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ORIGINAL ARTICLE

Comparison of long-term outcomes of laparoscopic and open sphincter-preserving total mesorectal excision for low rectal cancer

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Summary

Purpose: *The purpose of this study was to compare the long-term outcomes of laparoscopic and open sphincter-preserving total mesorectal excision (TME) for low rectal cancer (LRC) using propensity score matching (PSM).*

Methods: *The clinical and follow-up data of 169 patients with LRC who underwent sphincter-preserving TME at our institution between January 2011 and January 2014 were retrospectively analyzed. Patients were divided into laparoscopic and open group based on the surgical approach. PSM including age, sex, body mass index, clinical stage, and American Society of Anesthesiologists score with a 1:1 ratio was subsequently performed. Sixty-eight patients in each group were ultimately included, and short- and long-term outcomes were compared between groups.*

Results: *Compared with the open group, the laparoscopic group had less intraoperative blood loss, more rapid postoperative recovery, and lower incidence of 30-day postoperative complications. However, there were no significant differences in severity of postoperative 30-day complications between the two groups. Both groups had no intraoperative or 30-day postoperative mortality. Regarding survival outcome, tumor recurrence rate, tumor recurrence site, 5-year overall survival, and 5-year dis-ease-free survival, there were no significant differences between groups.*

Conclusion: *Laparoscopic sphincter-preserving TME can achieve long-term outcomes similar to those of open TME for LRC.*

Key words: *laparoscopic surgery, low rectal cancer, total mesorectal excision, sphincter-preservation surgery, minimally invasive surgery*

Introduction

Low rectal cancer (LRC) is defined as a tumor located below the pelvic peritoneal reflection [1-4]. For LRC, total mesorectal excision (TME) can be performed directly during the early stage, whereas neoad-juvant therapy is required for locally advanced rectal cancer [5-11]. The surgical procedure is more challenging and sphincter preservation is more difficult [12-14]. Since the first report of laparoscopic surgery for the treatment of rectal cancer in the 1990s [15], this procedure has become widely used [16-21]. As laparoscopic sphincter-preserving TME for LRC is more difficult, there are relatively few studies on such procedure, and most studies has been limited to short-term outcomes [22-26]. Only a few studies have compared the long-term outcomes of laparoscopic and open sphincter-preserving TME for LRC, which have been characterized by relatively short follow-up periods [25, 26]. Therefore, this study aimed to compare the long-term outcomes of laparoscopic and open sphinc-ter-preserving TME for LRC using propensity score matching (PSM) with a longer follow-up period of nearly 60 months.

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Methods

Patients

This study complied with the Declaration of Helsinki principles. This retrospective research was approved by the Ethics Committee of our hospital. The need for informed consent from all patients was waived be-cause this was a retrospective study.

From January 2011 to January 2014, a total of 179 patients with LRC who fulfilled the following criteria underwent sphincter-preserving TME at our institution. Inclusion criteria were as follows: (1) patients with rectal adenocarcinoma, (2) patients with clinical stage T1-3N0-2M0, (3) patients undergoing radical surgery, and (4) patients with complete data. Exclusion criteria were as follows: (1) patients undergoing emer-gency surgery, (2) patients with multiple tumors, and (3) patients with recurrent tumors. Patients were divided into laparoscopic and open groups based on the surgical approach used for TME. PSM including age, sex, body mass index (BMI), clinical stage, and American Society of An-esthesiologists (ASA) score was performed using R version 3.2.1 (The R Foundation, Vienna, Austria). Patients were matched with a 1:1 ratio, and 68 patients in each group were ultimately included. This study retrospec-tively compared the short- and long-term outcomes between groups.

Prior to treatment, patients had undergone colonoscopy with biopsy, pelvic magnetic resonance imaging, and chest and abdominal computed tomography for confirmation of clinical stage [27]. Laboratory and other tests, such as pulmonary function tests, electrocardiography, and echocar-diography were also performed preoperatively to determine whether pa-tients could tolerate surgery. Cancer staging was performed according to the 7th edition of the TNM classification of colorectal cancer, which was proposed by the Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) [28].

Patients with clinically locally advanced disease (cT3-4N+M0) were ad-ministered neoadjuvant chemotherapy (5-fluorouracil or Xeloda-based) and radiotherapy (45 Gy in 25 fractions over 5 weeks with a 5 Gy boost). Surgery with radical intent was performed 6-8 weeks after neoadjuvant therapy. Details of the surgical procedures are described in the relevant literature [24]. Laparoscopic surgery was performed only by the pure laparoscopic approach, not by hand or robot-assisted techniques. Thirty-day postoperative complications were graded according to the Clavien-Dindo classification system [29]. Major complications were de-fined as those of grades 3, 4, and 5, while minor complications were de-fined as those of grades 1 and 2 [29]. Operative death was defined as mortality occurring intraoperatively or within 30-days postoperatively. Postoperative adjuvant chemotherapy was recommended for patients with stage II with high risk or stage III disease. No patient received adjuvant radiotherapy in this study.

Follow-up

All patients were followed-up after discharge. Follow-up was con-ducted every 3 months in the first postoperative year, every 6 months in the second postoperative year, and annually in subsequent years. Each follow-up included a routine physical examination, tumor marker tests, and chest and abdominal imaging. Patients also underwent electronic colonoscopy on an annual basis [30-33]. Disease recurrence was defined as locoregional or distant metastasis confirmed by radiologic and/or pathologic methods, when available. The last documented follow-up visit was in May 2019.

Table 1. Baseline characteristics of the laparoscopic and open group

	Laparoscopic group (n=68)	*Open group (n=68)*	*p value*
Age (years, median and range)	61 (49-76)	64 (52-77)	0.259
Sex			0.468
Male	47	43	
Female	21	25	
BMI (kg/m^2, median and range)	22 (18-26)	23 (17-28)	0.247
ASA grade			0.142
I	42	49	
II	19	17	
III	7	2	
Clinical stage (cTNM, 7th)			0.616
I	35	38	
II	23	21	
III	10	9	
Preoperative CEA (ng/mL, median)			0.167
	25	33	
	43	35	
Distance to anal verge (cm, median, range)	4 (1-5)	4 (1-5)	0.584

BMI: body mass index, CEA: carcinoembryonic antigen

Statistics

All calculations were performed using IBM SPSS Statistics 22®. For variables with normal distribution, data have been presented as mean and standard deviations and were analyzed by Student's *t*-test. For variables with non-normal distribution, data are 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, where appropriate. Survival rates were analyzed using the Kaplan–Meier method, and differences were analyzed with the log-rank test. Univariate analyses were performed to identify prognostic variables related to over-all survival (OS) and disease-free survival (DFS). Univariate variables with probability values of <0.10 were selected for inclusion in the multi-variate Cox proportional hazard regression model. Hazard ratios (HR) along with the corresponding 95% confidence intervals (CI) were calcu-lated. P<0.05 indicated statistical significance.

Table 2. Short-term outcomes of the laparoscopic and open group

	Laparoscopic group (n=68)	*Open group (n=68)*	*p value*
Operative time (min, median and range)	200 (180-280)	170 (150-250)	0.030
Blood loss (ml, median and range)	170 (140-310)	200 (180-340)	0.021
Conversion to open surgery	6	-	-
Reasons for conversion		-	
Adhesions	2	-	
Bleeding	3	-	
Inadequate margins of resection	1		
Time to pass first flatus (h, median and range)	50 (40-90)	80 (60-100)	0.038
Postoperative hospital stay (d, median and range)	10 (7-23)	11 (8-24)	0.158
Patients with postoperative 30-day complications	10	21	0.025
Patients with major complications	1	1	1.000
Postoperative 30-day death	0	0	-

Table 3. Pathological outcomes of the laparoscopic and open group

	Laparoscopic group (n=68)	*Open group (n=68)*	*p value*
Pathological stage (pTNM)			0.488
pCR	8	11	
I	13	14	
II	34	31	
III	13	12	
Tumor differentiation			0.553
Well	37	36	
Moderately	23	18	
Poorly	8	14	
Circumferental resection margin			0.699
Positive (≤1mm)	3	4	
Negative (>1mm)	65	64	
Residual tumor			1.000
R0	68	68	
R1	0	0	
R2	0	0	
Harvested lymph nodes, median (range)	17 (6 –31)	18 (7 –30)	0.254
TME grading (Quirke classification)			1.000
1	0	0	
2	4	5	
3	64	63	

pCR: pathological complete response after neoadjuvant therapy, TME: total mesorectal excision

Results

There were no significant differences in baseline data, including age, sex, BMI, clinical stage, and ASA score, between the 2 groups (Table 1).

Compared with the open group, operating time in the laparoscopic group was longer (Table 2). However, the laparoscopic group demon-strated several advantages, including less intraoperative blood loss, faster postoperative recovery, and lower incidence of 30-day postoperative complications (Table 2). In addition, the incidence of postoperative wound infection and urinary tract infection was lower in the laparoscopic group than in the open group (Table 2). There were no significant differ-ences between groups in the incidence of 30-day postoperative major complications (Table 2) or pathologic data, including TNM stage, tumor differentiation, surgical margin, and circumferential resection margin (Table 3).

Long-term outcomes

Median follow-up time for the laparoscopic and open groups was 57 months and 59 months, respectively, which was not significantly different (p=0.374). During the follow-up period, 23 and 24 patients in the laparo-scopic and open groups died (p=0.857) (Table 4). Five-year overall sur-vival rates in the laparoscopic and open groups were 69% and 66%, re-spectively, with no significant difference (Figure 1, p=0.826). Multivari-ate Cox regression analysis of OS in all patients revealed that tumor status of T3 or T4, lymph node status of N2, and poor tumor differentia-tion were significant predictors of worse OS (Table 5).

During the follow-up period, 27 and 30 patients in the laparoscopic and open groups, respectively, suffered tumor recurrence, with most cases involving distant metastases. Five-year DFS rates in the laparoscopic and open groups were 59% and

Table 4. Follow-up data

	Laparoscopic group (n=68)	*Open group (n=68)*	*p value*
Tumor recurrence during follow-up			0.602
Locoregional alone	27	30	
Distant alone	2	1	
Both locoregional and distant	24	28	
Port site	1	1	-
	0	-	
Time to first recurrence (months, median and range)	22 (11-53)	19 (13-50)	0.268
Mortality during follow-up	23	24	0.857
Died of cancer recurrence	21	23	
Died of non-oncological causes	2	1	

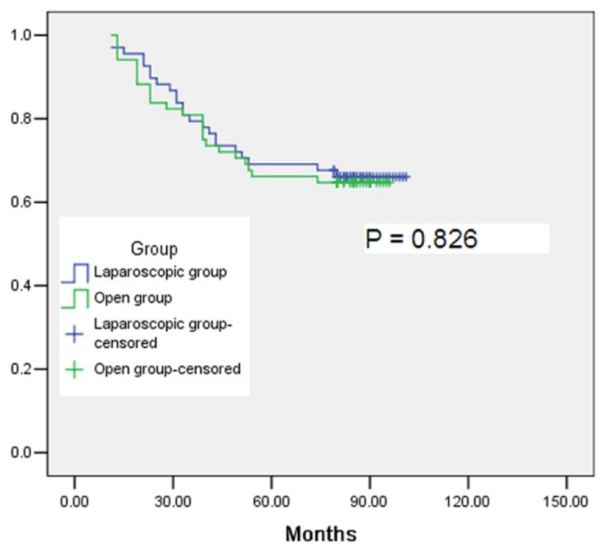

Figure 1. Comparison of overall survival rate between laparoscopic and open group. There was no significant difference between the two groups (p=0.826).

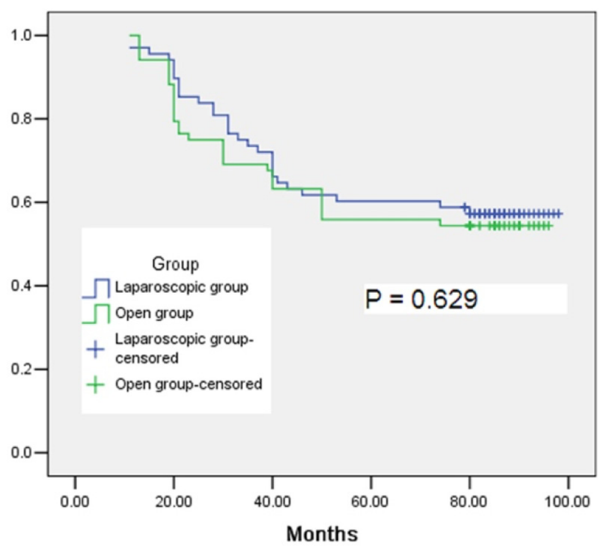

Figure 2. Comparison of disease-free survival rate between laparoscopic and open group. There was no significant difference between the two groups (p=0.629).

Table 5. Multivariate analysis of overall survival

Regression variables	*Adjusted hazard ratio*	*95% CI*	*p value*
Pathological T stage			
T_0-T_2	1.00		
T_3-T_4	2.54	1.55–3.55	0.028
Pathological N stage			
N_0-N_1	1.00		
N_2	2.02	1.55–2.87	0.020
Differentiation grade			
Well–Moderate	1.00		
Poor	1.87	1.25–2.08	0.041

Table 6. Multivariate analysis of disease-free survival

Regression variables	*Adjusted hazard ratio*	*95% CI*	*p value*
Age at surgery (years)			
<70	1.00		0.040
≥70	1.58	1.21–1.98	
Pathological T stage			
T_0-T_2	1.00		0.018
T_3-T_4	2.01	1.35–4.21	
Pathological N stage			
N_0-N_1	1.00		0.025
N_2	2.18	1.45–3.00	

55%, respectively, with no significant differ-ence (Figure 2, p=0.629). Multivariate Cox regression analysis of DFS in all patients revealed that age ≥70 years, tumor status of T3 or T4, and lymph node status of N2 were significant predictors of worse DFS (Table 6).

Discussion

In this study, the minimally invasive char-acteristics of laparoscopic surgery were mainly manifested as reduced blood loss, faster postop-era-tive recovery, and lower incidence of postop-erative 30-day complications, which are similar to the results reported in previous studies [32-35]. Op-erating time in the laparoscopic group was longer than that in the open group, which could be attributed to the fact that laparoscopic sphinc-ter-preserving TME for LRC is more complicated. We believe that oper-ating time will be shortened in the future with sustained improvements in surgical instruments and continuous accumulation of experience in surgi-cal techniques.

Previous studies have reported that the most common complication of laparoscopic sphincter-preserving TME for LRC is anastomotic leak-age [32-35], which has a typical incidence rate of 5% to 15% [32-35]. In this study, the incidence of anastomotic leakage in the laparoscopic and open groups were 7% and 8%, respectively. Therefore, laparoscopic sphincter-preserving TME did not increase the incidence of anastomotic leakage, which is consistent with previous studies [32-35]. Some studies have indicated that the incidence of postoperative complications after laparoscopic TME was lower than after open surgery [32,33], while other studies have reported similar incidence for laparoscopic and open TME [34,35]. Such a discrepancy could be due to different definitions of com-plications across studies [32-35]. In this study, the reason for the lower incidence of 30-day postoperative complications in the laparoscopic group compared with the open group was the lower incidence of both postoperative wound infection and urinary tract infection in the laparoscopic group. For major complications, the incidence rates were compa-rable between groups.

Several randomized controlled trials have shown that laparoscopic TME for the treatment of rectal cancer can achieve long-term outcomes similar to those of open surgery [35-37]. In this study, tumor recurrence and local recurrence rates were similar for laparoscopic and open surgery, with the majority of recurrences being distant metastases. In addition, 5-year OS and DFS rates were similar between groups and in-line with previous randomized controlled trials [35-37]. These findings demon-strate that laparoscopic sphincter-preserving TME for LRC can achieve long-term outcomes similar to those of open surgery [35-37]. To the best of our knowledge, this study is the first study with a median follow-up period of nearly 60 months in English literature.

In previous studied on the use of laparoscopic TME for locally ad-vanced LRC, Japanese authors have reported the adoption of lateral pel-vic lymph node dissection (LPLD) as a standard practice [38-44]. How-ever, LPLD increases surgical difficulty, imposes great demands on sur-geons, and is not supported by evidence-based medicine. Results of a randomized controlled trial carried out by Japanese researchers for the purpose of comparing TME + LPLD with TME for locally advanced rec-tal cancer showed that the TME + LPLD group had a lower local recur-rence rate, but the 5-year OS and DFS rates were similar between groups [45,46]. As laparoscopic LPLD requires an additional operating time of approximately 1 hour, [45,46] has no effect on long-term outcomes, and is not a recommended procedure in the European Society for Medical Oncology and National Comprehensive Cancer Network guidelines. LPLD was not performed in patients in this study.

One of the characteristics of rectal cancer in China is the higher proportion of LRC, with surgery being the only treatment method that offers hope for cure for such patients. In the past, abdominoperineal re-section (APR) was deemed the only effective surgical method for the radical treatment of LRC [12]. After the concept of TME was first de-scribed by the British researcher Heald in the British Journal of Surgery in 1982 [13], TME became a globally accepted gold standard for rectal cancer surgery [13]. TME can significantly reduce the local recurrence rate of rectal cancer and substantially improve the 5-year OS rate. In some countries, the long-term prognosis of patients with rectal cancer has exceeded that of colon cancer [13]. With improvement of the 5-year sur-vival rate, the demand for sphincter preservation has become greater as well. Pathologic studies have reported that intramural distal spread >2 cm is seen in only 3.6% of LRC cases, and that the main lymphatic drainage directions are upward and lateral, thus establishing a theoretical basis for sphincter-preservation surgery [47]. The good field of vision and magni-fication during laparoscopy are fully harnessed in this procedure, as they provide operational advantages in the narrow operating field of the pelvic floor, thereby resulting in better identification and preservation of the pelvic autonomic plexus, as well as greater precision in the separation of layers, which are conducive to the surgical process [27]. Previous large-size studies have shown a downward trend in the proportion of pa-tients undergoing APR, which have ranged from 20 to 40% of patients with LRC [47].

To overcome selection bias as much as possible, PSM was employed. The propensity score model reduced the different distribution of covariates among individuals allocated to each intervention. Although a ran-domized controlled trial can provide the most unbiased evidence for clinical science, it is unlikely to recruit patients and obtain consent when patients have to choose from surgical procedures with obvious differences. A propensity score model is closest to reality and decreases the variance of an estimated exposure effect without increasing the bias.

The major drawback of this study is that patients were not random-ized into treatment arms. Although PSM is a useful method for decreasing selection bias between groups, there are still inevitable selection biases from unmatched variables. In addition, our population had longer dura-tions of hospital stay than those reported in other series. This phenome-non may be related to different socioeconomic health systems with vary-ing hospital stays.

Conclusion

In conclusion, laparoscopic sphincter-preserving TME for the treat-ment of LRC can achieve good short-term outcomes, as well as patho-logic and long-term outcomes comparable to those of open sphinc-ter-preserving TME.

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Conflict of interests

None of the authors have any financial interest relevant to the work pre-sented in this manuscript.

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