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The diagnosis and oncological outcomes of obturator and internal iliac lymph node metastasis in middle–low rectal cancer: results of a multicenter Lateral Node Collaborative Group study in China

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Received: 3 September 2024 / Accepted: 1 November 2024
Published online: 04 November 2024

Abstract

Background Lateral lymph node dissection (LLND) can decrease local recurrence to lateral compartments in middle-low rectal cancer, but pathological evidence for optimal surgical indications, especially after neoadjuvant (chemo)radiotherapy (nCRT), is lacking. This study aimed to identify the predictive factors and oncological outcomes for different LLN locations associated with pathological metastasis.

Method In this multicenter study, patients from 19 centers who underwent total mesorectal excision (TME) with LLND for locally advanced mid-/low rectal cancer from January 2012 to December 2021 were included.

Results All 566 included patients underwent TME with LLND surgery; 241 (37.4%) of the largest LLNs were located in the obturator area, and 403 (62.6%) of the largest LLNs were located in the internal iliac area. Multivariate analysis revealed that a short-axis size of 9 mm for the obturator area and 6 mm for internal iliac nodes constituted a reliable indicator of pathological LLN metastasis in non-CRT patients. In nCRT patients, a short-axis node size of 7 mm for obturator nodes and 4 mm for internal iliac nodes could be used to accurately predict pathological LLN metastasis. In contrast to pathological internal iliac node metastasis, pathological obturator node metastasis was associated with lower distant metastasis-free survival (DMFS) ($P=0.001$), cancer-specific survival (CSS) ($P=0.043$), and overall survival (OS) ($P=0.009$), but lower lateral local recurrence-free survival (LRFS) ($P>0.05$) was not statistically significant.

Conclusions The obturator and internal iliac nodes may be two completely different types of LLNs, and the optimal cutoff value for predicting pathological LLN metastasis is inconsistent regardless of nCRT.

Clinical trial registration The protocol of the current study was registered on ClinicalTrials.gov (NCT04850027), and the protocols were in accordance with the standards set by the World Medical Association Declaration of Helsinki.

Keywords Lateral lymph node · Pathological features · Survival · Rectal cancer

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Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12672-024-01500-4.

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1 Introduction

The widespread acceptance of neoadjuvant chemoradiotherapy (nCRT) and standardized surgical procedures involving total mesorectal excision (TME) has significantly diminished postoperative local recurrence rates in middle/low rectal cancer patients over the past four decades, but 5% to 10% of patients still experience local recurrence [1–3]. Recent studies highlight lateral local recurrence (LLR) as the primary type of local recurrence, constituting up to 50–82.7%, with lateral lymph node (LLN) metastasis emerging as a prevalent and intricate clinical challenge [4, 5]. The treatment strategy for LLN metastasis has long differed between Western and Eastern countries. Western surgeons consider LLN metastasis to be indicative of systemic disease and feared complications and neurological dysfunction associated with lateral lymph node dissection (LLND); thus, nCRT and TME have always been the standard treatments. Surgeons in Japan consider LLNs as regional lymph nodes; therefore, the guidelines published by the Japanese Society for Cancer of the Colon and Rectum (JSCCR) advocate routine prophylactic LLND without nCRT for rectal cancers staged T3 to T4 and located below the peritoneal reflection [6]. Currently, the more consistent view is that LLND can significantly reduce local recurrence in the lateral pelvic region [7, 8], especially for patients with obvious enlarged LLNs before the operation [9–11].

With the advent of the era of precision medicine, the treatment and prevention of LLN metastasis need to be more individualized and precise to avoid overtreatment and morbidity. A multicenter study from 12 institutions across 7 countries in both Eastern and Western countries revealed divergent recurrence patterns and oncological outcomes among patients with node metastases in the internal iliac and obturator regions [11]. Notably, patients with internal iliac metastasis were at high risk of local reoccurrence after surgery, whereas patients with obturator metastasis were more likely to have distant metastasis. However, only 90 patients underwent LLND in the present study, and LLN metastasis was diagnosed based only on malignant features on preoperative pelvic magnetic resonance imaging (MRI), lacking confirmation from the final pathology. In addition, distant metastases are also detected in patients with LLN metastasis, and the survival benefit regarding local recurrence and long-term survival after LLND remains ambiguous. Although our previous studies established size-based criteria for LLNs after preoperative nCRT [12], it is necessary to clarify the recurrence patterns and prognostic characteristics of patients with LLN metastasis in different regions and carry out targeted and precise treatment to improve the prognosis of patients with LLN metastasis.

In this study, all patients underwent LLND with or without preoperative nCRT. Our primary objectives were to delineate diagnostic size criteria for obturator and internal iliac LLN metastasis before or after nCRT and to explore their correlation with various oncological outcomes, with the goal of identifying survival benefits associated with LLND.

2 Patients and methods

2.1 Study design and patient selection

Patient information was retrieved from a multicenter, prospective registry study performed at 19 hospitals across China from January 2012 to December 2021. The protocol was approved by the central ethics committee of the Chinese National Cancer Center/Cancer Hospital, the Chinese Academy of Medical Sciences and Peking Union Medical College, and the local ethics committees of all the participating hospitals. The protocol of the current study was registered on ClinicalTrials.gov (NCT04850027), and the procedures were performed in accordance with the ethical standards of the World Medical Association Declaration of Helsinki.

The inclusion criteria were patients aged 18–75 years with histologically confirmed rectal adenocarcinoma of stage II or III, who underwent TME combined with LLND surgery, and whose main lesion was located within the peritoneum from the anal verge confirmed in the intraoperative records. The exclusion criteria were patients with other malignant tumor diseases within 5 years, the absence of (high-quality) MRI scans for evaluating LLN status preoperatively, a noncurative (R1 and R2) resection, and a surgical procedure that did not follow the JSCCR guidelines for colorectal cancer whereby only part of the LLN was dissected instead of a standard LLND [13]. Given the objectives of this study, patients with both internal iliac and obturator enlarged nodes were also excluded. All the enrolled patients were divided into the nCRT group and the nonnCRT group according to preoperative treatment. Among the patients in the nCRT group, only those who had undergone restaging MRI were included.

2.2 Assessment of LLN

Two independent radiologists specializing in rectal malignancies examined the clinical stage and LLN status before and after treatment, and MRI was used to evaluate the characteristics of the enlarged LLNs, including the largest short-axis (SA), quantity, edge, location, and presence of malignant features (e.g., internal heterogeneity or border irregularity). LLN details in the nCRT group were re-evaluated by MRI 8 to 12 weeks after treatment. Clinically suspected LLN metastasis was diagnosed according to one or more of the following criteria: (1) SA diameter ≥ 5 mm before nCRT or SA diameter ≥ 3 mm after nCRT; (2) inhomogeneous or intense enhancement; and (3) irregular shape and rough edges. Furthermore, the location of the LLN was divided into the internal iliac and obturator areas and was defined as the lateral boundary of the main trunk of the internal iliac vessels. The assessment did not include the benign, long-stretched lymph nodes just behind the external iliac vein. An enlarged LLN was defined as a lymph node with the largest SA on one side, whether in the obturator or internal iliac area. Bilateral enlarged LLNs were defined as lymph nodes in the lateral areas on both sides (obturator or internal iliac area) and were analyzed individually on each side. Local recurrence was defined as the recurrence of new rectal tumors confirmed by imaging within the pelvis after previous resectional surgery [14].

2.3 Treatment strategies

nCRT was performed in patients with circumferential margin (CRM) involvement, multiple lymph node metastases, or a strong desire to preserve sphincter function. A long-term regimen was administered in the nCRT group, with a total radiotherapy dosage of 50 Gy in 25 fractions with two cycles of concurrent oral capecitabine. A combination of oxaliplatin and 5-FU/LV or capecitabine (i.e., FOLFOX or CAPOX) and 1 to 6 cycles of chemotherapy were subsequently administered, regardless of the pathological stage. Patients in the nonnCRT group with stage III and high-risk stage II disease underwent standard National Comprehensive Cancer Network (NCCN) postoperative adjuvant chemotherapy. Due to the treatment strategy standard update for clinical LLN metastasis during the study period, patients with suspected lateral lymph node metastasis before 2018 received surgical treatment without preoperative chemoradiotherapy. Since 2018, preoperative nCRT has been recommended before LLND for patients with an LLN SA ≥ 10 mm.

All surgeries were generally similar at each hospital and were performed by Chinese Medical Doctor Association-certified colorectal surgeons, who often perform LLND operations, whether open or laparoscopic. Unilateral or bilateral LLND was performed according to the location of the enlarged LLNs found on preoperative MR images after total mobilization of the rectum and distal rectal transection. The extent of the surgery was in accordance with the guidelines set by the JSCCR [13]. In this study, LLND was defined as the removal of all lymphatic tissue from the lateral area, including the internal iliac and obturator areas. All the autonomic nerves were preserved because lymph node metastasis around these nerves is rare in patients without clinical lateral pelvic lymph node metastasis [15]. The surgical procedure details were in accordance with previously reported methods. [16]

2.4 Outcomes and follow-up

Each lymph node was examined pathologically individually and correlated with its size measured on preoperative pelvic MR images by referring to its anatomical location. The correlation between the lymph node SA diameter and pathological LLN metastasis was analyzed, and the sensitivity, specificity, positive predictive value, and negative predictive value were calculated. For bilaterally enlarged LLNs, each side was compared individually. The oncological outcomes included lateral local recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), cancer-specific survival (CSS), and overall survival (OS). Follow-up was performed according to National Comprehensive Cancer Network-recommended schemes and included postoperative outpatient or telephone interviews. The last follow-up date was the patient's death or November 31, 2022, whichever occurred first.

2.5 Statistical analysis

The $\chi 2$ test and t test were used for comparisons between continuous variables and categorical variables. Multivariate analysis of variables that had a statistically significant effect (P value < 0.05) on pathological LLN metastasis was performed via Cox and multiple logistic regression models. The Kaplan−Meier method was used to calculate the LRFS, DMFS, CSS, and OS curves, which were compared via the log-rank test. All the statistical analyses were carried out via SPSS version 24.0 for Windows (IBM Corp., Armonk, NY).

3 Results

3.1 Clinical and pathological characteristics

A total of 566 patients who had LLNs with a preoperative SA diameter of at least 5 mm and underwent TME combined with LLND were included in the study (Fig. 1); 342 (60.4%) were male, and the mean ± SD age was 57.5 ± 10.8 years (Table 1). There were 488 patients (86.2%) with unilateral enlarged LLNs and 78 patients (13.8%) with bilateral enlarged LLNs. The average number of removed LLNs was 9.1, and a total of 161 (28.4%) were confirmed to have LLN metastasis through pathology. Among these 161 patients, 110 (19.4%) had LLN metastasis in the internal iliac vessel area, 41 (7.2%) had LLN metastasis in the obturator area, and 10 (1.8%) had LLN metastasis in both the internal iliac vessels and the obturator area.

3.2 Size criteria for LLN metastasis in the nCRT cohort

Table 2 describes the sensitivity, specificity, and positive and negative predictive values in the nCRT cohort for diagnosing LLN metastasis based on each size criterion. A total of 294 LLNs were dissected from 258 patients, and 80 (27.2%) were pathologically confirmed to have LLN metastasis. The sensitivity, specificity, positive predictive value, negative predictive value, and area under the curve (AUC) of an internal iliac area SA diameter of 4 mm for predicting pathological LLN metastasis were 95.7%, 56.9%, 42.7%, 97.5%, and 0.763, respectively. The corresponding values for the obturator area cutoff LLN size of 7 mm were 94.1%, 90.9%, 81.6%, 95.9%, and 0.910, respectively. Furthermore, univariate and multivariate analyses were performed to identify the independent predictive factors of LLN metastasis in patients who underwent nCRT. As shown in Supplementary Table S1, poor histological grade (HR 2.62; 95% CI 1.11–6.17; $P = 0.028$), ycT3/4 stage (HR 3.35; 95% CI 1.15–9.75; $P = 0.027$), and post-CRT LLN SA diameter > 4 mm (HR 18.20; 95% CI 4.03–82.09; $P < 0.001$) were independent and significant predictors of internal iliac LLN metastasis. An LLN SA diameter > 7 mm (HR 70.84; 95% CI 18.13–276.91; $P < 0.001$) was the only independent and significant

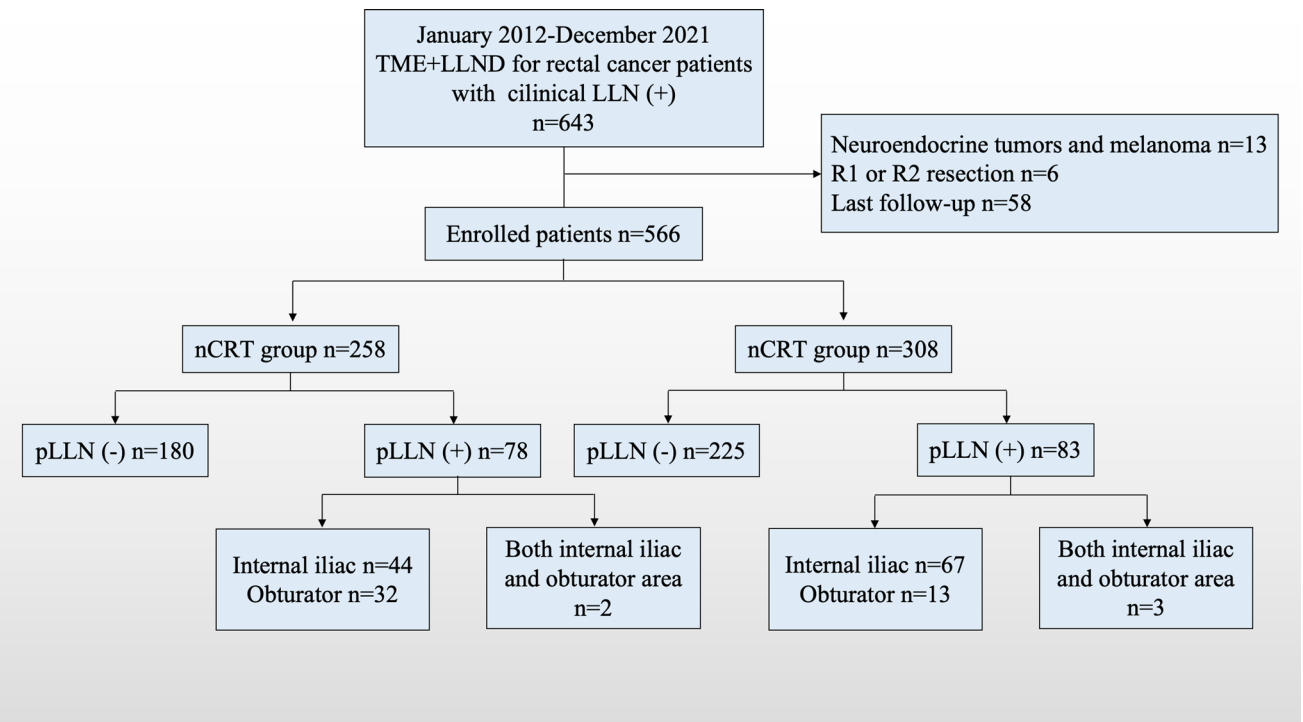

Fig. 1 Flow chart showing lateral lymph node patterns in patients with middle/low rectal cancer. *TME* total mesorectal excision, *pLLN* pathological lateral lymph node, *LLND* lateral lymph node dissection

Table 1 Baseline Clinical and pathological characteristics of all enrolled patients

Characteristics	Overall cohort (n = 566) N(%)
Age (y, mean ± SD) (range)	57.5 ± 10.8 (18–85)
Gender (%)	
Male	342 (60.4)
Female	224 (39.6)
Distance of tumor from the AV (cm, mean ± SD) (range)	4.4 ± 2.1 (1–8)
BMI (Kg/m^2, mean ± SD)(range)	24.0 ± 3.0 (16.1–38.0)
Neoadjuvant chemoradiotherapy	258 (45.6)
Types of operation	
Low anterior resection	303 (53.5)
Abdominoperineal resection	203 (35.9)
Hartmann procedure	31 (5.5)
Total pelvic exeraction	29 (5.1)
Swollen LLN	
Unilateral enlarged LLN	488 (86.2)
Bilateral enlarged LLN	78 (13.8)
Location of largest LLN on each side	
Internal iliac vessels area	403 (62.6, 403/644)
Obturator area	241 (37.4, 241/644)
Pathological LLN metastasis	161 (28.4)
Location of LLN metastasis	
Internal iliac vessels area	111 (19.6)
Obturator area	45 (8.0)
Both Internal iliac vessels and obturator area	5 (0.9)
Bilateral LLN metastasis	5 (0.9)
Pathological T stage (%)	
Complete response or T1-T2	150 (26.5)
T3-T4	416 (73.5)
Pathological mesorectal LN metastasis (%)	
N0	275 (48.6)
N1-N2	291 (51.4)
Histology (%)	
Moderate	301 (53.2)
Poor/Mucinous/signet	265 (46.8)
LLNs removed (n, mean ± SD)	9.1 ± 6.8 (0–28)
Mesorectal LN removed (n, mean ± SD)	16.4 ± 9.2 (3–48)
Adjuvant therapy	425 (75.1)

AV anal verge, *BMI* body mass index, *LLN* lateral lymph node, *LN* lymph node

predictor of obturator LLN metastasis. Thus, it is plausible to adopt LLN SA diameters of 4 and 7 mm in the internal iliac and obturator areas post-CRT as cutoff values for predicting metastatic LLNs (Fig. 2A, B).

3.3 Size criteria for LLN metastasis in the nonnCRT cohort

In total, 350 LLNs were dissected from 308 patients who did not undergo nCRT, and 104 (29.7%) were pathologically confirmed to have LLN metastasis (Table 3). The sensitivity was 84.3%, specificity was 81.3%, positive predictive value was 67.8%, negative predictive value was 91.7%, and AUC was 0.828 for an SA diameter of 6 mm in the internal iliac area for predicting pathological LLN metastasis. A cutoff obturator area LLN size of 9 mm had a sensitivity of 94.1%, a specificity of 90.9%, a positive predictive value of 81.6%, a negative predictive value of 95.9%, and an area under the curve of 0.978. In univariate and multivariate analyses (Supplementary Table S2), an LLN SA

Table 2 Diagnosis of LLN metastasis by short diameter in nCRT cohort [n = 258 patients; 294 LLNs)

Cutoff value	Sensitivity	Specificity	Positive predictive value	Negative predictive value	AUC
Internal iliac area (183 LLNs)					
3 mm	100% (46/46)	20.4% (28/137)	29.7% (46/155)	100% (28/28)	0.602
4 mm	95.7% (44/46)	56.9% (78/137)	42.7% (44/103)	97.5% (78/80)	0.763
5 mm	73.9% (34/46)	75.9% (104/137)	50.7% (34/67)	89.7% (104/116)	0.749
6 mm	54.3% (25/46)	86.9% (119/137)	58.1% (25/43)	85.0% (119/140)	0.706
7 mm	41.3% (19/46)	94.9% (130/137)	73.1% (19/26)	82.8% (130/157)	0.681
8 mm	36.9% (17/46)	96.4% (132/137)	77.3% (17/22)	82.0% (132/161)	0.667
Obturator area (111 LLNs)					
3 mm	100% (34/34)	13.0% (10/77)	33.7% (34/101)	100% (10/10)	0.565
4 mm	100% (34/34)	26.0% (20/77)	37.4% (34/91)	100% (20/20)	0.630
5 mm	100% (34/34)	39.0% (30/77)	42.0% (34/81)	100% (30/30)	0.695
6 mm	97.1% (33/34)	59.7% (46/77)	51.6% (33/64)	97.9% (46/47)	0.784
7 mm	94.1% (31/34)	90.9% (70/77)	81.6% (31/38)	95.9% (70/73)	0.910
8 mm	85.3% (29/34)	94.8% (73/77)	87.9% (29/33)	93.6% (73/78)	0.900

nCRT neoadjuvant chemoradiotherapy, *LLN* lateral lymph node, *AUC* area under curve

diameter > 6 mm (HR 38.32; 95% CI 14.71–99.79; $P < 0.001$) in the internal iliac area and an LLN SA diameter > 9 mm (HR 51.35; 95% CI 10.41–204.55; $P < 0.001$) in the obturator area were found to be independent and significant predictors of LLN metastasis. Therefore, these findings further validate the reasonableness of using LLN SA diameters of 6 and 9 mm in the internal iliac and obturator regions as non-nCRT cutoffs for predicting metastatic LLNs (Fig. 2C, D).

3.4 Associations between the use of obturators or internal iliac lymph nodes and oncologic outcomes

Table 4 shows the multivariable analyses, and Supplementary Table S3 shows the univariable analyses of oncological outcomes and survival in all 161 patients with pathological LLN metastasis. According to the multivariate Cox regression analyses, circumferential resection margin status ($P = 0.020$) and pT stage ($P = 0.004$) significantly affected LRFS, age at operation significantly ($P = 0.001$) affected CSS, and positive lymphatic invasion ($P < 0.001$) was associated with a worse OS. Compared with patients with internal iliac lymph node metastasis, those with pathological obturator lymph node metastasis had greater DM (HR 2.90, 1.54 to 5.44; $P = 0.001$), CSS (HR 3.76, 1.04 to 13.55; $P = 0.043$), and OS (HR 3.83, 1.40 to 10.47; $P = 0.009$), but there was no difference in LRFS ($P > 0.05$). These results were similar to those of separate analyses of patients with internal iliac and obturator lymph node metastasis (Fig. 3A–D). By analyzing all the lymph nodes (including mesorectal lymph nodes), we found that patients with pN1/2 disease had worse DM (HR 2.90, 1.54 to 5.44; $P = 0.001$), CSS (HR 3.76, 1.04 to 13.55; $P = 0.043$), and OS (HR 3.83, 1.40 to 10.47; $P = 0.009$), but there was no difference in LRFS ($P > 0.05$). In addition, according to the optimal predictive cutoff values of lateral lymph nodes determined in Tables 2 and 3, a further subgroup analysis of patients was performed (Supplementary Table S4, Supplementary Table S5, Supplementary Fig. 1), and the results showed a strong association between the groups with OS and LRFS.

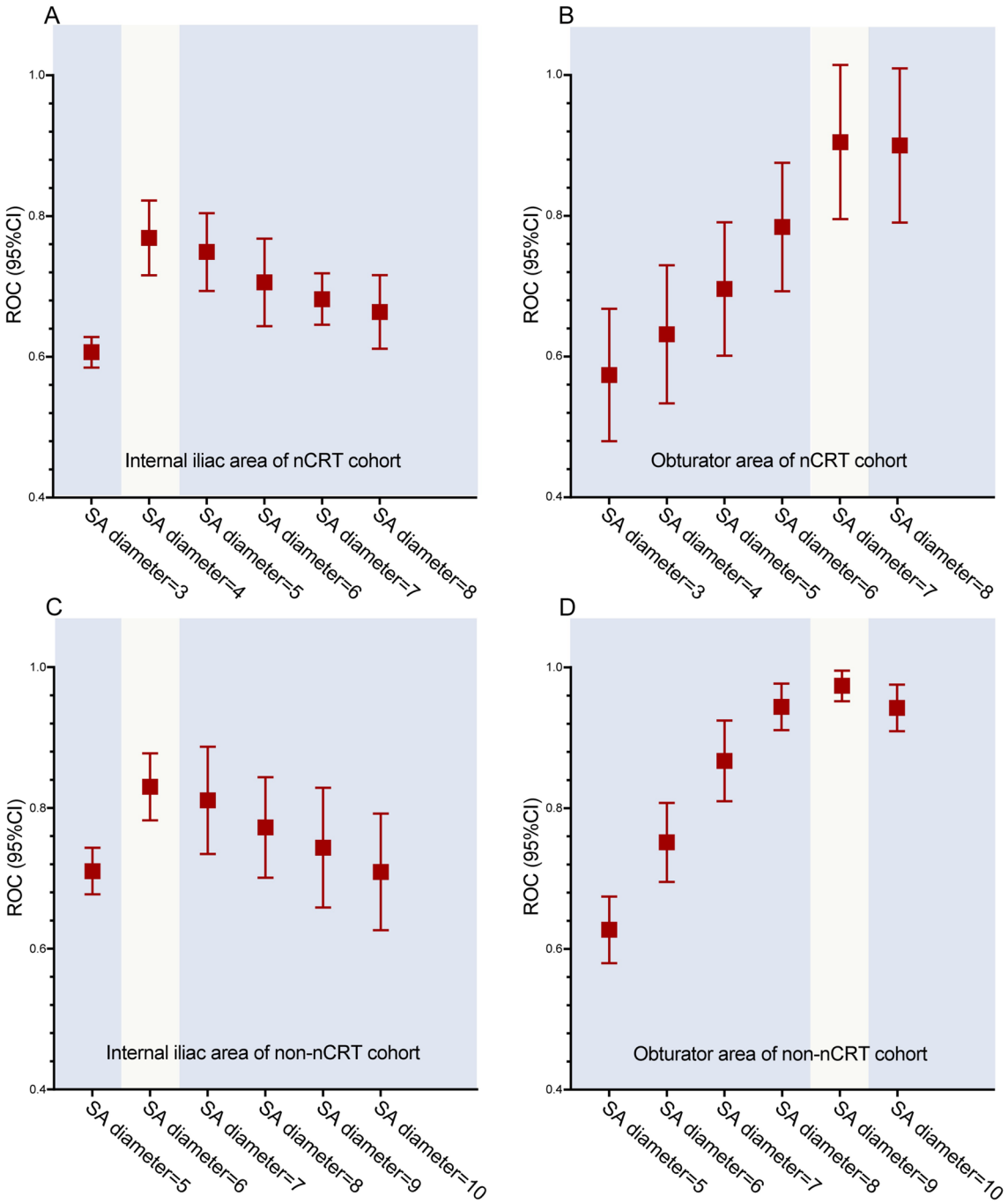

Fig. 2 The area under the curve values of different LLN diameters. *LLN* lateral lymph node

4 Discussion

The results of this study, which included 566 patients from 19 centers who underwent LLND operations for stage II/III middle/low rectal cancer, demonstrated that the SA diameter cutoff values for diagnosing obturator and internal iliac LLN metastasis are different. In this study, an SA diameter of 9 mm or more for obturator lymph nodes and a diameter of 6 mm or more for internal iliac lymph nodes were shown to be accurate predictors of pathological LLN metastasis in non-nCRT patients, and an SA diameter of 7 mm or more for obturator lymph nodes and 4 mm or more for internal iliac lymph nodes could accurately predict pathological LLN metastasis in nCRT patients. In addition,

Table 3 Diagnosis of LLN metastasis by short diameter in non-nCRT group (n = 308 patients; 350 LLNs)

Cutoff value	Sensitivity	Specificity	Positive predictive value	Negative Predictive value	AUC
Internal iliac area (220 LLNs)					
5 mm	94.3% (66/70)	48.7% (73/150)	46.2% (66/143)	94.8% (73/77)	0.715
6 mm	84.3% (59/70)	81.3% (122/150)	67.8% (59/87)	91.7% (122/133)	0.828
7 mm	75.7% (53/70)	86.7% (130/150)	72.6% (53/73)	88.4% (130/147)	0.812
8 mm	61.4% (43/70)	93.3% (140/150)	81.1% (43/53)	83.8% (140/167)	0.774
9 mm	51.4% (36/70)	98.7% (148/150)	94.7% (36/38)	81.3% (148/182)	0.750
10 mm	44.3% (31/70)	98.7% (148/150)	93.9% (31/33)	79.1% (148/187)	0.715
Obturator area (130 LLNs)					
5 mm	100% (16/16)	25.4% (29/114)	15.8% (16/101)	100% (29/29)	0.627
6 mm	100% (16/16)	49.1% (56/114)	21.6% (16/74)	100% (56/56)	0.746
7 mm	100% (16/16)	72.8% (83/114)	34.0% (16/47)	100% (83/83)	0.864
8 mm	100% (16/16)	87.7% (100/114)	53.3% (16/30)	100.0% (100/100)	0.939
9 mm	100% (16/16)	95.6% (109/114)	76.2% (16/21)	100.0% (100/109)	0.978
10 mm	87.5% (14/16)	100.0% (114/114)	100.0% (14/14)	98.3% (114/116)	0.938

nCRT neoadjuvant chemoradiotherapy, *LLN* lateral lymph node, *AUC* area under curve

oncological outcomes were inconsistent between patients with obturator and internal iliac LLN metastasis. LLN metastasis in the internal iliac area was related to better DMFS, CSS, and OS rates. However, the LRFS rate was not significantly different between the internal iliac and obturator areas.

LLND is a complicated and challenging technique for LLN metastasis that needs to be performed by skeletonizing the pelvic blood vessels and nerve plexus. The complex anatomy of the pelvic lateral wall, especially the tissue fibrosis and edema caused by nCRT, can reduce the clarity of the surgical field, even when surgery is performed by experienced surgeons. It may increase the risk of complications, such as urinary and sexual dysfunction [15]. In recent years, with increasing research evidence, especially from international multicenter investigations conducted across Asia, Europe, and North America, it has been confirmed that for patients with LLN metastasis identified via preoperative imaging, a comprehensive treatment strategy combining nCRT and selective LLND can improve patient prognosis [10, 11, 17]. China was one of the first countries in which surgeons performed lateral lymph node dissection, and the initial expert consensus on lateral lymph nodes in the country was released in 2019 [18]. Therefore, our research population consisted entirely of patients receiving LLND, which can be used to determine whether there is pathological metastasis in the lateral lymph nodes. We previously explored the feasibility, indications, and prognostic importance of LLND for middle/low rectal cancer and reported that a post-CRT LLN short-axis diameter ≥ 7 mm could be used for predicting LLN metastasis. [12] The diameter of the LLN is significantly associated with lateral local recurrence [19]; even following nCRT in patients with rectal cancer, the presence of enlarged LLNs and a larger diameter before surgery are crucial risk factors for poor prognosis and lateral local recurrence [5]. However, the size-based optimal SA diameter threshold for LLN metastasis varies among studies, especially the cutoff value for diagnosis after nCRT. Multiple studies in recent years have shown that an SA diameter of LLNs greater than 7 mm on MRI in newly diagnosed cases is an independent risk factor for local recurrence and lateral local recurrence, with a 5-year LLR rate of 19.5%, which is significantly greater than that in patients with an LLN SA diameter ≤ 7 mm (4.9%, $P < 0.001$). [11, 20] When the number of enlarged LLNs is < 5 mm, the metastasis rate is low, ranging from 3.5% to 5.0% [21, 22]. When MRI detects lateral lymph nodes ≤ 3 mm, the negative predictive value can reach 99% [23]. In several studies that involve measuring the diameter of LLNs through gross pathological specimens,

Table 4 Multivariable regression analyses of risk factors for local recurrence-free survival, distant metastasis-free survival, cancer-specific survival, and overall survival in 161 patients with pathological LLN metastasis

Variables	Local recurrence-free survival		Distant metastasis-free survival		Cancer-specific survival		Overall survival	
	Multivariate analysis		Multivariate analysis		Multivariate analysis		Multivariate analysis	
	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
Sex: male/female					0.43 (0.16–1.17)	0.098		
Age at operation (≥ 60 years vs < 60 years)			0.90 (0.49–1.63)	0.716	0.18 (0.06–0.50)	0.001		
Lymphatic invasion (positive/negative)							6.39 (2.26–18.01)	< 0.001
Circumferential Resection Margin (positive/negative)	4.04 (1.25–13.04)	0.020						
pT stage (T3–T4/T1-T2)	5.93 (1.77–19.86)	0.004			2.51 (0.59–10.64)	0.212	1.83 (0.62–5.37)	0.272
pN stage (mesorectal LN) (N1-N2/N0)			2.09 (1.18–3.69)	0.011	8.67 (1.72–43.75)	0.009	4.54 (1.61–12.79)	0.004
Pathological LLN metastasis								
Internal iliac LN metastasis			1.00 (Reference)	-	1.00 (Reference)	-	1.00 (Reference)	-
Obturator LN metastasis			2.90 (1.54–5.44)	0.001	3.76 (1.04–13.55)	0.043	3.83 (1.40–10.47)	0.009
Both Internal iliac and obturator LN metastasis			4.37 (1.74–10.98)	0.002	11.81 (2.13–65.44)	0.005	5.38 (1.45–19.94)	0.012
Grade 3–5 postoperative complication (yes/no)	2.31 (0.90–5.98)	0.084						

LN lymph node, *LLN* lateral lymph node

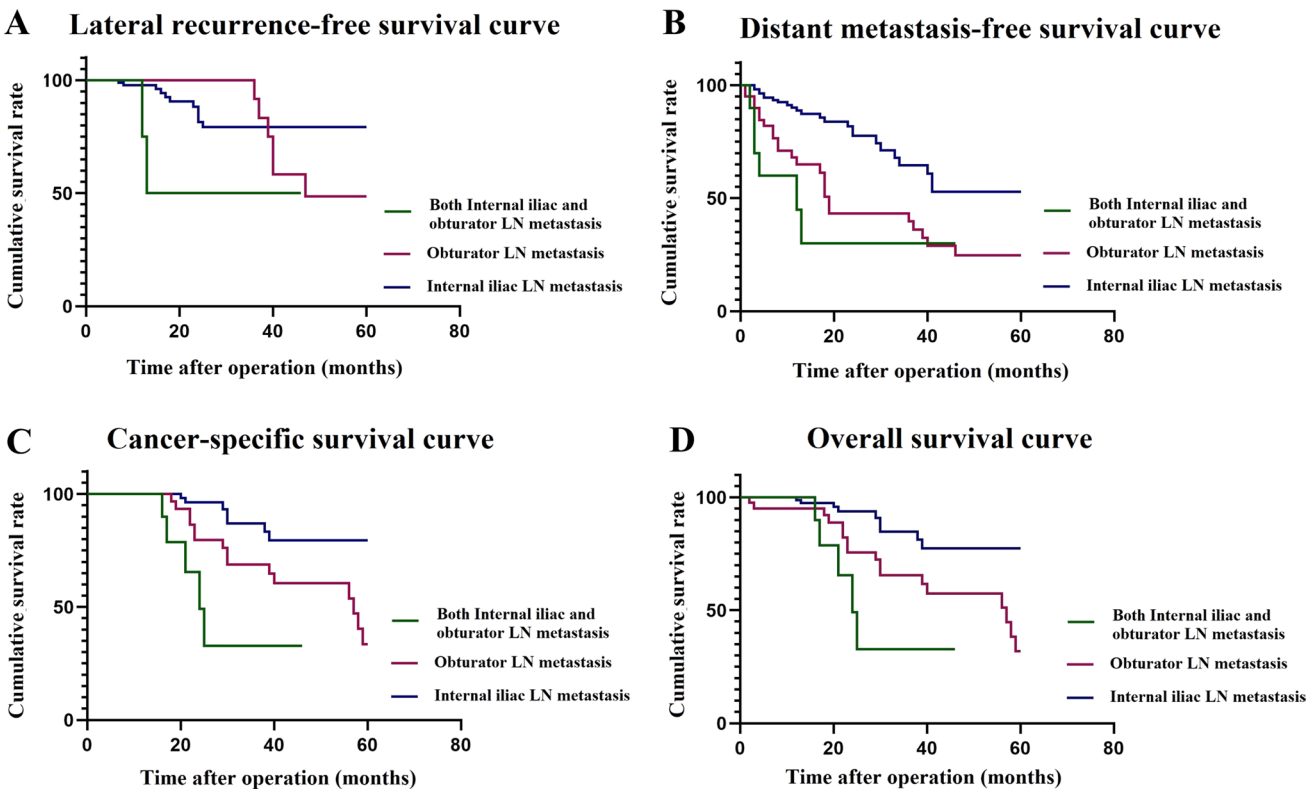

Fig. 3 LRFS (**A**), DMFS (**B**), CSS (**C**), and OS (**D**) according to the location of the pathological LLN metastasis. *LRFS* lateral local recurrence-free survival, *DMFS* distant metastasis-free survival, *CSS* cancer-specific survival, *OS* overall survival, *LLN* lateral lymph node

the most accurate cutoff value for predicting LLN metastasis was shown to be 5 mm [24]. Notably, a recent international multicenter study led by a Japanese hospital revealed that thresholds for detecting LLN metastasis differ across various lateral regions. In patients whose SA of LLNs is 7 mm or greater before nCRT, there is no 3-year LLR for obturator lymph nodes 6 mm or less and internal iliac lymph nodes 4 mm or less after treatment [19]. In the present study, preoperative nCRT was omitted in 54.4% (308/566) of patients who underwent LLND with suspected LLN metastasis. Regarding the initial LLN size without nCRT, when a cutoff value of 9 mm was used for the obturator lymph nodes and 6 mm for the internal iliac lymph nodes, the sensitivity was 94.1% and 84.3%, respectively. However, based on the post-CRT LLN size, when a cutoff value of 7 mm was used for the obturator lymph nodes and 4 mm for the internal iliac lymph nodes, the sensitivities were 94.1% and 95.7%, respectively, which means that only approximately 5% of patients may not have benefited from LLND. Therefore, we believe that for different locations of LLN metastasis and preoperative treatment strategies, a more accurate LLN size should be developed as a more appropriate standard for LLND.

The second main finding from this study is that oncological outcomes differ based on the lateral lymph node metastasis area. In a multicenter study [11], post-CRT LLNs still behaved aggressively, and internal iliac nodes with a post-SA > 4 mm resulted in a 5-year LLR of 52.3%, whereas this value was 17.8% in patients with obturator nodes with a post-SA > 6 mm. The scholars in that study also demonstrated that internal iliac nodes are less likely to respond to nCRT than obturator nodes (22% and 63%, respectively), which suggests that enlarged obturator nodes are more likely to be reactive. Our results indicated that approximately 25.5% (41/161) of the visible pathological LLN metastases were located in the obturator area (Table 1), but they tended to be a surrogate marker of more advanced disease than internal iliac LLN metastasis, with a lower DMFS (P = 0.001), CSS (P = 0.043), and OS (P = 0.009) but no statistically significant difference in LRFS. However, why obturator area LLN metastasis results in much poorer oncologic outcomes remains unknown. One theory to consider is that pathological obturator LLN metastasis may be more active, aggressive, and destructive, while the internal lymph nodes act as sentinel nodes and are more likely to respond after treatment. However, in general, performing LLND of both the internal iliac and obturator areas in China is standard, irrespective of where the involved node is located. It should be noted that the duration of this study spans 8 years, and the treatment strategies for LLN metastasis in rectal cancer are constantly being optimized and improved. In the early years of the study, the treatment strategies in our institution were still being explored, and we performed LLND for all patients with clinical evidence

of LLN metastasis and conducted an exploratory analysis. In recent years, we have gradually established effective and practical indications for LLND and we believe that patients with LLN diameter ≥ 7 mm after nCRT or poor differentiation should be supplemented with LLND. This can avoid overtreatment while reducing local recurrence. As previously stated, this exploratory and hypothesis-generating study is prospective and multi-institutional, leading to heterogeneity in patients and treatments; therefore, the results must be interpreted cautiously [18]. For example, most LLND procedures are performed in patients from Chinese National Cancer Center centers. Second, there are surgical thresholds for TME with LLND, and different surgeons may perform surgical procedures with subtle differences. Although the sample size in our study was relatively large, this is the result of ten years of research, and there may be differences in the quality of surgical procedures and pathology reports.

This multicenter cohort study revealed that an SA node size of 9 mm for obturator nodes and 6 mm for internal iliac nodes is a reliable indicator of pathological LLN metastasis in non-CRT patients. For post-CRT patients, an SA node size of 7 mm for the obturator nodes and 4 mm for the internal iliac nodes may be used to accurately predict pathological LLN metastasis. In contrast with the internal iliac area, pathological obturator LLN metastasis is associated with more advanced disease with reduced DMFS, CSS, and OS rates but does not increase LRFS.

Acknowledgements The authors thank the Chinese Lateral Node Collaborative Group for supporting and reviewing the present study, especially for their help in data collection.

Author contributions (I) conception and design: QL, WX, and FH; (II) administrative support: QL and WX; (III) provision of study materials or patients: FH, RW, SCZ, SWM, and TXX; (IV) collection and assembly of data: FH, and RW; (V) data analysis and interpretation: QL, WX, FH, and RW. All authors read and approved the final.

Funding This study was supported by the National Key Research and Development Program/Prevention and Treatment Research on Commonly Occurring and Prevalent Diseases (No. 2022YFC2505003) and the Medicine and Health Technology Innovation Project of the Chinese Academy of Medical Sciences (No. 2017-12 M-1e006).

Data availability The data that support the findings of this study are available from the authors but restrictions apply to the availability of these data, which were used under license from the Cancer Hospital, Chinese Academy of Medical Sciences for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission from the Cancer Hospital, Chinese Academy of Medical Sciences.

Declarations

Ethics approval and consent to participate The study protocol and all amendments were approved by the ethics committee of the Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (NCC2022C-325). Written informed consent was obtained from individual or guardian participants.

Animal studies Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

References

1. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet. 1986;1(8496):1479–82. https://doi.org/10.1016/s0140-6736(86)91510-2.
2. Taylor FG, Quirke P, Heald RJ, et al. Preoperative magnetic resonance imaging assessment of circumferential resection margin predicts disease-free survival and local recurrence: 5-year follow-up results of the MERCURY study. J Clin Oncol. 2014;32(1):34–43. https://doi.org/10.1200/JCO.2012.45.3258.

3. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351(17):1731–40. https://doi.org/10.1056/NEJMoa040694.
4. Sluckin TC, Couwenberg AM, Lambregts D, et al. Lateral lymph nodes in rectal cancer: do we all think the same? a review of multidisciplinary obstacles and treatment recommendations. Clin Colorectal Cancer. 2022;21(2):80–8. https://doi.org/10.1016/j.clcc.2022.02.002.
5. Kim TH, Jeong SY, Choi DH, et al. 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(3):729–37. https://doi.org/10.1245/s10434-007-9696-x.
6. Yagi R, Shimada Y, Kameyama H, et al. Clinical significance of extramural tumor deposits in the lateral pelvic lymph node area in low rectal cancer: a retrospective study at two institutions. Ann Surg Oncol. 2016;23(Suppl 4):552–8. https://doi.org/10.1245/s10434-016-5379-9.
7. Shiraishi T, Sasaki T, Tsukada Y, et al. Radiologic factors and areas of local recurrence in locally advanced lower rectal cancer after lateral pelvic lymph node dissection. Dis Colon Rectum. 2021;64(12):1479–87. https://doi.org/10.1097/DCR.0000000000001921.
8. Sammour T, Chang GJ. Lateral node dissection in low rectal cancer: time for a global approach? Ann Surg. 2017;266(2):208–9. https://doi.org/10.1097/SLA.0000000000002273.
9. Kawai K, Shiratori H, Hata K, et al. Optimal size criteria for lateral lymph node dissection after neoadjuvant chemoradiotherapy for rectal cancer. Dis Colon Rectum. 2021;64(3):274–83. https://doi.org/10.1097/DCR.0000000000001866.
10. Ogura A, Konishi T, Cunningham C, et al. Neoadjuvant (Chemo)radiotherapy with total mesorectal excision only is not sufficient to prevent lateral local recurrence in enlarged nodes: results of the multicenter lateral node study of patients with low cT3/4 rectal cancer. J Clin Oncol. 2019;37(1):33–43. https://doi.org/10.1200/JCO.18.00032.
11. Schaap DP, Boogerd LSF, Konishi T, et al. Rectal cancer lateral lymph nodes: multicentre study of the impact of obturator and internal iliac nodes on oncological outcomes. Br J Surg. 2021;108(2):205–13. https://doi.org/10.1093/bjs/znaa009.
12. Zhou S, Zhang H, Liang J, et al. Feasibility, indications, and prognostic significance of selective lateral pelvic lymph node dissection after preoperative chemoradiotherapy in middle/low rectal cancer: results of a multicenter lateral node study in China. Dis Colon Rectum. 2023. https://doi.org/10.1097/DCR.0000000000002640.
13. Hashiguchi Y, Muro K, Saito Y, et al. Japanese society for cancer of the colon and rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. Int J Clin Oncol. 2020;25(1):1–42. https://doi.org/10.1007/s10147-019-01485-z.
14. Beyond TME Collaborative. Consensus statement on the multidisciplinary management of patients with recurrent and primary rectal cancer beyond total mesorectal excision planes. Br J Surg. 2013;100(8):1009–14. https://doi.org/10.1002/bjs.9192.
15. Fujita S, Akasu T, Mizusawa J, Saito N, Kinugasa Y, Kanemitsu Y, 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(6):616–21. https://doi.org/10.1016/S1470-2045(12)70158-4.
16. Wang P, Zhou S, Zhou H, et al. Evaluating predictive factors for determining the presence of lateral pelvic node metastasis in rectal cancer patients following neoadjuvant chemoradiotherapy. Colorectal Dis. 2019;21(7):791–6. https://doi.org/10.1111/codi.14595.
17. Fujita S, Mizusawa J, Kanemitsu Y, et al. 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(2):201–7. https://doi.org/10.1097/SLA.0000000000002212.
18. Laparoscopic Surgery Committee of the Endoscopist Branch in the Chinese Medical Doctor Association (CMDA); Laparoscopic Surgery Committee of Colorectal Cancer Committee of Chinese Medical Doctor Association (CMDA); Colorectal Surgery Group of the Surgery Branch in the Chinese Medical Association (CMA). [Chinese expert consensus on the diagnosis and treatment for lateral lymph node metastasis of rectal cancer (2019 edition)]. Zhonghua Wei Chang Wai Ke Za Zhi. 2019;22(10):901–912. https://doi.org/10.3760/cma.j.issn.1671-0274.2019.10.001.
19. Ogura A, Konishi T, Beets GL, et al. Lateral nodal features on restaging magnetic resonance imaging associated with lateral local recurrence in low rectal cancer after neoadjuvant chemoradiotherapy or radiotherapy. JAMA Surg. 2019;154(9): e192172. https://doi.org/10.1001/jamasurg.2019.2172.
20. Bae JH, Song J, Kim JH, et al. Lateral lymph node size and tumor distance from anal verge accurately predict positive lateral pelvic lymph nodes in rectal cancer: a multi-institutional retrospective cohort study. Dis Colon Rectum. 2023;66(6):785–95. https://doi.org/10.1097/DCR.0000000000002528.
21. 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(1):80–7. https://doi.org/10.1097/01.sla.0000225359.72553.8c.
22. Ogawa S, Itabashi M, Hirosawa T, et al. Lateral pelvic lymph node dissection can be omitted in lower rectal cancer in which the longest lateral pelvic and perirectal lymph node is less than 5 mm on MRI. J Surg Oncol. 2014;109(3):227–33. https://doi.org/10.1002/jso.23478.
23. Akasu T, Iinuma G, Takawa M, et al. Accuracy of high-resolution magnetic resonance imaging in preoperative staging of rectal cancer. Ann Surg Oncol. 2009;16(10):2787–94. https://doi.org/10.1245/s10434-009-0613-3.
24. Hatano S, Ishida H, Ishiguro T, et al. Prediction of metastasis to mesorectal, internal iliac and obturator lymph nodes according to size criteria in patients with locally advanced lower rectal cancer. Jpn J Clin Oncol. 2015;45(1):35–42. https://doi.org/10.1093/jjco/hyu162.