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Original Article

Clinical efficacy of preoperative neoadjuvant chemotherapy combined with laparoscopic radical surgery for locally advanced esophageal cancer

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Abstract: Objective: To investigate the efficacy of preoperative neoadjuvant chemotherapy combined with laparoscopic radical surgery for locally advanced esophageal cancer. Methods: A total of 136 patients with locally advanced esophageal cancer scheduled for laparoscopic radical resection were included in this study and they were divided into two groups: observation group (n = 68, preoperative neoadjuvant chemotherapy combined with laparoscopic radical surgery) and control group (n = 68, laparoscopic radical surgery). The operation related indicators, postoperative recovery profile, the incidences of postoperative complications and adverse reactions to chemotherapy, recurrence and metastasis were observed. Results: There were no statistical differences in general information, operation time, intraoperative blood loss, the number of lymph nodes dissected, the time to postoperative thoracic duct extraction, the length of postoperative hospital stay, postoperative feeding time and the incidences of postoperative complications between the two groups (all $P > 0.05$). There were statistical differences in the rates of postoperative lymph node metastasis, the degrees of lymph node metastasis, and surgical resection margin between the two groups (all $P < 0.05$). In the observation group, hair loss was the most common adverse reaction after chemotherapy, followed by gastrointestinal symptoms, and no serious adverse reaction above grade 4 occurred. The total effective rate in the observation group was 57.35%, and the total control rate was 92.65%, which were significantly higher than those in the control group (38.24%, $P = 0.026$; 80.88%, $P = 0.040$). The number of deaths, recurrence and metastasis in the observation group was lower than those in the control group respectively (all $P < 0.05$). Conclusion: Preoperative neoadjuvant chemotherapy combined with laparoscopic radical surgery can increase the R0 resection rate, decrease the degree and rate of lymph node metastasis, and reduce postoperative recurrence and metastasis.

Keywords: Esophageal cancer, neoadjuvant chemotherapy, laparoscopic radical surgery, clinical efficacy

Introduction

Esophageal cancer has a high incidence in China, and patients over 50 years old are often affected and the incidence of male is higher than that of female. With high malignancy and poor prognosis, esophageal cancer has a high mortality [1]. Currently, treatment of esophageal cancer mainly depends on surgery [2], and surgical treatment for patients with locally advanced esophageal cancer has been accepted in clinic [3, 4]. With the continuous development and improvement of surgical techniques, minimally invasive endoscopic surgery has also been applied in the treatment of esophageal cancer [5]. Minimally invasive therapy is characterized by small trauma, rapid recovery and low incidences of postoperative complications [6, 7]. However, since most patients are already in the middle and advanced stages of esophageal cancer at the time of treatment and are prone to local and distant recurrence and metastasis after surgical resection, the 5-year survival rate of surgery alone is relatively low (less than 30%) [1]. Therefore, preoperative neoadjuvant chemotherapy combined with laparoscopic radical surgery is now used as the treatment standard for locally advanced esophageal cancer [8]. Studies have shown that preoperative neoadjuvant chemotherapy can decrease tumor stage, reduce the incidence of metastasis and improve the R0 resection rate

Table 1. Comparison of general information

Item	Observation group (n = 68)	Control group (n = 68)	χ^2/t	P
Gender (male/female)	38/30	40/28	0.120	0.729
Age (year old)	53.60 ± 9.09	53.19 ± 8.10	0.279	0.781
Tumor location (n)			0.118	0.943
Upper thoracic portion	18	17		
Middle thoracic portion	31	33		
Lower thoracic portion	19	18		
cTMN staging (n)			0.746	0.689
I B	35	30		
II A	17	20		
III B	16	18		
Pathological differentiation (n)			-0.515	0.773
High differentiation	22	26		
Middle differentiation	35	32		
Low differentiation	11	10		

[9], with deficiencies as small sample size and retrospective design. In this paper, a randomized controlled study was conducted to analyze the clinical efficacy of preoperative neoadjuvant chemotherapy combined with laparoscopic radical surgery for locally advanced esophageal cancer, in order to provide more evidences for clinical practice.

Materials and methods

Clinical information

A total of 136 patients with locally advanced esophageal cancer scheduled for laparoscopic radical resection admitted in Affiliated Hospital of Chengde Medical University from October 2012 to October 2016 were included in this study and they were divided into two groups according to the random number table method: observation group (n = 68, preoperative neoadjuvant chemotherapy combined with laparoscopic radical surgery) and control group (n = 68, laparoscopic radical surgery). Patients were aged 44-79 years old, with an average of 53.40 ± 8.58 years old. This study was approved by the Ethics Committee of Affiliated Hospital of Chengde Medical University and all patients signed the informed consent.

Inclusion criteria: Patients accorded with the diagnosis of locally advanced esophageal cancer, and patients with American Joint Commission on Cancer stage II-III [10]; the lesion was located in the thoracic region; no other relevant cancer therapy was given prior to surgery and patients with normal coagulation, and bone marrow functions.

Exclusion criteria: Patients with serious heart and lung disease; patients combined with other primary malignant tumors; patients with liver and kidney dysfunction; patients allergic to chemotherapy drug and uncooperative patients.

Methods

Preoperative neoadjuvant chemotherapy was conducted on the observation group and the details were as follows. On the first day, patients were given intravenous drip of paclitaxel (135 mg/m^2; Jiangsu Aosaikang Pharmaceutical Co., Ltd., China) for over 2 h, which was combined with intravenous drip of platinum drugs including oxaliplatin (85 mg/m^2; Nanjing Pharmaceutical Factory Co., Ltd., China), nedaplatin (85 mg/m^2; Jiangsu Aosaikang Pharmaceutical Co., Ltd., China), or lobaplatin (50 mg/m^2; Hainan Changan International Pharmaceutical Co., Ltd., China). Patients were given intravenous injection of dexamethasone (20 mg; Shanghai Modern Hasen Pharmaceutical Co., Ltd., China) 12 h before chemotherapy, and they were given intramuscular injection of promethazine (25 mg; Shanghai Harvest Pharmaceutical Co., Ltd., China) 30 min before chemotherapy to prevent allergy. In addition, patients were given intravenous drip of cimetidine (300 mg; Guangdong South Land Pharmaceutical Co., Ltd., China) 30 min before chemotherapy to protect the stomach. A course of treatment was 21 days, and 2 courses of chemotherapy were conducted. Laparoscopic radical surgery of total mesoesophagus esophageal cancer was performed in the two groups.

Outcome measures

According to National Cancer Institute Common Toxicity Criteria 4.0 toxicity rating [11], toxic side effects of chemotherapy drugs were recorded and divided into grade 0-4 on the basis of toxic reactions, including toxicity of leukocyte

Table 2. Comparison of intraoperative indicators

Item	Observation group (n=68)	Control group (n=68)	χ^2/t	P
Operation time (min)	245.19±30.92	246.51 ± 29.95	-0.245	0.800
Intraoperative blood loss (mL)	146.57 ± 41.14	145.79 ± 43.04	0.108	0.914
Number of dissected lymph node	32.79 ± 11.92	33.81 ± 12.14	0.492	0.624
Rate of postoperative lymph node metastasis (%)	51.47 (35/68)	69.12 (47/68)	4.435	0.035
Degree of lymph node metastasis (%)	5.61 (138/2,458)	7.17 (168/2,342)	4.884	0.027
Number of case of resection margin			4.847	0.028
R0 resection margin	66	59		
R1/R2 resection margin	2	9		

Table 3. Comparison of postoperative indicators

Item	Observation group (n = 68)	Control group (n = 68)	χ^2/t	P
Time to postoperative thoracic duct extraction (d)	6.74 ± 2.16	6.84 ± 2.11	0.281	0.779
Length of postoperative hospital stay (d)	14.29 ± 3.73	14.27 ± 3.82	0.023	0.982
Postoperative feeding time (d)	11.25 ± 2.52	11.44 ± 2.48	-0.446	0.656
Postoperative complication (n, %)				
Pulmonary infection	19 (27.94)	16 (23.53)	0.346	0.556
Chylothorax	1 (1.47)	1 (1.47)		1.000
Anastomotic fistula	3 (4.41)	8 (11.76)	2.473	0.116
Delayed gastric emptying	0	2 (2.94)		0.496
Recurrent laryngeal nerve injury	3 (4.41)	1 (1.47)		0.619
Arrhythmia	3 (4.41)	3 (4.41)	0.000	1.000
Anastomotic stricture	3 (4.41)	2 (2.94)	0.208	0.649
Anastomotic bleeding	1 (1.47)	0		1.000
Transferred to ICU	0	1 (1.47)		1.000
Total case of complication	27 (39.71)	22 (32.35)	0.798	0.372

Note: ICU, intensive care unit.

and hemoglobin in the blood system, nausea and vomiting, diarrhea, constipation, liver dysfunction, kidney dysfunction, heart dysfunction, hair loss and peripheral nervous system toxicity.

Operation related indicators: Operation time, intraoperative blood loss, the time to postoperative thoracic duct extraction, surgical resection margin (R0 or R1/R2), the number of lymph nodes dissected, the rates of lymph node metastasis, and the degrees of lymph node metastasis. Degree of lymph node metastasis = Number of positive lymph nodes/total number of lymph nodes dissected; rate of lymph node metastasis = number of case of positive lymph nodes/total number of cases).

Postoperative recovery profile of patients was observed and recorded, including the time of gastrointestinal function recovery, the length of postoperative hospital stay, the incidences of postoperative complications, and mortality, etc.

Assessment of efficacies

Efficacies were divided into complete remission (CR), partial remission (PR), disease stability (SD), and disease progression (PD). Effective rate = Number of case (CR + PR)/total number of cases * 100%. Disease control rate = Number of case (CR + PR + SD)/total number of cases * 100% [12].

Follow-up

Regular outpatient follow-up was performed in the patients for 2 years (deadline of October 2018) to monitor relapse, survival and metastasis of the patients.

Table 4. Adverse reactions of the observation group after chemotherapy (n, %)

Adverse reaction	NCI-CTC rating				Incidence
	Grade 1	Grade 2	Grade 3	Grade 4	
Leukopenia	12 (17.65)	3 (4.41)	0	0	15 (22.06)
Decrease in hemoglobin	13 (19.12)	1 (1.47)	0	0	14 (20.59)
Nausea and vomiting	31 (45.59)	9 (13.24)	0	0	40 (58.82)
Diarrhea	7 (10.29)	1 (1.47)	0	0	8 (11.76)
Constipation	9 (13.24)	3 (4.41)	0	0	12 (17.65)
Liver dysfunction	19 (27.94)	3 (4.41)	0	0	22 (32.35)
Kidney dysfunction	1 (1.47)	0	0	0	1 (1.47)
Heart dysfunction	7 (10.29)	0	0	0	7 (10.29)
Hair loss	4 (5.88)	44 (64.71)	9 (13.24)	0	57 (83.82)
Peripheral nervous system toxicity	13 (19.12)	4 (5.88)	0	0	17 (25.00)

Note: NCI-CTC, national cancer institute common toxicity criteria.

Table 5. Comparison of efficacies (n, %)

Croup	CR	PR	SD	PD	Total effective rate (%)	Total control rate (%)
Observation group (n=68)	13 (19.12)	26 (38.24)	24 (35.29)	5 (7.35)	57.35	92.65
Control group (n=68)	5 (7.35)	21 (30.88)	29 (42.65)	13 (19.12)	38.24	80.88
χ^2	8.115				4.980	4.098
P	0.044				0.026	0.043

Note: CR, complete remission; PR, partial remission; SD, disease stability; PD, disease progression.

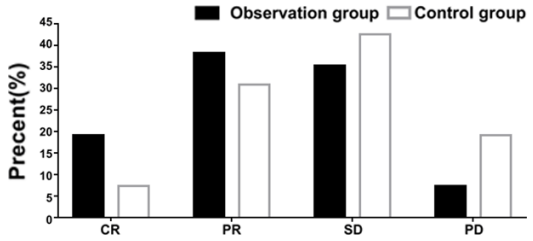

Figure 1. Comparison of efficacies. The disease control of the two groups was tested by chi-square test. χ^2=8.115, P=0.044. CR, complete remission; PR, partial remission; SD, disease stability; PD, disease progression.

Statistical analysis

Statistical analysis was performed using SPSS 17.0 software. Continuous variables were denoted by mean ± standard deviation ($\bar{x}$ ± sd); data accorded with normal distribution and homogeneity of variance were compared by t-test, conversely by rank sum test. Count data were expressed as percent (%) and were analyzed by chi-square test or Fisher exact test. P < 0.05 was considered statistically significant.

Results

General information

There was no statistical difference in general information including gender, age, tumor location, cTMN staging and pathological differentiation between the two groups (all P > 0.05). See **Table 1**.

Operative indicators

There were no statistical differences in operation time, intraoperative blood loss, the number of lymph nodes dissected (all P > 0.05). But there were statistical differences in the rates of postoperative lymph node metastasis, the degrees of lymph node metastasis, and the number of case with R0 or R1/R2 resection margin between the two groups (all P < 0.05). See **Table 2**.

Postoperative indicators

There were no statistical differences in the time to postoperative thoracic duct extraction, the length of postoperative hospital stay, post-

Table 6. Comparison of prognosis (n, %)

Group	Death	Recurrence	Metastasis
Observation group (n = 68)	6 (8.82)	5 (7.35)	7 (10.29)
Control group (n = 68)	15 (22.06)	14 (20.59)	16 (23.53)
χ^2	4.561	4.955	4.239
P	0.033	0.026	0.040

operative feeding time and the incidences of postoperative complications between the two groups (all P > 0.05). See **Table 3**.

Adverse reactions of the observation group after chemotherapy

All the 68 patients in the observation group underwent surgical treatment after the completion of chemotherapy. Hair loss was the most common adverse reaction after chemotherapy, followed by gastrointestinal symptoms, and no serious adverse reaction above grade 4 occurred. The aforesaid adverse reactions improved after symptomatic treatment. See **Table 4**.

Efficacy

The total effective rate in the observation group was 57.35%, and the total control rate was 92.65%, which were significantly higher than those in the control group respectively (38.24%, P = 0.026; 80.88%, P = 0.040). See **Table 5** and **Figure 1**.

Prognosis

The number of deaths, recurrence and metastasis in the observation group was fewer than those in the control group respectively (all P < 0.05). See **Table 6**.

Discussion

As the age of esophageal cancer patients is older and this disease has a high degree of malignancy and mortality, surgical treatment had not been advocated for patients with locally advanced esophageal cancer in the past. However, an increasing number of studies have found that surgery combined with neoadjuvant chemotherapy is beneficial to the survival rate of these patients [13, 14]. Therefore, this study analyzed the clinical efficacy of preoperative neoadjuvant chemotherapy combined with laparoscopic radical surgery for locally advanced esophageal cancer.

Comparison of intraoperative indicators found that R0 surgical resection rate of the observation group was higher than that of the control group, and lymph node metastasis rate and lymph node metastasis degree in the observation group were significantly lower than those in the control group while the other indicators showed no statistical difference. Metastasis of locally advanced esophageal cancer is through lymph nodes, and lymph node metastases around the lesions have been removed as far as possible during surgery, but lesions that cannot be recognized by the naked eye in the subclinical state may not been removed. Previous studies have found that neoadjuvant chemotherapy can eliminate subclinical lesions in this case, thereby increasing the resection rate and reducing the occurrence of recurrence and metastasis, which is consistent with the results of this study [15-17]. Comparisons of intraoperative and postoperative indicators showed that there were no statistical differences in operative time and postoperative complications. Some studies have found that preoperative neoadjuvant chemotherapy can decrease the tumor stage, make the tumor shrunk and reduce the operation difficulty [9]. However, there was no difference in the efficacy of two groups in this study, which is inconsistent with the results of the above studies. This may be related to the application of laparoscopy in the surgery, because laparoscopy has an amplification effect, not making the removal of lymph nodes more difficult [6, 7].

In this study, hair loss was the most common adverse reaction after neoadjuvant chemotherapy, followed by gastrointestinal symptoms, and no serious adverse reaction above grade 4 occurred. Some studies believe that neoadjuvant chemotherapy can increase the incidence of complications [18, 19]. In this study, patients with neoadjuvant chemotherapy had mild adverse reactions, which could be relieved after active intervention without affecting subsequent surgical treatment.

In the aspect of efficacy, the total effective rate in the observation group was 57.35%, and the total control rate was 92.65%, which were significantly higher than those in the control group

(38.24%, 80.88%). A previous single-center phase II clinical study also found that the efficacy of preoperative neoadjuvant chemotherapy combined with laparoscopic radical surgery was more obvious [20], which is consistent with the results of this study.

As for prognosis, a single-center retrospective study of esophageal cancer patients who underwent preoperative neoadjuvant chemotherapy reported that, the total survival period and survival rate of the patients were observed to be higher than those of the single surgery group [21]. In addition, a meta-analysis at home has found that preoperative chemotherapy or radiotherapy for patients with esophageal cancer can benefit the survival of patients [18]. This study found that the number of deaths, recurrence and metastasis respectively in the observation group were lower, which is consistent with previous studies [22].

The limitation of this study is small sample size. Therefore, the sample size needs to be expanded and further multicenter prospective study should be conducted to observe the efficacy of preoperative neoadjuvant chemotherapy combined with laparoscopic radical surgery.

In conclusion, preoperative therapy combined with laparoscopic radical surgery can increase R0 resection rate, decrease degree and rate of lymph node metastasis, and reduce postoperative recurrence and metastasis.

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Disclosure of conflict of interest

None.

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