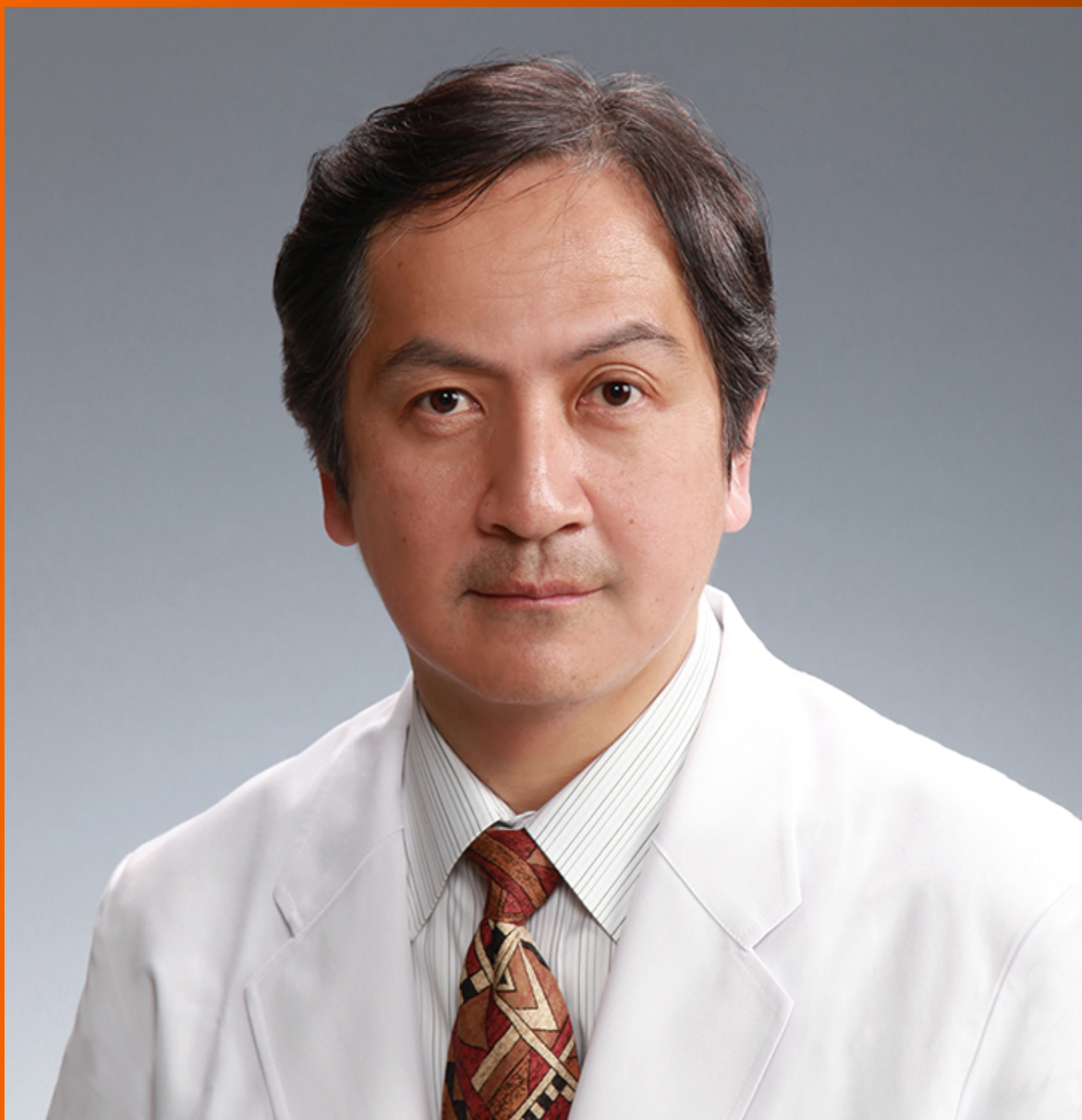


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Contents

Weekly Volume 28 Number 38 October 14, 2022

REVIEW

- 5515 Gastrointestinal and liver disease in patients with schizophrenia: A narrative review
Grant RK, Brindle WM, Donnelly MC, McConville PM, Stroud TG, Bandieri L, Plevris JN

MINIREVIEWS

- 5530 Ultrasound-based artificial intelligence in gastroenterology and hepatology
Liu JQ, Ren JY, Xu XL, Xiong LY, Peng YX, Pan XF, Dietrich CF, Cui XW
- 5547 Oxidative stress bridges the gut microbiota and the occurrence of frailty syndrome
Chen SY, Wang TY, Zhao C, Wang HJ

ORIGINAL ARTICLE

Basic Study

- 5557 Effect of low-dose radiation on thyroid function and the gut microbiota
Tong JY, Jiang W, Yu XQ, Wang R, Lu GH, Gao DW, Lv ZW, Li D
- 5573 Hypoxia inducible factor 1 α promotes interleukin-1 receptor antagonist expression during hepatic ischemia-reperfusion injury
Wang ZY, Liu Y, Li SP, Li JJ, Zhang Z, Xiao XC, Ou Y, Wang H, Cai JZ, Yang S

Retrospective Cohort Study

- 5589 No long-term survival benefit with sustained-release 5-fluorouracil implants in patients with stages II and III gastric cancer
Wu YZ, Wu M, Zheng XH, Wang BZ, Xue LY, Ding SK, Yang L, Ren JS, Tian YT, Xie YB
- 5602 Timing of endoscopic retrograde cholangiopancreatography in the treatment of acute cholangitis of different severity
Huang YC, Wu CH, Lee MH, Wang SF, Tsou YK, Lin CH, Sung KF, Liu NJ

Retrospective Study

- 5614 Clearance of the liver remnant predicts short-term outcome in patients undergoing resection of hepatocellular carcinoma
Miki A, Sakuma Y, Ohzawa H, Saito A, Meguro Y, Watanabe J, Morishima K, Endo K, Sasanuma H, Shimizu A, Lefor AK, Yasuda Y, Sata N
- 5626 A new scoring system to evaluate adjuvant chemotherapy for patients with T2N0M0 gastric cancer after D2 gastrectomy
Xu Q, Kang WZ, Xiong JP, Shao XX, Li WK, Hu HT, Tian YT

Observational Study

- 5636** Red blood cell distribution width derivatives in alcohol-related liver cirrhosis and metabolic-associated fatty liver disease

Michalak A, Guz M, Kozicka J, Cybulski M, Jeleniewicz W, Lach T, Cichoż-Lach H

SCIENTOMETRICS

- 5648** Comparison of evaluation indexes for Gastroenterology and Hepatology journals in different databases

Li JY, Yan ZH, Xiang Z, Gao C, Wu J

ABOUT COVER

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The primary aim of *World Journal of Gastroenterology* (WJG, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. WJG mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

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Retrospective Cohort Study

No long-term survival benefit with sustained-release 5-fluorouracil implants in patients with stages II and III gastric cancer

Yun-Zi Wu, Ming Wu, Xiao-Hao Zheng, Bing-Zhi Wang, Li-Yan Xue, Shi-Kang Ding, Lin Yang, Jian-Song Ren, Yan-Tao Tian, Yi-Bin Xie

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Abstract

BACKGROUND

The prognosis of gastric cancer in an advanced stage remains poor. The exact efficacy of the use of intraoperative sustained-release chemotherapy with 5-fluorouracil (5-FU) in advanced-stage gastric cancer is still unelucidated.

AIM

To explore the long-term survival benefit of using sustained-release 5-FU implants

in stage II and stage III gastric cancer patients.

METHODS

Patients with gastric cancer in a locally advanced stage and who underwent an R0 radical resection between Jan 2014, to Dec 2016, in this single institution were included. Patients with pathological diagnoses other than adenocarcinoma were excluded. All included patients were grouped according to whether intraoperative sustained-release (SR) chemotherapy with 5-FU was used or not (NSR). The primary end-point was 5-year overall survival. Kaplan-Meier method with log-rank test was used to analyze the overall survival of patients and Cox analysis was used to analyze prognosis factors of these patients.

RESULTS

In total, there were 563 patients with gastric cancer with locally advanced stage, who underwent an R0 radical resection. 309 patients were included in the final analysis. 219 (70.9%) were men, with an average age of 58.25 years. Furthermore, 56 (18.1%) received neoadjuvant chemotherapy, and 191 (61.8%) were in TNM stage III. In addition, 158 patients received intraoperative sustained-release chemotherapy with 5-FU and were included in the SR group, while the other 161 patients were included in the NSR group. The overall complication rate was 12.94% in the whole group and 10.81%, 16.46% in SR and NSR groups, respectively. There were no significant differences between the two groups in overall survival and complication rate ($P > 0.05$). The multivariate cox analysis indicated that only N Stage and neoadjuvant therapy were independent influencing factors of survival.

CONCLUSION

Intraoperative sustained-release chemotherapy usage with 5-FU, did not improve the survival of patients who underwent an R0 radical resection in locally advanced stage of gastric cancer.

Key Words: Sustained-release 5-fluorouracil implants; Gastric cancer; 5-year survival rate; Safety; Prognostic factor; R0 radical resection

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Core Tip: Intraoperative drug administration shows promise in preventing the recurrence of gastric cancer. Sustained-release 5-fluorouracil (5-FU) implant is a new convenient and continuous drug release method that ensures locally high drug concentration for approximately 1 mo. 5-FU implants are widely used to treat various gastric tumors. However, presently, only retrospective research and a small-scale clinical study conducted in China have reported on its use in patients with gastric cancer. In our real-world study, we collected complete datasets, making this the largest study in China. Unfortunately, 5-FU implants did not improve the long-term survival of gastric cancer patients.

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INTRODUCTION

Gastric cancer is the fifth most common newly diagnosed cancer and the third most common cause of cancer mortality worldwide[1-3]. In China, there are approximately 400000 new patients with gastric cancer, and nearly 300000 people die of gastric cancer every year[4]. At present, locally advanced gastric cancer with the American Joint Committee on Cancer TNM stages II and III accounts for the majority of these cases[5]. For locally-advanced gastric cancer patients, the current standard treatment is D2 gastrectomy, followed by adjuvant chemotherapy[6]. However, even in those who received standard treatment, 30-60% of them may relapse either locally or distantly[7].

Patients with stages II and III gastric cancer have been found to have a tendency to relapse after treatment[8]. According to the findings of a study by Yago *et al*[9], the 5-year recurrence-free survival rate was 88.3% for stage IIA, 73.8% for stage IIB, 67.4% for stage IIIA, 55.7% for stage IIIB, and 29.9% for stage IIIC. Of the three major recurrence patterns namely hematogenous, peritoneal, and lymph nodal

recurrences after curative gastrectomy, the latter two account for the majority of the cases[10-13]. In order to decrease local recurrence after resection, methods, such as extended peritoneal lavage[14], hyperthermic intraperitoneal perfusion chemotherapy[15], peritoneal lavage with 5-FU, and continuous intraperitoneal chemotherapy using a retained tube or pump, have been developed[16]. Furthermore, it has been reported that intraoperative intraperitoneal chemotherapy can reduce the mortality risk[17]. In addition, increasing the temperature of chemotherapeutic drugs has a synergistic effect with the increase of intraperitoneal chemotherapy. The CYTO-CHIP study group reported that compared with the routine method of cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy, it can improve median overall survival time and increase the 3-and 5-year overall survival rates [18]. In another study, the use of catheter-based intraperitoneal chemotherapy showed similar results of increased the 5-year overall survival rate and reduced the peritoneal recurrence rate[19]. The use of sustained-release 5-FU implants intraoperatively is a relatively newly developed method and has been used widely in almost all types of digestive tract cancer in China[20]. When this drug was placed intraoperatively into the tumor bed, it was released continuously, and it maintained a locally high drug concentration for approximately 1 mo[21]. The potential remnant tumor tends to grow quickly in the first year after resection owing to the decreased immunity and absence of adjuvant chemotherapy[9]. This is the theoretical basis for the use of sustained-release 5-FU implants.

Moreover, optimistic results concerning the use of sustained-release 5-FU implants in the treatment of gastric cancer have been shown. Recently, a multi-center, randomized, open-label, controlled clinical study showed that for cTNM stage III gastric cancer patients, the use of intraoperative 5-FU implants, combined with postoperative adjuvant chemotherapy, may reduce the risk of peritoneal recurrence and prolong progression-free survival significantly[22]. Another retrospective study with 5-FU implants in advanced gastric cancer patients showed that the use of 5-FU implants may improve 5-years overall survival (OS) and progression-free survival rates after surgery in gastric cancer patients[21]. However, these studies had limitations. The sample size of these studies was limited, the follow-up times were insufficient, and the rate of loss of follow-up was extremely high. In order to explore the long-term survival benefit of the use of sustained-release 5-FU implants, we conducted a real-world study using our own clinical data from a single institution.

MATERIALS AND METHODS

Data Collection and Primary Outcomes

In total, we treated 563 stages II and III gastric cancer patients between January 2014 and December 2016. The inclusion criteria were the presence of clinical TNM stage II and stage III, pathologically diagnosed adenocarcinoma of the stomach, a complete record of history, and age between 18–80 years. The exclusion criteria were the presence of gastric remnant cancer, distant metastases, positive peritoneal cytology, palliative resection, and any unsuitable condition for 5-FU chemotherapy. The primary clinical outcome was 5-year OS. Information on the patients' age, sex, body mass index, tumor (TNM Stage, Borrmann classification, Lauren classification, pathological classification, differentiation, number of resected lymph nodes, number of positive lymph nodes, as well as the extent of nerve invasion, and presence of a vascular tumor thrombus), treatment (resections, neoadjuvant therapy, and use of 5-FU implants), postoperative complications (pulmonary infections, anastomotic fistulas, bleeding, abdominal infections, intestinal obstructions, and admissions to the intensive care unit), and their follow-up results were extracted from our hospital's electronic records.

Treatment methods

All our patients underwent a standard D2 gastric resection with or without neoadjuvant therapy. In addition, all the patients received 6–8 cycles of adjuvant chemotherapy with an S-1 + oxaliplatin regimen. In the sustained-release (SR) group, sustained-release 5-FU implants in a fixed dosage of 1000 mg were placed intraoperatively near the tumor bed after resection. Other patients were divided into non-sustained-release (NSR) group. The placement of 5-FU implants near vessels and anastomotic stoma should be avoided.

Statistical analyses

The continuous variables were presented as central tendencies (means or medians) and dispersions (standard deviations or interquartile ranges). For the group comparisons of the numeric variables, the Student's *t*-test was used when the data were normally distributed, and the Mann-Whitney test for the variables in which distribution was not normal. When the categorical predictors were compared between the groups, we used Pearson's χ^2 test or Fisher's exact test. The survival analysis included the use of the Kaplan-Meier estimator for OS. A Cox regression analysis was performed to obtain the crude and adjusted hazard ratios for OS. Significance level for all tests was reached when the two-tailed *P* value was < 0.05. Statistical analyzes were performed using the IBM SPSS Statistics (version 26.0, IBM Inc., Armonk, NY, United States), and Prism software (version 9, GraphPad Software Inc., San Diego, CA, United States).

RESULTS

Clinicopathological characteristics

In total, 241 patients with incomplete data and 13 patients with a pathological diagnosis of gastric neuroendocrine tumor were excluded. Finally, 309 patients were included in this study, and they were divided into two groups according to whether sustained-release 5-FU was used or not. Therefore, there were 158 patients in the SR group and 164 patients in the NSR group (Figure 1).

The average age of the whole group was 58.25 ± 11.2 years, with male patients being the majority (70.9%). All the patients were diagnosed pathologically as having a stomach adenocarcinoma of TNM stages II and III. Furthermore, 32.4% of patients had signet ring cell carcinoma. All of the patients underwent an R0 resection surgery. As shown in Table 1, we compared the differences in the clinicopathological characteristics between the two patient cohorts. There were no significant differences between the two groups with respect to age, sex, body mass index, and TNM stage. Similarly, there were no differences between the two groups with respect to their pathological characteristics such as the Borrmann classification, Lauren classification, and differentiation. Although the number of resected lymph nodes in the SR group was higher than that in the NSR ($P = 0.0145$), the number of positive lymph nodes number was similar ($P = 0.2319$). Lymph node dissection was satisfactory in both groups, even though there was a gap between the two groups (Table 1).

Postoperative complications in patients

Table 2 shows the major postoperative complications, such as pulmonary inflections, anastomotic fistulas, postoperative bleeding, abdominal infections, and intestinal obstructions. There were no significant differences between the two groups with respect to the incidence of postoperative complications ($P > 0.05$).

Prognostic factors in gastric cancer patients

Figure 2 shows the results of the univariate and multivariate Cox analyses. From the univariate analysis, N stage ($P < 0.001$), T stage ($P = 0.001$), TNM stage ($P < 0.001$) neoadjuvant therapy ($P < 0.001$), Borrmann classification ($P = 0.001$), and resection type ($P = 0.002$) were found to be influencing prognostic factors in this group of patients. As per the multivariate Cox analysis, only N stage ($P = 0.030$) and neoadjuvant therapy were found to be independent influencing prognostic factors (Figure 2 and Table 3). The use of sustained-release 5-FU implants was not an independent influencing prognostic factor in this group ($P = 0.786$).

Survival outcomes

The 5-years OS rate of the SR and NSR groups were 68.2% and 67.9%, respectively ($P = 0.9850$). The median survival time for both groups was not obtained, as patient mortality numbers were too low to calculate. Furthermore, we performed subgroup comparisons according to the patient's age, sex, and TNM stage. There were no significant differences in any of the subgroups ($P > 0.05$) (Figures 3 and 4, Table 3).

DISCUSSION

Gastric cancer remains one of the most lethal cancers in China[23,24]. Almost 70% of the relapses occur within 2 years and more than 90% within 5 years[7,25]. In clinical practice, the recurrence patterns are classified as locoregional, peritoneal, and hematogenous. As reported by Wu, approximately all of the recurrences (99.5%) occurred within 7 years after the surgery, with 53.5% having had peritoneal dissemination, 43.3% hematogenous metastases, and 28.6% distant lymphatic spread[26]. The locoregional and peritoneal recurrences, which usually occur in gastric cancer patients, were found to be a critical problem. Peritoneal recurrence has been reported as the most common recurrence pattern in locally advanced gastric cancer patients, which accounts for 50% of the cases and occurs within 2 years after surgery[27]. In another study, almost 60% of the gastric cancer patients experienced a recurrence, which included 32.4% locoregional recurrences, 13.7% peritoneal metastases, and 44.3% distant metastases[28].

To reduce locoregional recurrences, intraperitoneal chemotherapy has been used widely worldwide. Different from other methods, the use of intraoperative sustained-release 5-FU is promising because of the convenient usage and a long effective time of approximately 1 mo. The use of sustained-release 5-FU implants has shown survival benefits in different types of digestive system tumors such as colon cancer and primary hepatic cellular cancer[29,30]. Furthermore, a few studies on the treatment of gastric cancer, which showed similar results, were also reported by Chinese researchers[21,22]. However, P values of survival benefits obtained in previous studies on gastric cancer were lower, but close to 0.05. Therefore, we conducted this real-world study to confirm the findings.

In the present study, the use of sustained-release 5-FU implants did not improve the long-term survival of gastric cancer patients with either TNM stage II or III. The estimated 5-year survival of patients with gastric cancer with TNM stage III in SR and NSR group was 50% and 49%, respectively (P

Table 1 Clinicopathological characteristics of different gastric cancer group

	SR group (n = 148)	NSR group (n =161)	P value
Age (yr)	57.15 ± 10.71	59.27 ± 11.52	0.2917
Gender, n (%)			0.781
Male	106 (71.6)	113 (70.2)	
Female	42 (28.4)	48 (29.8)	
BMI (kg/m ²)	23.97 ± 3.591	23.68 ± 3.488	0.9716
Neoadjuvant therapy, n (%)			0.52
Yes	29 (19.6)	27 (16.8)	
No	119 (80.4)	134 (83.2)	
Cardiovascular disease, n (%)			0.503
Yes	32 (21.6)	40 (24.8)	
No	116 (78.4)	121 (75.2)	
Diabetes, n (%)			0.093
Yes	10 (6.8)	20 (12.4)	
No	138 (93.2)	141 (87.6)	
T stage, n (%)			0.699
T1 and T2	23 (15.5)	21 (13.0)	
T3 and T4	96 (64.9)	113 (70.2)	
yp T1 and T2	5 (3.4)	3 (1.9)	
yp T3 and T4	24 (16.2)	24 (14.9)	
N stage, n (%)			0.533
N0 and N1	44 (29.7)	51 (31.7)	
N2 and N3	75 (50.7)	83 (51.6)	
yp N0 and yp N1	11 (7.4)	15 (9.3)	
yp N2 and yp N3	18 (12.2)	12 (7.5)	
M stage, n (%)			> 0.999
M0	148 (100.00)	161 (100)	
TNM stage, n (%)			0.91
Stage II	57 (38.5)	61 (37.9)	
Stage III	91 (61.5)	100 (62.1)	
Borrmann classification, n (%)			0.207
Superficial type	3 (2.0)	1 (0.6)	
Type I	10 (6.8)	9 (5.6)	
Type II	41 (27.7)	36 (22.4)	
Type III	73 (49.3)	78 (48.4)	
Type IV	2 (1.4)	9 (5.6)	
NA	19 (12.8)	28 (17.4)	
Lauren classification, n (%)			0.782
Intestinal type	42 (28.4)	48 (29.8)	
Diffuse type	64 (43.2)	69 (42.9)	
Mixed type	34 (23.0)	39 (24.2)	
NA	8 (5.4)	5 (3.1)	

Differentiation, <i>n</i> (%)			0.666
Low	88 (59.5)	91 (56.5)	
Low-medium	36 (24.3)	39 (24.2)	
Medium	19 (12.8)	26 (16.1)	
Medium-high and high	2 (1.4)	4 (2.5)	
NA	3 (2.0)	1 (0.6)	
Nerve invasion, <i>n</i> (%)			0.26
Yes	73 (49.3)	92 (57.1)	
No	24 (16.2)	27 (16.8)	
NA	51 (34.5)	42 (26.1)	
Vascular tumor thrombus, <i>n</i> (%)			0.23
Yes	57 (38.5)	57 (38.5)	
No	40 (27.0)	54 (33.5)	
NA	51 (34.5)	42 (26.1)	
Pathological classification, <i>n</i> (%)			0.481
Signet-ring cell carcinoma	45 (30.4)	55 (34.2)	
Another adenocarcinoma	103 (69.6)	106 (65.8)	
Resection type, <i>n</i> (%)			0.057
Total gastrectomy	53 (35.8)	54 (33.5)	
Proximal gastrectomy	7 (4.7)	20 (12.4)	
Distal gastrectomy	88 (59.5)	87 (54.0)	
R0 resection	148 (100.00)	161 (100)	> 0.999
Resected lymph nodes number	39.21 ± 14.13	35.73 ± 13.53	0.0145
Positive lymph nodes number	7.393 ± 8.864	6.856 ± 9.743	0.2319

SR: Sustained-release; NSR: Not sustained-release; BMI: Body mass index; NA: Not available.

Table 2 Postoperative complications in patients

	SR group (<i>n</i> = 148), <i>n</i> (%)	NSR group (<i>n</i> = 161), <i>n</i> (%)	<i>P</i> value
Pulmonary infection	3 (2.0)	6 (3.8)	0.583
Anastomotic fistula	6 (4.0)	6 (3.8)	0.882
Postoperative bleeding	1 (0.7)	3 (1.9)	0.675
Abdominal infection	3 (2.0)	9 (5.6)	0.105
Intestinal obstruction	3 (2.0)	1 (0.6)	0.556

SR: Sustained-release; NSR: Not sustained-release.

= 0.775), slightly higher than that of previous studies[31,32]. This may have been due to the R0 radical resection decreasing the risk of local-regional recurrence and compromising the effects of the sustained-release drug. Therefore, we may hypothesize that in cases of incomplete resections, such as an R1 resection, or if the lymph node dissection did not reach the D2 resection standard, the use of a sustained-release drug may improve survival. Previous results of drug use in the treatment of unresectable tumors, such as pancreatic cancer and colorectal cancer, provided evidence for this hypothesis[33].

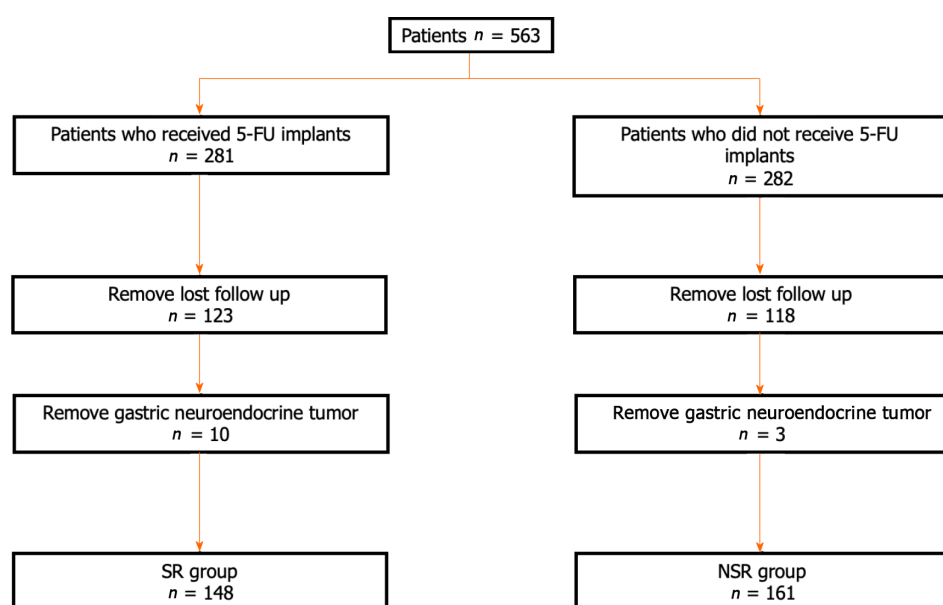
Similar to the findings of previous studies, the use of the sustained-release 5-FU implants did not increase postoperative complications, and systemic toxicity was rare in the present study. The use of 5-FU implants is usually recommended in gastric cancer patients, particularly at TNM stage T4 or N1-3

Table 3 Univariate and multivariate Cox analysis of patients

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95%CI	P value	HR	95%CI	P value
Gender						
Male	Reference					
Female	1.058	0.712-1.572	0.781			
Age, yr						
< 60	Reference					
≥ 60	1.03	0.717-1.481	0.872			
Neoadjuvant therapy						
No	Reference					
Yes	2.188	1.448-3.306	< 0.001	2.118	1.194-3.759	0.01
BMI						
Normal < 24	Reference					
Abnormal ≥ 24	0.752	0.516-1.098	0.14			
Cardiovascular disease						
No	Reference					
Yes	0.943	0.606-1.467	0.794			
Diabetes						
No	Reference					
Yes	0.891	0.479-1.658	0.715			
Drug administration						
No	Reference					
Yes	1.052	0.731-1.513	0.786			
Resection type						
Total gastrectomy	Reference					
Partial gastrectomy	0.558	0.387-0.804	0.002	0.663	0.428-1.027	0.066
Borrmann classification						
Superficial type, Type I and II	Reference					
Type III and IV	2.203	1.378-3.522	0.001	1.562	0.951-2.566	0.078
Lauren classification						
Intestinal type	Reference					
Others	1.158	0.762-1.762	0.492			
Differentiation type						
Low	Reference					
Others	0.874	0.535-1.430	0.593			
TNM stage						
Stage II	Reference					
Stage III	3.12	1.977-4.926	< 0.001	1.315	0.561-3.084	0.528
T stage						
T1 and T2	Reference					
T3 and T4	3.382	1.649-6.937	0.001	1.9	0.777-4.645	0.159
N stage						

N0 and N1	Reference					
N2 and N3	2.516	1.636-3.869	< 0.001	2.224	1.082-4.572	0.03
Signet-ring cell carcinoma						
Yes	Reference					
No	1.188	0.736-1.916	0.481			
Nerve invasion						
No	Reference					
Yes	1.703	0.938-3.093	0.08			
Vascular tumor thrombus						
No	Reference					
Yes	1.099	0.701-1.722	0.681			

HR: Hazard ratio; CI: Confidence interval; BMI: Body mass index.



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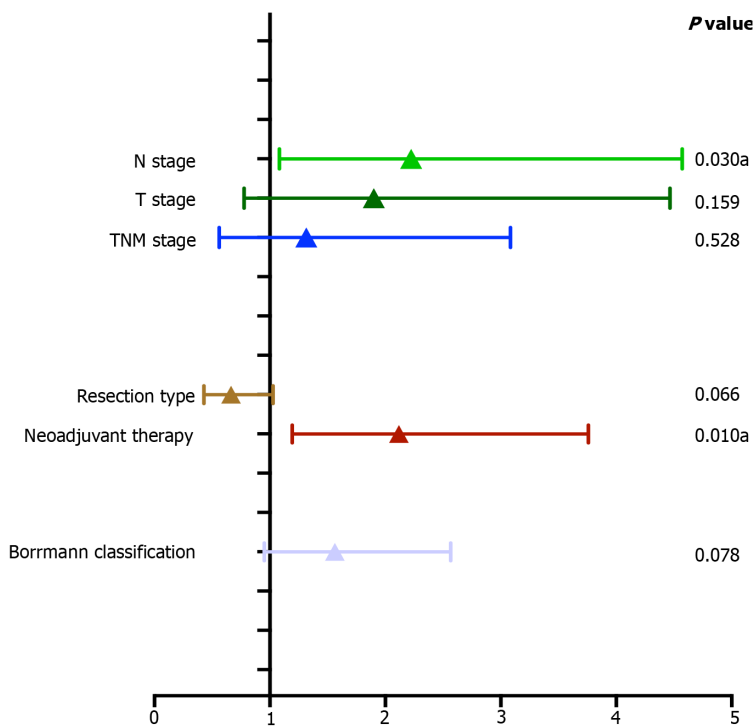
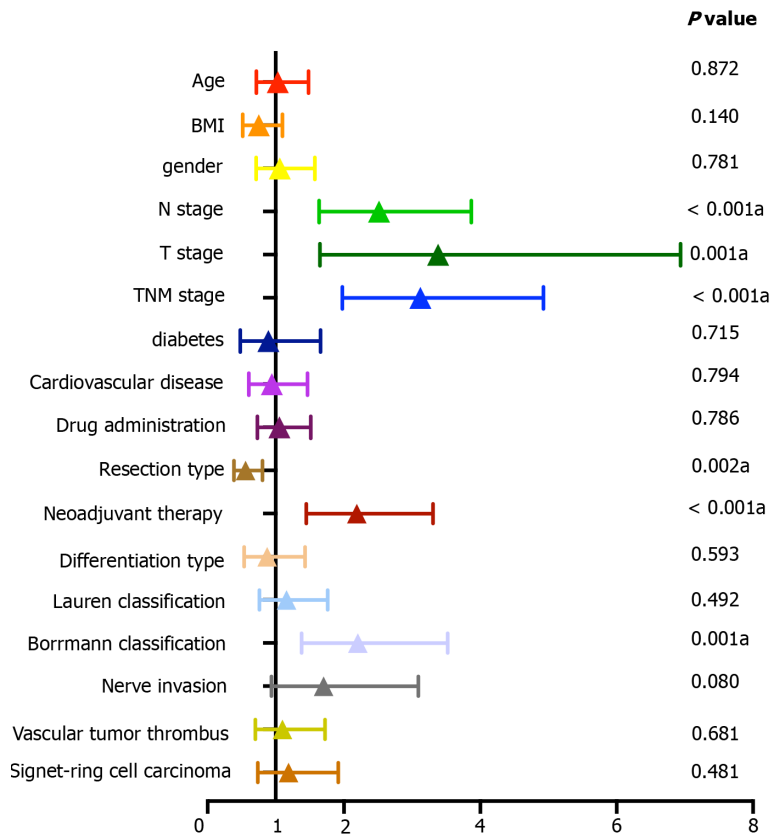
Figure 1 Flowchart of the selection of gastric cancer patients. 5-FU: 5-fluorouracil; NSR: Non-sustained-release.

[34]. In our study, the selection criteria were based on preoperative image examinations. Patients treated with 5-FU implants were in stage II and III, which is in accordance with the recommendations from the Chinese expert consensus[34].

Our study had some limitations. First, the sample size was insufficient. However, to date it remains the largest group studied. Second, selection biases existed. Many patients had incomplete history records, which may have contributed to a contrary result. Finally, the exact relapse time and the first site of recurrence were recorded incompletely. Owing to a lack of analysis of the relapses, the results were compromised. In order to understand the survival benefit of the sustained-release 5-FU plants on gastric cancer, a randomized controlled large-scale study is needed.

CONCLUSION

While the use of intraoperative sustained-release chemotherapy with 5-FU did not improve the survival of patients in an advanced stage of gastric cancer who underwent an R0 radical resection, it was a safe method, and it did not increase the complication rate.



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Figure 2 Univariate and Multivariate Cox analyses of prognostic factors of 5-year survival in this group. N stage (N0 and N1 vs N2 and N3), T stage (T1 and T2 vs T3 and T4), TNM stage (stage II and stage III), surgery type (Total gastrectomy vs Partial gastrectomy), Neoadjuvant therapy (No vs Yes) and Borrmann classification (Superficial Type, Type I and Type II vs Type III and Type IV) are the prognosis factor of gastric cancer patients.

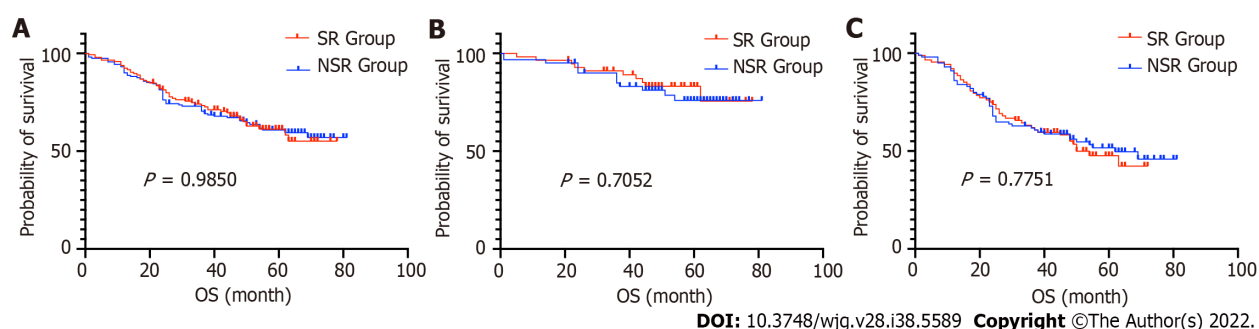


Figure 3 Survival Outcomes in gastric cancer patients. A: Overall survival analysis in all gastric cancer patients; B: Overall survival analysis in stage II gastric cancer patients; C: Overall survival analysis in stage III gastric cancer patients. NSR: Non-sustained-release.

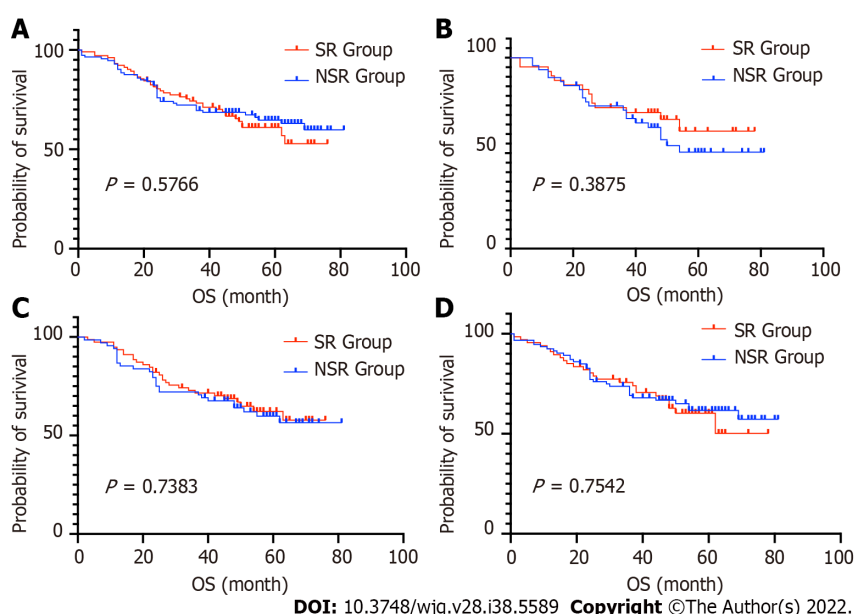


Figure 4 Survival analysis in the age and gender subgroups. A: Survival analysis in male gastric cancer patients; B: Survival analysis in female gastric cancer patients; C: Survival analysis in gastric cancer patients less than 60 years old; D: Survival analysis in gastric cancer patients is more than 60 years old. NSR: Non-sustained-release.

ARTICLE HIGHLIGHTS

Research background

The prognosis of gastric cancer in an advanced stage remains poor. The exact efficacy of the use of intraoperative sustained-release chemotherapy with 5-fluorouracil (5-FU) in advanced-stage gastric cancer is still unelucidated.

Research motivation

To explore the long-term survival benefit of using sustained-release 5-FU implants in stage II and stage III gastric cancer patients.

Research objectives

To explore the long-term survival benefit of using sustained-release 5-FU implants in stage II and stage III gastric cancer patients.

Research methods

All included patients were grouped according to whether intraoperative sustained-release (SR) chemotherapy with 5-FU was used or not (NSR). The primary end-point was 5-year overall survival. Kaplan-Meier method with log-rank test was used to analyze the overall survival of patients and Cox analysis was used to analyze prognosis factors of these patients.

Research results

309 patients were included in the final analysis. In addition, 158 patients received intraoperative sustained-release chemotherapy with 5-FU and were included in the SR group, while the other 161 patients were included in the NSR group. The overall complication rate was 12.94% in the whole group and 10.81%, 16.46% in SR and NSR groups, respectively. There were no significant differences between the two groups in overall survival and complication rate ($P > 0.05$).

Research conclusions

Intraoperative sustained-release chemotherapy usage with 5-FU, did not improve the survival of patients who underwent an R0 radical resection in locally advanced stage of gastric cancer.

Research perspectives

5-FU implants did not improve survival.

FOOTNOTES

Author contributions: Wu YZ and Xie YB contributed to the manuscript writing; Wu YZ, Zheng XH, Ming Wu, and Ding SK contributed to the data collection; Wu YZ and Ren JS contributed to the data analysis; Wang BZ and Xue LY contributed to the pathological diagnosis; Xie YB, Tian YT, and Yang L contributed to the clinical treatment and manuscript modification; all the authors contributed to the manuscript and approved the submitted version.

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