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Original Article

Preoperative neoadjuvant chemotherapy favors advanced gastric cancer treated with laparoscopic radical surgery

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Abstract: Objective: Gastric cancer is a common clinical malignancy, and it is often treated with surgery plus chemotherapy. This study aimed to explore the efficacy of laparoscopic radical surgery plus NACT (neoadjuvant chemotherapy) for patients with advanced gastric cancer. Methods: A total of 131 eligible cases of advanced gastric cancer who received laparoscopic radical surgery were recruited and by random number table method divided into the observation group (n=68, patients treated with preoperative NACT) and the control group (n=63, patients treated without preoperative chemotherapy). Surgery related indicators, postoperative recovery status, KPS (Karnofsky Performance Status) score, efficacy and postoperative complications were observed. Results: There are statistical differences between the two groups in surgical margins after postoperative chemotherapy (all P<0.05). The KPS scores in the observation group were higher than those in the control group at three and six weeks after surgery (both P<0.05). Total effective rate and control rate of the observation group were significantly higher than those of the control group (P<0.05). The numbers of death, recurrence and metastasis and the incidence of adverse reaction in the observation group were significantly less than those in the control group (P<0.05). Conclusion: Laparoscopic radical surgery plus NACT can increase the resection rate of surgery with negative surgical margins (R0), reduce recurrence and metastasis of advanced gastric cancer, and improve patients' quality of life.

Keywords: Laparoscopic radical resection, neoadjuvant chemotherapy, advanced gastric cancer, efficacy

Introduction

Gastric cancer is a common clinical malignancy and the third leading cause of death from cancer. In 2015, nearly 1.3 million cases suffered from this cancer in the world [1]. Gastric cancer incidence rates vary dramatically by world region with East Asia having the highest rate. In China, gastric cancer incidence rate ranks the second among tumors, and China is a high-incidence country in East Asia [2]. At present, surgery is the main strategy for treatment of gastric cancer [3]. With the development of surgical techniques, an increasing number of patients with gastric cancer have been treated with laparoscopic radical surgery, but surgical treatment alone for the cancer cannot achieve a desired outcome due to the low resection rate and postoperative 5-year survival rate and the high recurrence and metastasis rates after surgery [4]. In order to improve clinical efficacy, postoperative adjuvant chemotherapy is applied for treating gastric cancer to reduce the recurrence and metastasis, but patients are at a relatively higher risk for chemotherapy intolerance due to the variable efficacy of chemotherapy between human bodies [5]. In the continuous clinical exploration, neoadjuvant chemotherapy (NACT) is used to treat patients with cancer before and after the surgery. Previous studies have shown that NACT can effectively reduce the risks of recurrence and metastasis and improve survival, and can also reduce adverse reactions after chemotherapy [6, 7]. The present study aimed to explore the efficacy of laparoscopic radical surgery combined with NACT for patients with advanced gastric cancer.

Materials and methods

Patients

The study was approved by the Medical Ethics Committee of the First Hospital of Zibo City, and informed consents were obtained from all the patients or their families.

In this study, a total of 131 patients who underwent laparoscopic radical surgery for advanced gastric cancer from October 2012 to July 2017 in The First Hospital of Zibo City, were enrolled and by random number table method divided into two groups, observation group (n=68) and control group (n=63). Patients in the observation group underwent laparoscopic radical surgery with preoperative NACT, while patients in the control group received laparoscopic radical surgery without the preoperative chemotherapy. The age of all the patients ranged from 44 to 89 years old with an average age of 63.47 years (SD=8.67).

Patients who met with the following criteria were included: 1) diagnosed as primary gastric cancer and advanced gastric cancer (T2-T4 or N1+), 2) without receiving other tumor-related treatment before the treatment in this study, 3) with normal cardiopulmonary function, 4) normal coagulation, and normal bone marrow function as well as 5) complete clinical data [8]. Patients with the following conditions were excluded: 1) had received or were receiving other chemotherapy, or who had 2) severe heart and lung disease, or 3) other primary malignant tumors, or 4) abnormal blood coagulation or bone marrow function, or 5) liver and kidney dysfunction, or 6) who were allergic to chemotherapy drugs, or who had 7) poor coordination, or 8) incomplete clinical data.

Clinical and pathological staging

Clinical staging and pathological staging were evaluated according to the seventh edition of the UICC (Union for International Cancer Control)/AJCC (American Joint Committee on Cancer) staging system for gastric cancer [9].

Chemotherapy

The FNCLCC/FFCD clinical trial based on NACT for gastric cancer was successfully reported [10]. Preoperative NACT was performed in the observation group with the chemotherapy regimens including FOLFOX6 (Oxaliplatin/Calcium folinate/5-Fu), XELOX (Oxaliplatin/Capecitabine) and SOX (Oxaliplatin/S-1). Taking FOLFOX6 as an example, the details were as follows: oxaliplatin (Nanjing Pharmaceutical Co., Ltd., China) was intravenously infused on the 1st day at a dose of 80 mg/m^2 for more than two hours, and at the same time the tetrahydrofolic acid (Chongqing Yaoyou Pharmaceutical Co., Ltd., China) was intravenously infused at a dose of 400 mg/m^2; the next day, fluorouracil (Tianjin Jinyao Pharmaceutical Co., Ltd., China) was intravenously infused at a dose of 2,400 mg/m^2. The total infusion time was more than 46 hours. The above chemotherapy regimens were administrated two times a week, which were defined as one treatment cycle. Ultrasound gastroscopy was performed on the patients who received three cycles of chemotherapy; the ones who had no increase in tumor size and no metastasis and infiltration shown through the gastroscopy were then scheduled to receive laparoscopic radical surgery. If increase in tumor size and metastasis and infiltration were detected by the gastroscopy, two more cycles of chemotherapy were given to the patients before the surgery.

Surgical technique

Operation plan of laparoscopic radical gastrectomy was chosen and performed with reference to Expert consensus on quality control of the laparoscopic radical resection for gastric cancer in China (2017 edition) [8]. Ligation of blood vessels, dissection of surrounding lymphs, separation of surrounding tissues, reconstruction of the digestive tract and complete resection of the tumor were carried out during the surgery followed by gastrointestinal decompression, nutritional support and anti-infective treatment.

After surgery, all the patients received postoperative chemotherapy one week later. Oxaliplatin was intravenously infused at a dose of 130 mg/m^2 for more than two hours and capecitabine tablets (Roche, Shanghai, China) were administrated to all the patients on the days 1-14, twice a day, 100 mg each time. A treatment cycle was 21 days. The control group shared the same time point for laparoscopic radical surgery. The operations and postoperative chemotherapy in the control group were the same as those in the observation group. Outcome measures such as liver and kidney function and the blood routine of the two groups were monitored.

Outcome measures

Operative measurements in this study included operation time, the amount of intraoperative blood loss, the number of cases who received laparotomy converted from laparoscopic surgery, the number of cases who underwent palliative operations, surgical margin (R0 or R1/

R2 resection), and excision extension (total gastrectomy or distal gastrectomy). Postoperative recovery status was evaluated by several measures including postoperative gastrointestinal function recovery time (time of first flatus after surgery), postoperative off-bed time, length of hospital stays after surgery and postoperative complications. Postoperative complications included surgical site infection, pulmonary infection, intestinal obstruction, anastomotic leakage and pleural effusion.

The KPS score was used to evaluate the physical condition of patients on the day of admission and at three weeks and six weeks after surgery [11]. The total score for the evaluation was 100 points. The higher score indicates a better physical condition; conversely, the lower score indicates a worse physical condition. The score below 60 points referred to a poor physical condition that was not conducive to the treatments for the tumor.

Grade III or higher adverse reactions in all patients in one-cycle chemotherapy after surgery were observed. The adverse reactions in this study included reduction of all three hematopoietic cell lines (red blood cells, white blood cells and platelets), upper respiratory tract infection, gastrointestinal dysfunction, and peripheral neuritis.

Evaluation of efficacy

Postoperative efficacy was evaluated by the degree of remission or the degree of development of the disease, according to which efficacy was described as four conditions including CR (complete remission), PR (partial remission), SD (stable disease), and PD (progressive disease) [12]. Efficacy (%) = (the number of CR cases + the number of PR)/total number of cases ×100. Disease control rate (%) = (the number of CR + the number of PR + the number of SD)/total number of cases ×100.

Follow-up

The patients included in the study were followed up each month after discharge at the out-patient clinic, and examinations like gastroscopy, routine blood test, and blood biochemistry test were carried out. The follow-up was periodically performed after discharge. During the follow-up, conditions including recurrence, survival and metastasis were monitored in all patients. The deadline for the follow-up was July 2018.

Statistical analysis

The data obtained in this study were analyzed using the SPSS software version 17.0. The continuous variables were expressed as mean ± standard deviation ($\bar{\chi}$ ± sd). The independent-samples t-test was performed to analyze the continuous variables that conformed to the normal distribution and the homogeneity of the variance. The repeated measures analysis of variances was performed for measurement of multiple time points. Pearson chi-square test and Fisher exact probability test were performed to analyze the enumeration data. For all analyses, $P<0.05$ was considered statistically significant.

Results

No significant differences in baseline characteristics between two groups

Comparison of the baseline characteristics of the patients in the two groups showed that there were no significant differences in gender, age, tumor size, pathological type, and UICC stage between the two groups (all $P>0.05$). Of the 68 patients in the observation group, five patients who were evaluated as progressive gastric cancer in the third cycle of NACT underwent the surgery earlier, and the remaining 63 patients received the surgery after five cycles of NACT (**Table 1**).

Observation group surpassed control group in surgery related indicators

There were no significant differences in operation time, the amount of intraoperative blood loss, the number of cases who received laparotomy converted from laparoscopic surgery, excision extension, and the number of cases who underwent palliative operations between the two groups (all $P>0.05$). But there were differences in the number of negative surgical margins (R0) and the number of positive surgical margins (R1 or R2) between the two groups (both $P<0.05$, **Table 2**).

No significant differences in postoperative recovery status between two groups

There were no significant differences in the postoperative off-bed time, length of hospital stays after surgery, time of first flatus after surgery and total incidence of postoperative complications between the two groups (all $P>0.05$, **Table 3**).

Table 1. Baseline characteristics

	Observation group (n=68)	Control group (n=63)	χ^2/t	P
Male/female	38/30	37/26	-0.328	0.743
Age (years)	53.60±9.09	53.33±8.27	0.177	0.860
BMI (kg/m^2)	25.71±3.76	25.59±4.28	0.110	0.913
Duration of disease	3.17±1.05	3.97±0.65	0.534	0.128
Education level				
Junior high school or below	20	19	0.532	0.767
Senior high school or secondary specialized school	38	32		
Junior college or above	10	12		
Complications				
Hyperlipidemia (yes/no)	24/44	21/42	0.055	0.813
Hypertension (yes/no)	33/35	31/32	0.006	0.938
Coronary heart disease (yes/no)	12/56	10/53	0.074	0.786
Obesity (yes/no)	22/46	20/43	0.006	0.941
Systolic pressure (mmHg)	142.16±7.19	142.03±8.20	0.067	0.949
Diastolic pressure (mmHg)	88.18±7.19	88.20±7.82	0.017	0.984
Tumor size (cm)			-0.388	0.698
>5 cm	39	34		
≤5 cm	29	29		
Pathological type			-0.284	0.777
Differentiated type	64	60		
Undifferentiated type	4	3		
UICC stage			-0.651	0.515
IIB	21	18		
IIIA	19	16		
IIIB	13	13		
IIIC	15	16		

Table 2. Surgery related indicators between the two groups

	Observation group (n=68)	Control group (n=63)	t/Z	P
Operation time (min)	245.66±22.68	243.79±26.86	0.431	0.667
Intraoperative blood loss (mL)	148.81±64.79	143.71±54.79	0.467	0.641
Conversion from laparoscopic surgery to laparotomy (case)	10	13	0.888	0.375
Excision extension			1.688	0.091
Total gastrectomy	40	29		
Distal gastrectomy	23	24		
Palliative operation (case)	5	10		
Surgical margin			4.404	0.000
R0 margin	58	33		
R1/R2 margin	8	30		

KPS scores at six weeks surpassed that at three weeks in observation group

Analysis of variance through repeated measurements found that there was a statistically significant difference in KPS score between the two groups (P<0.001). There was no difference in KPS score between the two groups on admission (P=0.247), while differences between KPS scores at three weeks and the scores at six

Table 3. Postoperative recovery status between the two groups

	Observation group (n=68)	Control group (n=63)	t/χ^2	P
Postoperative off-bed time (d)	3.47±1.55	3.56±1.77	0.348	0.728
Length of hospital stay after surgery (d)	11.75±4.93	12.63±6.63	1.077	0.284
Time of first flatus after surgery (d)	4.22±1.60	4.27±1.79	0.166	0.868
Postoperative complications (d)	8	13	1.912	0.167
Surgical site infection (case)	5	7	0.772	0.440
Pulmonary infection (case)	1	1	0.054	0.957
Intestinal obstruction (case)	1	3	1.090	0.276
Anastomotic leakage (case)	0	1	1.039	0.299
Pleural effusion (case)	1	1	0.054	0.957

Table 4. PKPS score between the two groups

	Observation group	Control group	t	P
On admission	68.53±5.58	67.08±5.24	1.167	0.247
Three weeks after surgery	85.35±5.46*	73.35±5.46*	9.627	0.000
Six weeks after surgery	90.05±2.81*,#	74.19±3.17*	23.203	0.000
F	140.481			
P	0.000			

Note: intra-group comparisons of KPS scores at three weeks, six weeks after operation with KPS scores before operation, *P<0.001; Intra-group comparisons of KPS scores at three weeks after operation with KPS scores at six weeks after operation, #P<0.001. KPS, Karnofsky Performance Status.

Table 5. Adverse reactions of postoperative chemotherapy (n, %)

	Observation group (n=68)	Control group (n=63)	χ^2	P
Erythropenia	1 (1.47)	3 (4.76)		0.351
Leukopenia	4 (5.88)	3 (4.76)		0.543
Thrombocytopenia	2 (2.94)	4 (6.35)		0.427
Gastrointestinal dysfunction	1 (1.47)	3 (4.76)		0.351
Abnormal liver function	1 (1.47)	4 (6.35)		0.159
Peripheral neuritis	0	2 (3.17)		0.229
Hand-foot syndrome	0	1 (1.59)		0.481
Total cases	9 (13.24)	20 (31.75)	2.450	0.011

weeks after surgery were significant (both P= 0.000). Comparisons at different time points in both groups showed that the KPS scores at three and six weeks after intervention were higher than those before surgery (both P= 0.000); the KPS scores at six weeks were significantly higher than the scores at three weeks after surgery in the observation group (P=0.000). In contrast, there was no significant difference between the KPS scores at three weeks and the scores at six weeks after surgery in the control group (P>0.05, **Table 4**).

Observation group presented less adverse reactions from postoperative chemotherapy

A total of 29 cases had adverse reaction after postoperative chemotherapy in both groups, while the observation group (13.24%) showed significantly lower adverse reaction incidence than the control group (31.75%, P=0.011, **Table 5**).

Observation group presented higher efficacy than control group

The total effective rate and the total control rate of the observation group (57.35%, 92.65%, respectively) were significantly higher than those of the control group (39.68%, 84.13%, respectively; both P<0.05, **Table 6**).

Observation group had better prognosis over control group

The numbers of death, recurrence and metastasis in the observation group were lower than those in the control group (P<0.05, **Table 7**).

Discussion

Gastric cancer is a common malignant tumor. Treatments for gastric cancer are still based on surgery. With the introduction of minimally invasive laparoscopic techniques, more and more

Table 6. Tumor response rate and resection rate (n, %)

	CR	PR	SD	PD	Total effective rate	Total control rate
Observation group (n=68)	11 (16.18)	28 (41.18)	24 (35.29)	5 (7.35)	57.35	92.65
Control group (n=63)	5 (7.94)	20 (31.74)	28 (44.44)	10 (15.87)	39.68	84.13
χ^2	2.294				2.014	2.002
P	0.022				0.044	0.047

Note: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 7. Efficacy between the two groups (n, %)

	Death	Recurrence	Metastasis
Observation group (n=68)	6 (8.82)	5 (7.35)	7 (10.29)
Control group (n=63)	14 (22.22)	13 (20.63)	14 (22.22)
χ^2	2.122	2.198	2.060
P	0.034	0.028	0.039

patients with gastric cancer have been treated by laparoscopic radical gastrectomy. The laparoscopic radical surgery is widely applied in clinical operations because it is less traumatic to patients, but the efficacy of laparoscopic radical surgery for patients with advanced gastric cancer is still in controversy [13-15]. NACT refers to a method of preoperative chemotherapy. Previously studies have shown that NACT before surgery can eliminate small lesions of patients with gastric cancer, thus increasing the resection rate and survival rate of patients [16-18]. Therefore, we conducted this study to explore the efficacy of laparoscopic radical surgery combined with NACT for patients with advanced gastric cancer.

As to intraoperative related indicators in the two groups, the resection rate of surgery with negative surgical margins (R0) of the observation group was higher than that of the control group, while the other intraoperative related indicators between the two groups showed no differences. These results may be related to lymph node metastasis in advanced gastric cancer. Although the metastatic lymph nodes around the tumor have been dissected as much as possible during the surgery, the minimal residual lesions in the subclinical state cannot be excluded. Previous studies have found that the application of NACT can eliminate sub-clinically minimal residual lesions to increase resection rate and reduce recurrence and metastasis, which was consistent with the results of this study [19, 20].

Among all the comparisons of surgery related indicators between the two groups, no significant differences were shown in operative time and complications, while previous studies indicated that scar hyperplasia induced by preoperative chemotherapy in tissues surrounding gastric tumor increased the risk and difficulty of surgery [21, 22]. The result is inconsistent with what has been found in this study. In this study, laparoscopic amplification and harmonic scalpel were used for sharp dissection and dissection of lymph node in surgical procedures, which showed no increase in the difficulty of surgery. Moreover, the number of cases who received laparotomy converted from laparoscopic surgery in the observation group was lower than that in the control group, and the KPS scores after surgery in the observation group were higher than those in the control group, which may be related to the improvement of surgical resection rate that was more beneficial to the recovery of the disease in the observation group.

In terms of efficacy, the total effective rate and the total control rate of the observation group were significantly higher than those of the control group. In previous MAGIC trials, NACT followed by radical resection was found to be more effective [23], consistent with the findings of this study. NACT has been recommended as class I evidence for the treatment of advanced gastric cancer in the NCCN guidelines [24].

In terms of prognosis, a French study indicated that overall survival and survival rate of patients with operable gastric cancer or pancreatic cancer who underwent NACT before surgery were higher than those of counterparts who received the same surgery without preoperative chemotherapy [25]. The European EORCT study found that radical resection combined with NACT did

not increase survival rate, but its subgroup study showed significant improvement in the survival rate [26]. This study found that the numbers of death, recurrence and metastasis in the observation group were less than those in the control group, which was consistent with previous studies [27, 28].

However, the sample size of this study is small, and the size requires expansion for further research. Furthermore, this study was conducted retrospectively; therefore, a multicenter prospective study needs to be performed to further verify the efficacy of laparoscopic radical surgery combined with NACT.

In conclusion, laparoscopic radical surgery combined with NACT can increase the resection rate of surgery with negative surgical margins (R0), reduce recurrence and metastasis of advanced gastric cancer, and improve patients' quality of life.

Disclosure of conflict of interest

None.

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