

Original Article

Laparoscopic TME associated with neoadjuvant chemoradiation towards aggressive colorectal cancer

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Abstract: Objective: This study aims to investigate the clinical synchronization of the neoadjuvant chemoradiation (NC) and the laparoscopic total mesorectal excision (TME) in the treatment of locally aggressive colorectal cancer (LACC). Methods: 92 LACC patients were selected for the research, among who 46 cases, who were performed the synchronized NC, were divided into the treatment group, after having rest for 4-6 weeks after the treatment, the 40 patients of the treatment group, who were performed the laparoscopic surgery, formed the laparoscopy group. The rest 46 patients were divided into the control group, who were performed the conventional treatment. The intraoperative conditions, postoperative recoveries, postoperative complications and recurrence rates of the two groups were compared. Results: The stage-declining rate of the treatment group was 67.3%, and the surgical resection rate, anal preservation rate and postoperative complications were 86.9%, 69.6% and 26%, respectively, which were significantly higher than the control group; while the long-term recurrence rate significantly decreased to 21.7%, and the difference was statistically significant ($P < 0.05$). Conclusion: The NC could effectively achieve the stage-declining purpose against the LACC, improve the resection rate and reduce the postoperative recurrence rate.

Keywords: Laparoscopy, neoadjuvant chemoradiation, aggressive colorectal cancer

Introduction

The colorectal cancer is a common malignancy, and 60%-80% patients would already be in the middle and advanced stages when diagnosed. Currently, the combination of NC and TME against the LACC has been widely recognized and written into the colorectal cancer treatment guidelines. The NC could improve the radical resection rate of colorectal cancer, lower the tumor stage, and reduce the local recurrence, therefore it has been much more clinically applied in recent years [1-3]. With the development of laparoscopic technology, the laparoscopic technology has been increasingly used into the colorectal cancer radical resection, and further affirmed by the clinical efficacy [4]. Currently, the laparoscopic TEM, after the combination of NC in the middle and advanced colorectal cancer, has become more and more, while the postoperative long-term effects have rarely been reported. In this research, 46 patients, who were selected and performed the NC after the discussion of the multi-disciplinary

team (MDT) of our hospital, were performed the synchronous laparoscopic TME after the NC, aiming to discuss the effects in the resection rate, the anal preservation rate, the postoperative complications and the long-term recurrence rate, etc.

Materials and methods

General information

The subjects were the 92 LACC patients admitted into our department, among who 46 patients were performed the synchronous NC (the treatment group, $n=46$), then rested for 4-6 weeks after the treatment, 40 patients, whose tumor stages declined after the NC, were selected and performed the laparoscopic surgery (the laparoscopic surgery group, LS). The rest 46 patients were performed the conventional surgery (the control group, $n=46$), 40 patients, who had the similar general information with the patients in the LS, were divided into the control group, namely the open surgery

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Table 1. Tumor-stage declining situations of the 46 patients before and after the surgery

Time	T0N0	T1N0	T2N0	T2N1	T3N0	T3N1	T4N0	T4N1	T4N2	Declining rate (%)
Before	0	0	0	0	22	16	5	2	1	46
After	0	1	5	7	14	15	3	0	1	31 (67%)

Table 2. Basic surgical situations of the two groups

Basic surgical situations	LS group (n=40)	OS group (n=40)	P
Dixon method (cases)	32	24	0.068*
Miles method (cases)	8	12	0.072*
Surgical time (min)	150±35	95±28	0.0095 [▲]
Intraoperative bleeding volume (ml)	50±10	200±25	0.000 [▲]
Dial terminal ileum pre-colostomy in Dixon method	16	22	0.351*

Note: [▲]P<0.05, *P>0.05.

group (OS), including 52 males and 44 females, with the mean age as (60±3.5) years old, the average distance of the lower tumor edge to the anal was (5.1±1.5) cm; 62 cases were in the preoperative stage III (T₃₋₄N₀M₀), and 34 cases were in the stage IV (T₁₋₄N₁₋₂M₀). This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Hubei Provincial Cancer Hospital. Written informed consent was obtained from all participants.

Inclusion criteria

The inclusion criteria were as follows: 1) diagnosed as the colorectal cancer by the colonoscopy and pathological biopsy; 2) examined by CT, MRI or transrectal ultrasound, and the clinical stage was in T₃₋₄N₀M₀ or T₁₋₄N₁₋₂M₀; 3) excluded the tumor dista metastasis; 4) the patient should not receive any radiation therapy previously; 5) the general condition was acceptable, the nutritional status was good, and the hepatonephric function, the blood routine and the cardiopulmonary function were normal; 6) no history of other malignancy.

Therapy

The 46 patients were all performed the preoperative synchronous chemoradiation. The small-dose conventional fractionation radiotherapy was applied, with the total dose as 40-50 Gy, and a single dose as 2 Gy/times for 5 times a week. During the radiotherapy, the systemic chemotherapy was administrated synchronously with 5-FU-based chemotherapy (FOLFOX₄; oxaliplatin, 85 mg/m², intravenously

instilled for 2 h on Day 1; leucovorin, 200 mg/m², intravenously instilled for 2 h on Day 1; fluorouracil, 400 mg/m², intravenously injected on Day 1; fluorouracil, 2.0 g/m², maintained 48 h through the chemotherapy pump; Above drugs were provided by Jiangsu Hengrui Medicine Co., Ltd., Lianyungang, China). The therapy was repeated every 3 weeks [5]. After the chemoradiation, the preoperative evaluation was performed, and after rested 4-6 weeks, 40 patients, who exhibited the tumor stage declining, were performed the laparoscopic TME and the lymph node dissection; according to the intraoperative situation, the terminal ileum pre-colostomy was performed, with 5-hole operation method, and the protective bag was used to protect the incision and obtain the specimen. The 40 patients in the control group were performed the open TME surgery. The intraoperative lymph node dissection included the inferior mesenteric lymph nodes, the rectal vascular roots and the rectal perirectal lymph nodes. The postoperative adjuvant chemotherapy was determined according to the chemoradiation efficacy and the tumor staging postoperatively. The specific surgical methods were shown in **Table 1**.

Efficacy evaluation

The intraoperative situation, the postoperative recovery, the postoperative complications and the recurrence rate were compared. The efficacy of the LS group could be divided, according to the GHO standards [6], into: 1) complete remission (CR); 2) partial remission (PR); 3) stable disease (SD); 4) progressive disease (PD). The tumor regression degree was judged

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Table 3. Comparison of Postoperative complications and recovery of the 2 groups

Postoperative complications and recovery	LS group (n=40)	OS group (n=40)	P
Intestinal recovery time (days)	2.8±0.6	4.5±1.2	0.032 [▲]
Hospitalization time (days)	10.2±0.7	15.4±1.5	0.027 [▲]
Incision infection (cases)	2	1	0.000
Anastomotic fistula (cases)	4	2	0.000
Recto-vaginal fistula (cases)	1	0	0.000
Rectovesical fistula (cases)	0	1	0.000
Intestinal obstruction (cases)	1	1	0.000

Note: [▲]P<0.05.

Table 4. Comparison of the treatment efficacy of the 2 groups

Groups	Resection rate	Reoccurrence rate	Preservation rate	Complication rate (%)
Treatment	6 (86.9%) [★]	10 (21.7%)	32 (69.6%) [★]	12 (26%) [★]
Control	10 (65.2%)	18 (39.1%) [★]	24 (52.2%)	6 (10.8%)

Note: [★]P<0.05.

according to the postoperative pathological section, and performed the stage-declining analysis according to the semi-quantitative classification method reported by Birbeck [7], and the colorectal cancer staging was performed according to the standards in the 2010 NCCN colorectal cancer treatment guidelines.

Follow-up

Before and after the chemoradiation, and before the surgery, the pelvic imaging examination was performed. After the enrollment, the adverse reactions of the chemoradiation, the tumor marker changes and the quality of life were observed, and the postoperative follow-up was performed towards the long-term complications and the postoperative recurrence.

Statistical analysis

All the measurement data were expressed as the mean ± standard deviation ($\bar{x}\pm s$), and the SPSS16.0 statistical analysis software was used. The normally-distributed intergroup data were compared with the t test, and the χ^2 test was used to compare the rate, with P<0.05 considered as the statistical significance.

Results

Neoadjuvant chemoradiation

Two patients in the treatment group appeared the incomplete intestinal obstruction, thus per-

formed the surgical treatment, while the other 44 patients could complete the designed chemoradiation, among who 24 cases (54.5%) exhibited the adverse reactions, mainly as: bone marrow suppression, malignant vomiting, diarrhea, peripheral neurotoxicity. The postoperative pathologic results showed that: there was no significant difference in the total number of lymph nodes obtained postoperatively; the postoperative positive lymph nodes in the treatment group and the control group were (1.5±0.8) and (4.5±1.2) pieces, respectively, indicating that after the treatment, the positive lymph nodes obtained from the treatment group were significantly reduced when compared with the control group, and the difference was statistically significant (P<0.05).

Pathological staging

1 case of T1N0, 5 cases of T2N0, 7 cases of T2N1, 14 cases of T3N0, 15 cases of T3N1, 3 cases of T4N0 and 1 case of T4N2; according to the literature, 31 cases achieved the effect of tumor-stage declining, with the stage-declining rate as 67.3%, among who 35 cases were PR (76.1%), 9 cases were SD (19.5%) and 2 cases were PD (4.3%) (Table 1).

Basic surgical situations

Compared with the OS group, there was no significant change in the LS group (P>0.05); as for the surgery time, the LS group prolonged than the OS group, while in the term of the intraop-

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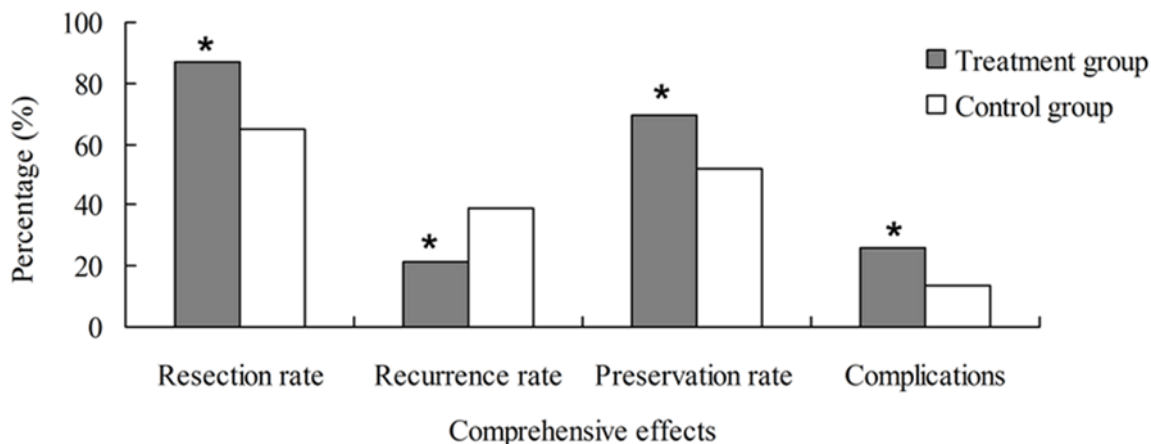


Figure 1. Comprehensive effects in two groups. * $P < 0.05$, versus the control group.

erative bleeding volume, the OS group significantly increased, and the difference was statistically significant ($P < 0.05$). The number of the patients, who were chosen the Hartmann's operation instead of the radical resection due to the age, multiple basic diseases and partial obstruction in the locally advanced tumor, were 6 and 10 in the treatment group and the control group, respectively (Table 2).

Postoperative complications and recovery

The postoperative intestinal recovery time of the LS group was (2.8 ± 0.6), and the mean hospitalization time was (10.2 ± 0.7), significantly shorter than those of the OS group ($P < 0.05$). In the view of the complications, there were 8 cases in the LS group, while 5 cases in the OS group, detailed in Table 3. There was no perioperative death in both groups.

Comprehensive effects

The two groups all obtained the effective follow up, and the follow-up time was (20 ± 4.5) months. The resection rate and the anal preservation rate in the treatment group were 86.9% and 69.6%, significantly higher than the control group ($P < 0.05$). But in the field of the postoperative complications, the incidence in the treatment group increased significantly than the control group, with the statistically significant difference ($P < 0.05$). In the term of long-term efficacy, the long-term recurrence rate on the treatment group significantly decreased to 21.7%, which was significantly lower than the control group, and the difference was statistically significant ($P < 0.05$) (Table 4; Figure 1).

Discussion

The new combined model of NC and surgical resection in the treatment of aggressive colorectal cancer has been widely recognized, written into the NCCN treatment guidelines and widely used in clinics [5]. In the recent years, with the development of laparoscopic technology, the surgical indications of laparoscopy has increasingly developed, including many malignant tumors such as colon cancer, colorectal cancer, stomach cancer and kidney cancer, etc. the laparoscopic TME has such advantages as clear vision, less invasive, faster recovery and shorter hospital stay, etc., and the efficacy is equal to the abdomen surgery, therefore it has been recognized by the domestic and foreign experts [8]. This study further investigated the clinical problems which might appear in the combination of laparoscopic TEM and NC against the advanced colorectal cancer.

Currently, the FLFOX4 scheme has been considered as the first-line chemotherapy in the preoperative synchronous neoadjuvant chemotherapy, while the preoperative neoadjuvant radiotherapy exists two methods: one is the conventional fractionation radiotherapy, in which the duration is long, and the surgery might be performed after having rested 4-6 weeks after the radiotherapy; the other is the short-range high-dose radiotherapy, in which the duration is short, and the surgery could be performed a week after the radiotherapy. There is still some controversy about these two kinds of preoperative radiotherapy. At present, the conventional fractionation radiotherapy is the most accepted method domestically, and the advan-

tage lie in the reduced radiation side effects, and the tumor might obtain the further stage-declining. In this study, the conventional fractionation radiotherapy was used, with the total dose as 40-50 Gy, and the single dose as 2Gy/time, 5 times a week for 5 weeks; at the same time, the synchronous FOLFOX₄ chemotherapy was performed, the results revealed that 35 cases obtained PR (76.1%), 9 cases obtained SD (19.5%), and the stage-declining rate was 67.3%. Meanwhile, compared with the control group, the surgical resection rate of the treatment group improved, and the anal preservation rate was increased, with statistically significant difference ($P<0.05$). The outcomes were improved, and the patient's quality of life was also improved. Among the patients, 2 cases exhibited the progression of tumor, the patient, who exhibited the incomplete intestinal obstruction and was older, were changed to the Hartmann method, followed by the continuous postoperative chemotherapy. 2 cases exhibited the stage III bone marrow suppression, which was improved after the active treatment. Whether the anal preservation should be performed in the low colorectal cancer depends on the fact that whether the tumor violates the external sphincter [9]. The preoperative neoadjuvant therapy could affect the metastasis and distribution of the lymph nodes in the ultralow colorectal cancer regions, and reduce the involvement of the external anal sphincter, thus improving the anal preservation rate [10, 11].

Whether the preoperative neoadjuvant therapy would increase the incidence of postoperative complications is still controversial. The results of the neoadjuvant therapy-related complications in the treatment of advanced colorectal cancer showed that: the neoadjuvant therapy would be conducive to control the tumor locally, and improve the long-term survival, while the incidence of the postoperative complication did not increase [12-14]. The present study found that the incidence of the postoperative complications in the treatment group was much higher than the control group, with statistically significant difference ($P<0.05$). The complications included the anastomotic leakage, wound infection, bowel obstruction, and rectovaginal fistula, and the possible reasons might be: 1. the local intestinal blood vessels were damaged, therefore the poor blood circulation around the stoma affected the healing; 2. the preoperative radiotherapy caused the local inflammation

edema, ischemia and hypoxia, which increased the incidence of anastomotic leakage; 3. the preoperative chemotherapy decreased the patients' immunity, and delayed the wound healing. Certain report figured out that: the long-range radiotherapy program should be used as much as possible in order to avoid the short-range high-dose irradiation-caused tissue edema and intestinal canal injury, which might cause the occurrence of postoperative anastomotic leakage [15]. Giuliani pointed out that after the neoadjuvant therapy, the intraoperative preventive intestinal stoma could prevent the anastomotic leakage rate [16]. We tried the short-range high-dose radiotherapy program commonly accepted in Europe, and the surgery was performed 1 week after the radiotherapy, and no postoperative fistula and wound infection occurred. Because of the fewer cases, the specific mechanism still needed the large amount cases for the further study.

Literature showed that more positive lymph nodes could be obtained after the neoadjuvant therapy, and the 5-year survival was worse [17, 18]. In this study, it was found that: the total numbers of lymph nodes obtained postoperatively in both groups were not statistically significant; while the positive lymph nodes number obtained from the treatment group was (1.5 ± 0.8), significantly less than the control group, and the difference was statistically significant ($P<0.05$). A study of 454 patients showed that: compared with the pure surgery, the recurrence rate dropped significantly when the preoperative neoadjuvant chemotherapy was performed, and the long-term survival rate improved [19, 20], which was consistent with the present study, the local recurrence rate of the treatment group decreased significantly than the control group, which might be associated with the facts that after the neoadjuvant therapy, the tumor shrank, the stage declined, the positive lymph nodes reduced, at the same time, the laparoscopic vision became clearer, the local amplification effect allowed a much more thorough TME surgery, which would all lower the local recurrence rate. Meanwhile, the neoadjuvant therapy was also one of the reasons which decreased the positive rate of cancer embolus in the rectal cancer [21].

In short, the rectal TME surgery improved the survival of colorectal cancer patients [22], the development of the laparoscopic technology

made the surgery more sophisticated, and made the postoperative recovery much more faster, while the neoadjuvant therapy helped the patients with advanced colorectal cancer to obtain more benefit. This study demonstrated that after the neoadjuvant therapy, the resection rate and the anal preservation rate in the advanced colorectal cancer were improved, while the recurrence rate reduced. As for the postoperative complications, we were still exploring further.

Disclosure of conflict of interest

None.

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