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ORIGINAL ARTICLE

Comparison of the long-term outcomes of patients who underwent laparoscopic versus open surgery for rectal cancer

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Summary

Purpose: *Survival data of patients who underwent laparoscopic surgery compared with those who underwent open surgery for rectal cancer are limited. We compared long-term outcomes of laparoscopic surgery with those of open surgery in patients with rectal cancer.*

Methods: *Between April 2007 and December 2013, a series of 879 patients with rectal cancer underwent surgery with curative intent (287 patients via laparoscopic surgery and 592 patients via open surgery). Age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) score, clinical stage and type of resection were matched by propensity scoring, and 382 patients (191 patients by laparoscopic surgery and 191 patients by open surgery) were selected for analysis. Intraoperative factors, postoperative data, long-term survival were evaluated.*

Results: *There was no significant difference in preoperative data between the two patient groups. Blood loss was significantly lower in the laparoscopy group than in the open group, while operation time was significantly longer in the laparoscopy group than the open group. There were no significant differences in overall survival or recurrence-free survival. The patterns of recurrence were not different between the two groups.*

Conclusion: *Laparoscopic surgery for patients with rectal cancer produces the same long-term results compared with open surgery in terms of survival and recurrence.*

Key words: *laparoscopy, long-term outcomes, minimally invasive surgery, rectal cancer*

Introduction

Rectal cancer is one of the most common causes of cancer-related death in the world [1]. The use of laparoscopic surgery for rectal cancer was first reported in 1990s and, since then, many studies have reported benefits of laparoscopic surgery such as better cosmetic results, reduced blood loss, decreased pain, early recovery of bowel movements, and short hospital stay [2-9]. Other studies have focused on its oncologic equivalency to open surgery [10-12]; however, the technique does involve a steep surgical learning curve, especially for patients with long-course neoadjuvant chemoradiotherapy. Small retrospective series and randomized prospective trials have compared outcomes between laparoscopic and open surgery for rectal cancer [10-15]. However, many of these studies were based on surgical outcomes and the long-term outcomes are scarce.

The purpose of this study, therefore, was to compare early and long-term surgical outcomes via a statistically generated case-control study between laparoscopic and open surgery for curatively resected rectal cancer at a single institute.

Methods

This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of Tianjin Third Central Hospital. The need for informed consent from all patients was waived due to its retro-

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spective nature, being not a prospective randomized controlled trial.

Between April 2007 and December 2013, a series of 879 patients with rectal cancer underwent surgery with curative intent at our institute. Data were retrieved from operative and pathological reports, with follow-up data being obtained from the outpatient follow-up database. Of these 879 patients, 287 underwent laparoscopic surgery and 592 patients underwent open surgery. Patients of both groups were matched for age, gender, BMI, ASA score, clinical stage and type of resection by a propensity scoring system using SAS software. Finally, 382 patients (191 by laparoscopic surgery and 191 by open surgery) were selected for analysis. All patients had undergone endoscopy, magnetic resonance imaging of the pelvis, computed tomographic scans of brain, chest, pelvis and abdomen, and abdominal ultrasonography to determine the clinical stage. Positron emission tomography-computerized tomography (PET-CT), staging laparosocpy and bone scanning were performed in selected cases, when necessary [16].

The clinical stage of rectal cancer was based on the 7th edition of the TNM classification of colorectal cancer which was proposed by the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC). For those patients operated before 2010, their staging was reassessed to match the 7th TNM classification by UICC and AJCC [17].

Neoadjuvant chemotherapy and radiotherapy

Neoadjuvant chemoradiotherapy was used in patients with clinical T3, T4 or N+ disease. Radiotherapy was delivered to the whole pelvis at a dose oft 45Gy in 25 fractions, followed by a boost to the primary tumor of 5.4Gy in 3 fractions during 5.5 weeks. Chemotherapy was 5-fluorouracil or Xeloda-based [18].

Surgery

Surgery with curative intent was performed 6-8 weeks after neoadjuvant therapy. Laparoscopic surgery was performed with 5 trocars. The rectum was mobilized and dissected between the visceral and parietal pelvic fascia without injuring the hypogastric nerves. A detailed procedure of laparoscopic surgery or open resection has been described elsewhere [19].

Morbidity

The severity of morbidity was graded according to the Clavien-Dindo classification. Major complications were defined as grades 3, 4 and 5 [20,21]. Minor complications were classified as 1, and 2. The definition of Clavien–Dindo system was as follows: Grade 1: oral medication or bedside medical care required; Grade 2: intravenous medical therapy required; Grade 3: radiologic, endoscopic, or operative intervention required; Grade 4: chronic deficit or disability associated with the event; and Grade 5: death related to surgical complication.

Follow up and endpoints

After discharge, all patients underwent blood exams every 3–4 months, a CT scan every 6 months, and an annual endoscopic examination. If gastrointestinal symptoms were reported, additional examinations were carried out when necessary. The last follow up was December 2014.

The primary endpoints of the study were overall survival and recurrence-free survival. Peritoneal recurrences were defined as carcinomatosis or ovarian metastasis. Other metastases were defined as lymph node recurrence outside the lymph node dissection field, liver metastases, or metastases at other extra-abdominal sites without other sites of malignancy. Cancer recurrence was defined as positive radiological evidence of recurrence. All cases of recurrence were documented pathologically and/or by radiologic imaging. Overall survival was assessed from the date of surgery until the last follow up or death of any cause. Recurrence-free

Table 1. Demographic data

	Laparoscopy (N=191)	*Open (N=191)*	*p value*
Age (years)	59 (41-76)	58 (44-74)	0.502
Gender (male:female)	132:59	128:63	0.661
BMI (kg/m^2, range)	23 (17-27)	24 (21-26)	0.568
Clinical stage (cTNM)			0.690
I	34	32	
II	19	21	
III	-	-	
ASA score			0.837
I	78	74	
II	81	87	
III	32	30	
Surgical procedure			0.762
Low anterior resection	167	165	
Abdominoperineal resection	24	26	

BMI: body mass index

Table 2. Surgical and pathological data

	Laparoscopy (N=191)	*Open (N=191)*	*p value*
Operative time (min, range)	170 (140-250)	150 (130-210)	0.010
Blood loss (ml, range)	170 (110-280)	250 (170-320)	0.020
Histologic differentiation			
Good	45	46	0.568
Moderate	121	126	
Poor	25	19	
Circumferential resection margin (mm)			
Positive (≤1)	7	5	0.558
Negative (>1)	184	186	
Retrieved lymph nodes, mean (range)	16 (8-20)	16 (7-25)	0.250
Pathological stage			
0	11	13	
I	69	73	0.515
II	85	81	
III	26	24	
Residual tumor (R0/R1/R2)	191/0/0	191/0/0	1.000

survival was calculated from the date of surgery until the date of disease recurrence or death of any cause.

Statistics

Statistical analyses was performed using SPSS 13.0 software (SPSS Inc., Chicago, Ill, USA). Variables were presented as mean±standard deviation for variables following normal distribution which were analyzed by Student's *t* test. For variables following non-normal distribution, data were expressed as median and range and were compared by Mann-Whitney *U* test. Differences of semiquantitative results were analyzed by Mann–Whitney *U* test. Differences of qualitative results were analyzed by chi-square test or Fisher's exact test. Survival rates were analyzed using the Kaplan-Meier method and differences between the two groups were assessed with the log-rank test. Cox's proportional hazards regression model was used to adjust the results for other factors of prognostic importance. All statistical tests were two-sided, with the threshold of significance set at $p<0.05$ level.

Results

Patient characteristics of the 382 case-matched patients are listed in Table 1. There were no significant differences in age, gender, BMI, ASA physical status classification, clinical stage and type of resection.

Significant differences were noticed in volume of blood loss and operation time between the two groups. In the laparoscopy group, blood loss was significantly reduced (p=0.020) and operation time significantly longer (p=0.010) than in the open group. However, the distribution of histologic differentiation, circumferential resection margin, excised lymph nodes, surgical margins and pathological TNM stage did not differ between the two groups (Table 2).

Postoperative 30-day mortality was zero in either group. Postoperative 30-day morbidity and severity of morbidity were similar between the laparoscopy and open group (Table 3). Also there was no significant difference in the postoperative hospital stay between the two groups.

The median follow-up period was 42 months for the laparoscopy group and 46 months for the open group (p=0.782).The 5-year overall survival rate in the laparoscopy group was 70%, compared to 66% in the open group (Figure 1, p=0.395). As shown in Figure 2, the 5-year recurrence-free survival rate was 65% in the laparoscopy group and 61% in the open group, respectively (Figure 2, p=0.273). Recurrent tumors developed in 7.5% of the patients in laparoscopy group and in 11.3% of the patients in open group. There were no significant differences with respect to the sites of recurrence (Table 4).

The results of uni and multivariate analyses for predictive factors of the patient overall survival are shown in Table 5. In univariate analysis, factors affecting the overall survival rate were pathological T stage, pathological N stage, histologic grade, and the presence of lymphatic and venous invasion (data not shown). Multivariate analysis identified pathological T stage and pathological N stage as the factors with independent effects on overall survival. The type of operative approach (laparoscopy vs open) did not influence the overall survival.

Table 3. Postoperative complications

Complications	*Laparoscopy (N=191)*	*Open (N=191)*	*p value*
Postoperative complications	19	23	
Anastomotic leakage	7	11	
Ileus	5	5	
Hernia	1	2	0.513
Heart failure	2	1	
Intra-abdominal bleeding	2	1	
Atelectasis	2	3	
Severity of complications			
Major (3b, 4a, 4b and 5)	3	5	0.629
Minor (1, 2 and 3a)	16	18	
Postoperative hospital stay (days, range)	7 (5-20)	8 (5-21)	0.525

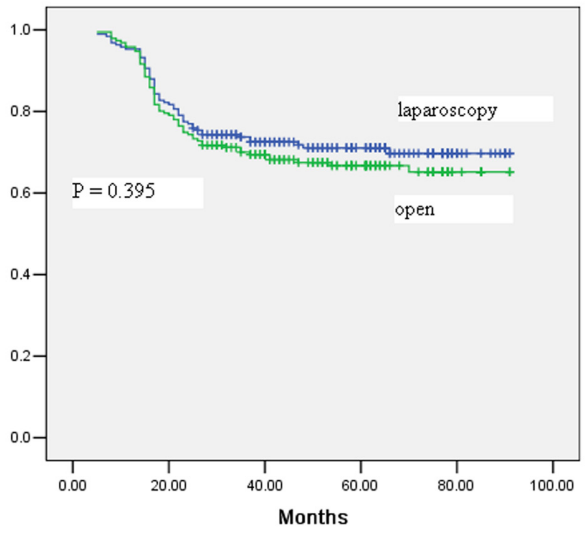

Figure 1. Kaplan-Meier overall survival of the laparoscopy group and open group. There was no significant difference between the 2 groups (p=0.395).

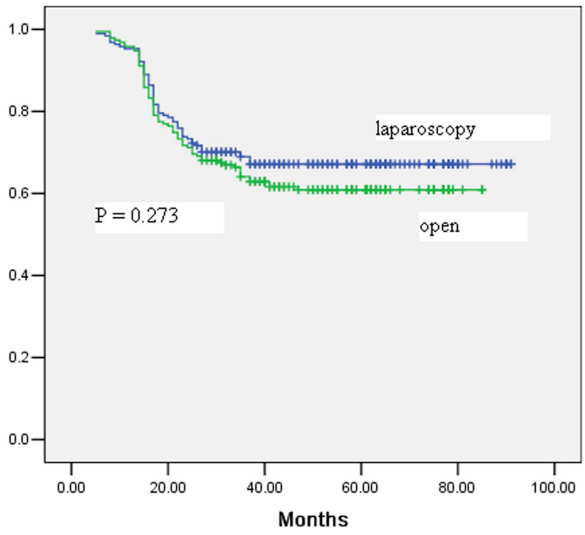

Figure 2. Kaplan-Meier disease-free survival of the laparoscopy group and the open group. No significant difference was observed (p=0.273).

The results of uni and multivariate analyses for predictive factors of recurrence-free survival in the patients are shown in Table 6. In univariate analysis, factors affecting the recurrence-free survival rate were pathological T stage, pathological N stage, histologic grade, and venous invasion (data not shown). Multivariate analysis identified pathological T stage, pathological N stage and histologic grade as the factors with independent effects on recurrence-free survival. The type of operative approach (laparoscopy vs open) did not influence the recurrence-free survival.

Discussion

In this study, we compared the long-term outcomes of patients with rectal cancer after laparoscopic and open surgery with curative intent. The main findings of this study were as follows: the long-term overall survival and recurrence-free survival was similar in both groups; the short-term outcomes were better in the laparoscopy group.

The long-term oncologic result is very important concerning the use of laparoscopic surgery for rectal cancer. Nowadays, there are several multicenter, randomized controlled clinical trials, focused on the laparoscopic and open surgery with radical intent in the treatment of patients with operable rectal cancer. However, the long-term outcomes are still awaited [10,11]. Thus, before conducting a large multicenter phase III

Table 4. Tumor recurrence data

Recurrence data	*Laparoscopy (N=191)*	*Open (N=191)*	*p value*
Tumor recurrence, N (%)	28 (14.7)	33 (17.3)	0.485
Recurrence site			
Brain	1	2	
Lung	2	4	
Liver	5	7	0.932
Locoregional	6	6	
Distant lymph nodes	1	2	
Peritoneum	13	12	
Time to recurrence (median)	19	14	0.188

Table 5. Prognostic factors related to overall survival

Regression variables	*Adjusted hazard ratio*	*95%CI*	*p value*
Pathological T stage			
T_{is}-T_2	1.00		
T_3-T_4	2.35	1.87-3.75	0.008
Pathological N stage			
N_0-N_1	1.00		
N_2	4.88	2.24-8.54	0.015

Table 6. Prognostic factors related to recurrence-free survival

Regression variables	*Adjusted hazard ratio*	*95%CI*	*p value*
Pathological T stage			
T_{is}-T_2	1.00		
T_3-T_4	1.87	124-1.99	0.020
Pathological N stage			
N_0-N_1	1.00		
N_2	2.38	1.47-2.15	0.031
Differentiation grade			
Good-Moderate	1.00		
Poor	3.88	1.88-4.98	0.005

randomized controlled clinical trial comparing laparoscopic surgery with open surgery for rectal cancer, it would be good to have the basis of a retrospective study on the long-term outcomes for rectal cancer after laparoscopic surgery. Marks and his colleagues [22] analyzed 132 consecutive patients who underwent laparoscopic surgery for rectal cancer with greater than 5-year follow up period, and found that the 5-year overall survival rates were 84.8%, and 5-year recurrence-free survival rates were also 84.8%. Their results indicated that laparoscopic surgery for rectal cancer had good long-term oncologic outcomes. To date, oncologic outcomes after laparoscopic vs open surgery for the treatment of rectal cancer have been reported in some studies [23-26]. In these studies, although the oncologic safety seemed to be identical between the groups, the sample size was relatively small (<100 patients) and the follow-up period short (<24 months). In the present study, we analyzed the surgical outcomes of a series of 382 consecutive patients treated either with laparoscopic surgery or open resection. The long-term oncologic results showed that the laparoscopic approach was similar to the open conventional approach for the treatment of rectal cancer.

Peritoneal spread is the major route of rectal cancer metastasis. Although the similarity of recurrence pattern has already been shown between open and laparoscopic gastrectomy for gastric cancer, the potential for peritoneal metastasis after laparoscopic surgery for rectal cancer remains an issue of concern because of different behaviors in cancer cell biology. We observed that not only

were the laparoscopic surgery recurrence-free survival rates similar to conventional open surgery, but so were the recurrence patterns in each group, which indicates that the laparoscopic procedure did not increase the rates of local and peritoneal recurrence.

In our series, no significant difference in the postoperative hospital stay between the two groups was observed, although many studies reported shorter postoperative hospital stay with laparoscopic surgery compared with open surgery, especially in Western centers [27-29]. We applied the same clinical path for each rectal resection in our institute and as a result postoperative courses were similar between the two groups in this study. Moreover, because hospitalization costs are covered by the insurance system, patients hesitate to be discharged earlier. It is therefore difficult to compare the length of hospital stay between China and Western countries. However, minimally invasive surgery yielded better short-term outcomes in this study; shorter hospital stay will impel the laparoscopic approach in the future.

The incidence of postoperative morbidity in the laparoscopy group in the present series was similar to that of other previous reports, and there was no difference in the severity of morbidity according to the Clavien-Dindo system between the laparoscopy and open groups. Therefore, laparoscopic surgery for rectal cancer may be safe from this viewpoint. Anastomotic leakage was the most common postoperative 30-day morbidity in this cohort. A stable and safe technique should therefore be developed in the future, irrespective of the surgical approach [30].

The major limitation of this study was its retrospective nature, and as such, the treatment strategy was not based on random assignment. In other words, selection bias for choosing the treatment modality might have occurred despite the use of a propensity-matching cohort.

In conclusion laparoscopic surgery for rectal cancer was oncologically safe with comparable overall survival and recurrence-free survival rates to open resection, and there were no differences in recurrence patterns between the two procedures, suggesting the radical nature of laparoscopic resection.

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