritoneal metastasis is the most common type of GC metastasis. In our analysis, 79 (67.5%) patients were diagnosed with peritoneal cavity metastasis (PPCM) after gastrectomy, 11 (9.4%) had liver metastasis, and 5 (4.3%) had lung metastasis. We selected the other 22 patients without postoperative metastasis as a non-PPCM group. Positive pN stage was the only factor ($P = 0.005$) correlated with PPCM in circumscribed B-4 patients by Pearson correlation analyses (Table 3). Notably, there was no difference in the PPCM rate between different pT stages (pT3 *vs* pT4). In addition, although chemotherapy did not seem to be associated with PPCM according to the results shown in Table 3, we further explored the association of chemotherapy and PPCM in different gastrectomy types. As shown in Table 4, postoperative chemotherapy was useful for suppressing PPCM in patients with subtotal gastrectomy ($P = 0.018$) but not in those with total gastrectomy ($P = 0.281$).

DISCUSSION

In this study, we first defined B-4 patients without distant metastasis as circumscribed B-4 patients. By multivariate analysis, we revealed that subtotal/total gastrectomy, pN stage, and postoperative chemotherapy were independent prognostic factors for these patients. pN stage, but not pT stage, was crucial for predicting the prognosis of circumscribed B-4 patients. In a previous study, we suggested classifying B-4 patients into pT4b stage according to prognosis^[4]. According to the statistical analysis, subtotal gastrectomy combined with chemotherapy can effectively improve the prognosis of circumscribed B-4. Even for the patients ($n = 13$) with positive pN, the combination therapy also improved the 3-year OS rate to 57.1%.

Surgical resection remains the main therapeutic method for GC, but the role of curative resection in B-4 is controversial^[10,13,14]. Luo *et al*^[8] and Kim *et al*^[10] reported that the 3- to 5-year OS of curative (R0) patients was higher than that of noncurative patients, but surgical curability was not an independent predictor of prognosis, particularly for B-4 patients. In addition, studies found that total gastrectomy had no advantages of long-term prognosis and led to nutritional deficiency and worse quality

Table 3 Factors associated with postoperative peritoneal cavity metastasis in Borrmann type IV patients

Variable	PPCM (79)	Non-PPCM (22)	Pearson <i>P</i> value
Tumor location			0.497
Upper 1/3–1/2 (U or MU)	13	4	
Lower 1/3–1/2 (M or L or ML)	41	13	
Total (LAU or LMU)	25	5	
Radical degree			0.107
R0	28	12	
R1+	51	10	
Gastrectomy type			0.112
Subtotal gastrectomy	13	7	
Total gastrectomy	66	15	
Venous/lymphatic infiltration			0.416
Yes	50	16	
No	29	6	
pT stage			0.559
pT3	23	5	
pT4	56	17	
pN stage			0.005 ^b
pN0	9	8	
pN1-3	70	14	
Chemotherapy			0.105
Yes	46	17	
No	33	5	

^b*P* < 0.01. PPCM: Postoperative peritoneal cavity metastasis; U: Upper; M: Middle; L: Lower; pT: Tumor invasion depth; pN: Lymph node status.

Table 4 Role of chemotherapy in suppressing postoperative peritoneal cavity metastasis in patients who underwent different gastrectomy procedures

Subtotal gastrectomy (20)		Total gastrectomy (81)			
	PPCM (13)	Non-PPCM (7)	Pearson <i>P</i> value	PPCM (66)	Non-PPCM (15)
Chemotherapy	4	6	0.018 ^a	45	8
Non-chemotherapy	9	1		21	7

^a*P* < 0.05. PPCM: Postoperative peritoneal cavity metastasis.

of life for advanced GC compared with subtotal gastrectomy^[15-20]. In our analysis, we also found that no survival benefit existed in the R0 patients compared with the R1 patients, and subtotal gastrectomy could significantly improve the prognosis of circumscribed B-4 patients compared with total gastrectomy. The pathological features of B-4 GC suggested that the lesion invaded the whole layers of the gastric wall, and even if there was no venous or lymphatic infiltration, some micrometastases had occurred before macroscopic distant metastasis. Thus, it is difficult to restrict metastasis and improve survival by surgical resection. The results from circumscribed B-4 patients provided more evidence for this conclusion.

Considering the limited effect of surgery, adjuvant chemotherapy was also found to

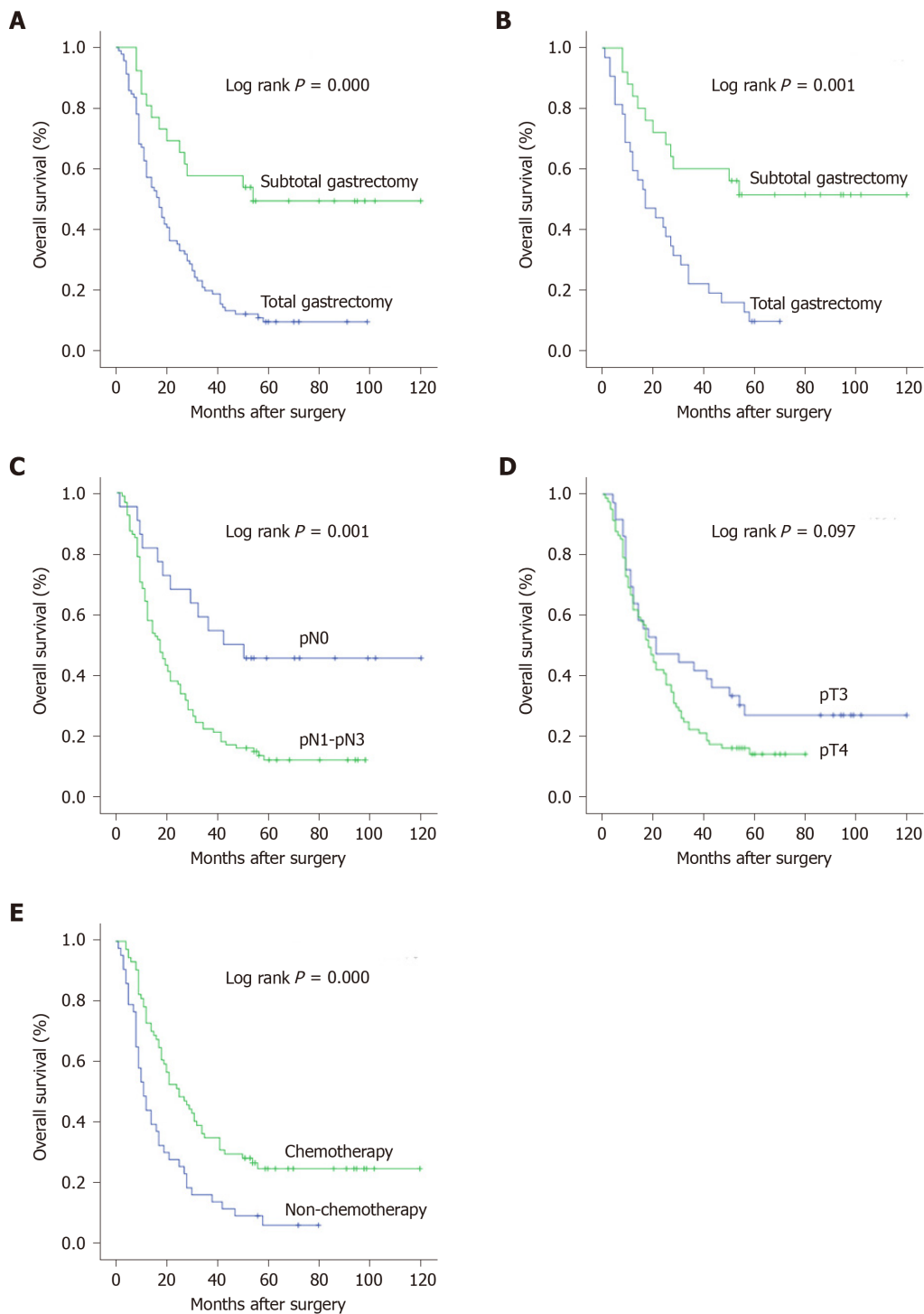


Figure 1 Survival curves of 117 patients according to the independent prognostic factors. A: Subtotal vs total gastrectomy; B: Subtotal vs total gastrectomy (lower-middle lesions); C: Lymph node status (pN stage); D: Tumor invasion depth (pT stage); E: Postoperative chemotherapy. pN: Lymph node status; pT: Tumor invasion depth.

be beneficial for survival in advanced GC. In a meta-analysis, 5-FU plus oxaliplatin (OXA) and 5-FU plus docetaxel (DOC) were recommended as postoperative chemotherapy regimens for advanced GC according to the efficacy^[21]. In this study, chemotherapy, including 5-FU and platinum, significantly improved the prognosis of local B-4, serving as one of the independent factors, even for patients who were older than 65 years. Notably, as shown in [Supplementary Table 1](#), significant differences in age and pT stage existed between the chemotherapy and nonchemotherapy groups ($P < 0.01$). Thus, we revealed that elderly patients with advanced GC stage seem to have a lower tendency to receive postoperative chemotherapy in the clinic, which should be rectified according to our conclusions. In addition, studies found that although S-1 or S-1/cisplatin might have positive effects against B-4, the prognostic role of

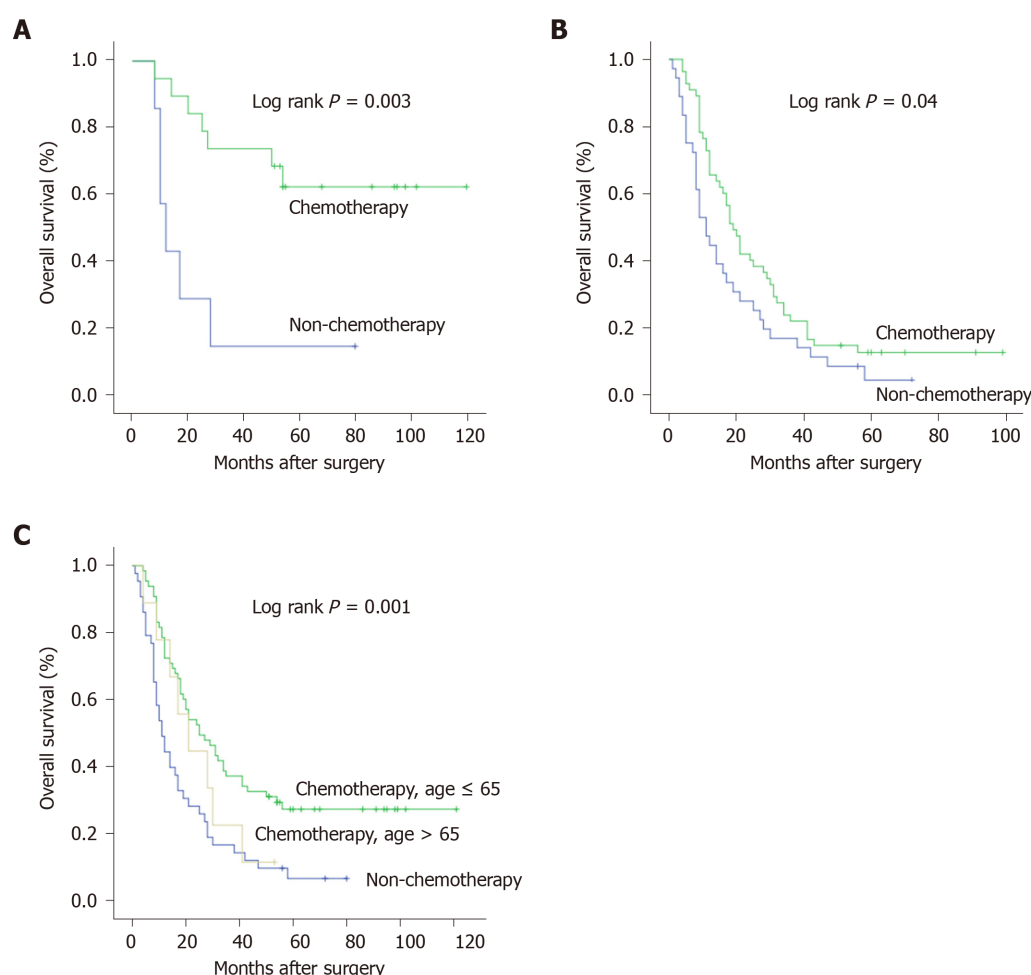


Figure 2 Survival curves of chemotherapy for different Borrmann type IV patients. A: Patients with subtotal gastrectomy; B: Patients with total gastrectomy; C: Patients of different ages.

neoadjuvant chemotherapy did not reach the expected survival rate, with a median survival of only 17.3 mo and a 3-year OS rate of 24.5%^[22-24]. Therefore, neoadjuvant chemotherapy was not included and analyzed in our study.

Above all, as shown in Figure 2, the survival time and OS rates of the two groups were significantly different, and there was an obvious tendency. Subtotal gastrectomy with chemotherapy improved the median survival of negative and positive pN patients to 77.7 mo and 51.0 mo, respectively. Thus, for advanced GC patients, after confirmation as circumscribed B-4, we recommend striving for subtotal gastrectomy and performing postoperative chemotherapy, especially for the lower 1/3-1/2 lesions, regardless of whether the patient has lymph node metastases.

Additionally, our results showed that positive pN was correlated with the occurrence of PPCM in circumscribed B-4 patients, which indicated that lymph node metastasis was an important course for peritoneal metastasis. Some newly developed methods like endoscopic ultrasound guided fine needle aspiration may provide cytological confirmation for lymph node and other metastases^[25-27]. Of course, serosal invasion and the shedding of cancer cells are also important routes for peritoneal metastasis.

There were also some limitations in our study. First, this is a retrospective, single-center and small-sample study, which reduced the significance of our study. For example, only one patient was divided in a group, as shown in Figure 3. Second, no data of neoadjuvant or targeted therapy were referred to in our study. Thus, a prospective study on a larger scale is necessary in the future.

CONCLUSION

Lymph node metastasis is an independent risk factor for poor prognosis in

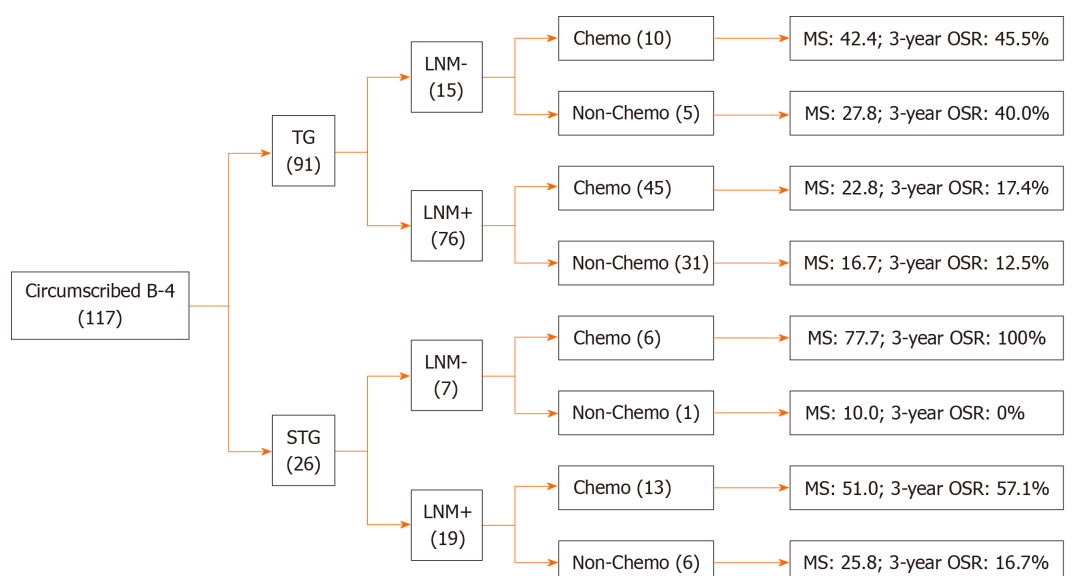


Figure 3 Mean survival and 3-yr overall survival rates of different groups of 117 patients according to Cox multivariate analysis. TG: Total gastrectomy; STG: Subtotal gastrectomy; LNM: Lymph node metastasis; Chemo: Chemotherapy; MS: Median survival (mo); OSR: Overall survival rate.

circumscribed B-4 patients. Subtotal gastrectomy combined with postoperative chemotherapy could significantly improve the long-term OS rate and median survival time for circumscribed B-4 patients.

ARTICLE HIGHLIGHTS

Research background

Borrmann type IV (B-4) gastric cancer (GC) accounts for about 10% of all GC cases in Asia. Some B-4 patients were found to have no distant metastasis by preoperative detection and underwent curative surgery, which was defined as circumscribed B-4 in our study.

Research motivation

Research of clinicopathological characteristics and prognosis in B-4 is rare, especially for the circumscribed B-4 patients.

Research objectives

In this study, we aimed to identify the factors related to prognosis and postoperative peritoneal cavity metastasis (PPCM) for circumscribed B-4 patients and to further explore the appropriate therapeutic strategies.

Research methods

A total of 117 circumscribed B-4 patients were included in this study. Survival analysis and Pearson correlation analyses were performed to identify the factors related to prognosis.

Research results

Subtotal gastrectomy combined with chemotherapy could significantly improve the long-term survival time for circumscribed B-4. Positive lymph node status was the only factor correlated with PPCM, and chemotherapy was useful for suppressing PPCM in patients with subtotal gastrectomy but not in those with total gastrectomy.

Research conclusions

Lymph node status is an independent prognostic factor for circumscribed B-4 patients. Subtotal gastrectomy and chemotherapy could effectively improve prognosis and suppress PPCM.

Research perspectives

This study recommended reasonable treatment schedules for circumscribed B-4 patients, but a multi-center study on a larger scale is necessary in the future.

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