

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2020 June 7; 26(21): 2877-2888

DOI: 10.3748/wjg.v26.i21.2877

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Observational Study Selective lateral lymph node dissection after neoadjuvant chemoradiotherapy in rectal cancer

Jia-Nan Chen, Zheng Liu, Zhi-Jie Wang, Shi-Wen Mei, Hai-Yu Shen, Juan Li, Wei Pei, Zheng Wang, Xi-Shan Wang, Jun Yu, Qian Liu

ORCID number: Jia-Nan Chen (0000-0002-6673-6884); Zheng Liu (0000-0002-8831-0761); Zhi-Jie Wang (0000-0002-930-4668); Shi-Wen Mei (0000-0002-9735-3261); Hai-Yu Shen (0000-0002-2961-5098); Juan Li (0000-0002-1839-7857); Wei Pei (0000-0002-1839-7857); Wei Pei (0000-0002-9021-7160); Xi-Shan Wang (0000-0002-1675-5083); Jun Yu (0000-0003-3435-6550); Qian Liu (0000-0003-2510-3113).

Author contributions: Chen JN and Wang ZJ designed the research; Mei SW, Shen HY, and Li J collected the data; Pei W, Wang Z, and Liu Z analyzed the data; Chen JN drafted the article; Liu Q, Yu J, and Wang XS revised the paper.

Supported by the Medicine and Health Technology Innovation Project of Chinese Academy of Medical Sciences, No. 2017-12M-1-006; and China Scholarship Council, No. CSC201906210471.

Institutional review board

statement: The study was reviewed and approved by the Institutional Review Board of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College.

Informed consent statement: All patients signed informed consent forms.

Conflict-of-interest statement: The authors declare there is no conflict of interest in regard to this research.

Jia-Nan Chen, Zheng Liu, Zhi-Jie Wang, Shi-Wen Mei, Hai-Yu Shen, Juan Li, Wei Pei, Zheng Wang, Xi-Shan Wang, Qian Liu, Department of Colorectal Surgery, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union College, Beijing 100021, China

Jun Yu, Departments of Surgery, the Johns Hopkins University School of Medicine, Baltimore, MD 21218, United States

Corresponding author: Qian Liu, MD, Chief Doctor, Professor, Surgeon, Department of Colorectal Surgery, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 17 Panjiayuan Nanli, Chaoyang District, Beijing 100021, China. fcwpumch@163.com

Abstract

BACKGROUND

Lateral lymph node metastasis is one of the leading causes of local recurrence in patients with advanced mid or low rectal cancer. Neoadjuvant chemoradiotherapy (NCRT) can effectively reduce the postoperative recurrence rate; thus, NCRT with total mesorectal excision (TME) is the most widely accepted standard of care for rectal cancer. The addition of lateral lymph node dissection (LLND) after NCRT remains a controversial topic.

AIM

To investigate the surgical outcomes of TME plus LLND, and the possible risk factors for lateral lymph node metastasis after NCRT.

METHODS

This retrospective study reviewed 89 consecutive patients with clinical stage II-III mid or low rectal cancer who underwent TME and LLND from June 2016 to October 2018. In the NCRT group, TME plus LLND was performed in patients with short axis (SA) of the lateral lymph node greater than 5 mm. In the non-NCRT group, TME plus LLND was performed in patients with SA of the lateral lymph node greater than 10 mm. Data regarding patient demographics, clinical workup, surgical procedure, complications, and outcomes were collected. Multivariate logistic regression analysis was performed to evaluate the possible risk factors for lateral lymph node metastasis in NCRT patients.

RESULTS

LLN metastasis was pathologically confirmed in 35 patients (39.3%): 26 (41.3%) in



WJG https://www.wjgnet.com

Data sharing statement: No additional data are available.

STROBE statement: The authors have carefully read the STROBE statement checklist of items and prepared the manuscript based on the requirements of the STROBE statement checklist of items.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licen

ses/by-nc/4.0/
Manuscript source: Unsolicited

manuscript source: Unsolicited manuscript

Received: January 7, 2020 Peer-review started: January 7, 2020

First decision: February 19, 2020 Revised: April 17, 2020 Accepted: April 28, 2020 Article in press: April 28, 2020 Published online: June 7, 2020

P-Reviewer: Antolino L, Rim CH, Silecchia G S-Editor: Dou Y L-Editor: Filipodia E-Editor: Ma YJ



the NCRT group and 9 (34.6%) in the non-NCRT group. The most common site of metastasis was around the obturator nerve (21/35) followed by the internal iliac artery region (12/35). In the NCRT patients, 46% of patients with SA of LLN greater than 7 mm were positive. The postoperative 30-d mortality rate was 0%. Two (2.2%) patients suffered from lateral local recurrence in the 2-year follow up. Multivariate analysis showed that cT4 stage (odds ratio [OR] = 5.124, 95% confidence interval [CI]: 1.419-18.508; *P* = 0.013), poor differentiation type (OR = 4.014, 95% CI: 1.038-15.520; *P* = 0.044), and SA \geq 7 mm (OR = 7.539, 95% CI: 1.487-38.214; *P* = 0.015) were statistically significant risk factors associated with LLN metastasis.

CONCLUSION

NCRT is not sufficient as a stand-alone therapy to eradicate LLN metastasis in lower rectal cancer patients and surgeons should consider performing selective LLND in patients with greater LLN SA diameter, poorer histological differentiation, or advanced T stage. Selective LLND for NCRT patients can have a favorable oncological outcome.

Key words: Rectal neoplasms; Neoadjuvant therapies; Lateral lymph node dissection; Locoregional recurrence; Lymphatic metastasis; Total mesorectal excision

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Lateral lymph node metastasis is one of the leading causes of local recurrence in patients with advanced mid or low rectal cancer. Lateral local recurrence remains a significant clinical problem associated with severe morbidity and low salvage likelihood. There is an East (mainly Japan)-West divide regarding the management of lateral lymph nodes associated with lower rectal cancer. Preoperative chemoradiotherapy followed by total mesorectal excision is a standard procedure in the west. Our study shows that lateral lymph node metastasis cannot be eradicated by neoadjuvant chemoradiotherapy. Selective total mesorectal excision plus lateral lymph node dissection should be performed in advanced mid or low rectal cancer patients.

Citation: Chen JN, Liu Z, Wang ZJ, Mei SW, Shen HY, Li J, Pei W, Wang Z, Wang XS, Yu J, Liu Q. Selective lateral lymph node dissection after neoadjuvant chemoradiotherapy in rectal cancer. *World J Gastroenterol* 2020; 26(21): 2877-2888 **URL**: https://www.wjgnet.com/1007-9327/full/v26/i21/2877.htm **DOI**: https://dx.doi.org/10.3748/wjg.v26.i21.2877

INTRODUCTION

Lateral lymph node metastasis in mid and low rectal cancer was first described in 1895 by Gerota^[1] using dye injection. Since then, many anatomical and pathological studies have divided the rectal lymphatic drainage into three main directions: Upward, lateral, and downward. Among them, lateral lymphatic drainage nodes comprise an important rectal approach below the peritoneal reflection^[2-4]. According to the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma: The 3rd English Edition, lateral lymph nodes are two groups of lymph nodes: One group along the internal iliac arteries and the obturator vessels and nerves, and the other along the common iliac, external iliac, and median sacral arteries^[5]. The incidence of lateral lymph node metastasis from lower rectal cancer is about 15%^[6], whereas the incidence of lateral lymph node metastasis in T3 and T4 patients is reported in more than 20% of cases^[7,8]. Local recurrence of rectal cancer, specifically lateral local recurrence, remains a significant clinical problem associated with severe morbidity, low salvage likelihood, and eventual death in the majority of patients^[9]. There is a lack of consensus leading to an East (mainly Japan)-West division concerning the management of lateral lymph nodes associated with lower rectal cancer. In western practice, patients with locally advanced (stage II-III) rectal cancer are treated with neoadjuvant chemoradiotherapy (NCRT) and total mesorectal excision (TME) as the standard. This is based on the interpretation that lymph node involvement is considered a systemic disease^[10]. Furthermore, lateral lymph node dissection (LLND)



« WJG | https://www.wjgnet.com

inevitably results in a longer operative time and increased blood loss compared to TME alone. The adoption of NCRT followed by TME has demonstrated increased local control resulting in local recurrence in less than 10% of cases^[11]. On the other hand, the Japanese Society for Cancer of the Colon and Rectum cites different guidelines for the treatment of rectal cancer and recommends LLND for advanced rectal cancer that extends below the peritoneal reflection to address the possibility of LLN metastasis^[12]. Several studies from Japan argue that LLN metastasis should be considered a local disease rather than systemic disease, and that LLND can significantly reduce local recurrence rates^[6,13]. In recent years, a growing body of evidence has supported conflicting standard strategies in both Japan and Western countries, culminating in similar local recurrence rates^[14]. Recent studies have suggested that perhaps a middle-ground selective LLND should be considered after preoperative chemoradiotherapy based on magnetic resonance imaging/computed tomography (MRI/CT) findings^[15,16].

In China, preoperative chemoradiotherapy followed by TME is still the standard of care, as most surgeons do not perform an LLND most commonly citing extended operative time and potential nerve damage as the reason. We collected data from 89 consecutive patients with mid or low rectal cancer who underwent TME plus LLND in this study to investigate the therapeutic effect of preoperative CRT on LLN metastasis and identify the associated risk factors.

MATERIALS AND METHODS

Patients

The study was approved by the ethics committee of the National Cancer Center and conformed to the ethical standards of the World Medical Association Declaration of Helsinki. All patients signed an informed consent form. A total of 89 mid or low rectal cancer patients who underwent TME plus LLND at the National Cancer Center/National Sciences Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College from June 2016 to October 2018 were consecutively collected in this study. The inclusion criteria of this study were as follows: (1) Histologically confirmed adenocarcinoma of the middle or low rectum (the distal verge of the tumor located below the peritoneal reflection); (2) All patients were confirmed to have clinical tumor-node-metastasis stage II-III by MRI/CT at the time of diagnosis; and (3) All patients underwent TME plus LLND. Patients with distant metastasis were excluded.

Treatment strategy

Treatment strategies for each patient were determined by a multidisciplinary meeting and the patient's wishes. In the NCRT group, patients received short-course radiotherapy for a total dose of 25 Gy or received 5-fluorouracil-based NCRT, with a total dose of 45 Gy or 50.4 Gy before surgery. Both the obturator and internal iliac compartments were included in the standard radiation field. MRI after 4 wk of NCRT were done to evaluate swollen lymph nodes. Patients with swollen lymph nodes with an SA \geq 5 mm underwent LLND plus TME. The operation was carried out within 1 wk after short-course radiotherapy or 8 wk after the end of a long-course NCRT. For patients without NCRT, if the lateral swollen lymph nodes with an SA \geq 10 mm, TME plus LLND were performed.

All patients were placed in the modified lithotomy position after anesthesia. They all underwent TME with LLND. The pelvic peritoneum was opened, and the hypogastric nerves were identified and preserved. LLND included six regions: Common iliac, internal iliac, external iliac node, obturator, aortic bifurcation, and median sacral regions^[17]. Typically, the external iliac node and median sacral region are not dissected because of a low metastatic incidence. The probability of bilateral lymph node metastasis is extremely low and results in a significantly higher postoperative complication rate, longer operation time, and more bleeding. Thus, bilateral lymph node dissection is not routinely performed unless the MRI/CT strongly suggests bilateral lymph node involvement^[18-20].

Pathological diagnosis

After resection of the surgical specimens, LLNs are separated according to the anatomical position, fixed in formalin, and sent for pathological examination. The tumor stage was decided by professional pathologists according to the 7th and 8th edition of the American Joint Committee on Cancer.

Statistical analysis

The Statistical Package for the Social Sciences version 21.0 for Windows (IBM Corp,



« WJG https://www.wjgnet.com

Armonk, NY, United States) was used for data analyses. Quantitative data are shown as the mean ± standard deviation and were analyzed by a *t*-test. Categorical data are shown as frequencies and percentages and were analyzed by the χ^2 or Fisher's exact test as appropriate. Univariate logistic regression analysis was used to evaluate the association between lateral lymph node metastasis and various parameters. Multivariate logistic regression analysis was performed to examine the predictors of lateral lymph node metastasis to calculate the 95% confidence intervals (CIs) for each risk factor, and differences were considered statistically significant when *P* < 0.05. The data were statistically reviewed by a biomedical statistician from the National Cancer Center.

RESULTS

The demographics of 89 rectal cancer patients treated with TME plus LLND at the National Cancer Center/Chinese Academy of Medical Sciences are summarized in Table 1. Clinical T3 and T4 rectal cancer accounted for 60.7% and 39.3% of the cases, respectively, and clinical N1 and N2 stage accounted for 56.2% and 43.8%, respectively. Among the 89 patients, 63 received neoadjuvant therapy. Of those, three received short-course radiotherapy (25 Gy administered doses of 5 Gy over 5 d) and underwent TME plus LLND within 1 wk. Sixty patients received 5-fluorouracil-based long-course NCRT (45-50.4 Gy administered in 25-28 fractions), and then surgery after an 8-wk interval. Twenty-six patients were treated with TME plus LLND directly without receiving any NCRT. Table 2 shows the surgery-related data. Two patients initially received laparoscopic surgery that was subsequently converted to open surgery, while the others underwent a laparoscopic TME plus LLND. Low anterior resection was done in 44 (49.4%) patients. Unilateral and bilateral LLNDs were performed in 76 (85.4%) and 13 (14.6%) patients, respectively. Nine (10.1%) patients received a temporary ileum stoma during the surgery.

Fifteen patients (16.8%) had postoperative complications reported after LLND (Table 3). According to the Clavien-Dindo classification^[21], most of the patients developed to Grade II or Grade III complications, there were no grade IV or grade V postoperative complications. Four (4.5%) patients suffered an anastomotic leakage, three of which received an ileostomy while the fourth recovered after conservative treatment. Two (15.4%) of thirteen bilateral LLND patients were discharged from the hospital with an indwelling catheter due to urinary retention. In both cases, after 4 wk of bladder training, the catheter was successfully removed. Tissue liquefaction occurred in three (3.4%) patients, after a careful dressing change, and the wound finally healed well. Four (4.5%) patients had small bowel obstruction, and they all recovered with conservative medical treatment.

The median follow-up duration was 24.5 mo (range 6-38 mo). During follow-up, mortality occurred in 8 (9.0%) patients due to distant metastasis and the 2-year disease-free survival was 80.9%. Two (2.2%) patients suffered lateral local recurrence during follow-up and both underwent unilateral LLND.

Table 4 describes the pathological outcomes. Thirty-five (39.3%) patients were pathologically confirmed with lateral lymph node metastasis. Of these, 26 (41.3%, 26/63) patients received NCRT before surgery, while 9 (34.6%, 9/26) did not receive NCRT. Moreover, the pathological results revealed that the obturator region was the location with the highest lymph node metastasis involvement, accounting for 60.0% in the 35 patients. Twelve (34.3%) cases of LLNs metastasis were in the internal iliac region and two (5.7%) were located at the bifurcation of the abdominal aorta. An R0 margin status was observed in 87 (97.8%) cases, while the other 2 patients had a positive circumferential resection margin.

Table 5 depicts an LLN metastatic rate for different cutoff values along the short axis (SA) in patients who received preoperative (chemo)radiotherapy. Patients with a SA of LLN \geq 10 mm after NCRT had the highest positive LLN metastasis rate (51.9%). The pathological positive rates of the SA of 5-7 mm and 7-10 mm were 23.1% and 39.1%, respectively.

Table 6 summarizes the univariate analysis, which revealed that the clinical T stage (P = 0.003), histological type (P = 0.183), and the SA diameter of LLN after NCRT (P = 0.135) were candidate variables that may be associated with LLN metastasis. After multivariate analysis, clinical T4 stage (95% CI: 1.419-18.508; P = 0.013), poor histological type (95% CI: 1.038-15.520; P = 0.044), and SA diameter of LLN after NCRT (95% CI: 1.487-38.214; P = 0.015) were independent risk factors associated with LLN metastasis.

, ideng® WJG https://www.wjgnet.com

Variables	Value
Gender, n (%)	
Male	51 (57.3)
Female	38 (42.7)
Age in yr, mean ± SD	54.4 ± 10.1
BMI in kg/m ² , mean \pm SD	24.9 ± 4.6
ASA score, n (%)	
ASA I	13 (14.6)
ASA II	56 (62.9)
ASA III	20 (22.5)
cT stage	
cT3	54 (60.7)
cT4	35 (39.3)
cN stage	
N1	50 (56.2)
N2	39 (43.8)
Neoadjuvant chemoradiotherapy	
No	26 (29.2)
Short-course radiotherapy	3 (3.4)
Long-course radiotherapy + chemotherapy	60 (67.4)

ASA: American Society of Anesthesiologists; BMI: Body mass index; SD: Standard deviation.

DISCUSSION

This study supports the importance of selective LLND after preoperative chemoradiotherapy. Clinical T4 stage, poor histological type, and an SA diameter of LLNs \geq 7 mm after NCRT were independent and significant risk factors associated with LLNs metastasis in patients with advanced mid or low rectal cancer treated with NCRT. Since the LLN metastatic rate in NCRT patients can be as high as 41.3%, we suggest that selective LLND be performed.

It has been reported that LLN metastasis occurs in 10%-25% of all mid or low rectal cancer patients who did not receive preoperative chemoradiotherapy treatment^[8,22,23]. Fujita *et al*^[6] suggested that the incidences of local recurrence in patients without</sup>NCRT were 7% and 13% after TME plus LLND or TME alone, respectively. The European MERCURY Study Group similarly reported that 11.7% of rectal cancer patients suffer from LLN metastasis^[24]. Still, in western surgical practice, it remains uncommon to perform an LLND in advanced rectal cancer patients as preoperative CRT and TME is the standard protocol^[25]. The addition of NCRT has decreased 5-year local recurrence rates from > 25% to approximately 5% to $10\%^{[26]}$. Yet, a study in South Korea enrolled 366 patients with advanced rectal tumor and showed that TME following preoperative CRT is not enough to control LLNs metastasis. The reported incidence of LLNs metastasis was 12.5% in patients with lymph node SA of 5-9.9 mm and 68.8% in patients with an SA \geq 10 mm. The LLNs accounted for 82.7% of all local recurrences^[27]. Oh et al^[28] published a multicenter retrospective cohort study that included 36 patients with lateral lymph nodes greater than 5 mm after NCRT. All patients received LLND and the pathological results showed 22 (61.1%) patients had LLNs metastasis. These findings indicate that NCRT plus TME or TME plus LLND alone is not sufficient to eradicate LLN metastasis, and LLND should be considered if LLN metastasis is suspected even after chemoradiotherapy. Our data show that the incidence of LLNs metastasis in NCRT patients with SA \geq 5 mm is 41.3% (26 of 63) and 51.9% (14 of 27) in patients with lymph nodes SA \geq 10 mm. If these pathological metastases had not been removed by LLND, they may subsequently lead to local recurrence^[29]. In the 2-year follow-up period, 2 (2.2%) patients developed local recurrence. Thus, our results suggest that there is an oncological benefit when performing LLND for patients with clinically suspected LLN metastasis after preoperative CRT^[29]. In addition, in the present study, after LLND 80.9% of patients did not have a systemic recurrence. Therefore, we believe that LLN metastasis can be regarded as a locoregional disease rather than a systemic one^[30].

Laparoscopic LLND for rectal cancer patients after NCRT is a challenging

« WJG https://www.wjgnet.com

Table 2 Surgery-related data			
Variables	Value		
Type of operation, <i>n</i> (%)			
Low anterior resection	44 (49.4)		
Intersphincteric resection	2 (2.2)		
Hartmann's procedure	6 (6.7)		
Abdominoperineal resection	37 (41.6)		
Conversion to open, <i>n</i> (%)	2 (2.2)		
Operation time in min, mean ± SD	290.7 ± 89.5		
Estimated blood loss in mL, mean ± SD	79.2 ± 146.7		
Temporary stoma, n (%)	9 (10.1)		
Type of LLND, <i>n</i> (%)			
Unilateral	76 (85.4)		
Bilateral	13 (14.6)		
Hospital stay after operation (d, mean \pm SD)	8.5 ± 4.2		
30 d post-operative mortality, <i>n</i> (%)	0		
2-yr lateral local recurrence, n (%)	2 (2.2)		
2-yr disease-free survival	80.90%		
2-yr overall survival	91.00%		

LLND: Lateral lymph node dissection; SD: Standard deviation.

procedure because of the complicated anatomy of the pelvic sidewall. The JCOG0212 study showed that the operation time was significantly longer in the TME + LLND group compared with the TME alone group (360 min *vs* 254 min, *P* < 0.0001), and also blood loss was significantly higher in the TME + LLND group (576 mL *vs* 337 mL, *P* < 0.0001). In addition, the overall postoperative complication in the LLND + TME group was higher than that in the TME alone group, but without statistical difference (22% *vs* 16%, *P* = 0.007)^[31]. In our study, the most common postoperative complications were anastomotic leakage (4.5%) and bowel obstruction (4.5%), and the overall postoperative complication rate was 16.8%, similar to a previously reported study (18%-38%)^[32].

Some studies have pointed out that longer operative time and increased blood loss may increase the postoperative complication rate and thus the criteria for selecting patients for LLND is crucial^[6]. Several studies have suggested that LLN size after NCRT is a powerful indicator of pathological LLNs metastasis. The European Society of Gastrointestinal and Abdominal Radiology recommended that size (SA diameter) is a reliable criterion for lymph node staging after neoadjuvant treatment, and should remain the prime criterion for malignancy in that location^[33]. Akiyoshi *et al*^[34] analyzed the data of 77 patients with advanced low rectal cancer and suspected LLNs involvement were undergone NCRT and LLND. LLNs metastasis was confirmed in 40.3% of patients. They showed that LLN metastasis was significantly higher in patients with LLN SA > 5 mm. Oh *et al*^[28] as previously described, demonstrated that an LLN greater than 5 mm on post-NCRT MRI was significantly associated with residual tumor metastasis as 61.1% (22 of 36) of patients were found to be pathologically positive. This was comparable to the 41.2% positive rate found in our center where the criteria for LLND if the SA of LLNs greater than 5 mm after NCRT or greater than 10 mm without NCRT. Furthermore, we performed receiver operating characteristic analysis for the sizes of dissected LLNs, and the area under the curve value was 0.686 for the prediction of pathological metastasis (data not shown), which was regarded as low accuracy. In order to identify risk factors correlated with LLN metastasis after CRT, we performed multivariate analysis that revealed that clinical T4 stage (95% CI: 1.419-18.508; *P* = 0.013), poor histological type (95% CI: 1.038-15.520; *P* = 0.044), and SA diameter of LLN after NCRT ≥ 7 mm (95%CI: 1.487-38.214; *P* = 0.015) were independently associated with LLN metastasis.

The performance of TME plus LLND dates back to the 1970s when it was associated with favorable oncological results, but had a high urinary and sexual dysfunction rate^[35,36]. To preserve the function of the autonomic nerves, nerve-preserving LLND was developed in the mid-1980s in order to obtain local control with an acceptable quality of life^[37]. Georgiou *et al*^[38] conducted a meta-analysis investigating the outcomes of an extended lymphadenectomy *versus* conventional surgery for rectal

ور» WJG https://www.wjgnet.com

Table 3 Postoperative complications, n = 89			
Variables	Value, <i>n</i> (%)		
Anastomotic leakage	4 (4.5)		
Urinary retention	2 (2.2)		
Wound infection	3 (3.4)		
Bowel obstruction	4 (4.5)		
Lymphatic leakage	1 (1.1)		
Pelvic hemorrhage	1 (1.1)		

cancer. Their results suggested that LLND was associated with increased urinary and sexual dysfunction incidence, as one of its included studies suggested that the urinary retention happened in the LLND + TME and TME along group were 16% and 4%, respectively. However, many of the retrospective studies included did not perform nerve-preservation surgeries. The Japanese Research Committee for Colorectal Cancer has emphasized that an autonomic nerve-preserving technique results in better urinary and sexual function^[17]. JCOG0212 was the largest randomized clinical trial that has compared postoperative urinary and sexual dysfunction between TME and TME plus LLND in lower rectal cancer patients. They suggested that blood loss was the only independent predictor of early urinary dysfunction and that LLND did not increase sexual dysfunction incidence after rectal cancer surgery. Sexual dysfunction was independently associated with increased age^[39,40]. In our study, 2 (2.2%) patients experienced urinary retention, both received bilateral lymph node metastasis and after 4 wk of bladder practice, their catheters were successfully removed. These acceptable functional results might be explained by the relatively mature nervepreserving techniques in the laparoscopic rectal cancer surgeries. Longer operative time and increased blood loss may associate with higher postoperative complication rates according to some study results^[41,42]. Thus, we do not recommend routine bilateral lymph nodes dissection unless there is strong suspicion of bilateral LLNs metastasis^[6].

This study had several limitations. First, it was a single-center retrospective analysis and the sample size was relatively small; thus, a multi-center study should be conducted to confirm our conclusions. Additionally, we did not evaluate lateral lymph nodes metastasis in non-NCRT patients due to the small sample size. Next, the rectal cancer patients received either short-course or long-course radiotherapy, which might have caused heterogeneity in the pathological outcomes of the lateral lymph nodes. Third, the follow-up duration was short, because of the low local recurrence rate after NCRT, so longer follow-up may be necessary to evaluate more recurrences. Fourth, we did not study the effect of LLND on sexual functions because of poor medical records.

In conclusion, the present study showed that LLN metastasis cannot eradicate by NCRT and that selective TME plus LLND should be considered in mid or low rectal cancer patients. Our results showed satisfying perioperative and oncological outcomes.



Table 4 Pathological outcomes			
Variables	Value		
Tumor size in cm, mean ± SD	4.9 ± 2.3		
Differentiation degree, n (%)			
Poor	28 (31.5)		
Moderate/well	61 (68.5)		
Pathological LLN metastasis, n (%)			
With NCRT	26 (41.3)		
Without NCRT	9 (34.6)		
Position of metastasis, <i>n</i> (%)			
Internal iliac	12 (34.3)		
Obturator	21 (60.0)		
Bifurcation of abdominal aorta	2 (5.7)		
R status, n (%)			
R0	87 (97.8)		
R1	2 (2.2)		

LLN: Lateral lymph node; NRCT: Neoadjuvant chemoradiotherapy; SD: Standard deviation.

Table 5 Lateral lymph node metastatic rate for different cutoff values in short-axis in patients who received (chemo)radiotherapy, <i>n</i> = 63					
Variables	Positive, <i>n</i> = 26	Negative, <i>n</i> = 37	P value		
SA 5-7 mm, n (%)	3 (23.1)	10 (76.9)	0.216		
SA 7-10 mm, n (%)	9 (39.1)	14 (60.9)			
$SA \ge 10 \text{ mm}, n (\%)$	14 (51.9)	13 (48.1)			

SA: Short-axis.



Table 6 Risk factors for pathological lateral lymph node metastasis after neoadjuvant chemoradiotherapy, n = 63

Variables	Univariate analysis	Multivariate analysis	
	<i>P</i> value	95%CI	<i>P</i> value
Sex	0.259	0.184-2.697	0.609
Male			
Female			
Age	0.987	0.242-3.269	0.889
≥ 60			
< 60			
cT stage	0.003	1.419-18.508	0.013
cT3			
cT4			
Histological type	0.183	1.038-15.520	0.044
Poor			
Moderate/well			
Short-axis	0.135	1.487-38.214	0.015
5-7 mm			
≥7 mm			
Mixed signal intensity of LLN	0.739	0.342-4.894	0.705
Yes			
No			
Border irregularity of LLN	0.315	0.119-1.675	0.232
Yes			
No			

LLN: Lateral lymph node.

ARTICLE HIGHLIGHTS

Research background

Lateral lymph node metastasis is one of the leading causes for local recurrence in patients with advanced mid or low rectal cancer. The addition of lateral lymph node dissection (LLND) after neoadjuvant chemoradiotherapy (NCRT) remains a controversial topic.

Research motivation

There is a lack of consensus leading to an East (mainly Japan)-West division concerning the management of lateral lymph nodes after NCRT associated with lower rectal cancer. There are few data regarding surgical outcomes of total mesorectal excision (TME) plus LLND after NCRT.

Research objectives

The main aim of this study was to investigate the surgical outcomes of TME plus LLND, and the possible risk factors for lateral lymph node metastasis after NCRT.

Research methods

We performed an observational study and enrolled patients who underwent TME plus LLND. Information regarding the clinicopathologic features and clinical outcomes was collected and analyzed. Multivariate logistic regression analysis was performed to evaluate the possible risk factors for lateral lymph node metastasis in the NCRT patients.

Research results

Lateral lymph node metastasis can be found in lower rectal cancer patients with enlarged lymph node size. Advanced T stage, poor differentiation type, and short axis \geq 7 mm were statistically significant risk factors associated with LLN metastasis.

Research conclusions

Preoperative chemoradiotherapy is not sufficient as a stand-alone therapy to eradicate LLN metastasis in lower rectal cancer patients and surgeons should consider performing selective LLND in patients with greater lateral lymph node short axis diameter, poorer histological differentiation or advanced T stage. Selective LLND for NCRT patients can have a favorable oncological outcome.

aishideng[®] WJG | https://www.wjgnet.com

Research perspectives

Larger prospective multicenter clinal studies need to be performed so that standard managements regarding lateral lymph nodes in rectal cancer can be established.

REFERENCES

- 1 Gerota D. Die Lymphgefaesse des Rektums und Anus. Arch Anat Physiol 1895; 240-256
- 2 Sauer I, Bacon HE. A new approach for excision of carcinoma of the lower portion of the rectum and anal canal. *Surg Gynecol Obstet* 1952; **95**: 229-242 [PMID: 14950656]
- 3 Blair JB, Holyoke EA, Best RR. A note on the lymphatics of the middle and lower rectum and anus. Anat Rec 1950; 108: 635-644 [PMID: 14799884 DOI: 10.1002/ar.1091080402]
- 4 Stearns MW, Deddish MR. Five-year results of abdominopelvic lymph node dissection for carcinoma of the rectum. *Dis Colon Rectum* 1959; 2: 169-172 [PMID: 13652786 DOI: 10.1007/bf02616711]
- 5 Japanese Society for Cancer of the Colon and Rectum. Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma: the 3d English Edition [Secondary Publication]. J Anus Rectum Colon 2019; 3: 175-195 [PMID: 31768468 DOI: 10.23922/jarc.2019-018]
- Fujita S, Akasu T, Mizusawa J, Saito N, Kinugasa Y, Kanemitsu Y, Ohue M, Fujii S, Shiozawa M, Yamaguchi T, Moriya 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: 616-621 [PMID: 22591948 DOI: 10.1016/S1470-2045(12)70158-4]
- 7 Yano H, Moran BJ. The incidence of lateral pelvic side-wall nodal involvement in low rectal cancer may be similar in Japan and the West. Br J Surg 2008; 95: 33-49 [PMID: 18165939 DOI: 10.1002/bjs.6061]
- 8 Ueno M, Oya M, Azekura K, Yamaguchi T, Muto T. Incidence and prognostic significance of lateral lymph node metastasis in patients with advanced low rectal cancer. *Br J Surg* 2005; 92: 756-763 [PMID: 15838895 DOI: 10.1002/bis.4975]
- 9 Harris CA, Solomon MJ, Heriot AG, Sagar PM, Tekkis PP, Dixon L, Pascoe R, Dobbs BR, Frampton CM, Harji DP, Kontovounisios C, Austin KK, Koh CE, Lee PJ, Lynch AC, Warrier SK, Frizelle FA. The Outcomes and Patterns of Treatment Failure After Surgery for Locally Recurrent Rectal Cancer. *Ann Surg* 2016; 264: 323-329 [PMID: 26692078 DOI: 10.1097/SLA.000000000001524]
- 10 Georgiou P, Tan E, Gouvas N, Antoniou A, Brown G, Nicholls RJ, Tekkis P. Extended lymphadenectomy versus conventional surgery for rectal cancer: a meta-analysis. *Lancet Oncol* 2009; 10: 1053-1062 [PMID: 19767239 DOI: 10.1016/S1470-2045(09)70224-4]
- 11 Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, Martus P, Tschmelitsch J, Hager E, Hess CF, Karstens JH, Liersch T, Schmidberger H, Raab R; German Rectal Cancer Study Group. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004; **351**: 1731-1740 [PMID: 15496622 DOI: 10.1056/NEJMoa040694]
- 12 Watanabe T, Itabashi M, Shimada Y, Tanaka S, Ito Y, Ajioka Y, Hamaguchi T, Hyodo I, Igarashi M, Ishida H, Ishiguro M, Kanemitsu Y, Kokudo N, Muro K, Ochiai A, Oguchi M, Ohkura Y, Saito Y, Sakai Y, Ueno H, Yoshino T, Fujimori T, Koinuma N, Morita T, Nishimura G, Sakata Y, Takahashi K, Takiuchi H, Tsuruta O, Yamaguchi T, Yoshida M, Yamaguchi N, Kotake K, Sugihara K; Japanese Society for Cancer of the Colon and Rectum. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2010 for the treatment of colorectal cancer. *Int J Clin Oncol* 2012; 17: 1-29 [PMID: 22002491 DOI: 10.1007/s10147-011-0315-2]
- 13 Akiyoshi T, Watanabe T, Miyata S, Kotake K, Muto T, Sugihara K; Japanese Society for Cancer of the Colon and Rectum. Results of a Japanese nationwide multi-institutional study on lateral pelvic lymph node metastasis in low rectal cancer: is it regional or distant disease? *Ann Surg* 2012; 255: 1129-1134 [PMID: 22549752 DOI: 10.1097/SLA.0b013e3182565d9d]
- 14 Kusters M, Beets GL, 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: 229-235 [PMID: 19212175 DOI: 10.1097/SLA.0b013e318190a664]
- 15 Ishihara S, Kawai K, Tanaka T, Kiyomatsu T, Hata K, Nozawa H, Morikawa T, Watanabe T. Oncological Outcomes of Lateral Pelvic Lymph Node Metastasis in Rectal Cancer Treated With Preoperative Chemoradiotherapy. *Dis Colon Rectum* 2017; 60: 469-476 [PMID: 28383446 DOI: 10.1097/DCR.000000000000752]
- 16 Kim MJ, Kim TH, Kim DY, Kim SY, Baek JY, Chang HJ, Park SC, Park JW, Oh JH. Can chemoradiation allow for omission of lateral pelvic node dissection for locally advanced rectal cancer? J Surg Oncol 2015; 111: 459-464 [PMID: 25559888 DOI: 10.1002/jso.23852]
- 17 Watanabe T, Muro K, Ajioka Y, Hashiguchi Y, Ito Y, Saito Y, Hamaguchi T, Ishida H, Ishiguro M, Ishihara S, Kanemitsu Y, Kawano H, Kinugasa Y, Kokudo N, Murofushi K, Nakajima T, Oka S, Sakai Y, Tsuji A, Uehara K, Ueno H, Yamazaki K, Yoshida M, Yoshino T, Boku N, Fujimori T, Itabashi M, Koinuma N, Morita T, Nishimura G, Sakata Y, Shimada Y, Takahashi K, Tanaka S, Tsuruta O, Yamaguchi T, Yamaguchi N, Tanaka T, Kotake K, Sugihara K; Japanese Society for Cancer of the Colon and Rectum. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2016 for the treatment of colorectal cancer. *Int J Clin Oncol* 2018; 23: 1-34 [PMID: 28349281 DOI: 10.1007/s10147-017-1101-6]
- 18 Kim DJ, Chung JJ, Yu JS, Cho ES, Kim JH. Evaluation of lateral pelvic nodes in patients with advanced rectal cancer. *AJR Am J Roentgenol* 2014; 202: 1245-1255 [PMID: 24848821 DOI: 10.2214/AIR 13.11228]
- 19 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: 2779-2786 [PMID: 19626377 DOI: 10.1245/s10434-009-0546-x]
- 20 Kanemitsu Y, Komori K, Shida D, Ochiai H, Tsukamoto S, Kinoshita T, Moriya Y. Potential impact of lateral lymph node dissection (LLND) for low rectal cancer on prognoses and local control: A comparison of 2 high-volume centers in Japan that employ different policies concerning LLND. *Surgery* 2017; 162: 303-314 [PMID: 28366499 DOI: 10.1016/j.surg.2017.02.005]



- 21 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; 240: 205-213 [PMID: 15273542 DOI: 10.1097/01.sla.0000133083.54934.ae]
- 22 Shimoyama M, Yamazaki T, Suda T, Hatakeyama K. Prognostic significance of lateral lymph node micrometastases in lower rectal cancer: an immunohistochemical study with CAM5.2. *Dis Colon Rectum* 2003; 46: 333-339 [PMID: 12626908 DOI: 10.1007/s10350-004-6552-y]
- 23 Hida J, Yasutomi M, Fujimoto K, Maruyama T, Okuno K, Shindo K. Does lateral lymph node dissection improve survival in rectal carcinoma? Examination of node metastases by the clearing method. J Am Coll Surg 1997; 184: 475-480 [PMID: 9145067]
- 24 MERCURY Study Group. Shihab OC, Taylor F, Bees N, Blake H, Jeyadevan N, Bleehen R, Blomqvist L, Creagh M, George C, Guthrie A, Massouh H, Peppercorn D, Moran BJ, Heald RJ, Quirke P, Tekkis P, Brown G. Relevance of magnetic resonance imaging-detected pelvic sidewall lymph node involvement in rectal cancer. *Br J Surg* 2011; **98**: 1798-1804 [PMID: 21928408 DOI: 10.1002/bjs.7662]
- 25 Smith JJ, Garcia-Aguilar J. Advances and challenges in treatment of locally advanced rectal cancer. J Clin Oncol 2015; 33: 1797-1808 [PMID: 25918296 DOI: 10.1200/JCO.2014.60.1054]
- 26 Ludmir EB, Palta M, Willett CG, Czito BG. Total neoadjuvant therapy for rectal cancer: An emerging option. Cancer 2017; 123: 1497-1506 [PMID: 28295220 DOI: 10.1002/cncr.30600]
- 27 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 preoperative chemoradiotherapy and curative resection. *Ann Surg Oncol* 2008; 15: 729-737 [PMID: 18057989 DOI: 10.1245/s10434-007-9696-x]
- 28 Oh HK, Kang SB, Lee SM, Lee SY, Ihn MH, Kim DW, Park JH, Kim YH, Lee KH, Kim JS, Kim JW, Kim JH, Chang TY, Park SC, Sohn DK, Oh JH, Park JW, Ryoo SB, Jeong SY, Park KJ. Neoadjuvant chemoradiotherapy affects the indications for lateral pelvic node dissection in mid/low rectal cancer with clinically suspected lateral node involvement: a multicenter retrospective cohort study. *Ann Surg Oncol* 2014; 21: 2280-2287 [PMID: 24604580 DOI: 10.1245/s10434-014-3559-z]
- Fujita S, Mizusawa J, Kanemitsu Y, Ito M, Kinugasa Y, Komori K, Ohue M, Ota M, Akazai Y, Shiozawa M, Yamaguchi T, Bandou H, Katsumata K, Murata K, Akagi Y, Takiguchi N, Saida Y, Nakamura K, Fukuda H, Akasu T, Moriya Y; Colorectal Cancer Study Group of Japan Clinical Oncology Group. Mesorectal Excision With or Without Lateral Lymph Node Dissection for Clinical Stage II/III Lower Rectal Cancer (JCOG0212): A Multicenter, Randomized Controlled, Noninferiority Trial. *Ann Surg* 2017; 266: 201-207 [PMID: 28288057 DOI: 10.1097/SLA.00000000002212]
- 30 Akiyoshi T, Watanabe T, Miyata S, Kotake K, Muto T, Sugihara K; Japanese Society for Cancer of the Colon and Rectum. Results of a Japanese nationwide multi-institutional study on lateral pelvic lymph node metastasis in low rectal cancer: is it regional or distant disease? *Ann Surg* 2012; 255: 1129-1134 [PMID: 22549752 DOI: 10.1097/SLA.0b013e3182565d9d]
- 31 Fujita S, Akasu T, Mizusawa J, Saito N, Kinugasa Y, Kanemitsu Y, Ohue M, Fujii S, Shiozawa M, Yamaguchi T, Moriya 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: 616-621 [PMID: 22591948 DOI: 10.1016/S1470-2045(12)70158-4]
- 32 Tevis SE, Kohlnhofer BM, Stringfield S, Foley EF, Harms BA, Heise CP, Kennedy GD. Postoperative complications in patients with rectal cancer are associated with delays in chemotherapy that lead to worse disease-free and overall survival. *Dis Colon Rectum* 2013; 56: 1339-1348 [PMID: 24201387 DOI: 10.1097/DCR.0b013e3182a857eb]
- 33 Beets-Tan RG, Lambregts DM, Maas M, Bipat S, Barbaro B, Caseiro-Alves F, Curvo-Semedo L, Fenlon HM, Gollub MJ, Gourtsoyianni S, Halligan S, Hoeffel C, Kim SH, Laghi A, Maier A, Rafaelsen SR, Stoker J, Taylor SA, Torkzad MR, Blomqvist L. Magnetic resonance imaging for the clinical management of rectal cancer patients: recommendations from the 2012 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus meeting. *Eur Radiol* 2013; 23: 2522-2531 [PMID: 23743687 DOI: 10.1007/s00330-013-2864-4]
- 34 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 Preoperative Chemoradiotherapy in Patients with Advanced Low-Rectal Cancer. Ann Surg Oncol 2015; 22 Suppl 3: S614-S620 [PMID: 25896145 DOI: 10.1245/s10434-015-4565-5]
- 35 Nagawa H, Muto T, Sunouchi K, Higuchi Y, Tsurita G, Watanabe T, Sawada T. Randomized, controlled trial of lateral node dissection vs. nerve-preserving resection in patients with rectal cancer after preoperative radiotherapy. *Dis Colon Rectum* 2001; 44: 1274-1280 [PMID: 11584199 DOI: 10.1007/bf02234784]
- 36 Hojo K, Sawada T, Moriya Y. An analysis of survival and voiding, sexual function after wide iliopelvic lymphadenectomy in patients with carcinoma of the rectum, compared with conventional lymphadenectomy. *Dis Colon Rectum* 1989; **32**: 128-133 [PMID: 2914526 DOI: 10.1007/bf02553825]
- Moriya Y, Sugihara K, Akasu T, Fujita S. Nerve-sparing surgery with lateral node dissection for advanced lower rectal cancer. *Eur J Cancer* 1995; **31A**: 1229-1232 [PMID: 7577028 DOI: 10.1016/0959-8049(95)00164-e]
- 38 Georgiou P, Tan E, Gouvas N, Antoniou A, Brown G, Nicholls RJ, Tekkis P. Extended lymphadenectomy versus conventional surgery for rectal cancer: a meta-analysis. *Lancet Oncol* 2009; 10: 1053-1062 [PMID: 19767239 DOI: 10.1016/S1470-2045(09)70224-4]
- 39 Saito S, Fujita S, Mizusawa J, Kanemitsu Y, Saito N, Kinugasa Y, Akazai Y, Ota M, Ohue M, Komori K, Shiozawa M, Yamaguchi T, Akasu T, Moriya Y; Colorectal Cancer Study Group of Japan Clinical Oncology Group. Male sexual dysfunction after rectal cancer surgery: Results of a randomized trial comparing mesorectal excision with and without lateral lymph node dissection for patients with lower rectal cancer: Japan Clinical Oncology Group Study JCOG0212. *Eur J Surg Oncol* 2016; 42: 1851-1858 [PMID: 27519616 DOI: 10.1016/j.ejso.2016.07.010]
- 40 Ito M, Kobayashi A, Fujita S, Mizusawa J, Kanemitsu Y, Kinugasa Y, Komori K, Ohue M, Ota M, Akazai Y, Shiozawa M, Yamaguchi T, Akasu T, Moriya Y; Colorectal Cancer Study Group of Japan Clinical Oncology Group. Urinary dysfunction after rectal cancer surgery: Results from a randomized trial comparing mesorectal excision with and without lateral lymph node dissection for clinical stage II or III lower rectal cancer (Japan Clinical Oncology Group Study, JCOG0212). Eur J Surg Oncol 2018; 44: 463-



468 [PMID: 29428473 DOI: 10.1016/j.ejso.2018.01.015]

- 41 Palmerola R, Hartman C, Theckumparampil N, Mukkamala A, Fishbein J, Schwartz M, Kavoussi LR. Surgical Complications and Their Repercussions. *J Endourol* 2016; 30 Suppl 1: S2-S7 [PMID: 26971898 DOI: 10.1089/end.2015.0705]
- 42 Cheng H, Clymer JW, Po-Han Chen B, Sadeghirad B, Ferko NC, Cameron CG, Hinoul P. Prolonged operative duration is associated with complications: a systematic review and meta-analysis. *J Surg Res* 2018; **229**: 134-144 [PMID: 29936980 DOI: 10.1016/j.jss.2018.03.022]





Published by Baishideng Publishing Group Inc 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA Telephone: +1-925-3991568 E-mail: bpgoffice@wjgnet.com Help Desk:http://www.f6publishing.com/helpdesk http://www.wjgnet.com



© 2020 Baishideng Publishing Group Inc. All rights reserved.