

Received: 2018.01.25
Accepted: 2018.01.29
Published: 2018.06.11

Feasibility of Extended Dissection of Lateral Pelvic Lymph Nodes During Laparoscopic Total Mesorectal Excision in Patients with Locally Advanced Lower Rectal Cancer: A Single-Center Pilot Study After Neoadjuvant Chemotherapy

Department of Digestive Surgery, Tenri Hospital, Tenri, Nara, Japan

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BCDEF **Yuki Aisu***
DF **Shigeru Kato**
DF **Yoshio Kadokawa**
DF **Daiki Yasukawa**
DF **Yusuke Kimura**
DF **Yuichi Takamatsu**
DF **Taku Kitano**
ABCDEF **Tomohide Hori***

Corresponding Authors:
Source of support:

* Yuki Aisu and Tomohide Hori contributed equally to this work
Yuki Aisu, e-mail: aisuyuki@tenriyorozu.jp, Tomohide Hori, e-mail: horitomo@tenriyorozu.jp
Departmental sources

Background: The feasibility of additional dissection of the lateral pelvic lymph nodes (LPLNs) in patients undergoing total mesorectal excision (TME) combined with neoadjuvant chemotherapy (NAC) for locally advanced rectal cancer (LARC) is controversial. The use of laparoscopic surgery is also debated. In the present study, we evaluated the utility of laparoscopic dissection of LPLNs during TME for patients with LARC and metastatic LPLNs after NAC, based on our experience with 19 cases.

Material/Methods: Twenty-five patients with LARC with swollen LPLNs who underwent laparoscopic TME and LPLN dissection were enrolled in this pilot study. The patients were divided into 2 groups: those patients with NAC (n=19) and without NAC (n=6). Our NAC regimen involved 4 to 6 courses of FOLFOX plus panitumumab, cetuximab, or bevacizumab.

Results: The operative duration was significantly longer in the NAC group than in the non-NAC group (648 vs. 558 minutes, respectively; $P=0.022$). The rate of major complications, defined as grade ≥ 3 according to the Clavien-Dindo classification, was similar between the 2 groups (15.8% vs. 33.3%, respectively; $P=0.4016$). No conversion to conventional laparotomy occurred in either group. In the NAC group, a histopathological complete response was obtained in 2 patients (10.5%), and a nearly complete response (Tis N0 M0) was observed in one patient (5.3%). Although the operation time was prolonged in the NAC group, the other perioperative factors showed no differences between the 2 groups.

Conclusions: Laparoscopic LPLN dissection is feasible in patients with LARC and clinically swollen LPLNs, even after NAC.

MeSH Keywords: **Colorectal Neoplasms • Colorectal Surgery • Laparoscopy • Lymph Node Excision • Neoadjuvant Therapy**

Full-text PDF: <https://www.medscimonit.com/abstract/index/idArt/909163>

 2943  3  4  78



Background

Rectal cancer often invades the bladder, uterus, sacrococcyx, and lateral pelvic lymph nodes (LPLNs). Locally-advanced rectal cancer (LARC) with LPLN metastasis is well known to have a poor prognosis. The LPLNs are an important metastatic site. However, the most effective therapeutic strategy for LARC has not been established. Local recurrence after total mesorectal excision (TME) without LPLN dissection may have untreated LPLN metastasis [1]. Surgical dissection for LPLN metastasis remains controversial. Some researchers have suggested that intentional LPLN dissection is associated with intractable complications [2,3], although some treatment guidelines suggest that intentional dissection of LPLNs surely has therapeutic potential for patients with LARC [4–7]. Combination therapy of preoperative chemoradiotherapy and TME without LPLN dissection was previously performed worldwide. However, this simple therapy only improved local control after TME [8], though it did not prolong survival [9,10]. Hence, a high rate of distant metastasis after TME remains a critical problem. Reinforced and/or stronger systemic chemotherapy in the preoperative period (i.e., systemic neoadjuvant chemotherapy [NAC]), has therapeutic potential in carcinogenic control for patients with LARC [11–14]. Surgical innovation by LPLN dissection for patients with LARC has been discussed since the early 1960s [15]; since then, this surgical therapy has been developed mainly in Japan [16–20]. However, advanced techniques and highly skilled procedures are required for LPLN dissection. We herein discuss the key points and pitfalls of laparoscopic LPLN dissection.

Overall, both systemic NAC for carcinogenic control and surgical dissection of LPLNs for local curability surely have therapeutic potential for patients with LARC. We believe that the combination of systemic NAC and intentional dissection of LPLNs results in adequate local curability, a reduction of distant metastasis, and a favorable long-term outcome. In our institution, 19 consecutive patients with LARC and LPLN metastasis underwent laparoscopic TME and LPLN dissection after NAC. Here, we report on our investigation of the therapeutic impact of this combined therapy, and also discussed the usefulness of laparoscopic surgery for LPLN dissection, even after NAC.

Material and Methods

Treatment strategy

Patients with LARC who develop postoperative local recurrence after TME without LPLN dissection may have untreated LPLN metastasis [1]. Surgical dissection for LPLN metastasis remains controversial. Aggressive and/or curative dissection of LPLNs is often associated with intractable complications

(i.e., urinary and sexual dysfunction) [2,3]. However, according to the 2016 Japanese guidelines for colorectal cancer [4,5], TME with LPLN dissection is recommended to improve both local curability and survival in patients with LARC in whom the lower border of the tumor is located distal to the peritoneal reflection and the tumor has invaded beyond the muscularis propria. Such tumors are categorized as advanced Rb cancer according to the 2013 Japanese classification of colorectal cancer [6]. If LPLN dissection is indicated based on the Japanese criterion, the percentage of intrapelvic recurrence is expected to decrease to 50% and the 5-year survival is expected to improve to 8% to 9% [7]. Hence, LPLN surely has therapeutic potential for patients with LARC.

A combination of TME accompanied not by LPLN dissection but by preoperative chemoradiotherapy was previously performed worldwide; LPLN dissection was not performed because it requires advanced surgical techniques even in conventional open surgical procedures. Some physicians expected that preoperative chemoradiotherapy targeting the pelvic region may effectively reduce intrapelvic recurrence [8]. However, this simple therapy only improved local control after TME; it did not prolong survival [9,10]. Reinforced and/or stronger systemic chemotherapy in the preoperative period is expected to effectively control existing micro-metastasis and improve survival [11]. Many physicians have suggested that systemic NAC has therapeutic potential in carcinogenic control for patients with LARC [12–14].

Twenty-seven patients with LARC who had clinical LPLN metastasis underwent laparoscopic LPLN dissection in our institution from 2011 to 2016. Two patients with preoperative para-aortic LN metastases were excluded from the present study. Nineteen patients underwent laparoscopic TME and LPLN dissection with NAC, and 6 patients underwent laparoscopic TME and LPLN dissection without NAC. The median follow-up term was 27.5 months (range, 8.6–71.0 months). The oncologic findings were assessed according to the 2013 Japanese classification of colorectal cancer and the 2016 Japanese guidelines for colorectal cancer [4,6].

NAC is indicated for patients with cT3-4 and/or N+ rectal cancer in our institution, and laparoscopic LPLN dissection is indicated in patients with LPLN with a short-axis diameter of >5 mm on pretreatment computed tomography and/or magnetic resonance imaging, regardless of the LN size after NAC. Fifty-five patients were treated with 4 to 6 courses of oxaliplatin-based NAC including a molecule-targeting drug; 19 of these patients then underwent laparoscopic TME and LPLN dissection with curative intent.

Patient classification and statistical analysis

The short- and mid-term oncological outcomes were compared between the 19 patients who underwent laparoscopic

TME and LPLN dissection with NAC (NAC group) and the 6 patients who underwent laparoscopic TME and LPLN dissection only (non-NAC group). Quantitative data are expressed as median (range). Statistical analyses were performed using statistical software (Stat View-J 5.0; SAS Institute, Cary, NC, USA). Differences between the 2 groups were evaluated using Fisher's exact test, the chi-square test, and the Mann-Whitney U test, as appropriate. Overall survival (OS) and relapse-free survival (RFS) were defined as the time from surgery to death from any cause and any recurrences, respectively.

Surgical procedures of LPLN dissection

Surgical innovation by LPLN dissection for patients with LARC has been documented [16–20]. However, the technical difficulty of LPLN dissection requires selection of skillful surgeons; advanced techniques and highly skilled procedures are required

for LPLN dissection, even under conventional laparotomy. In our institution, we employ laparoscopic surgery for LPLN dissection. We performed curative LPLN dissection (LNs 263P, 263D, and 283 according to the 2013 Japanese classification of colorectal cancer) [6] only for the metastatic side based on the findings of the imaging studies before NAC. Preventive LPLN dissection for the unaffected side was not conducted.

The patients were placed in the lithotomy position. Five ports were placed, including a 12-mm camera port at the umbilicus and 5- or 12-mm ports in the bilateral abdomen. LPLN dissection was performed after resection of the rectum and before anastomosis during low anterior resection. The surgical procedures performed during LPLN dissection are shown in Figures 1–3. The ureter was isolated and pulled with vessel tape. Once the external iliac artery and vein were exposed, dissection was performed along the surface of the iliopsoas and

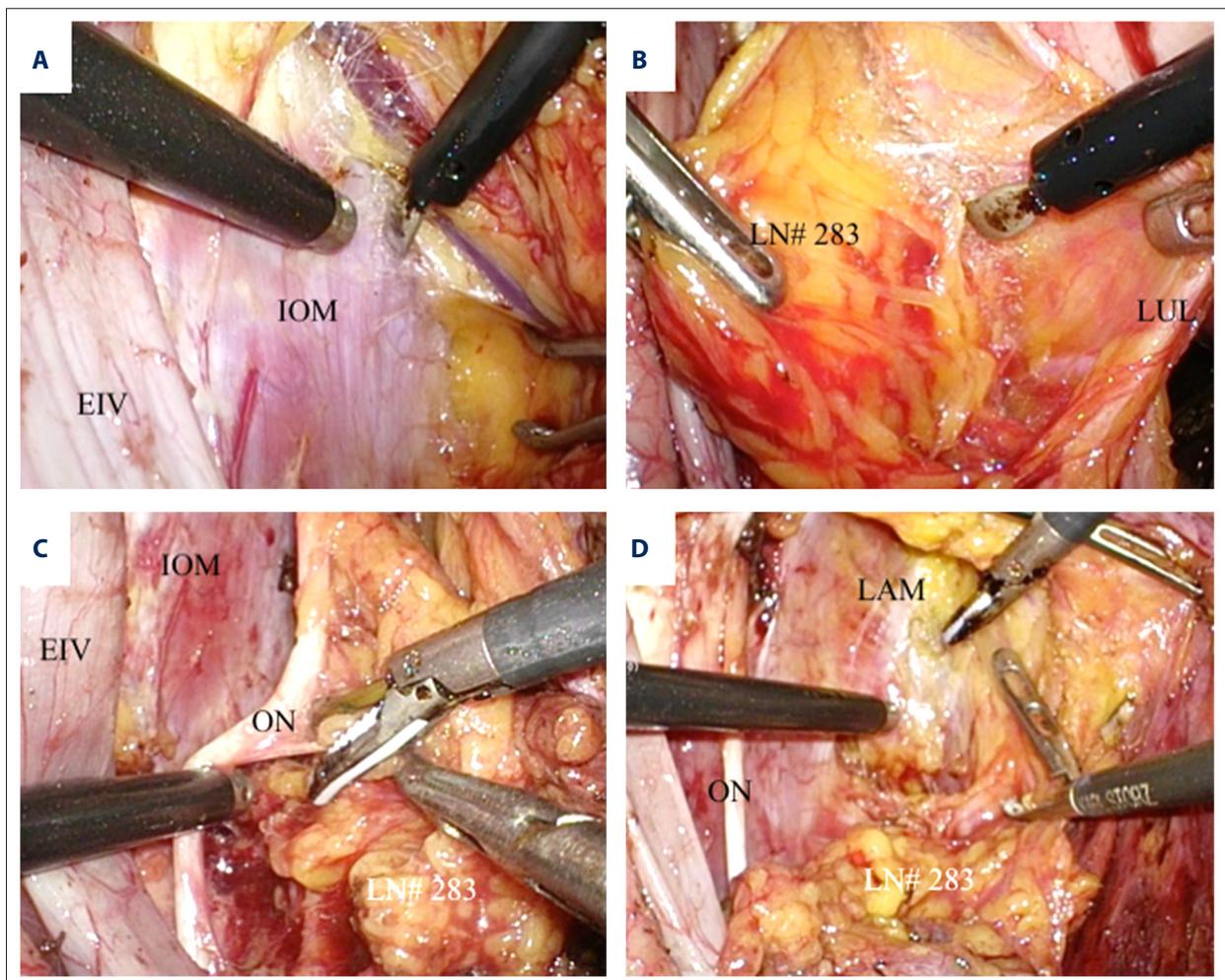


Figure 1. (A) Once the external iliac artery and vein were exposed, dissection was performed along the surface of the iliopsoas and internal obturator muscles. (B) LN #283 was dissected. (C, D) The obturator nerve was identified and preserved, but the obturator vessels were divided. EIV – external iliac vein; IOM – internal obturator muscle; LAM – levator ani muscle; LN – lymph node; LUL – lateral umbilical ligament; ON – obturator nerve.

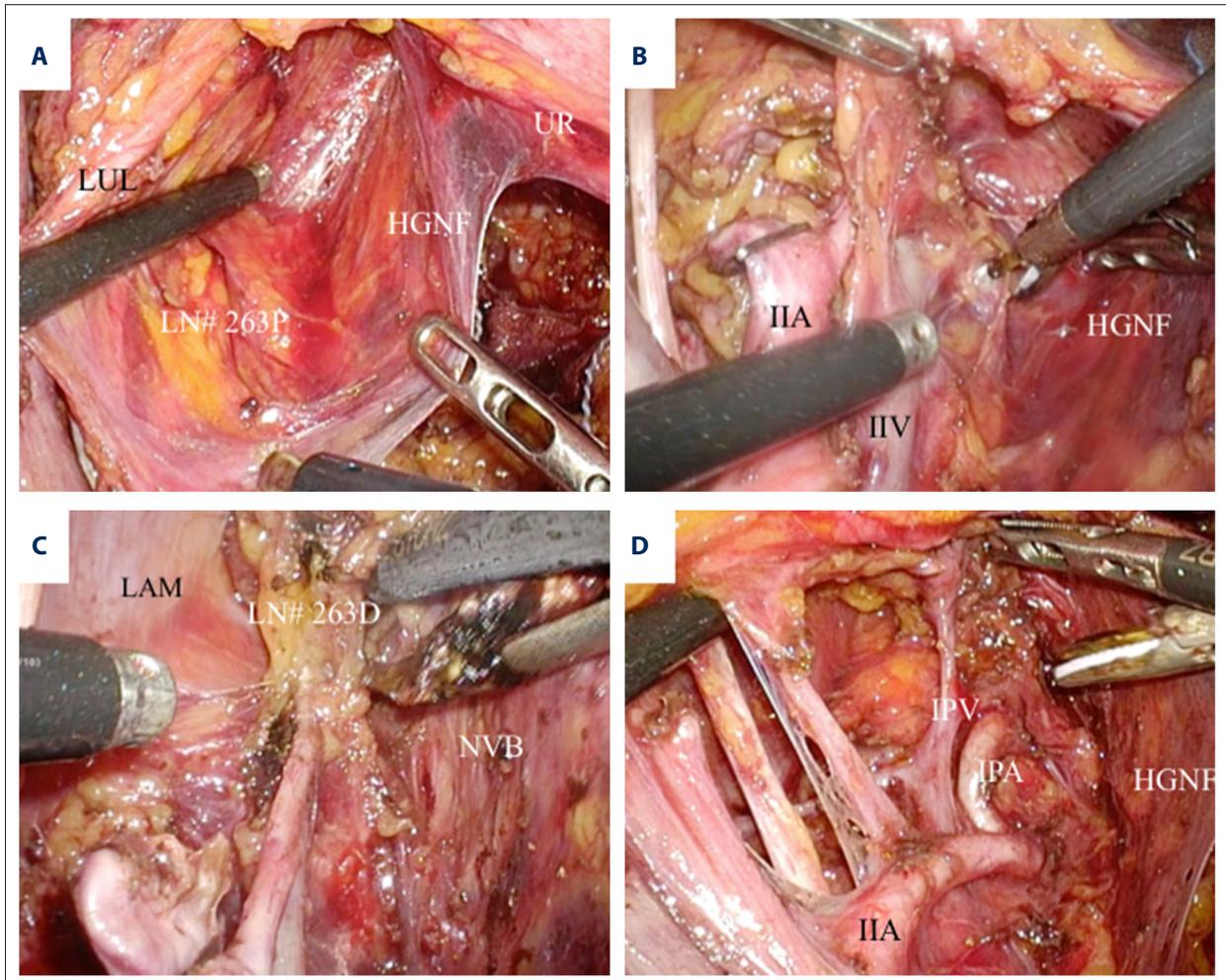


Figure 2. (A–C) The internal iliac artery was preserved, and its branches (i.e., the superior and inferior vesical arteries) were clipped and divided. (D) When bilateral dissection of the LPLNs was required, one of the bilateral superior and inferior vesical arteries was preserved to maintain blood flow into the bladder. HGNF – hypogastric nerve fascia; IIA – internal iliac artery; IIV – internal iliac vein; IPA – internal pudendal artery; IPV – internal pudendal vein; LAM – levator ani muscle; LN – lymph node; LPLN – lateral pelvic lymph node; LUL – lateral umbilical ligament; NVB – neurovascular bundle; UR – ureter.

internal obturator muscles. The obturator nerve was identified and preserved, but the obturator vessels were divided. The internal iliac artery was preserved, and its branches (i.e., the superior and inferior vesical arteries) were clipped and divided. If metastatic LPLNs had adhered or were close to the internal iliac artery, this artery was resected together. When bilateral dissection of the LPLNs was required, one or more of the bilateral superior and inferior vesical arteries was preserved to ensure blood flow into the bladder. The roots of the umbilical artery were clipped and divided. The surface of the internal iliac vein was exposed, and the confluence of the inferior vesical vein was divided. The sacral plexus was exposed as the dorsal landmark of the LPLN dissection, and the distal side of the internal iliac artery (internal pudendal artery) was divided at the level of the pudendal canal. The inferior vesical artery and vein were divided at their entrance into the bladder.

If the metastatic LPLNs had adhered to the pelvic plexus, this plexus was resected *en bloc*.

Results

Patient characteristics

The patient characteristics are summarized in Table 1. There were no significant differences between the 2 groups in terms of sex ($P=0.813$), age ($P=0.260$), distance from the anal verge ($P=0.2598$), pretreatment serum levels of carcinoembryonic antigen ($P=0.3481$), carbohydrate antigen 19-9 ($P=0.6154$), and tumor size ($P=0.8954$). The cT stage was significantly higher in the NAC than non-NAC group ($P=0.0278$). The cN stage and c stage were N3 and stage IIIb in all patients. In the NAC group,

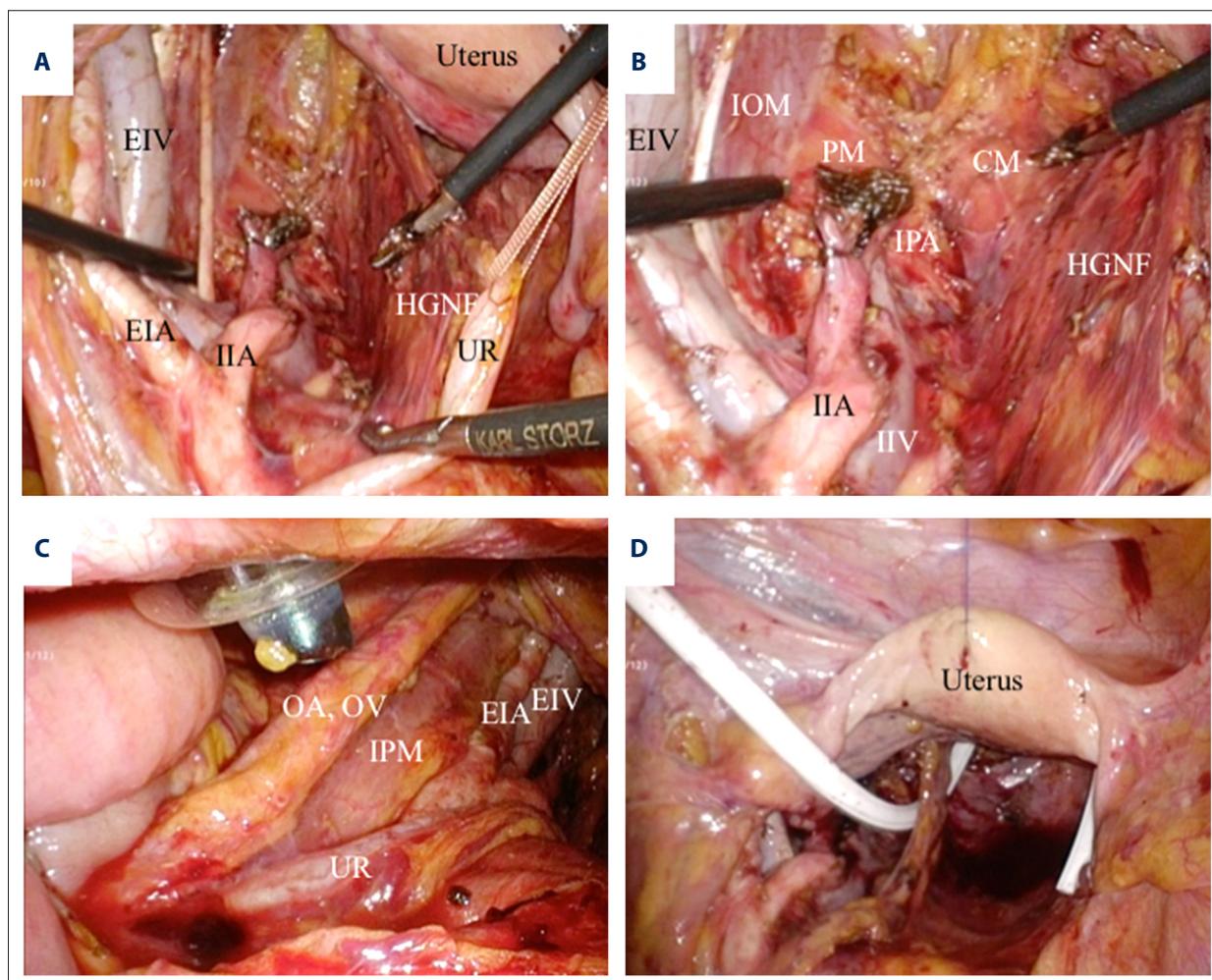


Figure 3. (A–C) Aggressive dissection of LPLNs was laparoscopically completed. (D) A drain was placed at the pelvic floor. CM – coccygeal muscle; EIA – external iliac artery; EIV – external iliac vein; HGNF – hypogastric nerve fascia; IIA – internal iliac artery; IIV – internal iliac vein; IPA – internal pudendal artery; IPM – iliopsoas muscle; IOM – internal obturator muscle; LPLN – lateral pelvic lymph node; OA – ovarian artery; OV – ovarian vein; PM – piriform muscle; UR – ureter.

the numbers of patients who underwent induction chemotherapy with the FOLFOX regimen (leucovorin, 5-fluorouracil, and oxaliplatin) accompanied by bevacizumab, panitumumab, or cetuximab were 13 (68.4%), 5 (26.3%), and 1 (5.2%), respectively. In the NAC group, details of the therapeutic effects of NAC were as follows: (i) the number of patients with ycT2, ycT3, and ycT4 cancer were 5 (26.3%), 8 (42.1%), and 6 (31.6%), respectively. (ii) The number of patients with ycN0, ycN1, ycN2, and ycN3 cancer were 6 (31.6%), 1 (5.0%), 1 (5.0%), and 11 (57.9%), respectively. (iii) The number of yc stage I, II, IIIa, and IIIb were 3 (15.8%), 3 (15.8%), 1 (5.0%), and 12 (63.2%), respectively. Overall, after NAC, the numbers of patients who achieved any downregulations of their T factor, N factor, and clinical stage were 5 (26.3%), 8 (42.1%), and 7 (36.8%), respectively. On the other hand, adjuvant chemotherapy after surgery was used in 14 patients (73.7%) in the NAC group and 2 patients (33.3%) in the non-NAC group.

Operative profiles

The operative courses are summarized in Table 2. Bilateral LPLN dissection was performed not in the non-NAC group (none, 0.0%) but in the NAC group (6 patients, 31.6%). In contrast, 13 patients in the NAC group (68.4%) and all patients in the non-NAC group (100.0%) underwent unilateral LPLN dissection. Temporary stoma construction, colostomy, or diverting ileostomy, was performed in all cases. The operative duration was significantly longer in the NAC than non-NAC group (648 vs. 558 minutes, respectively; $P=0.022$). There were no significant differences in the blood loss or postoperative hospital stay between the 2 groups. Neither conversion to conventional open surgery nor postoperative mortality occurred in either group.

Table 1. Patient characteristics.

	NAC group (n=19)	Non-NAC group (n=6)	The p value
Sex			0.8130
Male	11	3	
Female	8	3	
Age	66 (47–79)	71.5 (59–81)	0.2600
Distance from AV [mm] (range)	30 (0–120)	55 (30–150)	0.2598
Pretreatment serum level of CEA [ng/ml] (range)	4.5 (1.4–198)	3.1 (0.8–6.9)	0.3481
Pretreatment serum level of CA19-9 [ng/ml] (range)	10.6 (0.6–62.2)	11.9 (8.9–33.2)	0.6154
Tumor size [mm] (range)	40 (20–60)	39 (20–55)	0.8954
Pretreatment LPLN metastases			
Unilateral	15	6	
Bilateral	4	0	
cT stage			0.0278
2	1	3	
3	11	3	
4	7	0	
cN stage			
3	19	6	-
cStage			
IIIb	19	6	-
ycT stage			
2	5	N/A	
3	8	N/A	
4	6	N/A	
ycN stage			
0	6	N/A	
1	1	N/A	
2	1	N/A	
3	11	N/A	
ycStage			
I	3	N/A	
II	3	N/A	
IIIa	1	N/A	
IIIb	12	N/A	
NAC regimen			
FOLFOX + Bevacizumab	12	N/A	
FOLFOX + Panitumumab	6	N/A	
FOLFOX + Cetuximab	1	N/A	
Adjuvant chemotherapy			
Oxaliplatin-based	3	1	
5-FU-based	11	1	

AV – anal verge; CA19-9 – carbohydrate antigen 19-9; CEA – carcinoembryonic antigen; LPLN – lateral pelvic lymph node; N/A – not available; NAC – neoadjuvant chemotherapy; 5-FU – 5-fluorouracil.

Table 2. Important factors during and after surgery.

Variables	NAC group (n=19)	Non-NAC group (n=6)	The p value
Operative procedure			–
Low anterior resection	5	0	
Intersphincteric resection	0	1	
Abdominoperineal resection	13	3	
Hartmann's procedure	1	2	
LPLN dissection			0.1468
Unilateral	13	6	
Bilateral	6	0	
Simultaneous stoma construction			–
Colostomy	14	5	
Ileostomy	5	1	
Obturator nerve preservation			0.3938
Complete	17	6	
Incomplete	2	0	
Operative time [m] (range)	648 (550–892)	558 (537–654)	0.022
Blood loss [ml] (range)	100 (5–890)	105 (30–240)	0.3537
Conversion to conventional open surgery	0	0	–
Postoperative hospital stay [days] (range)	16 (10–80)	18 (9–48)	0.8528
Postoperative mortality	0	0	–

LPLN – lateral pelvic lymph node; NAC – neoadjuvant chemotherapy.

Postoperative outcomes

The postoperative complications are summarized in Table 3. Ten patients in the NAC group (52.6%) and 3 patients in the non-NAC group (50.0%) developed postoperative complications. Major complications, defined as grade ≥ 3 according to the Clavien-Dindo classification [21], occurred in 3 patients in the NAC group (reoperation for anastomotic leakage, resuture for perineum wound disruption, and percutaneous drainage for infectious lymphocele) and in 2 patients in the non-NAC group (reoperation for colon perforation and percutaneous drainage for pelvic abscess).

Pathological findings

The pathological findings are summarized in Table 4. There were no significant differences between the 2 groups in yp(p)T stage ($P=0.663$), yp(p) N stage ($P=0.661$), yp(p) stage ($P=0.500$), or the number of LNs harvested ($P=0.120$).

LPLN metastases were identified in 4 patients in the NAC group (21.1%) and in 2 patients in the non-NAC group (33.3%). A pathological complete response (CR) was achieved in 2 patients of

NAC group (10.5%). The circumferential resection margin was negative in all patients.

RFS and OS

The clinical course of all the study patients was followed for 27.5 months (range, 8.6–71.0 months) after surgery. Recurrence at the opposite side of the LPLN dissection was observed in 1 patient (5.3%) in the NAC group 13 months after surgery. There were no significant differences in RFS or OS between the 2 groups.

Discussion

LN dissection has a large impact on the prognosis and outcome in patients with rectocolon cancers [22–26]. Surprisingly, the number of investigated LNs is a predictive factor for prognosis even in patients with the same number of positive LNs, and patients with larger numbers of investigated LNs have a better prognosis [22–24]. Staging error is a critical problem [24]. Twelve or more LNs should be harvested and investigated [27–32]. Prognostic relevance of occult tumor cells in LNs has been suggested [33,34]. The number of positive LNs is

Table 3. Postoperative complications.

Variables	NAC group (n=19)	Non-NAC group (n=6)	The p value
All postoperative complications			
Anastomotic leakage	2	0	
Acute renal failure	1	0	
Wound infection	2	1	
Wound disruption	2	1	
Lymphocele	1	0	
Enteritis	1	0	
Pelvic abscess	0	1	
Obturator nerve disorder	2	0	
Portal vein embolism	1	0	
Urinary dysfunction	1	0	
Postoperative complications*			0.4016
Reoperation for anastomotic leakage	1	0	
Reoperation for colon perforation	0	1	
Resuture for perinium wound disruption	1	0	
Percutaneous drainage for infectious lymphocele	1	0	
Percutaneous drainage for pelvic abscess	0	1	

* Postoperative complications \geq Grade 3 according to the Clavien-Dindo classification. NAC – neoadjuvant chemotherapy.

considered as the most reliable prognostic factor [25,35–41]. However, aggressive dissection of LPLNs is accompanied by high rates of pelvic nerve injury, urination disturbance, sexual impairment, and defecation disorders [42,43]. Hence, a higher rate of postoperative complications is observed despite the fact that this surgery is performed with advanced surgical techniques supported by full knowledge of the pelvic anatomy [44].

Aggressive dissection of LPLNs is debated among rectocolon surgeons [45–48]. Based on the concept of the importance of extended dissection of regional LNs, aggressive dissection of LPLNs was established in Japan in 1982 [15] and in the United States in 1986 [49]. This surgical approach was thereafter developed mainly in Japan [50,51]; many important reports by Japanese surgeons have been published [17–19,52–55]. Some researchers have reported that aggressive dissection of LPLNs never improves the prognosis of patients with positive metastases of LPLNs [7,56,57], postoperative survival [58,59], or the local recurrence rate after surgery [60–62]. In Japan, however, this approach is generally considered the golden standard for lower rectal cancer. Notably, laparoscopic surgery for rectocolon cancer also has some advantages, such as less pain, faster recovery, shorter hospital stay, and earlier return to normal life [63–68]; therefore, many skillful surgeons currently focus on the laparoscopic approach for LPLN dissection [55,63,69,70].

Generally, NAC has an advantage over adjuvant chemotherapy with respect to the dose given. Briefly, a higher dosage is available for NAC because adjuvant therapy requires a period of recovery from perioperative damage. This reinforced and stronger chemotherapy will exterminate systemic micro-metastases, suppress postoperative recurrence, and consequently achieve prolonged survival. The safety and feasibility of laparoscopic TME with LPLN dissection has not been verified in patients with LARC after NAC [71]; therefore, we assessed our own results of laparoscopic TME combined with LPLN dissection after NAC. To the best of our knowledge, this pilot study is the first to analyze the safety and feasibility of laparoscopic LPLN dissection for patients with LARC after NAC.

As already described, downregulations were obtained by NAC induction. In previous studies, the reported CR rates after NAC for rectal cancer ranged from 3.8% to 25.0% [12–14,72]. In the present study, 2 patients (10.5%) achieved CR, and 1 patient (5.2%) was histopathologically categorized as having ypTis-NOM0 cancer. Although previous studies targeted cStage II–III rectal cancer, all of our patients were preoperatively categorized as having more advanced stages because of their metastatic LPLNs (i.e., cStage IIIb). Our CR rate of 10.5% is considered reasonable for patients with LARC.

Table 4. Pathological findings.

Variables	NAC group (n=19)	Non-NAC group (n=6)	The p value
yp(p)T			0.6633
0	2	0	
is	1	0	
1	1	0	
2	3	3	
3	12	3	
4	0	0	
yp(p)N			0.6608
0	11	3	
1	3	1	
2	1	0	
3	4	2	
yp(p)Stage			0.5044
0	3	0	
I	2	1	
II	6	2	
IIIa	3	1	
IIIb	5	2	
Pathological CR	2	N/A	0.3938
Histological type			
Well/moderate/papillary	16	6	
Mucinous/poor/signet	1	0	
Number of lymph nodes harvested	27 (14–48)	22 (13–25)	0.1202
Number of metastatic lymph nodes	0 (0–7)	1 (0–3)	
Location of lymph node metastasis			–
Only mesorectal	4	1	
Mesorectal and LPLN	2	0	
Only LPLN	2	2	
Circumferential resection margin			–
Positive	0	0	
Negative	19	6	

CR – complete response; LPLN – laterally pelvic lymph node; N/A – not available; NAC – neoadjuvant chemotherapy.

No consensus has been reached for NAC regimens in patients with LARC. We initially conducted NAC in 6 courses and performed a mid-term assessment using imaging studies and colonoscopy after 3 courses. However, no remarkable differences in the therapeutic effects between 3 and 6 courses were observed. We thereafter revised our NAC regimen to involve 4 courses without a mid-term assessment. Previous reports have suggested that 2 to 6 courses during a 2- to 3-month period are required for NAC and recommended surgery at 2 to 4 weeks after the last chemotherapy session [12–14,72]. The estimated serum half-life of bevacizumab is approximately 3 weeks [73,74], and adverse effects on wound healing persist for 6 weeks [75]. Bevacizumab was therefore omitted from the last course in our current regimen. Although prediction of the therapeutic effectiveness is ideal for selection of the chemotherapy regimen, accurate estimation of individual patients' responses to NAC is impossible. Only 1 patient was determined to have progressive disease after 3 courses because of metastatic enlargement of LNs. Although NAC was suspended, and surgery was performed in this patient, no recurrences were detected 3.1 years after surgery. When NAC is considered ineffective, intentional conversion to surgery should be considered.

Whether intentional bilateral dissection of LPLNs is necessary remains uncertain. Aggressive dissection of LPLNs may be omitted on the side without metastasis based on preoperative imaging studies because a national clinical trial in Japan suggested that metastatic LPLNs were observed in only 7.4% of patients on this side [76]. Hence, aggressive dissection of LPLNs was applied only on the side showing image-detected metastases. In the present study, 1 patient (5.3%) developed lymphogenic recurrence at the LPLN site without image-detected metastases before surgery. In fact, real metastases can be proven by histopathological evaluation, not by imaging study. Increasing dissection of lymph nodes may have a positive effect on prognosis [77,78]. We speculate that intentional or aggressive dissection of the bilateral LPLNs may be required in patients with LARC.

In this pilot study, the surgical duration was significantly longer in the NAC than the non-NAC group. There were no significant differences in blood loss or number of LNs harvested between the 2 groups. There are 2 possible explanations for the longer operative time in the NAC group. First, bilateral LPLN dissection was more frequently required in the NAC group. Second, dense or edematous tissues associated with NAC presented an obstacle to surgeons when attempting to identify the dissectible layers. The rates of postoperative major complications were similar between the 2 groups. No conversions to conventional open surgery occurred. The circumferential resection margin (i.e., tumor remnant) was negative in all patients. This study was designed as a comparative and retrospective study in a single institution, and our sample size was small. Also, this study was not a randomized controlled trial. Therefore, the problems of bias and potential limitation are inherent in this study. Of course, our conclusions must be interpreted with extreme caution. We believe that this pilot study suggests that laparoscopic TME with LPLN dissection for patients with LARC with metastatic LPLNs is acceptable even after NAC.

Aggressive dissection of LPLNs is a major research issue worldwide. Skillful surgeons should explore the difficult issues discussed in the present report. Our findings lead to one simple question: "Where should skillful rectocolon surgeons head in the next decade?" We consider that it is important to focus on aggressive dissection of metastatic LPLNs in patients with LARC using laparoscopy, even after NAC. We should never forget that rectocolon surgeons have a large frontier.

Conclusions

Even after NAC, laparoscopic TME with LPLN dissection is safe and feasible in patients with LARC and metastatic LPLNs, based on our own experience of 19 cases.

Conflict of interest

All authors have no conflict of interest.

References:

1. Kusters M, Slater A, Muirhead R et al: What to do with lateral nodal disease in low locally advanced rectal cancer? A call for further reflection and research. *Dis Colon Rectum*, 2017; 60: 577–85
2. Matsuoka H, Masaki T, Sugiyama M, Atomi Y: Impact of lateral pelvic lymph node dissection on evacuatory and urinary functions following low anterior resection for advanced rectal carcinoma. *Langenbecks Arch Surg*, 2005; 390: 517–22
3. Akasu T, Sugihara K, Moriya Y: Male urinary and sexual functions after mesorectal excision alone or in combination with extended lateral pelvic lymph node dissection for rectal cancer. *Ann Surg Oncol*, 2009; 16: 2779–86
4. Japanese Society for Cancer of the Colon and Rectum (Japan). *JSCCR Guidelines 2016 for the Treatment of Colorectal Cancer*. Tokyo: Kanehara, 2016
5. Watanabe T, Muro K, Ajioka Y et al: Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2016 for the treatment of colorectal cancer. *Int J Clin Oncol*, 2017 [Epub ahead of print]
6. Japanese Society for Cancer of the Colon and Rectum (Japan). *Japanese Classification of Colorectal Carcinoma*. Tokyo: Kanehara, 2013
7. Sugihara K, Kobayashi H, Kato T et al: Indication and benefit of pelvic sidewall dissection for rectal cancer. *Dis Colon Rectum*, 2006; 49: 1663–72

8. Ishihara S, Kawai K, Tanaka T et al: Oncological outcomes of lateral pelvic lymph node metastasis in rectal cancer treated with preoperative chemoradiotherapy. *Dis Colon Rectum*, 2017; 60: 469–76
9. Sauer R, Liersch T, Merkel S et al: Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: Results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J Clin Oncol*, 2012; 30: 1926–33
10. Folkesson J, Birgisson H, Pahlman L et al: Swedish Rectal Cancer Trial: Long lasting benefits from radiotherapy on survival and local recurrence rate. *J Clin Oncol*, 2005; 23: 5644–50
11. Hasegawa S, Goto S, Matsumoto T et al: A multicenter phase 2 study on the feasibility and efficacy of neoadjuvant chemotherapy without radiotherapy for locally advanced rectal cancer. *Ann Surg Oncol*, 2017; 24(12): 3587–95
12. Schrag D, Weiser MR, Goodman KA et al: Neoadjuvant chemotherapy without routine use of radiation therapy for patients with locally advanced rectal cancer: A pilot trial. *J Clin Oncol*, 2014; 32: 513–18
13. Uehara K, Hiramatsu K, Maeda A et al: Neoadjuvant oxaliplatin and capecitabine and bevacizumab without radiotherapy for poor-risk rectal cancer: N-SOG 03 Phase II trial. *Jpn J Clin Oncol*, 2013; 43: 964–71
14. Hasegawa J, Mizushima J, Mizushima T et al: Neoadjuvant capecitabine and oxaliplatin (XELOX) combined with bevacizumab for high-risk localized rectal cancer. *Cancer Chemother Pharmacol*, 2014; 73: 1079–87
15. Hojo K, Koyama Y: Postoperative follow-up studies on cancer of the colon and rectum. *Am J Surg*, 1982; 143: 293–95
16. Ogura A, Akiyoshi T, Nagasaki T et al: Feasibility of laparoscopic total mesorectal excision with extended lateral pelvic lymph node dissection for advanced lower rectal cancer after preoperative chemoradiotherapy. *World J Surg*, 2017; 41: 868–75
17. Ueno H, Mochizuki H, Hashiguchi Y et al: Potential prognostic benefit of lateral pelvic node dissection for rectal cancer located below the peritoneal reflection. *Ann Surg*, 2007; 245: 80–87
18. Moriya Y, Sugihara K, Akasu T, Fujita S: Importance of extended lymphadenectomy with lateral node dissection for advanced lower rectal cancer. *World J Surg*, 1997; 21: 728–32
19. Fujita S, Yamamoto S, Akasu T, Moriya Y: Lateral pelvic lymph node dissection for advanced lower rectal cancer. *Br J Surg*, 2003; 90: 1580–85
20. Hasegawa S, Takahashi R, Hida K et al: Revisiting the treatment strategy for rectal cancer through the pattern of local recurrence. *Eur J Surg Oncol*, 2016; 42: 1674–79
21. Clavien PA, Barkun J, de Oliveira ML et al: The Clavien-Dindo classification of surgical complications: Five-year experience. *Ann Surg*, 2009; 250: 187–96
22. Le Voyer TE, Sigurdson ER, Hanlon AL et al: Colon cancer survival is associated with increasing number of lymph nodes analyzed: A secondary survey of intergroup trial INT-0089. *J Clin Oncol*, 2003; 21: 2912–19
23. Ogino S, Noshio K, Irahara N et al: Negative lymph node count is associated with survival of colorectal cancer patients, independent of tumoral molecular alterations and lymphocytic reaction. *Am J Gastroenterol*, 2010; 105: 420–33
24. Moore J, Hyman N, Callas P, Littenberg B: Staging error does not explain the relationship between the number of lymph nodes in a colon cancer specimen and survival. *Surgery*, 2010; 147: 358–65
25. Vather R, Sammour T, Zargar-Shoshtari K et al: Lymph node examination as a predictor of long-term outcome in Dukes B colon cancer. *Int J Colorectal Dis*, 2009; 24: 283–88
26. Hida J, Yasutomi M, Maruyama T et al: Lymph node metastases detected in the mesorectum distal to carcinoma of the rectum by the clearing method: Justification of total mesorectal excision. *J Am Coll Surg*, 1997; 184: 584–88
27. Tekkis PP, Smith JJ, Heriot AG et al: A national study on lymph node retrieval in resectional surgery for colorectal cancer. *Dis Colon Rectum*, 2006; 49: 1673–83
28. Bilimoria KY, Palis B, Stewart AK et al: Impact of tumor location on nodal evaluation for colon cancer. *Dis Colon Rectum*, 2008; 51: 154–61
29. Kukreja SS, Esteban-Agusti E, Velasco JM, Hieken TJ: Increased lymph node evaluation with colorectal cancer resection: Does it improve detection of stage III disease? *Arch Surg*, 2009; 144: 612–17
30. Vather R, Sammour T, Kahokehr A et al: Lymph node evaluation and long-term survival in Stage II and Stage III colon cancer: A national study. *Ann Surg Oncol*, 2009; 16: 585–93
31. Lee S, Hofmann LJ, Davis KG, Waddell BE: Lymph node evaluation of colon cancer and its association with improved staging and survival in the Department of Defense Health Care System. *Ann Surg Oncol*, 2009; 16: 3080–86
32. Hashiguchi Y, Hase K, Ueno H et al: Prognostic significance of the number of lymph nodes examined in colon cancer surgery: Clinical application beyond simple measurement. *Ann Surg*, 2010; 251: 872–81
33. Doekhie FS, Kuppen PJ, Peeters KC et al: Prognostic relevance of occult tumour cells in lymph nodes in colorectal cancer. *Eur J Surg Oncol*, 2006; 32: 253–58
34. Chen G, McIver CM, Texler M et al: Detection of occult metastasis in lymph nodes from colorectal cancer patients: A multiple-marker reverse transcriptase-polymerase chain reaction study. *Dis Colon Rectum*, 2004; 47: 679–86
35. Rosenberg R, Friederichs J, Schuster T et al: Prognosis of patients with colorectal cancer is associated with lymph node ratio: A single-center analysis of 3,026 patients over a 25-year time period. *Ann Surg*, 2008; 248: 968–78
36. Wang J, Hassett JM, Dayton MT, Kulaylat MN: Lymph node ratio: Role in the staging of node-positive colon cancer. *Ann Surg Oncol*, 2008; 15: 1600–8
37. Vinh-Hung V, Verkooijen HM, Fioretta G et al: Lymph node ratio as an alternative to pN staging in node-positive breast cancer. *J Clin Oncol*, 2009; 27: 1062–68
38. Moug SJ, Saldanha JD, McGregor JR et al: Positive lymph node retrieval ratio optimises patient staging in colorectal cancer. *Br J Cancer*, 2009; 100: 1530–33
39. Vaccaro CA, Im V, Rossi GL et al: Lymph node ratio as prognosis factor for colon cancer treated by colorectal surgeons. *Dis Colon Rectum*, 2009; 52: 1244–50
40. Wang J, Kulaylat M, Rockette H et al: Should total number of lymph nodes be used as a quality of care measure for stage III colon cancer? *Ann Surg*, 2009; 249: 559–63
41. Huh JW, Kim YJ, Kim HR: Ratio of metastatic to resected lymph nodes as a prognostic factor in node-positive colorectal cancer. *Ann Surg Oncol*, 2010; 17: 2640–46
42. Sugihara K, Moriya Y, Akasu T, Fujita S: Pelvic autonomic nerve preservation for patients with rectal carcinoma. *Oncologic and functional outcome. Cancer*, 1996; 78: 1871–80
43. Hida J, Yasutomi M, Fujimoto K et al: Does lateral lymph node dissection improve survival in rectal carcinoma? Examination of node metastases by the clearing method. *J Am Coll Surg*, 1997; 184: 475–80
44. Di Matteo G, Mascagni D, Peparini N, Di Matteo FM: Lymphadenectomy and nerve sparing technique in radical surgery of rectal cancer. *Ann Ital Chir*, 1996; 67: 593–602
45. Ohue M, Iwasa S, Kanemitsu Y et al: A Phase II/III randomized controlled trial comparing perioperative versus postoperative chemotherapy with mFOLFOX6 for lower rectal cancer with suspected lateral pelvic node metastasis: Japan Clinical Oncology Group Study JCOG1310 (PRECIUS study). *Jpn J Clin Oncol*, 2017; 47: 84–87
46. Kim MJ, Chan Park S, Kim TH et al: Is lateral pelvic node dissection necessary after preoperative chemoradiotherapy for rectal cancer patients with initially suspected lateral pelvic node? *Surgery*, 2016; 160: 366–76
47. Akiyoshi T, Matsueda K, Hiratsuka M et al: Indications for lateral pelvic lymph node dissection based on magnetic resonance imaging before and after preoperative chemoradiotherapy in patients with advanced low-rectal cancer. *Ann Surg Oncol*, 2015; 22: S614–20
48. Funahashi K, Koike J, Shiokawa H et al: Potential tumor spread of lateral pelvic lymphatic flow in low rectal cancer. *Hepatogastroenterology*, 2014; 61: 2227–31
49. Enker WE, Pilipshen SJ, Heilweil ML et al: En bloc pelvic lymphadenectomy and sphincter preservation in the surgical management of rectal cancer. *Ann Surg*, 1986; 203: 426–33
50. Scholefield JH, Steup WH: Surgery for rectal cancer in Japan. *Lancet*, 1992; 340: 1101
51. Scholefield JH, Northover JM: Surgical management of rectal cancer. *Br J Surg*, 1995; 82: 745–48
52. Kobayashi H, Mochizuki H, Kato T et al: Outcomes of surgery alone for lower rectal cancer with and without pelvic sidewall dissection. *Dis Colon Rectum*, 2009; 52: 567–76
53. Shiozawa M, Akaike M, Yamada R et al: Lateral lymph node dissection for lower rectal cancer. *Hepatogastroenterology*, 2007; 54: 1066–70

54. Moriya Y, Hojo K, Sawada T, Koyama Y: Significance of lateral node dissection for advanced rectal carcinoma at or below the peritoneal reflection. *Dis Colon Rectum*, 1989; 32: 307-15
55. Furuhashi T, Okita K, Nishidate T et al: Clinical feasibility of laparoscopic lateral pelvic lymph node dissection following total mesorectal excision for advanced rectal cancer. *Surg Today*, 2015; 45: 310-14
56. Ueno M, Oya M, Azekura K et al: Incidence and prognostic significance of lateral lymph node metastasis in patients with advanced low rectal cancer. *Br J Surg*, 2005; 92: 756-63
57. Min BS, Kim JS, Kim NK et al: Extended lymph node dissection for rectal cancer with radiologically diagnosed extramesenteric lymph node metastasis. *Ann Surg Oncol*, 2009; 16: 3271-78
58. Watanabe T, Tsurita G, Muto T et al: Extended lymphadenectomy and preoperative radiotherapy for lower rectal cancers. *Surgery*, 2002; 132: 27-33
59. Kim JC, Takahashi K, Yu CS et al: Comparative outcome between chemoradiotherapy and lateral pelvic lymph node dissection following total mesorectal excision in rectal cancer. *Ann Surg*, 2007; 246: 754-62
60. Georgiou P, Tan E, Gouvas N et al: Extended lymphadenectomy versus conventional surgery for rectal cancer: A meta-analysis. *Lancet Oncol*, 2009; 10: 1053-62
61. Kusters M, Beets GL, van de Velde CJ et al: 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
62. Nagawa H, Muto T, Sunouchi K et al: Randomized, controlled trial of lateral node dissection vs. nerve-preserving resection in patients with rectal cancer after preoperative radiotherapy. *Dis Colon Rectum*, 2001; 44: 1274-80
63. Nagayoshi K, Ueki T, Manabe T et al: Laparoscopic lateral pelvic lymph node dissection is achievable and offers advantages as a minimally invasive surgery over the open approach. *Surg Endosc*, 2016; 30: 1938-47
64. Kennedy GD, Heise C, Rajamanickam V et al: Laparoscopy decreases postoperative complication rates after abdominal colectomy: Results from the national surgical quality improvement program. *Ann Surg*, 2009; 249: 596-601
65. Degiuli M, Mineccia M, Bertone A et al: Outcome of laparoscopic colorectal resection. *Surg Endosc*, 2004; 18: 427-32
66. Lacy AM, Garcia-Valdecasas JC, Pique JM et al: Short-term outcome analysis of a randomized study comparing laparoscopic vs. open colectomy for colon cancer. *Surg Endosc*, 1995; 9: 1101-5
67. Stage JG, Schulze S, Moller P et al: Prospective randomized study of laparoscopic versus open colonic resection for adenocarcinoma. *Br J Surg*, 1997; 84: 391-96
68. Milsom JW, Bohm B, Hammerhofer KA et al: A prospective, randomized trial comparing laparoscopic versus conventional techniques in colorectal cancer surgery: A preliminary report. *J Am Coll Surg*, 1998; 187: 46-54
69. Akiyoshi T, Nagata J, Nagasaki T et al: Laparoscopic salvage lateral pelvic lymph node dissection for locally recurrent rectal cancer. *Colorectal Dis*, 2015; 17: O213-16
70. Park JS, Choi GS, Lim KH et al: Laparoscopic extended lateral pelvic node dissection following total mesorectal excision for advanced rectal cancer: Initial clinical experience. *Surg Endosc*, 2011; 25: 3322-29
71. Liang JT: Technical feasibility of laparoscopic lateral pelvic lymph node dissection for patients with low rectal cancer after concurrent chemoradiotherapy. *Ann Surg Oncol*, 2011; 18: 153-59
72. Ishii Y, Hasegawa H, Endo T et al: Medium-term results of neoadjuvant systemic chemotherapy using irinotecan, 5-fluorouracil, and leucovorin in patients with locally advanced rectal cancer. *Eur J Surg Oncol*, 2010; 36: 1061-65
73. Ignoffo RJ: Overview of bevacizumab: A new cancer therapeutic strategy targeting vascular endothelial growth factor. *Am J Health Syst Pharm*, 2004; 61: 521-26
74. Etxano J, Insausti LP, Elizalde A et al: Analysis of the changes induced by bevacizumab using a high temporal resolution DCE-MRI as prognostic factors for response to further neoadjuvant chemotherapy. *Acta Radiol*, 2015; 56: 1300-7
75. Bose D, Meric-Bernstam F, Hofstetter W et al: Vascular endothelial growth factor targeted therapy in the perioperative setting: Implications for patient care. *Lancet Oncol*, 2010; 11: 373-82
76. Fujita S, Akasu T, Mizusawa J et al: 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
77. Isik A, Peker K, Firat D et al: Importance of metastatic lymph node ratio in non-metastatic, lymph node-invaded colon cancer: A clinical trial. *Med Sci Monit*, 2014; 20: 1369-75
78. Isik A, Okan I, Firat D et al: A new prognostic strategy for gastric carcinoma: Albumin level and metastatic lymph node ratio. *Minerva Chir*, 2014; 69: 147-53