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• COLORECTAL CANCER •

Comparative evaluation of immune response after laparoscopical and open total mesorectal excisions with anal sphincter preservation in patients with rectal cancer

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Abstract

AIM: The study of immune response of open *versus* laparoscopical total mesorectal excision with anal sphincter preservation in patients with rectal cancer has not been reported yet. The dissected retroperitoneal area that contacts directly with carbon dioxide is extensive in laparoscopic total mesorectal excision with anal sphincter preservation surgery. It is important to clarify whether the immune response of laparoscopic total mesorectal excision with anal sphincter preservation (LTME with ASP) in patients with rectal cancer is suppressed more severely than that of open surgery (OTME with ASP). This study was designed to compare the immune functions after laparoscopic and open total mesorectal excision with anal sphincter preservation for rectal cancer.

METHODS: This study involved 45 patients undergoing laparoscopic (n=20) and open (n=25) total mesorectal excisions with anal sphincter preservation for rectal cancer. Serum interleukin-2 (IL-2), interleukin-6 (IL-6), tumor necrosis factor α (TNF_α) were assayed preoperatively and on days 1 and 5 postoperatively. $CD3^+$ and $CD56^+$ T lymphocyte count, $CD3^-$ and $CD56^+$ natural killer cell (NK) count and immunoglobulin (IgG/IgM/IgA) were assayed preoperatively and on day 5 postoperatively. The numbers of $CD3^+$ and $CD56^+$ T lymphocytes and $CD3^-$ and $CD56^+$ NK cells were counted using flow cytometry. An enzyme-linked immunosorbent assay (ELISA) was used for IL-2, IL-6 and TNF_α determination. And IgG, IgM, and IgA were assayed using immunonephelometry.

RESULTS: The demographic data of the two groups had no difference. The preoperative levels of $CD3^+$ and $CD56^+$ T lymphocyte count, $CD3^-$ and $CD56^+$ NK count, serum IgG, IgM, IgA, IL-2, IL-6 and TNF_α also had no significant difference in the two groups (P>0.05). The $CD3^+$ and $CD56^+$ T lymphocyte counts had no obvious changes after surgery in laparoscopic (d=-0.79±3.83 %) and open (d=0.42±2.09 %) groups. The $CD3^-$ and $CD56^+$ NK counts were decreased postoperatively in both laparoscopic (d=-7.23±11.33 %) and open (d=-9.21±13.93 %) groups. The differences of the determined values of serum IgG, IgM and IgA on the fifth day after operation subtracted those before operation were -2.56±2.14 g/L, -252.35±392.94 mg/L, -506.15±912.24 mg/L in laparoscopic group, and -1.81±2.10 g/L, -282.72±356.75 mg/L, -252.20±396.28 mg/L in open group, respectively. The levels of IL-2 were decreased after operation in both groups. However, the levels of IL-6 were decreased after laparoscopic surgery (d_1=-23.14±263.97 ng/L and d_5=-40.08±272.03 ng/L), and increased after open surgery (d_1=27.38±129.14 ng/L and d_5=21.67±234.31 ng/L). The TNF_α levels were not elevated after surgery in both groups. There were no significant differences in the numbers of $CD3^+$ and $CD56^+$ T lymphocytes and $CD3^-$ and $CD56^+$ NK cells, the levels of IgG, IgM, IgA, IL-2, IL-6 and TNF_α between the two groups (P>0.05).

CONCLUSION: There are no differences in immune responses between the patients having laparoscopic total mesorectal excision with anal sphincter preservation and those undergone open surgery for rectal cancer.

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INTRODUCTION

General anesthesia, major surgery, and severe trauma are all known to cause significant inhibition of the immune response[1]. The immunosuppression associated with major surgery is believed to contribute to the increased risk of metastasis and sepsis in the postoperative period[1]. In order to improve the immune response of postoperative patients, minimally invasive surgery has been performed. Reduced hospital stay, less wound pain, earlier resumption of diet and recovery of bowel function are recognized as benefits of laparoscopic cholecystectomy or colectomy[2]. The effects of laparoscopic colorectal surgery on the immune system varied from study to study. Meanwhile, study on immune response of open *versus* laparoscopical total mesorectal excision with anal sphincter preservation in patients with rectal cancer has not been reported yet. The dissected retroperitoneal area that contacts directly with carbon dioxide is extensive in laparoscopic total mesorectal excision with anal sphincter preservation surgery. It is important to clarify whether the immune response of laparoscopic total mesorectal excision with anal sphincter preservation (LTME with ASP) in patients with rectal cancer is suppressed more severely than that of open surgery (OTME with ASP). The aim of this nonrandomized prospective study was to compare the effects of LTME and OTME on immune response.

MATERIALS AND METHODS

Patients selection

From October 2001 to July 2002, 49 patients admitted to the General Surgery Department of West China Hospital with the diagnosis of rectal cancer confirmed by pathology were prospectively evaluated. The criterion for inclusion in the study was patients diagnosed with biopsy as adenocarcinoma of the rectum localized below 15 cm from the anal margin. The criteria for exclusion included age older than 80 years and younger than 18 years, presence of a fixed palpable mass or cancer infiltrating adjacent organs, evidence of metastatic disease, neoadjuvant chemoradiotherapy, severe cardiovascular (New York Heart Association class 3 or more) or respiratory dysfunction, patients with previous abdominal operation, acute intestinal obstruction or perforation, any malignancy within the recent 5 years, synchronous multiple adenocarcinomas and pregnancy, any contraindication to pneumoperitoneum, and patients with unresectable tumor.

Preoperative examinations including flexible endoscopy as well as biopsy, ultrasonography, computed tomography scan, radiography of the chest, etc. were routinely performed. All patients underwent preoperative bowel preparation (1L 10 % mannite electrolyte solution). Prophylactic antibiotics of ciprofloxacin and metronidazole were routinely given orally for three days before operation. A urinary catheter and a nasogastric tube were routinely used.

Data collection

The parameters measured were demographic data, operating time, distance of the tumor from the anal margin, time of first passing flatus, time removing urinary catheter, duration of hospital stay, postoperative complications and death. Demographic data included age, sex, serum total protein (TP), albumin (Alb), hemoglobulin (Hb), weight, and underlying diseases.

Operation techniques

All patients were administrated general anesthesia and operations were carried out in lithotomy position with 15° head-down tilt. Premedication and anesthetic techniques were standardized. Induction was made by intravenous injection of 3-5 mg/kg thiopentone together with fentanyl. Anesthesia was maintained by ventilation with an O_2/N_2O mixture and isoflurane. Operations were performed by surgeons experienced in both laparoscopic and conventional surgeries. The rectal surgery was performed according to the principle of total mesorectal excision (TME)[3,4]. Our laparoscopic techniques were reported previously[5].

Pneumoperitoneum was introduced through subumbilical incision to maintain the pressure at 12-14 mmHg (1 mmHg= 0.133 kPa). Camera port with subumbilical trocar was first created, then one operative port in the right midclavicular line at the level of umbilicus, and other two operative ports in the left and right McBurney point were also created respectively under the guidance of laparoscopic view to facilitate dissection. A laparoscope with 25 or 30 curvy degree was inserted into the abdominal cavity via a subumbilical trocar, following the no-touch technique. Routine exploration was performed to ascertain whether the tumor metastasized to the organs in the abdominal cavity and infiltrated the serosa or implanted in the abdominal cavity. With the operation proceeding of total mesorectal excision, division was moved downward into the pelvis along the anatomic space between visceral and parietal endopelvic fascia. In order to extract the bowel loop of the tumor, the port at the left McBurney' s point was extended to about 3.5 cm long, the tumor was routinely isolated by inserting it into a sheath-shaped bacteria-free plastic bag through the incision, and the tumor as well as the proximal colon were extracted through the bag, and then the bowel was transected at the level of 10-15 cm above upper margin of the tumor. After the anvil of a 29 mm-sized circular stapler was inserted into the end of the proximal bowel and secured with 2/0 prolene purse-string suture, the proximal bowel was internalized and the extended incision was closed. Pneumoperitoneum was then induced again, and laparoscopic colo-anal or colo-rectal anastomosis was performed using a CDH 29 circular stapler.

Immunological studies

Seven milliliters of venous blood were taken by peripheral venipuncture before surgery and on days 1 and 5 after surgery into one plain vacutainer and one heparin vacutainer. The specimens were centrifuged and the collected serum was stored at -20 ℃ for the assay of interleukin-2 (IL-2), interleukin-6 (IL-6) and tumor necrosis factor α (TNF_α). IL-2, IL-6 and TNF_α were assayed preoperatively and on days 1 and 5 postoperatively. $CD3^+$ and $CD56^+$ T lymphocyte count, $CD3^-$ and $CD56^+$ natural killer cell (NK) count and immunoglobulin (IgG/IgM/IgA) were determined preoperatively and on day 5 postoperatively. The numbers of $CD3^+$ and $CD56^+$ T lymphocytes and $CD3^-$ and $CD56^+$ NK cells were counted using flow cytometry (Elite-Esp, Beckman-Coulter, USA). An enzyme-linked immunosorbent assay (ELISA) was used for IL-2, IL-6 and TNF_α determination (Bio-Rad system, Immune Company, France), and immunoglobulin (Ig) G, IgM, and IgA were assayed using immunonephelometry (Immage analyzer, Beckman-Coulter, USA).

Statistics analysis

All the data were collected on designed forms, and analyzed with SPSS version 10.0 software. The differences of the determinated values on fifth or first postoperative day subtracted those before operation were compared between laparoscopic and open groups. Student' s *t* test was used for quantitative variables and chi-square test for qualitative variables. All *P* values were two sided. Statistical significance was established as $P<0.05$. The data were expressed as mean ± standard deviation (SD).

RESULTS

A total of 49 patients were entered into the study. Four patients did not meet the eligibility criteria for the trial (three in laparoscopic group and one in open). Three were found to have hepatic metastasis and one did not receive resection because the cancer infiltrated several adjacent organs.

Patient characteristics

The demographic features of the patients are shown in Table 1. The two groups had no differences with respect to age, gender, TP, Alb, Hb, weight and Duke' s classification ($P>0.05$).

Surgical treatment

Table 2 shows the results of the two treatments. All the 45 patients received the curative anterior resection with total mesorectal excision, and the low/ultralow/colo-anal anastomosis was performed by laparoscopic or open surgery. In laparoscopic group, no one required conversion to open surgery.

There was no surgical death in both groups. Operation time was significantly longer in the laparoscopic group than that in the open group (226.75±46.15 min *versus* 146.40±38.09 min, $P<0.05$). The time of first passing flatus in laparoscopic group was significantly shorter than that in the open group (3.15±1.14 min *versus* 4.36±1.19 min, $P<0.05$). There were

no differences in time of removing urinary catheter, duration of hospital stay and distance of tumor from anal margin between the two groups (P>0.05).

The two groups of patients had comparable preoperative underlying diseases. As for the postoperative complications, one patient in the open group had anastomotic leakage and one in the same group experienced wound infection, both of them were successfully treated conservatively. There was no postoperative complication in the laparoscopic group. There were no local recurrence, port site recurrence, and mortality in any patients observed during follow-up ranged from 8 to 17 months.

Table 1 Demographic and clinical characteristics of patients (mean ±SD)

	LTME n=20	OTME n=25	P value
Age (year)	61.60±8.44	57.96±10.70	0.213
Sex (n)			>0.05
M	9	16	
F	11	9	
TP (g/L)	69.36±5.14	71.55±8.23	0.298
Alb (g/L)	41.70±4.16	43.36±4.49	0.199
Hb (g/L)	123.05±14.43	125.18±15.14	0.627
Weight (kg)	58.45±7.86	59.88±10.85	0.619
Duke's classification (n)			>0.05
A	10	6	
B	4	7	
C_1	3	7	
C_2	3	5	
Underlying diseases (n)			>0.05
Diabetes mellitus	1	0	
Hypertension	1	1	
Anemia	0	2	

Table 2 Surgical treatment of patients

	LTME n=20	OTME n=25	P value
Operating time (min)	226.75±46.15	146.40±38.09	0.000[b]
Time of first passing flatus (day)	3.15±1.14	4.36±1.19	0.001[b]
Time of removing urinary catheter (day)	7.35±2.18	6.28±1.59	0.065
Duration of hospital stay (day)	18.30±4.28	18.04±5.47	0.863
Distance of tumor from anal margin (cm)	8.35±3.72	7.00±3.93	0.247

[b]P<0.01 *vs* open group.

Immune response

As expected, the preoperative levels of $CD3^+$ and $CD56^+$ T lymphocyte count, $CD3^-$ and $CD56^+$ NK count, serum IgG, IgM, IgA, IL-2, IL-6 and TNF_α had no difference in the two groups (Table 3, P>0.05).

Table 3 Preoperative immune indicators of two groups (mean ±SD)

	LTME n=20	OTME n=25	P value
$CD3^+$ $CD56^+$ T (%)	4.56±5.08	3.74±4.19	0.556
$CD3^-$ $CD56^+$ NK (%)	20.87±13.76	25.41±16.79	0.335
IgG (g/L)	11.50±2.41	12.61±2.90	0.178
IgM (mg/L)	1 407.40±420.27	1 582.40±735.41	0.350
IgA (mg/L)	2 726.40±2 048.28	2 380.16±928.99	0.454
IL-2 (ng/L)	85.20±303.81	128.30±387.12	0.686
IL-6 (ng/L)	88.70±231.52	49.06±81.63	0.429
TNFα(ng/L)	7.69±5.71	12.99±26.61	0.387

Table 4 shows the differences of the values of IL-2, IL-6 and TNF_α on the fifth or first postoperative day subtracted those before operation, respectively. The TNF_α levels were not elevated after surgery, and there were no significant differences between the two groups (P>0.05). However, the levels of IL-6 were decreased after laparoscopic surgery (d_1=-23.14±263.97 ng/L and d_5=-40.08±272.03 ng/L), but there were no significant differences between the laparoscopic and open groups (P>0.05). The levels of IL-2 were decreased after operation in both groups, the differences were no significant in postoperative days between the two groups (P>0.05).

Table 4 Changes of IL-2, IL-6 and TNF_α after surgery in two groups (mean ±SD)

		LTME n=20	OTME n=25	P value
IL-2(ng/L)	d_1	-80.54±304.30	-98.82±412.38	0.869
	d_5	-27.55±344.29	-33.59±560.20	0.967
IL-6(ng/L)	d_1	-23.14±263.97	27.38±129.14	0.405
	d_5	-40.08±272.03	21.67±234.31	0.418
TNFα (ng/L)	d_1	2.23±12.78	-1.01±7.82	0.301
	d_5	1.84±12.84	0.56±9.86	0.705

(d_1=the differences of the values of IL-2, IL-6 and TNF_α on the first postoperative day subtracted those before operation, respectively. d_5= the differences of the values of IL-2, IL-6 and TNF_α on the fifth postoperative day subtracted those before operation, respectively).

Table 5 shows the differences of the values of $CD3^+$ and $CD56^+$ T lymphocyte count, $CD3^-$ and $CD56^+$ NK count, and serum IgG, IgM, and IgA on the fifth postoperative day from those before operation, respectively. There were no significant differences of $CD3^+$ and $CD56^+$ T lymphocyte count, $CD3^-$ and $CD56^+$ NK count, and serum IgG, IgM, and IgA levels after surgery between the two groups (P>0.05).

Table 5 Changes of $CD3^+$ $CD56^+$ T lymphocyte count, $CD3^-$ $CD56^+$ NK count, and serum immunoglobulin after surgery in two groups (mean ±SD)

	LTME n=20	OTME n=25	P value
$CD3^+$ $CD56^+$ T lymphocyte (%)	-0.79±3.83	0.42±2.09	0.214
$CD3^-$ $CD56^+$ NK (%)	-7.23±11.33	-9.21±13.93	0.609
IgG (g/L)	-2.56±2.14	-1.81±2.10	0.248
IgM (mg/L)	-252.35±392.94	-282.72±356.75	0.787
IgA (mg/L)	-506.15±912.24	-252.20±396.28	0.216

Numbers listed were the differences of the values of $CD3^+$ $CD56^+$ T lymphocyte count, $CD3^-$ $CD56^+$ NK count, and serum IgG, IgM, IgA on the fifth postoperative day subtracted those before operation, respectively.

DISCUSSION

Rectal cancer is the common malignance in our country. Studies on rectal cancer have made great progresses both in clinical practice[6-15] and in theoretical basis[16-26] during the latest years. Multiple clinical studies have demonstrated the correlation of high pelvic recurrence with the degree of mesorectal excision[27]. Residual mesorectum, especially inadequate excision of distal mesorectum (DMR), contributed to poor oncologic outcomes. In order to reduce the rate of local recurrence in the pelvis of rectal carcinoma, total mesorectal excision (TME) has been performed in many colorectal surgery centers. TME has been applied in clinical practice, and the local recurrence rate has decreased dramatically to 5-7.1 %[28,29],

while the mean local recurrence rate of conventional operative procedure for treatment of rectal cancer remained 18.5 %. TME has been claimed to improve not only local recurrence rate, but also long term survival[30-34]. With the improvement of laparoscopic technique, laparoscopic colorectal surgery has been attempted in many countries[4,35-39]. The laparoscopic colorectal surgery has been proposed to be less traumatic than open surgery. It has been demonstrated that laparoscopic-assisted colectomy has many advantages during immediate postoperative period over the open colectomy with regard to the disappearance of postoperative ileus, fewer analgesia, early ambulation, less postoperative complications, and shorter hospital stay[4,35-39]. In this study, the time of first flatus in the laparoscopic group was significantly shorter than that in the open group.

Some randomised clinical trials of open versus laparoscopically assisted colectomy on systematic immunity in patients with colorectal cancer have been performed. Delgado *et al*[40] found that the plasma levels of cortisol and prolactin were higher in postoperative period, but no significant differences were observed between both groups of the patients. The level of interleukin-6 was higher with significant differences at 4, 12 and 24 hours in the patients undergone open colectomy than that in laparoscopic group. The plasma level of C-reactive protein (CRP) was significantly lower at 72 hours in patients receiving laparoscopic-assisted colectomy than that in patients receiving open one. They suggested that acute phase systematic response was attenuated in patients undergone laparoscopic-assisted colectomy in comparison with those undergone open colectomy. Leung *et al*[41] clarified tissue trauma as reflected by systematic cytokine response, such as interleukin-1β, interleukin-6 and CRP, was less after laparoscopic resection than after open resection of rectosigmoid carcinoma. Nishiguchi *et al*[42] showed that interleukin-6 and CRP levels were significantly higher in the open group than those in the laparoscopic group one day and two days after surgery, respectively. Lymphocyte counts were significantly higher in the laparoscopic group than those in the open group two days after surgery. They concluded that laparoscopic surgery for colorectal carcinoma led to less postoperative stress than conventional open surgery. Some researchers verified that the levels of serum IL-2, CRP, and TNF_α were significantly lower after surgery in the laparoscopic group than those in the open group[43-45]. Braga *et al*[46] also found that laparoscopic colorectal surgery was associated with less pronounced immunosuppression and inflammatory response and lower consumption of analgesic drugs than open surgery. But Tang *et al*[47] and Mehigan *et al*[48] showed that there was no difference in the systematic immune response in patients having laparoscopically assisted colectomy compared with those undergone conventional open surgery for colorectal cancer. Sandoval *et al*[49] also revealed that the laparoscopic surgery did not affect natural antitumoral cellular immunity in an animal model. Moreover, Fukushima *et al*[50] found that serum IL-6 after surgery was significantly higher in laparoscopic sigmoid colectomy than in the open group. They proposed that early IL-6 response after surgery be associated with operation time.

Previous immune response studies were only performed in colorectal surgery. However, the study on immune response of open *versus* laparoscopical total mesorectal excision with anal sphincter preservation in patients with rectal cancer has not been reported yet. The dissected retroperitoneal area that contacted directly with carbon dioxide was extensive in laparoscopic total mesorectal excision with anal sphincter preservation surgery. It is important to clarify whether the immune response of laparoscopic total mesorectal excision with anal sphincter preservation in patients with rectal cancer is suppressed more severely than that of open surgery or not. In this study, TNF_α levels were not elevated after surgery, and there were no significant differences between the two groups (P>0.05). However, the levels of IL-6 were decreased after laparoscopic surgery (d_1=-23.14±263.97 ng/L and d_5=-40.08±272.03 ng/L), but there were no significant differences between the laparoscopic and open groups (P>0.05). The levels of IL-2 were decreased after operation in both groups, and the differences were not significant in postoperative days between the two groups (P>0.05). There were no significant differences in $CD3^+$ and $CD56^+$ T lymphocyte count, $CD3^-$ and $CD56^+$ NK count, and serum IgG, IgM, and IgA levels after surgery between the two groups (P>0.05). Based on the results of our study, it is concluded that there is difference in immune responses in patients having laparoscopic total mesorectal excision with anal sphincter preservation compared with those undergone open surgery for rectal cancer.

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