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Review Article

Neo-adjuvant chemotherapy combined with laparoscopic surgery can improve the efficacy and quality of life of patients with advanced gastric cancer

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Abstract: Objective: To analyze the effect of neo-adjuvant chemotherapy (NAC) combined with laparoscopic distal gastrectomy on the efficacy and quality of life of patients with advanced gastric cancer (AGC). Methods: From November 2014 to October 2016, 86 patients with AGC diagnosed and treated in our hospital were selected as research participants, and they were divided into observation group (OG) (45 cases) and control group (CG) (41 cases) in accordance with the treatment methods. In OG, patients received NAC combined with laparoscopic distal gastrectomy before operation, while patients in CG received laparoscopic distal gastrectomy only. The efficacy, operative situation, adverse reaction, postoperative recovery, KPS score and 3-year survival were compared and analyzed in both groups. Results: There was no obvious difference in the operation time, intraoperative blood loss, hospitalization time, adverse reactions, postoperative recovery and 3-year survival rate in both groups ($P > 0.05$). The therapeutic effect (total effective rate) in OG was significantly higher than that in CG. There was no obvious difference in KPS scores between the OG and CG ($P > 0.05$). After different operations for 3 months, KPS scores of patients were significantly increased in the two groups ($P < 0.05$), and it was obviously higher in the OG than that of the CG ($P < 0.05$). Conclusion: NAC combined with laparoscopic radical gastrectomy has a definite clinical effect for the treatment of AGC, which can ameliorate the curative effect and the quality of life of patients. It is therefore worthy of clinical promotion.

Keywords: Advanced gastric cancer, neo-adjuvant chemotherapy, laparoscopy, quality of life

Introduction

Gastric cancer (GC) is one of the common malignant tumors of digestive system. Because of the deterioration of the environment and the change of people's lifestyle, its morbidity and mortality have been high in recent years. Early detection and treatment are essential for prolonging the survival time of patients with GC [1-3].

At present, the surgical treatment is the main therapeutic method for GC. Open surgery is the main treatment for AGC [4, 5]. Laparoscopic surgery has the advantages of less trauma and quick recovery, and it is widely used in the resection of GC at present. Because early GC has no specific clinical symptoms and its onset is hidden, most patients are not confirmed until the advanced stage. Because of the wide distribution of the cancerous tissue, it is difficult to completely remove the cancerous tissue. Surgical treatment alone is often ineffective and has a high recurrence rate, and the 5-year survival rate is low [6-8]. NAC refers to systemic chemotherapy before the implementation of local treatment methods (such as operation or radiotherapy), with the aim of reducing the mass and killing invisible metastatic cells as soon as possible, so as to promote subsequent operation, radiotherapy and other treatments. It can also eliminate potential micrometastatic lesion and reduce postoperative recurrence rate [9, 10]. It is of great significance for the surgical efficacy and postoperative rehabilitation of patients with AGC [11]. Relevant studies have shown that NAC before tumor resection can effectively increase the tumor resection rate and improve the prognosis of patients, while laparoscopic distal gastrectomy combin-

ed with NAC has significant clinical efficacy and high safety in the treatment of early GC [12-14]. However, there are few studies on laparoscopic radical gastrectomy combined with NAC for the treatment of AGC.

This research was designed to seek the clinical effects of NAC combined with laparoscopic distal gastrectomy for the treatment of AGC by performing laparoscopic-assisted radical gastrectomy alone and NAC for patients with AGC in the two groups, providing scientific reference for clinical treatment.

Materials and methods

Baseline data

From November 2014 to October 2016, 86 patients with AGC diagnosed and treated in Chongqing University Central Hospital were selected as research participants, and they were divided into OG (45 cases) and CG (41 cases) according to the treatment methods. In OG, patients received NAC combined with laparoscopic distal gastrectomy before operation, while patients in CG received laparoscopic distal gastrectomy only. This research was approved by the ethics committee of Chongqing University Central Hospital, and it was performed in accordance with Helsinki Declaration. All subjects affixed informed consent.

Inclusion criteria: Patients were confirmed as AGC [15] by gastroscopy and biopsy, and the abdominal ultrasound and abdominal enhanced CT-MRI scan showed measurable lesions, and no distant metastasis was found. Patients were diagnosed as AGC in stage I~III by spiral CT and ultrasonic gastroscopy. ECOG score was 0~1. Before operation, patients did not receive radiotherapy, chemotherapy or other related treatment. Liver and kidney function and coagulation function were normal, and patients could tolerate operation and had no other contraindications to operation. There was no distant metastasis of liver, bone, lung, lymph node by detection of B-ultrasound and CT. Patients had indications for NAC and had no contraindications. Patients had the corresponding surgical indications, and radical distal subtotal gastrectomy, radical proximal gastrectomy and radical total gastrectomy with D2 lymph node dissection assisted by laparoscopy were feasible. Patients had no previous history of abdominal surgery.

Exclusion criteria: Patients were diagnosed as undifferentiated gastric carcinoma by histopathological examination of gastroscopic biopsy. There were basic diseases that affected this treatment. Adverse reactions of NAC were serious, which required symptomatic treatment and termination of chemotherapy. During the operation, it was confirmed that the tumor had infiltrated adjacent tissues or organs, which required extensive radical gastrectomy, that is, the patients were diagnosed as stage T4b during the operation. Patients suffered from severe heart, liver, kidney and hematological diseases.

Methods of treatment

In OG, patients received preoperative chemotherapy with XELOX regimen, namely capecitabine combined with oxaliplatin. From the first day to the 14th day, the capecitabine was given orally to the patients for 2500 mg/m^2 for 2 times/d, and 130 mg/m^2 of oxaliplatin was given intravenously for 3 hours, with 1 cycle of chemotherapy every 3 weeks and 2 consecutive courses of chemotherapy. After 2 cycles of chemotherapy, gastroscopy and enhanced CT were reexamined to observe the effect of chemotherapy. If the primary tumor lesion was significantly reduced, the patients continued chemotherapy for 2 cycles. During chemotherapy, blood routine, liver and kidney function and coagulation function were regularly checked. If the number of leukocytes was less than 3×10^9/L or the number of neutrophils was less than 1.5×10^9/L, recombinant human granulocyte colony stimulating factor was used to increase leukocytes. If the toxic side effects of liver and kidney function of the patient exceeded grade II and the toxic side effects of digestive tract exceeded grade III, chemotherapy was stopped and symptomatic treatment was given to the patients. Chemotherapy was continued after symptoms were relieved or relevant indexes were recovered, and the dosage of chemotherapeutic drugs was reduced as appropriate. Laparoscopic surgery was performed at 2~4 weeks after chemotherapy. In CG, patients were treated with laparoscopic surgery within 2 weeks of diagnosis. The operation mode in both groups was D2 radical gastrectomy. After operation, 34 cases received postoperative adjuvant chemotherapy according to the original scheme.

Table 1. Baseline data in OG and CG [n (%)]/($\bar{x}$ ± sd)

Classification	OG (n=45)	CG (n=41)	t/χ^2	P
Gender			0.952	0.329
Male	25 (55.56)	27 (65.85)		
Female	20 (44.44)	14 (34.15)		
Age/years old	54.17±9.48	55.33±8.93	0.583	0.562
BMI (kg/m^2)	23.14±4.98	23.58±4.20	0.441	0.661
Hemoglobin (g/L)	114.51±17.49	116.97±19.42	0.618	0.538
Serum albumin (g/L)	37.88±6.49	38.44±5.61	0.426	0.671
Tumor diameter (cm)	3.75±0.48	3.64±0.51	1.030	0.306
Tumor location			0.682	0.711
Upper stomach	12 (26.67)	8 (19.51)		
Middle stomach	11 (24.44)	12 (29.27)		
Lower stomach	22 (48.89)	21 (51.22)		
Differentiation degree			0.100	0.951
Well differentiated	8 (17.78)	7 (17.07)		
Middle differentiated	22 (48.89)	19 (46.34)		
Poorly differentiated	15 (33.33)	15 (36.59)		
TNM stages			0.038	0.845
Stage I-II	21 (46.67)	20 (48.78)		
Stage III	24 (53.33)	21 (51.22)		

Outcome measures

The operative situation indexes of patients were compared in the two groups, including operative time, operative blood loss, postoperative hospitalization time and other indexes. After treatment for one month, the efficacy of the patient was evaluated according to RECIST solid tumor efficacy judgment standard [16]: complete response (CR), partial response (PR), stable disease (SD) progressive disease (PD). Total effective rate = (CR+PR) cases/total cases × 100%. The postoperative recovery was compared in the two groups, including out of bed activity time and postoperative anus exhaust time. During treatment, the adverse reactions were compared, including postoperative complications, hematological toxic reactions and digestive system toxic reactions. Postoperative complications included abdominal infection, incision infection and lung infection. Hematological toxic reactions included anemia and leukopenia. Digestive system toxic reactions included oral mucositis and nausea and vomiting. The karnofsky performance status (KPS) score [17] was used to evaluate the recovery of quality of life after treatment for 3 months: the higher the score, the better the health status, and the more tolerable the side effects of treatment. Statistics were made on the 3-year survival of the patients after operation, and the 3-year survival of patients in both groups were compared by plotting the K-M survival curve.

Statistical processing

SPSS22.0 was used for statistical analysis. Normal distribution measurement data were represented by mean number ± standard deviation (x ± sd), and t test was used for comparison. The counting data were represented as percentages and compared with χ^2 test. Rank sum test was used for comparison of ranked data. The survival curve was drawn by K-M method, and the death risks in the two groups were compared by Log-Rank test. The difference was statistically significant with $P < 0.05$.

Results

Baseline data

There was no obvious difference in age, gender, body mass index (BMI), hemoglobin, serum albumin, tumor diameter, tumor location, degree of differentiation, TNM stage and other general data between the OG and CG ($P > 0.05$) (**Table 1**).

Comparison of efficacy between OG and CG

In OG, there were 21 cases of CR, 13 cases of PR, 9 cases of SD and 2 cases of PD, with a total effective number of 34 cases and a total effective rate of 75.56%. In CG, there were 14 cases of CR, 8 cases of PR, 13 cases of SD and 6 cases of PD, with a total effective number of 22 cases and a total effective rate of 53.66%. After χ^2 test, the therapeutic effect (total effective rate) in OG was obviously higher than that in CG ($P < 0.05$) (**Table 2**).

Comparison of operative situations in OG and CG

There was no obvious difference between the OG and CG in terms of operation time, intraoperative blood loss and hospitalization time ($P > 0.05$) (**Table 3**).

Table 2. Comparison of efficacy in both groups [n (%)]

Grouping	n	CR	PR	SD	PD	Total effective
OG	45	21 (46.67)	13 (28.89)	9 (20.00)	2 (4.44)	34 (75.56)
CG	41	14 (34.15)	8 (19.51)	13 (31.71)	6 (14.63)	22 (53.66)
χ^2	-	-	-	-	-	4.529
P	-	-	-	-	-	0.033

Table 3. Comparison of operative situations in both groups ($\bar{x}$ ± sd)

Grouping	n	Operation time	Intraoperative blood loss	Hospitalization time
OG	45	4.64±1.27	116.47±19.72	22.73±7.67
CG	41	4.53±1.85	122.11±15.86	23.72±8.75
t	-	0.324	1.452	0.559
P	-	0.747	0.150	0.578

Comparison of adverse reactions between OG and CG

In OG, there were 2 cases of abdominal infection, 3 cases of incision infection, 3 cases of lung infection, 1 case of nausea and vomiting, 2 cases of anemia, 1 case of oral mucositis and 1 case of leukopenia, with a total adverse reaction rate of 28.89%. In CG, there were 2 cases of abdominal infection, 4 cases of incision infection, 3 cases of lung infection, 3 cases of nausea and vomiting, 1 case of anemia, 2 cases of oral mucositis and 1 case of leukopenia, with a total adverse reaction rate of 33.33%. After χ^2 test, there was no obvious difference in adverse reactions between the OG and CG (P > 0.05) (**Table 4**).

Comparison of postoperative recovery between OG and CG

There was no obvious difference in postoperative out of bed activity time and anus exhaust time between OG and CG (P > 0.05) (**Table 5**).

Comparison of KPS scores in OG and CG at admission and 3 months after operation

There was no obvious difference in KPS score between OG and CG at admission (P > 0.05). After different operations for 3 months, the KPS scores of patients were significantly increased in the two groups (P < 0.05), and the OG was obviously higher than the CG (P < 0.05). Therefore, compared with the admission, the KPS scores of patients in OG were significantly increased at 3 months after operation (**Figure 1**).

Survival of patients in OG and CG during follow-up

Statistics were made on the survival of patients after operation for 3 years. All 86 patients were followed up. 7 patients died and 79 cases survived within 3 years, with a survival rate of 91.86%. Among them, 3 patients died and 42 patients survived in OG within 3 years, with a survival rate of 93.33%. 4 patients died and 37 patients survived in CG, with a survival rate of 90.24%. According to the 3-year survival conditions of patients in the two groups, the K-M survival curve was drawn and observed, and it was found that there was no statistical difference between the 3-year survival conditions of patients in the two groups (P > 0.05) (**Figure 2**).

Discussion

At present, GC is a common cancer in the world. More than 70% of the cases are in the advanced stage at the time of diagnosis. A large proportion of patients will have postoperative recurrence or metastasis after the first radical operation. The postoperative 5-year survival rate of patients with AGC is still hovering around 30% [18-20]. At present, the surgical resection is the main treatment for GC, in which patients with early GC can be effectively recovered after laparoscopic surgery, but patients with AGC are difficult to achieve ideal curative effect by alone surgical treatment due to many factors such as lymph node metastasis routes [21, 22].

NAC is a local or systemic treatment given to patients before surgery or radiotherapy for malignant tumors. It can not only kill tumor cells and reduce tumor size, but also has the advantages of eliminating potential micrometastatic lesion and reducing postoperative recurrence rate. It can lay the better foundation for subsequent surgical operations. Since tumor size is reduced, it is more conducive to radical resec-

Table 4. Comparison of adverse reactions in both groups [n (%)]

Grouping	n	Abdominal infection	Wound infection	Pulmonary infection	Nausea and vomiting	Anemia	Oral mucositis	Leukopenia	Total adverse reactions
OG	45	2 (4.44)	3 (6.67)	3 (6.67)	1 (2.22)	2 (4.44)	1 (2.22)	1 (2.22)	13 (28.89)
CG	41	2 (4.17)	4 (8.33)	3 (6.25)	3 (6.25)	1 (2.08)	2 (4.17)	1 (2.08)	16 (33.33)
χ^2	-				-				0.986
P	-				-				0.321

Table 5. Comparison of postoperative recovery between the two groups ($\bar{x} \pm sd$)

Grouping	n	Postoperative out of bed activity time	Postoperative anus exhaust time
OG	45	2.77±0.73	3.88±1.64
CG	41	2.86±0.67	3.72±1.51
t	-	0.594	0.469
P	-	0.554	0.640

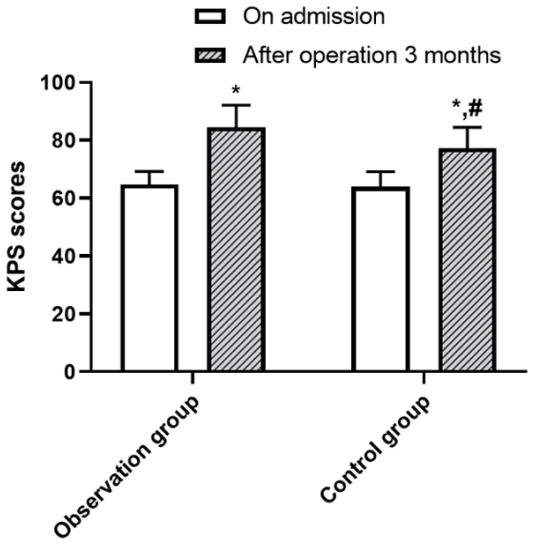

Figure 1. KPS scores in OG and CG at admission and 3 months after operation. There was no significant difference in KPS scores between OG and CG ($p > 0.05$). After different operations for 3 months, KPS scores of patients were significantly increased in the two groups ($P < 0.05$), and the OG was significantly higher than the CG ($P < 0.05$). Compared with admission, KPS scores of patients in OG increased more obviously after operation for 3 months. Note: Compared with admission, *$P < 0.05$; Compared with the OG after operation for 3 months, #$P < 0.05$.

tion and improve surgical efficacy [23, 24]. Currently, it has been widely used in the treatment of solid tumors such as rectal cancer and osteosarcoma. However, there are few studies on NAC in the treatment of patients with AGC [25]. Laparoscopic surgery results in a smaller

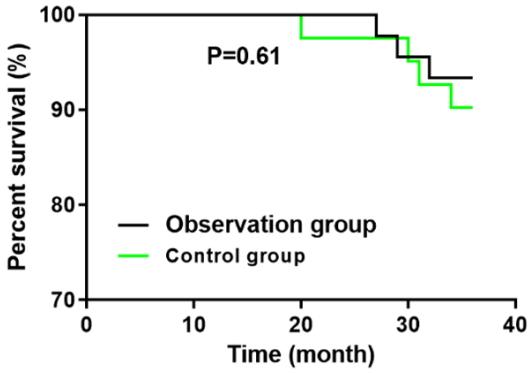

Figure 2. Survival of patients in OG and CG during follow-up. 3 patients died and 42 patients survived in OG within 3 years, with a survival rate of 93.33%. 4 patients died and 37 patients survived in CG, with a survival rate of 90.24%. There was no statistical difference in the 3-year survival of patients between the two groups ($P > 0.05$).

incision and it has lower requirements on patients' surgical tolerance, less damage to patients' autoimmune function and faster postoperative recovery, which expands the scope of the applicable population and can achieve the same therapeutic effect as traditional laparotomy, and the incidence of complications is much lower than traditional laparotomy. In addition, the amount of blood loss is less during laparoscopic surgery, which reduces the possibility of the exfoliation and metastasis of cancer cells, effectively reducing the recurrence rate and is beneficial to the rehabilitation of patients [26]. At present, the application of NAC combined with laparoscopic-assisted radical gastrectomy not only improves the clinical efficacy of surgical treatment alone, but also provides a new direction for the treatment of AGC in the future [27]. In this study, patients were treated with NAC combined with laparoscopic distal gastrectomy in OG. The results revealed that there was no significant difference in terms of operation time, number of lymph node dissection, intraoperative blood loss, intestinal exhaust time, time of getting out of bed after

operation, postoperative hospitalization time and other indicators between the two groups. It revealed that preoperative NAC had no effect on operation time, blood loss and number of lymph node dissection. Moreover, it had no obvious influence on postoperative recovery indexes such as intestinal exhaust time, time of getting out of bed after operation, postoperative hospitalization time. This might be that perioperative indexes were mainly related to the operation mode, and laparoscopic surgery had the advantages of small trauma, short operation time and less blood loss, so NAC was difficult to show obvious advantages. Comparing the efficacy of patients in both groups, it was found that the total effective rate of patients was 75.56% in OG, which was higher than 53.66% in CG. The intraoperative evaluation index showed that the incidence rate of omental adhesion and potential pyloric obstruction in OG was lower than that in CG, but the patients' gastric surrounding tissues were brittle and serosal congestion and edema were more obvious than that of CG. In terms of quality of life, we compared the KPS scores of patients in the two groups at admission and 3 months after operation, and found that the KPS scores of patients were obviously increased in the two groups ($P < 0.05$), and the OG was obviously higher than the CG ($p < 0.05$). This might be due to the higher rate of complete resection and the higher recovery of the patients in physiological and psychological aspects in OG. At the end of the study, we made statistics on the survival of the patients after operation for 3 years. According to the 3-year survival of patients in the two groups, the K-M survival curve was drawn and observed, and it revealed that there was no statistical difference in the 3-year survival of patients in both groups ($P > 0.05$). This results of Pattison et al. [28] have shown that there is no obvious difference in OS and PFS between NAC+radical gastrectomy group and radical gastrectomy alone group ($P > 0.05$), which is similar to our results. However, the analysis of their subgroup results has shown that the 5-year survival rate of NAC plus radical gastrectomy group is superior.

Although this study revealed the efficacy of NAC combined with laparoscopic-assisted radical gastrectomy in the treatment of AGC, we did not analyze the 5-year survival and quality of life of patients in the two groups, hoping to supplement this in future research.

To sum up, NAC combined with laparoscopic radical gastrectomy has a definite clinical effect for the treatment of AGC, which can ameliorate the curative effect and the quality of life of patients, so it is worthy of clinical promotion.

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Disclosure of conflict of interest

None.

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