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Original Article

Effect of transarterial chemotherapy on the outcome and prognosis of patients with locally advanced proximal gastric cancer

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Abstract: Objective: To investigate the effect of transarterial infusion chemotherapy on the prognosis of patients undergoing proximal radical gastrectomy for gastric cancer. Methods: In this retrospective study, 96 patients with locally advanced proximal gastric cancer diagnosed in Gansu Cancer Hospital from July 2014 to July 2017 were enrolled. Among them, 40 patients undergoing surgery after 4 cycles of intravenous + oral chemotherapy and 2-4 cycles of adjuvant chemotherapy after surgery were grouped as the control group (CG); the remaining 56 patients treated with left gastric artery infusion chemotherapy were grouped as the observation group (OG). The clinical efficacy, surgical regimen, adverse reactions (nausea, vomiting, and bone marrow suppression) after chemotherapy, improvement of clinical symptoms, 5-year survival, 5-year progression-free survival (PFS) and overall response rate (ORR) after treatment were compared between the two groups. Cox regression was used to analyze prognostic factors affecting PFS. Results: Compared to the CG, the OG exhibited a significantly higher overall response rate and smaller tumor volume ($P < 0.05$ or $P < 0.01$); the overall incidence of clinical symptoms in the OG was lower ($P < 0.05$); the proportion of patients who underwent radical resection in the OG was significantly higher ($P < 0.05$); nausea and vomiting symptoms were more common in the OG ($P < 0.05$), but there was no statistical difference in terms of bone marrow suppression ($P > 0.05$); and the OG had significantly higher 5-year progression-free survival and survival time of patients ($P < 0.05$). Cox regression analysis revealed that tumor stage, tumor type and treatment regimen were independent prognostic factors for PFS ($P < 0.01$). Conclusion: Regional arterial infusion chemotherapy is an ideal neoadjuvant therapy for gastric cancer, which can evidently reduce the tumor lesions in a short time, increase the resection rate, and significantly prolong the PFS of the patients. The gastrointestinal side effects are comparatively significant but tolerable.

Keywords: Neoadjuvant chemotherapy, arterial infusion chemotherapy, locally advanced proximal gastric cancer, progression-free survival, locally advanced gastric cancer, prognosis

Introduction

Gastric cancer is the fifth most common malignancy in the world and one of the leading causes of cancer-related death [1]. The latest statistics indicate there were more than 1 million new cases of gastric cancer and 760,000 related deaths worldwide in 2020 [2]. The mortality rate of gastric cancer in China is the highest throughout the world, and it ranks second in the incidence of all malignant tumors, second in the total incidence of male cancer and fifth in that of female cancer [3, 4]. The prognosis of gastric cancer patients mainly depends on their disease stage. Early gastric cancer is limited to the mucosa and submucosa, and the five-year survival rate can exceed 90% after endoscopic treatment or surgical treatment [5]. However, the clinical symptoms at this stage are occult, and most patients only have occasional epigastric discomfort, belching and acid reflux. Thus, the patients are normally at the advanced stages when diagnosed [6]. Even with surgery combined with S-1 adjuvant chemotherapy, the outcome of locally advanced gastric cancer remains unsatisfactory. There-

fore, it is particularly important to find new treatment options to improve patient outcomes.

Neoadjuvant chemotherapy has been gradually applied in the treatment of gastric cancer and has achieved good clinical efficacy in recent years [7]. Study has shown [8] that neoadjuvant chemotherapy can effectively shrink the tumor lesions, reduce the stage, and improve the radical resection rate. Earlier systemic therapy can also rapidly relieve the symptoms of patients, eliminate tumor micro-metastasis, prevent intraoperative dissemination and postoperative recurrence; meanwhile, it has certain reference value for the selection of postoperative adjuvant chemotherapy regimens and prognosis evaluation [9]. At present, neoadjuvant chemotherapy mainly includes intravenous and oral administration, but systemic administration has a relatively poor prognosis due to low effective drug concentration reaching the lesion, low downstaging rate, and low radical resection rate [10]. With the development of vascular interventional therapy techniques and equipment, selective arterial infusion chemotherapy has become a new route of neoadjuvant chemotherapy, which can directly pump chemotherapeutic drugs into target organs through feeding arteries. In addition, the concentration of chemotherapeutic drugs in the tumor area can be increased by more than 10 fold [11, 12]. It has been shown that when the local drug concentration is increased by a factor of 1, a 10-fold number of tumor cells can be killed [13]. Therefore, arterial infusion chemotherapy can significantly enhance the killing effect against tumor cells with mild adverse reactions.

However, studies about the effect of transarterial chemotherapy on the outcome of patients undergoing radical gastrectomy for gastric cancer remains quite limited. The aim of this study was to investigate the effect of transarterial chemotherapy on the outcome and prognosis of patients undergoing radical gastrectomy for gastric cancer, and to provide a reference for the selection of clinical treatment options.

Methods and materials

Clinical data

In this retrospective analysis, 96 patients with locally advanced proximal gastric cancer diagnosed in Gansu Cancer Hospital from July 2014 to July 2017 were enrolled. Forty patients undergoing surgery after 4 cycles of intravenous plus oral chemotherapy and 2-4 cycles of adjuvant chemotherapy after surgery were grouped as the control group (CG), while the remaining 56 patients with radical gastrectomy after 2 cycles of left gastric artery infusion chemotherapy plus 2 cycles of oral chemotherapy before surgery on the basis of CG patients were grouped as the observation group (OG). This study was approved by the medical ethics committee of Gansu Provincial Tumor Hospital (Ethical batch P-LW202204180001).

Inclusion and exclusion criteria

Inclusion criteria: Patients with symptoms in line with the diagnostic criteria for gastric cancer [14]; Patients with clinical stage IIIa-IV, and stage IV patients were limited to liver metastases (less than 5), with no extensive intra-abdominal metastasis; Patients that were endurable to surgery and chemotherapy; Patients with no previous history of other gastric surgery; and Patients with complete clinical data.

Exclusion criteria: Patients with participation in other treatment regimens before this study; Patients combined with other malignant tumors; Patients with upper gastrointestinal bleeding, gastrointestinal obstruction or other complications; Patients with heart, liver, lung, or kidney dysfunction, and KPS (Karnofsky, Karnofsky) score > 70 points.

Treatment regimen

The treatment plan of the OG patients: the Seldinger technique was used to puncture and intubate the femoral artery, and celiac artery and left gastric artery angiography were successively performed to determine the extent of the tumor lesion and blood supply. The left gastric artery was intubated for proximal gastric cancer, followed by perfusion chemotherapy. The arterial infusion chemotherapy regimen was fluorouracil (FU, Xi'an Haixin Pharmaceutical Co., Ltd., GYZZ H20050511) + irinotecan (CPT-11, Jiangsu Hengrui Medicine Co., Ltd., GYZZ H20213373) + oxaliplatin (OXA, Harbin Pharmaceutical Group Bioengineering Co., Ltd., GYZZ H20133094) (FU 400-500 mg/m^2, CPT-11 100-130 mg/m^2, OXA 85-100 mg/m^2), and within 1 week after arterial infusion chemother-

apy, tegafur capsules (Qilu Pharmaceutical Co., Ltd., GYZZ H20100151) 40 mg/m^2 bid were orally administered for 14 days when patient's nausea, vomiting and other gastrointestinal reactions were relieved, and the next cycle of treatment was performed after 1-2 weeks of rest; the patient's vital signs were closely monitored during the operation, and antiemetic, analgesic, gastric mucosal protection and supportive symptomatic treatment were routinely given before and after treatment. At the end of each cycle of chemotherapy, the efficacy of chemotherapy was assessed before the next cycle of treatment. Patients were given 2 additional cycles of systemic chemotherapy with SOX regimen if a complete remission (CR) was determined, and 2 cycles of systemic chemotherapy with the original arterial infusion regimen if a partial remission (PR) was determined, and patients were switched to systemic chemotherapy with docetaxel (Chenxin Pharmaceutical Co., Ltd., GYZZ H20093648) and tegafur capsules (Qilu Co., Ltd., GYZZ H20100151) for 2 cycles if stable disease (SD) or progressive disease (PD) was determined. Surgical treatment was performed 1-2 weeks after the end of chemotherapy, followed by intravenous + oral chemotherapy. All interventional procedures were performed in the same surgical group.

CG patients were treated with intravenous infusion of chemotherapy drugs, and the chemotherapy cycle, drugs, and evaluation criteria were consistent with those in the OG.

Outcome measures

Main outcome measures: Clinical efficacy was compared between the two groups after preoperative chemotherapy. Patients' survival information was obtained by querying patient clinic review records as well as electronic medical records. The 5-year progression-free survival (PFS) and overall survival (OS) rates after treatment were compared between the two groups. Cox regression was used to analyze prognostic factors affecting the PFS.

Secondary outcome measures: Clinical data, choice of surgical plan, and incidence of adverse reactions (nausea, vomiting and bone marrow suppression) after chemotherapy were compared between the two groups, as well as the improvement of clinical symptoms after treatment. Criteria for adverse reactions were evaluated using grading criteria and toxicity performance established by the National Cancer Institute [15]. The changes of tumor volume before and after chemotherapy were compared between the two groups.

Criteria for response assessment

Tumor volume was assessed by CT, and MRI was performed if necessary. The treatment effect was evaluated according to the response evaluation criteria for solid tumors issued by the World Health Organization [16] as follows: complete remission (CR, complete disappearance of local mass); partial remission (PR, lesion reduction of more than 50%); stable disease (SD, lesion reduction of less than 50%); progressive disease (PD, mass increase of more than 25% or appearance of new lesions); overall response rate (ORR) = CR + PR.

Statistical analysis

In this study, SPSS 20.0 (SPSS Inc., Chicago, USA) was used for statistical analysis of the collected data, and GraphPad Prism 8 (Graphpad software, San Diego, USA) was used for figure rendering. The enumeration data were expressed as rate (%) and Chi-square test was for data comparison. Measurement data were expressed as mean ± standard deviation (Means ± SD), Student t-test and Paired t-test were used for inter-group comparison and intra-group comparison, respectively. Rank sum test was used for rank data. The 5-year PFS and survival of patients were analyzed with K-M survival and log rank test, and the prognostic factors affecting PFS were determined with Multivariate Cox regression. $P < 0.05$ was considered statistically significant.

Results

Clinical data comparison

Comparison of the clinical data between the two groups showed no statistical difference in terms of age, gender, BMI, tumor stage, pathological type, past medical history and smoking history (all $P > 0.05$, **Table 1**).

Efficacy assessments

The clinical efficacy of preoperative chemotherapy in the two groups showed evidently higher

Table 1. Baseline data

Variables	Observation Group (n=56)	Control Group (n=40)	x^2 value	*P* value
Age				
≥ 55 years	24	15	0.277	0.598
< 55 years	32	25		
Gender				
Male	38	30	0.576	0.447
Female	18	10		
Tumor Staging				
Stage IIIa	22	16	0.517	0.915
Stage IIIb	17	12		
Stage IIIc	14	11		
Stage IV	3	1		
Pathological Type				
Well-differentiated adenocarcinoma	14	12	0.602	0.895
Moderately differentiated adenocarcinoma	16	10		
Poorly differentiated adenocarcinoma	20	15		
Signet ring cell carcinoma	6	3		
Past medical history				
Hypertension	17	15	0.535	0.464
Diabetes	16	12	0.023	0.879
Smoking history				
Yes	40	31	0.446	0.504
None	16	9		

Table 2. Efficacy assessments

Grouping	CR	PR	SD	PD	ORR
Observation Group (n=56)	5 (8.92)	489 (85.71)	1 (1.79%)	2 (3.58%)	53 (94.63)
Control Group (n=40)	2 (5.00)	30 (75.00)	7 (17.50)	1 (2.50%)	32 (80.00)
x^2 value					4.931
P value					0.026

Note: Complete Response (CR); Partial Response (PR); Stable Disease (SD); Progressive Disease (PD); Overall Response Rate (ORR).

Table 3. Tumor diameter before and after treatment

Grouping	Tumor size (cm^3)	
	Before treatment	After treatment
Observation Group (n=56)	5.29±1.76	2.24±1.41*
Control Group (n=40)	5.21±1.55	1.41±1.30*
t value	0.227	2.965
P value	0.820	0.003

Note: *means P < 0.05 compared with before treatment.

overall response rate (ORR) in the OG than in the CG (P < 0.05, **Table 2**). In addition, we compared the changes of tumor volume before and after chemotherapy between the two groups and found that the tumor size after chemotherapy in the OG was smaller than that in the CG (**Table 3**).

Clinical symptom relief

Statistical analysis of the clinical symptoms of the two groups revealed a lower total incidence of clinical symptoms in the OG than in the CG (P < 0.05, **Table 4**).

Surgical protocol

Statistical analysis of the choice of surgical options in the two groups revealed that the

Table 4. Clinical symptom statistics

Grouping	Abdominal distension, abdominal pain and discomfort	Anorexia	Pharyngeal sense of eating	Fecal occult blood positive	Total Occurrence
Observation Group (n=56)	3 (5.36%)	5 (8.93%)	1 (1.79%)	4 (7.14%)	13 (23.21%)
Control Group (n=40)	4 (10.00%)	8 (20.00%)	2 (5.00%)	6 (15.00%)	20 (50.00%)
x^2 value					7.421
P value					0.006

Table 5. Surgical options

Grouping	Radical surgery	Palliative surgery
Observation Group (n=56)	52 (92.86%)	4 (7.14%)
Control Group (n=40)	31 (77.50)	9 (22.50)
x^2 value	4.700	
P value	0.030	

number of patients treated with radical resection in the OG was significantly more than that in the CG (P < 0.05, **Table 5**).

Incidence of adverse reactions during preoperative chemotherapy

The statistical analysis of adverse reactions of preoperative chemotherapy indicated higher incidence of nausea and vomiting in the OG than in the OG (P < 0.05, **Table 6**), but there was no statistical difference in the incidence of bone marrow suppression between the two groups (P > 0.05, **Table 7**).

Comparison of 5-year OS and PFS between the two groups

Comparison of 5-year PFS and OS between the two groups showed that the 1-, 2-, 3-, 4- and 5-year PFS rates of the OG were 87.50%, 64.28%, 51.78%, 37.50% and 21.42%, respectively, and those in the CG were 72.50%, 42.50%, 37.50%, 15.00%, and 15.00%, respectively. The 1-, 2-, 3-, 4-, and 5-year OS rates of patients in the OG were 96.42%, 83.92%, 75.00%, 66.07%, and 55.53%, respectively, and those in the CG were 87.50%, 77.50%, 57.50%, 42.50%, and 30.50%, respectively. Statistically, the 5-year PFS and OS of the OG patients were markedly higher than those of CG patients (P < 0.05, **Figure 1**).

Prognostic factor analysis for PFS

Follow-up data were collected from 56 patients in the OG and 40 patients in the CG, with a follow-up rate of 100%. We found that tumor stage, tumor type, and treatment regimen were independent prognostic factors for PFS by Cox regression analysis (P < 0.01, **Figure 2**).

Discussion

Gastric cancer, as one of the most common malignant tumors in China, poses the highest mortality rate among malignant tumors of the digestive system [17]. With the continuous improvement of diagnosis and treatment techniques in China, the early diagnostic rate of gastric cancer has been evidently improved, striving for surgical treatment opportunities for most patients [18, 19]. How to improve the therapeutic effect of radical gastrectomy for gastric cancer remains the focus of gastroenterologist.

With the deepening of the biological research of gastric cancer and the improvement of medical technology, preoperative interventional therapy has become an effective method to improve the effect of surgical treatment [20]. Preoperative arterial infusion chemotherapy directly injects high concentrations of chemotherapeutic drugs into the lesion to kill tumor cells. The local drug concentration in the lesion is tens or even hundreds of times higher than systemic chemotherapy, therefore it poses stronger lethality and less systemic toxic side effects [21]. Studies have shown that the short-term efficacy and long-term survival rate of arterial infusion chemotherapy in the treatment of advanced gastric cancer are evidently better than those of systemic chemotherapy [22]. It can be seen that regional arterial infusion chemotherapy is a safe and effective neoadjuvant treatment modality for locally advanced gastric cancer.

In this study, the regimen selected for arterial infusion chemotherapy was 5-FU + CPT-11 + OXA, which is a third-generation platinum drug that can bind DNA more rapidly and firmly com-

Table 6. Nausea and vomiting statistics

Grouping	Grade 0	Grade I	Grade II	Grade III	Grade IV
Observation Group (n=56)	0 (0.00%)	0 (0.00%)	43 (76.78%)	9 (16.07%)	4 (7.14%)
Control Group (n=40)	2 (5.00%)	10 (25.00%)	19 (47.50%)	5 (12.50%)	4 (10.00%)
Z value			-2.250		
P value			0.024		

Table 7. Bone marrow suppression statistics

Grouping	Grade 0	Grade I	Grade II	Grade III	Grade IV
Observation Group (n=56)	31 (55.52%)	0 (0.00%)	18 (32.14%)	7 (12.5%)	0 (0.00%)
Control Group (n=40)	22 (55.00%)	0 (0.00%)	15 (37.50%)	3 (7.50%)	0 (0.00%)
Z value			-0.180		
P value			0.857		

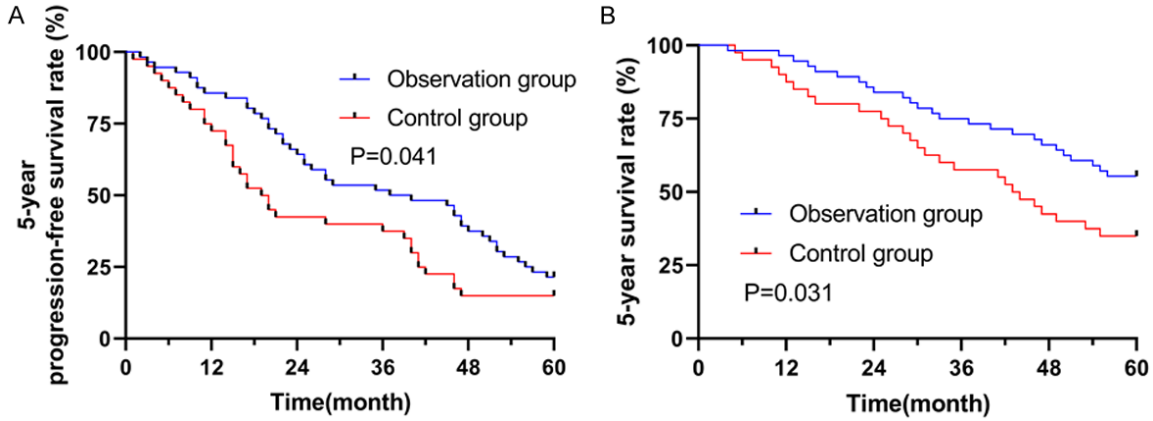

Figure 1. Comparison of 5-year progression-free survival and survival rates between the two groups. A. Comparison of 5-year progression-free survival. B. Comparison of 5-year survival.

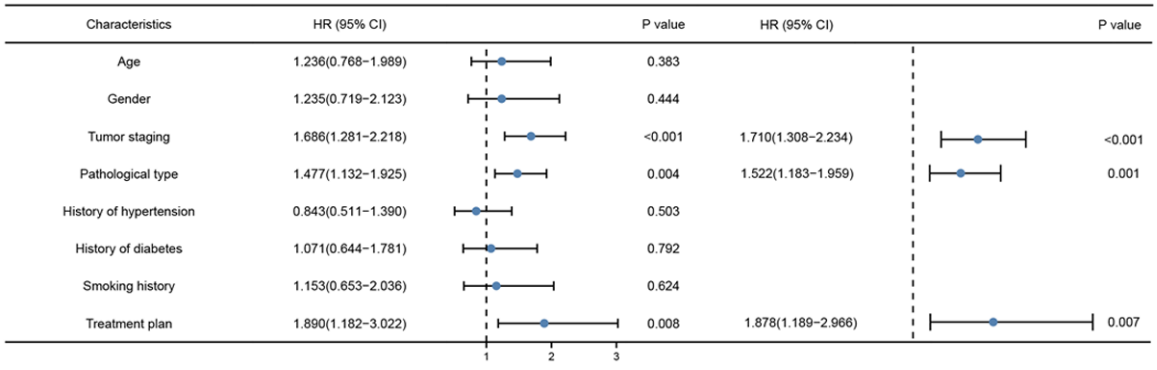

Figure 2. Cox regression analysis of prognostic factors affecting progression-free survival.

pared with cisplatin. It has a stronger cytotoxic effect, and has a synergistic effect with FU [23]. Study has shown that preoperative regional arterial infusion chemotherapy with OXA + FU regimen in advanced gastric cancer evidently increased the radical resection rate and long-term survival rate, with mild adverse reactions [24]. In this study, CPT-11 was also selected on

the basis of FU + OXA. CPT-11 can specifically inhibit DNA topoisomerase I, inhibit DNA replication and transcription, and has a strong antitumor effect. In addition, it has an evident effect in intravenous chemotherapy for advanced gastric cancer; however, the application of regional arterial infusion chemotherapy has not yet been reported in the literature [25]. Because 5-FU has a short plasma half-life, continuous intravenous administration is required in clinical practice; Tegafur is a novel oral anticancer drug of fluorouracil derivatives, which consists of two modulators, tegafur (FT) and gimeracil (CDHP), and oteracil potassium (Oxo); FT is a precursor of FU and can be converted to fluorouracil nucleoside *in vivo*, which plays an anti-tumor role by preventing protein synthesis [26]; CDHP can inhibit the catabolism of FU released from FT under the action of dihydropyrimidine dehydrogenase, increase the concentration of FU in the body, and enhance the anticancer effect [27]; Oxo can avoid or reduce the phosphorylation of FU in the intestine and reduce the toxic effects of FU drugs. Therefore, continuous intravenous infusion of tegafur and FU has similar efficacy and can be used as a supplement to arterial infusion chemotherapy. Our study found that the ORR, improvement of clinical symptoms, and the rate of radical resection of OG patients were all evidently higher than those of CG patients after preoperative chemotherapy. However, the incidence of nausea and vomiting after chemotherapy in the OG was higher than that in the CG. These results suggest that arterial infusion chemotherapy can significantly improve the clinical response rate of patients before surgery and ensure the best chance of radical resection, but it will increase the incidence of adverse reactions in patients. Our department has performed arterial infusion chemotherapy for locally advanced and advanced gastric cancer with liver metastasis since 1996, so that it has been continuously optimized in terms of chemotherapeutic drug dose and chemotherapy cycle. In the beginning, our department performed left gastric artery infusion chemotherapy and embolization therapy, but patients suffered from severe nausea, vomiting and upper abdominal pain after embolization, and some patients could only be relieved after about 10 days of treatment, thus embolization was abandoned considering the possibility of secondary perfusion chemotherapy. Embolization of liver metastases was only performed on patients with liver metastasis. Why should intravenous chemotherapy be performed after the downstaging of arterial infusion chemotherapy? Previously, some patients achieved PR or even CR after 1 or 2 times of infusion chemoembolization, while 2 weeks later, surgery revealed very severe perigastric adhesions, resulting in difficult surgery. Therefore, arterial infusion chemotherapy was selected followed by 2 cycles of intravenous chemotherapy before surgery, at which time perigastric adhesions were found to be easily released during surgery. Previously, Wu et al. [28] found that neoadjuvant chemotherapy by local arterial infusion could improve the pathological response rate to epirubicin, oxaliplatin plus capecitabine regimens in the treatment of advanced gastric cancer. However, the study by Li et al. [24] found that the tumor regression rate of patients with locally advanced gastric cancer after continuous arterial catheterization chemotherapy was 100%, and all patients survived without tumor recurrence or progression after 1 year of postoperative follow-up. These results suggest that arterial infusion chemotherapy can improve the clinical efficacy of patients with gastric cancer. The main reason is that high concentrations of chemotherapeutic drugs can also lead to tumor tissue ischemia and necrosis, which may not be conducive to immune escape caused by tumor cells but facilitate the killing effect of human immune cells.

In this study, we also compared the 5-year PFS and OS between the two groups and found that OG patients held markedly higher 5-year PFS and OS rates than CG patients. As reported earlier in the study of Lu et al. [29], arterial infusion chemotherapy after gastric cancer surgery was found to be significantly superior to systemic chemotherapy in improving the survival time of patients, which is consistent with our findings. In addition, in the study by He et al. [30], the 3-year survival time of patients who received preoperative arterial infusion chemotherapy and surgical treatment was evidently higher than that of patients who received arterial infusion chemotherapy alone. These results suggest that preoperative arterial infusion chemotherapy significantly improves patient survival compared with intravenous chemotherapy. At the end of the study, we analyzed the factors affecting PFS, and tumor stage, tumor type and

treatment regimen were found to be independent prognostic factors for PFS. Zhang et al. [31] revealed that the clinical stage and treatment regimen of patients receiving preoperative intra-arterial chemotherapy were independent prognostic factors for 5-year OS, which is consistent with our results. There are abundant nerves, lymphatic vessels and blood vessels from the mucosal layer to the outer serosa of the gastric wall. Tumor cells can cause hematogenous and lymph node metastasis with blood circulation and lymph node reflux. The deeper the TNM stage, the greater the probability of tumor cell invasion and metastasis to the peritumor [32]. Therefore, gastric cancer patients with higher TNM stage have worse prognosis and need medical intervention as early as possible.

In this study, we determined the effect of transarterial infusion chemotherapy on the treatment efficacy and prognosis of patients undergoing radical gastrectomy for gastric cancer. However, there were some limitations in this study. First, this study was a retrospective study and analysis of the results may be biased. Second, as a single-center study, this study had fewer patient samples. Therefore, we hope to include more samples in future studies and launch multi-center collaboration to refine our conclusions.

In summary, regional arterial infusion chemotherapy for gastric cancer is an ideal neoadjuvant therapy, which can significantly reduce the tumor lesions in a short time and increase the resection rate. However, it also increases the adverse reactions of patients, so patient condition needs to be considered when it comes to selection of protocol.

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Disclosure of conflict of interest

None.

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