Int J Clin Exp Med 2019;12(4):4250-4257
www.ijcem.com /ISSN:1940-5901/IJCEM0088211

Original Article

Feasibility and safety of laparoscopic lateral pelvic lymph node dissection following total mesorectal excision for advanced lower rectal cancer after pre-operative chemoradiotherapy

Sicheng Zhou, Jianwei Liang

Department of Colorectal Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Received November 10, 2018; Accepted December 7, 2018; Epub April 15, 2019; Published April 30, 2019

Abstract: Objective: The goal of this study was to evaluate the feasibility and safety of laparoscopic lateral pelvic lymph node dissection (LPLND) following total mesorectal excision (TME) in patients with advanced lower rectal cancer treated with pre-operative chemoradiotherapy (CRT). Methods: A total of 76 patients with lower rectal cancer without distant metastasis or recurrence who underwent laparoscopic TME + LPLND were reviewed and data including the clinical characteristics, peri-operative outcomes, and pathological outcomes were analyzed. Among them, the 18 patients who received CRT (CRT group) were compared with their matched controls (non-CRT group, n=18). Results: In all 76 patients, there were no conversions to open surgery and no postoperative mortality. The operation time was significant longer and the total blood loss was significant greater in CRT group than those in non-CRT group (P=0.012, P=0.027). The complication rate and postoperative hospitalization time were similar in the two groups (P=1.000, P=0.242). The two groups also had the same number of harvested lateral pelvic lymph nodes and harvested mesorectal lymph nodes (P=1.000, P=1.000). Conclusion: LPLND following TME is technically feasible, safe, and oncologically acceptable in patients with advanced lower rectal cancer treated with pre-operative CRT, with no significant increase in postoperative morbidity compared with TME + LPLND without pre-operative CRT.

Keywords: Laparoscopy, lateral pelvic lymph node dissection, pre-operative chemoradiotherapy, rectal cancer

Introduction

Lateral pelvic lymph node (LPLN) metastasis is an important factor for local recurrence after surgery in patients with advanced low rectal cancer as approximately 10% to 25% of patients with advanced rectal cancer have associated LPLN metastasis [1, 2]. However, the management of LPLN metastasis in such patients remain controversial between Japan and Western countries.

In Japan, there is a positive attitude towards LPLN dissection (LPLND), which has become a standard surgery for patients with advanced low rectal cancer when combining with total mesorectal excision (TME). LPLND can significantly decrease the recurrence rate and improve the long-term survival rate of patients with locally advanced low rectal cancer [3]. According to the Japan Society for Cancer of the Colon and Rectum 2010 Guidelines for the Treatment of Colorectal Cancer, it is recommended that patients with T3-T4 rectal cancer that extends below the peritoneal reflection undergo LPLND [4].

On the other hand, Western countries hold a different strategy as LPLN metastasis is generally considered systemic disease. Even if LPLND was performed, patients had a high distant metastasis rate, and the five-year survival rate was only 20-45% [5]. In addition, the technical difficulty and high incidence of surgical morbidities, such as urinary and sexual dysfunction, are also large obstacles for LPLND development [6-11]. In this case, some Western doctors perform pre-operative chemoradiotherapy (CRT) and believe that TME without LPLND can reduce the recurrence rate [5, 12]. However, a

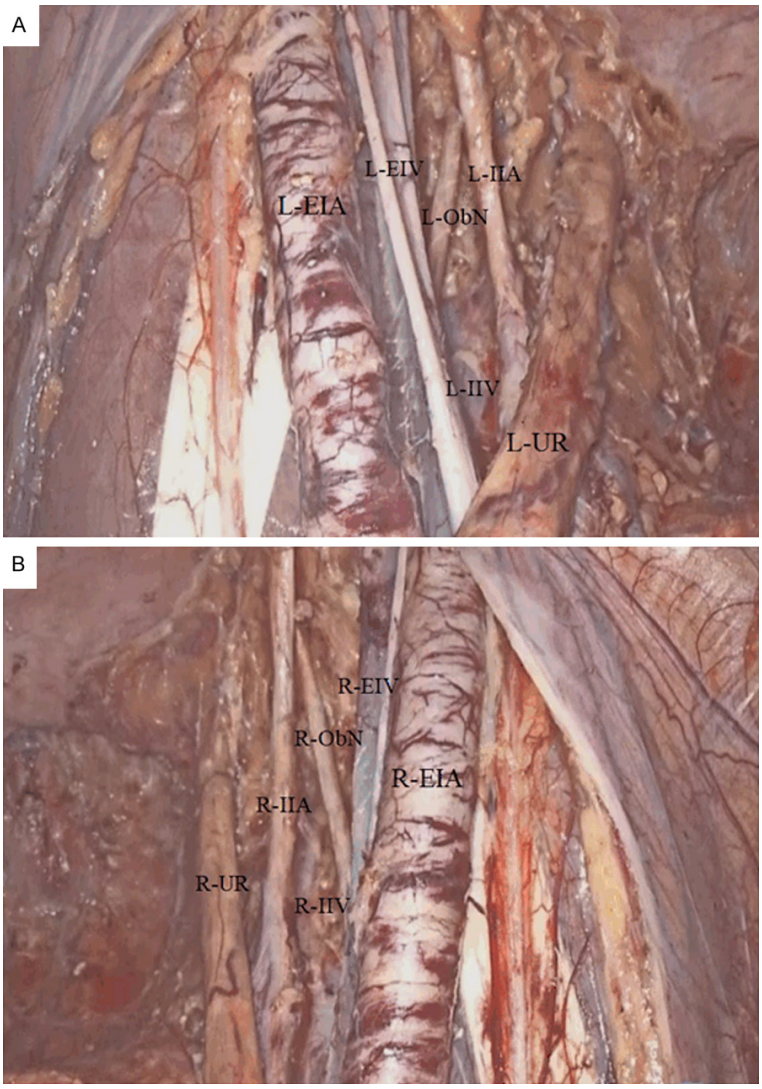

Figure 1. Intra-operative view of a dissected pelvic side wall with preservation of the vascular and nerve structures. A: Dissection of the left pelvic side wall; B: Dissection of the right pelvic side wall; UR, ureter; IIV, internal iliac vein; IIA, internal iliac artery; EIV, external iliac vein; EIA, external iliac artery; ObN, obturator nerve.

recent study showed that LPLN metastasis and local recurrence were unable to be controlled by pre-operative CRT without LPLND [13].

In addition, a few studies have confirmed that laparoscopic LPLND is feasible and safe, as the technique of laparoscopic LPLND is complex and requires masterful skills [14-16]. Therefore, it is necessary for surgeons to master the skills and indications for LPLND. However, these studies either had a small sample size or simply implemented TME + LPLND without pre-operative CRT. Therefore, the main purpose of this study is to examine the safety and feasibility of LPLND after pre-operative CRT for patients with advanced rectal cancer and swollen LPLNs.

Materials and methods

Case selection

Data of 76 patients with low (located below the peritoneal reflection) rectal cancer and swollen LPLNs who underwent TME + LPLND from January 2014 to February 2018 were analyzed retrospectively. This study was approved by the Ethics Committee of the National Cancer Center/Cancer Hospital. These patients had complete clinical information.

The indication for LPLND was that the long-axis diameter of the LPLNs was greater than 5 mm as assessed by magnetic resonance imaging (MRI) before treatment and the size of the LPLNs after pre-operative treatment was not referred to [17]. Among the 76 cases, 40 patients received pre-operative CRT in the present study. Among them, 31 were treated with a long-course of CRT with capecitabine and a total radiation dose of 50.4 Gy. Nine of these patients were treated with 4 cycles of chemotherapy (XELOX) followed by a short-course of radiotherapy (5 × 5 Gy).

Paired comparison was performed on 18 cases (CRT group) who were selected from the patents who received CRT and their matched controls (non-CRT group, n=18). The clinical characteristics, peri-operative outcomes and pathological findings were compared and analyzed.

Surgical procedure

All 76 patients in this study underwent surgery by one surgeon with more than 20 years of clinical experience. Each surgery was performed by one operator and two assistants.

Table 1. Clinical characteristics of the patients

Variable	Total (n=76)	CRT group (n=18)	Non-CRT group (n=18)	P
Sex (male/female, n)	38/38	8/10	10/8	
Age (years)	58.3±1.3	56.9±8.6	58.0±9.5	0.754
Distance from the AV (mm)	45.3±2.1	33.8±14.7	55.333±15.541	<0.001
BMI (kg/m^2) (range)	25.45±0.78	25.20±0.80	25.57±0.80	0.674
Pre-treatment CEA (ng/mL)	3.49±8.55	13.00±5.44	16.36±6.91	0.617
Pre-treatment CA19-9 (ng/mL)	15.41±6.47	20.52±4.79	16.50±5.45	0.621
cT stage (n)				
2	16	6	6	
3	48	8	8	
4	12	4	4	
cN stage (n)				
0	19	4	4	
1	20	5	5	
2	37	9	9	
Adjuvant therapy (n)				
Long course CRT	31	13		
Short course CRT	9	5		
Non-CRT	37		18	

Note: BMI body mass index, AV anal verge, CEA carcinoembryonic antigen, CA19-9 carbohydrate antigen 19-9, CRT chemoradiotherapy.

The surgical procedure was modified from the previous reports [15]. The five abdominal ports placed for laparoscopic LPLND were the same as those used for TME: first, a para-umbilical port was established for the laparoscope; then, two ports were established at the anterior axillary line in the right lower abdominal quadrant; and another two working ports were established in the left lower abdominal quadrant that were symmetrical to the right-sided ports.

When performing a left LPLND, the operator stood on the right side. When performing a right LPLND, the operator stood on the left side. Our routine choice is to perform the left LPLND first, because the operator does not need to adjust their position after extracting the specimen. LPLNs were defined as lymph nodes distributed outside the pelvic plexus, including lymph nodes surrounding the internal iliac vessels, obturator fossa, and external iliac vessels. When performing LPLND, the ureters and hypogastric nerve were first separated and elevated by an assistant in order to prevent damage to these structures. Then, the lymph nodes were dissected in order along the external iliac vessels and the common iliac vessels, in the obturator fossa and along the internal iliac vessels, separately and carefully, paying attention to protect the ureters and hypogastric nerve. See **Figure 1**.

Observation indicators

Basic clinical information was summarized and analyzed, including age, sex, body mass index (BMI), pre-treatment CEA, pre-treatment CA199, the distance from the anal verge and TNM stag. The peri-operative and pathological outcomes were observed the related indicators included operation procedure, LPLND (unilateral or bilateral), nerve preservation condition, temporary stoma application, operation time, blood loss volume, hospital stay, postoperative mortality, rates of en bloc resection of adjacent structures, complication, histological type, the removing number and metastatic number of mesorectal lymph nodes and LPLNs as well as location of lymph node metastasis and the positive rate of circumferential resection margins. TNM stag were classified according to the Union for International Cancer Control 7th edition. Urinary retention was evaluated by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Statistical analysis

All the data were analyzed by using SPSS software version 19.0 for Windows (IBM Crop, Armonk, NY, United States). Measurement data are expressed by the mean ± standard devia-

Table 2. Peri-operative outcomes of the patients

Variable	CRT group (n=18)	Non-CRT group (n=18)	P
Operative procedure (n)			0.513
Low anterior resection	12	10	
Abdominoperineal resection	4	7	
Hartmann's procedure	2	1	
LPLND (n)			1.000
Unilateral	15	15	
Bilateral	3	3	
Nerve preservation (n)			
Complete	18	18	
Incomplete	0	0	
Temporary stoma (n)	13	3	0.001
En bloc resection of adjacent structures (n)	3	3	1.000
Seminal vesicle	0	1	
Vagina	1	0	
Uterus	1	1	
Ovary	1	1	
Operative time (min)	298.23±68.31	200.78±48.94	0.012
Blood loss (ml)	130.29±23.04	50.14±711.98	0.027
Hospital stay (days)	7.56±2.33	7.34±0.89	0.242
Postoperative mortality (n)	0	0	
Conversion to open procedure (n)	0	0	
Postoperative complication (n)	5(27.78%)	3(16.67%)	1.000*
Anastomotic leakage	1	0	
Wound infection	1	1	
Bowel obstruction	0	0	
Lymphatic leakage	0	0	
Bleeding	2	1	
Obturator nerve injury	0	1	
Urinary retention	1	0	

Note: *Yate's continuity corrected Chi square test. LPLND lateral pelvic lymph node dissection.

tion and the comparison between the two groups were applied paired t test. Count data are expressed as percentage and the comparison between groups were performed using the X^2 test, Yate's continuity corrected Chi square test or Fisher exact test. A *P* value of <0.05 was considered statistically significant.

Results

Basic information

The clinical characteristics of the 76 patients and the two groups are summarized in **Table 1**. There were no significant differences between the two groups in terms of age, sex, BMI, pre-treatment CEA or pre-treatment CA199 (all P> 0.05), while there were significant difference in distance from the anal verge (P<0.001).

Peri-operative outcomes

The operation procedures were similar between the two groups (P=0.513). There was a significant difference between the two groups in operation time and blood loss (P=0.027). The temporary stoma was present significantly more often in CRT group than that in non-CRT group (P=0.001). There was no significant difference between the two groups in the percentage of en bloc resections of adjacent structures, total postoperative complication rate, hospital stay and urinary retention rate (all P>0.05). There were no cases of conversion to

Table 3. Pathological outcomes

Variable	CRT group (n=18)	Non-CRT group (n=18)	P
Histological type (n)			0.457
Moderate	14	12	
Mucinous/poor/signet	4	6	
pT (n)			0.526
pT1	1	1	
pT2	4	4	
pT3	9	12	
pT4	4	1	
pN (n)			0.757
pN0	7	8	
pN1	6	4	
pN2	5	6	
Mesorectal lymph nodes removed (n)	8	8	1.000
LPLNs removed (n)	3	4	1.000*
Metastatic LPLNs (n)	6	4	0.457
Metastatic mesorectal lymph nodes (n)	10	10	1.000
Location of lymph node metastasis			
Only mesorectal	8	8	
Mesorectal and LPLNs	2	2	
Only LPLNs	0	0	
Circumferential resection margins			1.000#
Positive	1	0	
Negative	17	18	

Note: *Yate's continuity corrected Chi square test; #Fisher's exact test; LPLNs lateral pelvic lymph nodes.

open surgery and no postoperative mortality in either group as shown in **Table 2**.

Pathological outcomes

No significant difference was found in histological type, pT stage, pN stage, or positive circumferential resection margins between the two groups (all P>0.05). There were 6 and 4 patients with identified LPLN metastasis and 10 and 10 patients with identified mesorectal metastasis in CRT group and non-CRT group, respectively (both P>0.05). The number of mesorectal lymph nodes and LPLNs removed were similar in both groups (both P>0.05) as shown in **Table 3**.

Discussion

Laparoscopic surgery has been generally accepted as a minimally invasive procedure and has been wildly used in treating patients with colorectal cancer [18-20]. However, laparoscopic LPLND is controversial due to its technical difficulties and the complicated anatomy of the pelvic sidewall. In addition, the tissue edema and fibrosis induced by chemoradiotherapy have further increased the difficulty of the surgery. Therefore, the present study aims to demonstrate the feasibility and safety of laparoscopic LPLND in patients who have received pre-operative CRT.

Nagayoshi et al. reported that the operation time in the laparoscopy group was much longer than that in the open group (641 VS. 312 min), but the amount of the intraoperative bleeding was significantly lower in the laparoscopy group than in the open group (252 VS. 815 ml) [21]. These findings might indicate that under clear and magnified visualization, the surgeon could perform laparoscopic LPLND more precisely, therefore, it can greatly reduce bleeding and the operation is safer and efficient. However, most patients in these studies did not receive pre-operative CRT. Some studies have reported that pre-operative CRT would increase intraoperative blood loss, which severely affected the clarity of surgical visualization. In addition, pre-operative CRT can inhibit the immune system and increase the probability of incision, lung and pelvic infection [22, 23]. In the present study, the operation duration was significant longer and the intraoperative bleeding loss was significant larger in patients who received pre-operative CRT than those did not receive pre-operative CRT, which were in accordance with the findings of above reports. Tissue edema and fibrosis caused by pre-operative CRT could be used to explain these differences, which further leading to tissue bleeding, unclear anatomical relation and prolonged operation duration. Ogura et al. reported that there were 107 patients performed laparoscopic LPLND + TME after pre-operative CRT, and the median operation dura-

tion and blood loss were 461 minutes and 115 ml, respectively [16].

The hospital stay in the two groups was similar in our study, but it was significantly shorter than that in a previous report [24]. Furthermore, the rates of major postoperative complications were similar in two group in the present study, and there were no cases of conversion to an open procedure and no postoperative mortality, in addition, there was no significant difference in morbidity between the CRT group and non-CRT group, suggesting that the addition of pre-operative CRT for patients with swollen LPLNs before LPLND is acceptable and feasible.

In terms of preserving urinary function, previous reports have reported the incidence of urinary retention after surgery in patients who underwent open TME + LPLND [7]. In this study, there was one case of grade 2 urinary retention that did not require catheterization in CRT group I and no cases in non-CRT group. This suggests that laparoscopic LPLND may have an advantage for preserving urinary function whether or not patients underwent pre-operative CRT. Furthermore, Kagawa et al. recently reported that robotic-assisted lateral lymph node dissection for patients with advanced lower rectal cancer achieved better short-term outcomes. This indicated that with the development of robot technology, the technology of LPLND will be more mature, and the safety and feasibility will be greatly improved [25].

Mesorectal lymph node metastasis is a significant poor prognostic factor and the number of lymph nodes resected is a key factor to determine the success of surgery [26, 27]. The total number of retrieved LPLNs and mesorectal lymph nodes per patient in CRT group was equal to that of non-CRT group, which is similar to the results reported by Atsushi Ogura [16]. Furthermore, only one patient who underwent pre-operative CRT had positive circumferential resection margins, suggesting that surgeons can overcome the difficulty of tissue edema and fibrosis caused by chemoradiotherapy through improved surgical skills and proficiency, and the same surgical treatment effect can be achieved after pre-operative CRT.

However, there are some limitations in the study, for example, long-term follow up was not performed and this is a single centre retrospective study. Therefore, a multi-centre prospective study with larger sample size are needed in the future. In conclusion, laparoscopic TME + LPLND after pre-operative CRT appears to be technically feasible and safe, as well as oncologically acceptable, however it may prolong the operation time and increase blood loss.

Acknowledgements

This work was supported by the Beijing Hope Run Special Fund of Cancer Foundation of China (LC2017A19).

Disclosure of conflict of interest

None.

Address correspondence to: Jianwei Liang, Department of Colorectal Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China. Tel: +86-010-87787110; Fax: +86-010-87787110, E-mail: liangjianwei7110@163.com

References

[1] Tamura H, Shimada Y, Kameyama H. Prophylactic lateral pelvic lymph node dissection in stage IV low rectal cancer. World Journal of Clinical Oncology 2017; 8: 412-419.

[2] Takahashi T, Ueno M, Azekura K, Ohta H. Lateral node dissection and total mesorectal excision for rectal cancer. Dis Colon Rectum 2000; 43.

[3] Sugihara K, Kobayashi H, Kato T, Mori T, Mochizuki H, Kameoka S, Shirouzu K, Muto T. Indication and benefit of pelvic sidewall dissection for rectal cancer. Dis Colon Rectum 2006; 49: 1663-72.

[4] Watanabe T, Itabashi M, Shimada Y, Tanaka S, Ito Y, Ajoka Y. Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2014 for treatment of colorectal cancer. Int J Clin Oncol 2015; 20: 207-239.

[5] Van Gijn W, Marijnen CA, Nagtegaal ID, Kranenbarg EM, Putter H, Wigger S, Rutten HJ, Pahlman L, Glimelius B, van de Velde CJ, Dutch Colorectal Cancer Group. Pre-operative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol 2011; 12: 575-582.

[6] Akiyoshi T, Nagata J, Nagasaki T, Konishi T, Fujimoto Y, Nagayama S, Fukunaga Y, Ueno M. Laparoscopic salvage lateral pelvic lymph node dissection for locally recurrent rectal cancer. Colorectal Dis 2015; 17.
[7] Yan CQ, Yao L, Zhang Z, Li XS, Cai L, He ZS, Zhou LQ. Laparoscopic enlarged pelvic lymphadenectomy for the treatment of high-risk prostate cancer. Practical Journal of Clinical Medicine 2017; 5-9.
[8] Kusters M, Beets GI, van de Velde CJ, Beets-Tan RG, Marijnen CA, Rutten HJ, Putter H, Moriya Y. A comparison between the treatment of low rectal cancer in Japan and the Netherlands, focusing on the patterns of local recurrence. Ann Surg 2009; 249: 229-35.
[9] Zhang J, Hu Q, W ZR. Clinical experience with laparoscopic pelvic lymph node dissection for prostate cancer. Journal of Minimally Invasive Urology 2017; 6: 207-209.
[10] Ozawa H, Kotake K, Hosaka M. Impact of lateral pelvic lymph node dissection on the survival of patients with T3 and T4 low rectal cancer. World J Surg 2016; 40: 1492-1499.
[11] Ishihara S, Kanemitsu Y, Murono K. Oncological benefit of lateral pelvic lymph node dissection for rectal cancer treated without pre-operative chemoradiotherapy: a multicenter retrospective study using propensity score analysis. International Journal of Colorectal Disease 2016; 31: 1-7.
[12] Bosset JF, Calais G, Mineur L, Maingon P. Fluorouracil-based adjuvant chemotherapy after pre-operative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. Lancet Oncol 2014; 15: 184-190.
[13] Kim TH, Jeong SY, Choi DH, Kim DY, Jung KH, Moon SH, Chang HJ, Lim SB, Choi HS, Park JG. Lateral lymph node metastasis is a major cause of locoregional recurrence in rectal cancer treated with pre-operative chemoradiotherapy and curative resection. Ann Surg Oncol 2008; 15: 729-37.
[14] Liang JT. Technical feasibility of laparoscopic lateral pelvic lymph node dissection for patients with low rectal cancer after concurrent chemoradiation therapy. Ann Surg Oncol 2011; 18: 153-159.
[15] Furuhata T, Okita K, Nishidate T, Ito T, Yamaguchi H, Ueki T, Akizuki E, Meguro M, Ogawa T, Kukita K, Kimura Y, Mizuguchi T, Hirata K. Clinical feasibility of laparoscopic lateral pelvic lymph node dissection following total mesorectal excision for advanced rectal cancer. Surg Today 2015; 45: 310-314.
[16] Ogura A, Akiyoshi T, Nagasaki T, Konishi T, Fujimoto Y, Nagayama S, Fukunaga Y, Ueno M, Kuroyanagi H. Feasibility of laparoscopic total mesorectal excision with extended lateral pelvic lymph node dissection for advanced lower rectal cancer after pre-operative chemoradiotherapy. World J Surg 2017; 41: 868-875.
[17] Akiyoshi T, Matsueda K, Hiratsuka M, Unno T, Nagata J, Nagasaki T, Konishi T, Fujimoto Y, Nagayama S, Fukunaga Y, Ueno M. Indications for lateral pelvic lymph node dissection based on magnetic resonance imaging before and after pre-operative chemoradiotherapy in patients with advanced low-rectal cancer. Ann Surg Oncol 2015; 22: 614-620.
[18] Buchanan GN, Malik A, Parvaiz A, Sheffield JP, Kennedy RH. Laparoscopic resection for colorectal cancer. Br J Surg 2008; 95: 893-902.
[19] Neudecker J, Klein F, Bittner R, Carus T, Stroux A, Schwenk W, LAPKON II Trialists. Short-term outcomes from a prospective randomized trial comparing laparoscopic and open surgery for colorectal cancer. Br J Surg 2009; 96: 1458-67.
[20] Fujita S, Akasu T, Mizusawa J, Saito N, Kinugasa Y, Kanemitsu Y, Colorectal Cancer Study Group of Japan Clinical Oncology Group. Postoperative morbidity and mortality after mesorectal excision with and without lateral lymph node dissection for clinical stage II or stage III lower rectal cancer (JCOG0212): results from a multicentre, randomised controlled, non-inferiority trial. Lancet Oncol 2012; 13: 616-21.
[21] Nagayoshi K, Ueki T, Manabe T, Moriyama T, Yanai K, Oda Y, Tanaka M. Laparoscopic lateral pelvic lymph node dissection is achievable and offers advantages as a minimally invasive surgery over the open approach. Surg Endosc 2016; 30: 1938-1947.
[22] Bai DL, Li Q. Study on the therapeutic effect of laparoscopic surgery after neoadjuvant chemoradiotherapy. Chinese Journal of the Frontiers of Medical Science (Electronic Version) 2016; 8: 50-53.
[23] Lirici MM, Hüscher CG. Techniques and technology evolution of rectal cancer surgery: a history of more than a hundred years. Minim Invasive Ther Allied Technol 2016; 25: 226-233.
[24] Park JS, Choi GS, Lim KH, Jang YS, Kim HJ, Park SY, Jun SH. Laparocscopic extended lateral pelvic node dissection following total mesorectal excision for advanced rectal cancer: initial clinical experience. Surg Endosc 2011; 25: 3322-9.
[25] Kagawa H, Kinugasa Y, Shiomi A. Robotic-assisted lateral lymph node dissection for lower rectal cancer: short-term outcomes in 50 consecutive patients. Surg Endosc 2015; 29: 995.
[26] Mori S, Baba K, Yanagi M, Kita Y, Yanagita S, Uchikado Y, Arigami T, Uenosono Y, Okumura H, Nakajo A, Maemuras K, Ishigami S, Natsug-

oe S. Laparoscopic complete temesocolic excision with radically lymph node dissection along the surgical trunk for right colon cancer. Surg Endosc 2015; 29: 34-40.

[27] Moon SH, Kim DY, Park JW, Oh JH, Chang HJ, Kim SY, Kim TH, Park HC, Choi DH, Chun HK, Kim JH, Park JH, Yu CS. Can the new American Joint Committee on Cancer staging system predict survival in rectal cancer patients treated with curative surgery following preoperative chemoradiotherapy? Cancer 2012; 118: 4961-4968.