ORIGINAL PAPER

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Lateral Lymph Node Dissection in Rectal Cancer; "Does Image Size of Lymph Node Really Matter?"

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ABSTRACT

Background: The probability of lateral compartment recurrence is significantly increased in rectal cancer diagnosed patients with clinical evidence of Lateral Pelvic Lymph Node (LPLN) metastases if they get Total Mesorectum Excision (TME) without LPLN dissection, even if they undergo combined-modality chemoradiation therapy (nCRT).
Objectives: The objective of this study is to determine the minimum post neoadjuvant chemoradiotherapy LPLN size that reliably predicts lymph node positivity.
Patients and Methods: This study is a prospective observational cohort study conducted at the National Cancer Institute NCI of Cairo University, Shifa AL-Orman Cancer Hospital, and Damanhur Cancer Center which included 39 Egyptian with lower rectum cancer patients who were evaluated after meeting the study's requirements; managed by TME and LPLN dissection in the period from January 2020 till the end of September 2022.
Results: lateral pelvic lymph Node size (post nCRT) ranged between (5-10) mm with median 6.5 mm and mean 7.0 ± 2.2 in negative LPLN group while ranged between (5-12) mm with median 8 mm and mean 8.0 ± 2.1in positive LPLN group with difference of no statistical significance at (p=0.184). To determine whether any of the two research groups has a positive lateral pelvic lymph node, a ROC curve of node size (post nCRT) was built, and the matching areas under curve (AUC) were determined to be 62%, (p=0.184). With sensitivity values of 73.9%, 37.5% and 50%, 8 mm was the ideal cut-off value for Node size (post nCRT) for identifying the lateral pelvic lymph node presence.
Conclusion: Our early experience indicate that residual lateral pelvic lymph nodes larger than 8 mm after nCRT in lower rectal cancer are suspicious of being metastasized, and we do recommend ipsilateral LPLN dissection for this group of patients. LLNs-involved systematic research is required, paying close attention to the anatomical placements, primary- and restaging sizes, and LLNs themselves.
Key words: lateral pelvic lymph node dissection, cancer rectum, neoadjuvant

Abbreviations:
LPLN: Lateral Pelvic Lymph Node;
TME: Total Mesorectum Excision;
nCRT: neoadjuvant Chemo Radiation Therapy;
NCI: National Cancer Institute;
AUC: Area Under Curve;
LLNs: Lateral Pelvic Lymph Nodes;
LR: Local Recurrence;
LLND: Lateral Pelvic Lymph Nodes Dissection;
CRM: Circumferential (Radial) Resection Margin;
SD: Standard Deviation;
BMI: Body Mass Index;
ECOG: Eastern Cooperative Oncology Group;
yp: Post neoadjuvant Pathology;
ROC: Receiver Operating Characteristic Curve

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BACKGROUND

The topic of lateral pelvic lymph node dissection (LLND) in locally advanced

rectal cancer (LARC) has drawn a lot of attention since it is believed that 10 to 25% of total involved patients with lower rectal involved cancer experience lateral nodal spread. Local recurrence (LR) rates can reach up to 35% in cases of lateral nodal spread, and these patients are frequently palliated (1). The East and West have different therapeutic paradigms for these pre-treatment metastatic LLNs. nCRT is not a common form of treatment in the East; instead, upfront rectal resection in accordance with total mesorectum excision (TME) principles and a LLND for tumor removal and any metastatic LLNs are the standard treatment methods (2). In contrast, the Western standard of treatment uses TME after nCRT without the use of an LLND (3). LLND indication should be clarified in the nCRT era, taking into account the improvements in preoperative evaluation brought about by the high-resolution rectal MRI adoption and the also development of more reliable LLN imaging (4).

PATIENTS AND METHODS

The aim of this study is to determine the minimum post neoadjuvant chemoradiotherapy lateral pelvic lymph node size that reliably predicts lymph node positivity. This study included 88 patients with mid or low primary rectal cancer who had lateral pelvic lymph node (LLN) metastasis (external iliac, internal iliac, or obturator node) 5 mm in size or more as determined by MRI before nCRT. Patients were assessed by the multi-disciplinary board at the National Cancer Institute NCI, Shifa AL-Orman Cancer Hospital and Damanhur Cancer Center including: surgical oncologist, medical oncologist, radiation oncologist, pathologist and interventional radiologist. Investigations included full labs, tumor markers as CEA and CA19.9, magnetic resonance imaging (MRI pelvis) for loco regional clinical staging, contrast enhanced computed tomography (whole body CT) as a metastatic work up for clinical staging. The type of imaging modality in the post neoadjuvant setting was MRI "preoperative MRI". All patients had a colonoscopy and tissue biopsy to confirm the diagnosis of rectal cancer, define tumor pathological type, tumor grade, tumor length, tumor location and exclude any synchronous colonic lesions. Patients were assigned for their plan of combined treatment modality in the form of either combined approach of nCRT and TME or combined approach of nCRT, TME, and LLND (*fig. 1, 2*). Postoperative pathology results are obtained including (pT stage, pN stage and LLN size if positive) and Immunohistochemistry tests by cytokeratin when was needed to confirm the histopathological results. Data were managed and analyzed using SPSS version 25.0. Numbers and Percentages described qualitative variables while mean and standard deviation for quantitative variables. ROC (Receiver Operating Characteristic) curve was used to select the best cut-off point for the lateral pelvic lymph node size to show positivity. All tests were two-tailed. A p-value < 0.05 was considered significant.

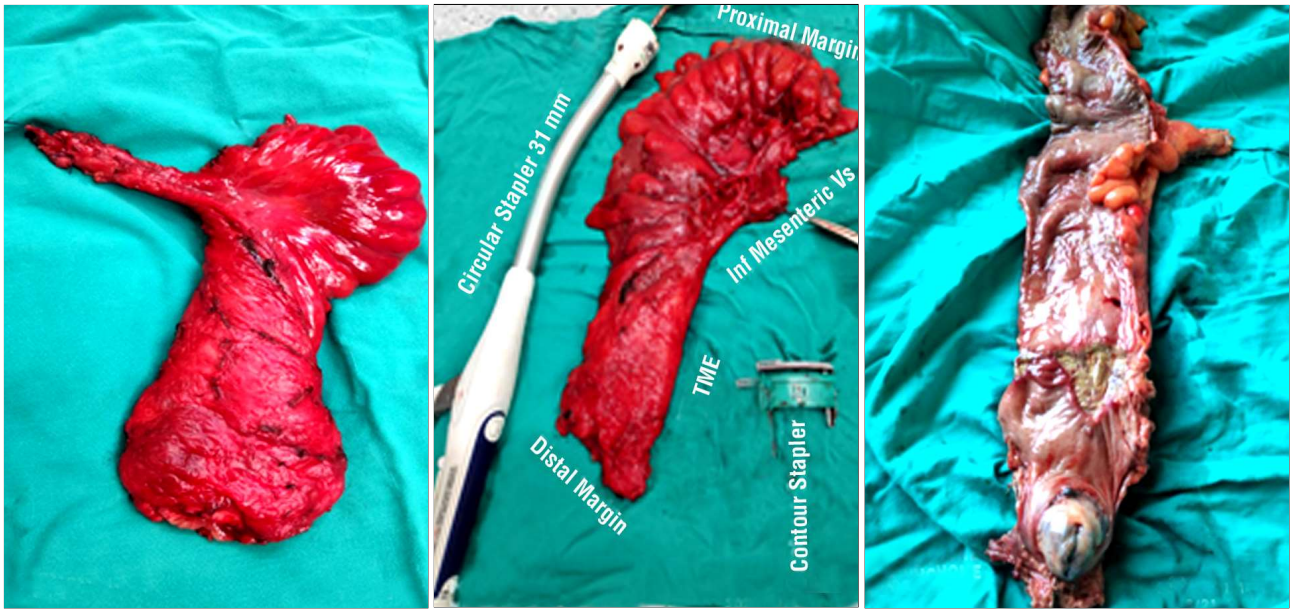

Figure 1 - Complete mesorectum excision showing smooth mesorectum surface with only minor irregularities; intact bulky mesorectum with a smooth surface with only minor irregularities of the mesorectum surface, no surface defects greater than 5 mm in depth, no coning towards the distal margin of the specimen, and smooth appearing CRM on transverse sectioning

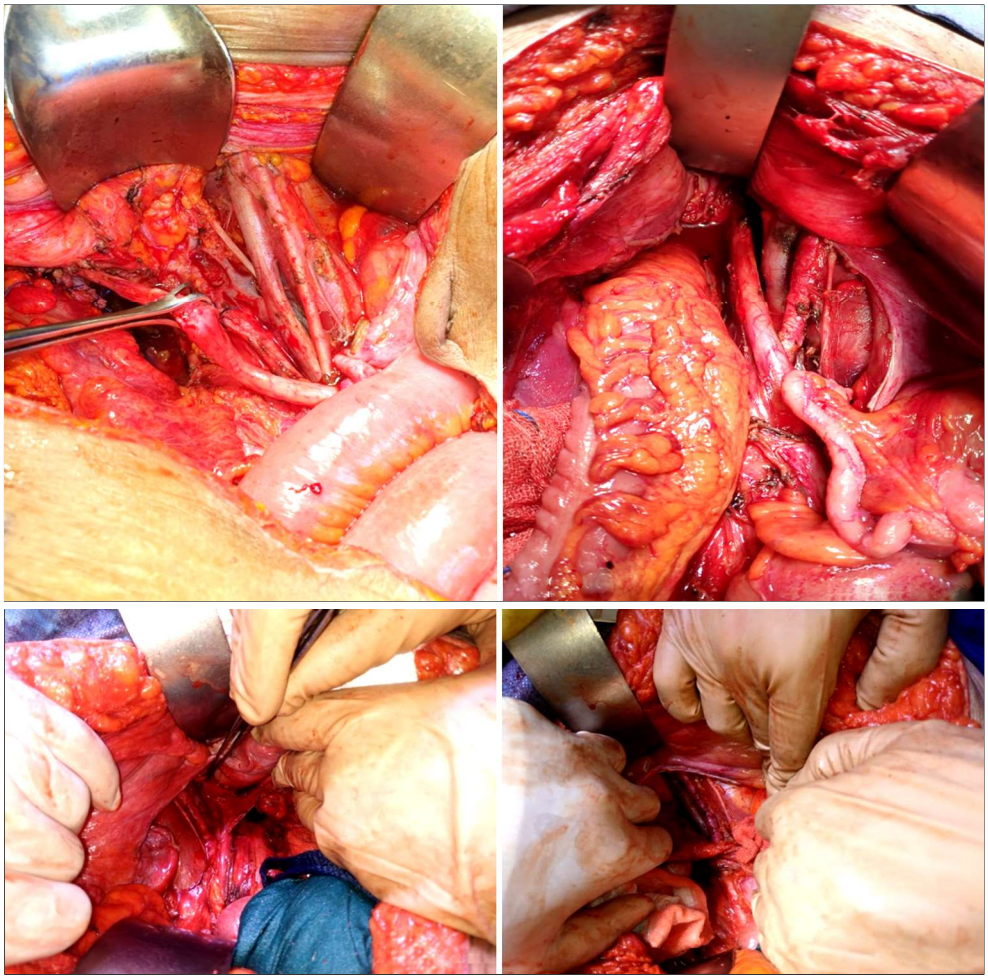

Figure 2 - Lateral pelvic lymph nodes dissection (LPLND) was done when the lateral pelvic lymph node size was equal or more than 5 mm in size.

RESULTS

We identified 88 patients suffering cancer in the rectum and underwent nCRT and TME with or without LLND between January 2020 and the end of September 2022 and who had suspected LPLN metastases. Forty nine (49) patients were excluded as they showed a good response to nCRT and LLN were either disappeared or turned less than 5mm in size by pre-operative MRI reassessment; managed by TME only, leaving thirty nine (39) Patients who were evaluated after meeting the study's requirements; managed by TME and LLND. Then were sorted forming 2 groups according to the final pathological results, 16 patients with negative LLN and 23 patients with positive LLN as displayed in *fig. 3*.

Depending on demographic characters, the age ranged between (30 – 64) years with mean ± SD (46.9 ± 9.3) in negative LN group and ranged between (28 – 76) years with mean ± SD (48.1 ± 13.8) in positive LN group. According to *table 1*; there was difference of no statistical significance among the two groups' ages at (p= 0.773). 11 patients (68.8%) were females and 5 patients (31.2%) were males in negative LN group while in the positive LN group, there were 9 patients (39.1%) who were male and 14 patients (60.9%) who were female, with a difference of no statistical significance at (p=0.869). BMI was with mean ± SD (26.8 ± 4.6) in negative LN group and with mean ± SD (28.7 ± 3.1) in positive LN group with difference of no statistical significance at (p=0.135). Performance status in the negative LN group was ECOG 0 in 9 patients (56.2%), ECOG 1 in 6 patients (37.5%), and ECOG 2 in 1 patient (6.2%), while the positive LN group was ECOG 0 in 10 patients (43.5%), ECOG 1 in 8 patients (34.8%), and ECOG 2 in 5 patients (21.7%). However, at (p=0.508), there was a difference of no statistical significance among the two groups as displayed in *table 1*. Regarding ypT classification, among 23 patients with positive LN, 14 patients (60.9%) and 6 patients (26.1%), respectively, received T3 and T4 diagnoses, with difference of no statistical significance among the two groups at (p=0.268). Regarding ypN classification, among 16 patients of negative LLN, 11 patients (68.8%)

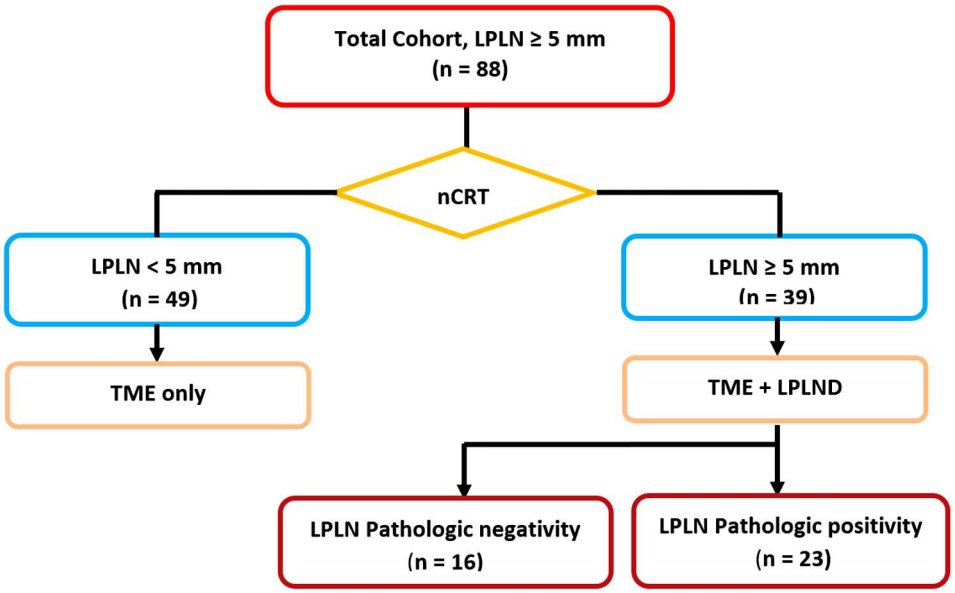

Figure 3 - Flowchart that illustrates the proportion of patients with pathogenic LPLN positivity before and after nCRT, broken down by LPLN size. LPLN = lateral pelvic lymph node; LPLND = lateral pelvic lymph node dissection; nCRT = neoadjuvant chemo-radiation therapy; TME = total mesorectum excision

Characteristic	LPLN negative (n = 16)		LPLN positive (n = 23)		P value
Age, y, mean ± SD	46.9 ± 9.3		48.1 ± 13.8		0.773
Gender, n (%)					0.869
male	5 (31.2%)		9 (39.1%)		
female	11 (68.8%)		14 (60.9%)		
BMI, kg/m^2 , mean ± SD	26.8 ± 4.6		28.7 ± 3.1		0.135
Performance Status (PS), n (%)					0.508
ECOG 0	9 (56.2%)		10 (43.5%)		
ECOG 1	6 (37.5%)		8 (34.8%)		
ECOG 2	1 (6.2%)		5 (21.7%)		
yp T classification, n (%)					
T10 (0.0%)	0 (0.0%)				
0.268					
T22 (12.5%)	3 (13.0%)				
T313 (81.2%)	14 (60.9%)				
T41 (6.2%)	6 (26.1%)				
yp N classification, n (%)	Axial LNs **	Axial LNs + (-LPLN)	Axial LNs **	Axial LNs + (+LPLN)	<0.001*
N0	11 (68.8%)	11 (68.8%)	1 (4.3%)	0 (0.0%)	
N1	4 (25.0%)	4 (25.0%)	10 (43.5%)	8 (34.8%)	
N2	1 (6.2%)	1 (6.2%)	12 (52.2%)	15 (65.2%)	
		0.046*		0.046*	^{MH}p0
yp Stage, n (%)					<0.001*
I		2 (12.5%)		0 (0.0%)	
II		9 (56.2%)		0 (0.0%)	
III		5 (31.2%)		21 (91.3%)	
IV		0 (0.0%)		2 (8.7%)	
Lymphovascular invasion, n (%) +++		8 (50.0%)		22 (95.7%)	0.001*
Perineural invasion, n (%) +++		5 (31.2%)		13 (56.5%)	0.218
Node size (post-nCRT) in mm, mean ± SD		7.0 ± 2.2		8.0 ± 2.1	0.184

Table 1 - Post-nCRT patient demographics by pathologic LPLN status

P values <0.05 were considered statistically significant. LPLN = lateral pelvic lymph node; nCRT = neoadjuvant chemo-radiation; yp = post-nCRT pathologic; MH: Marginal Homogeneity Test; p0: p value for comparing between Axial and Axial + LPLN

**Axial LNs = Superior, middle and inferior rectal, inferior mesenteric, mesorectal, lateral sacral, presacral, sacral promontory (Gerota) LN.

and 4 patients (25%) were diagnosed as N0 and N1 respectively while 15 patients (65.2%) and 8 patients (34.8%) of the 23 patients with positive LLN were identified as N2 and N1, respectively, with a difference that was highly statistically significant at (p0.001). As a regard of yp stage, the most common stages were II in 9 individuals (56.2%) and III in 5 patients (31.2%) in the group of patients with negative LN whereas stage III was seen in 21 patients (91.3%) and IV was seen in 2 patients (8.7%), with a highly statistically significant difference at (p0.001), as displayed in *table 1*. Lymphovascular invasion was detected in 8 patients (50%) in negative LN group and in 22 patients (95.7%) in positive LN group with high significant difference that was statistically analyzed (p=0.001). Perineural invasion was detected in 5 patients (31.2%) in negative LN group and in 13 patients (56.5%) in positive LN group with no significant difference at (p=0.218). Node size (post nCRT) ranged between (5-10) mm with median 6.5 mm and mean 7.0 ± 2.2 in negative LN group while ranged between (5-12) mm with median 8 mm and mean 8.0 ± 2.1 in positive LN group with difference of no statistical significance at (p=0.184) as displayed in *table 1*. To determine whether any of the two research groups has a positive lateral pelvic lymph node, a ROC curve of node size (post nCRT) was built, and the matching areas under curve (AUC) were determined to be 62%, (p=0.184). As indicated in *table 2*, *fig. 4*, with sensitivity values of 73.9%, 37.5%, and 50%, 8 mm was the ideal cut-off value for Node size (post nCRT) for identifying the lateral pelvic lymph node presence.

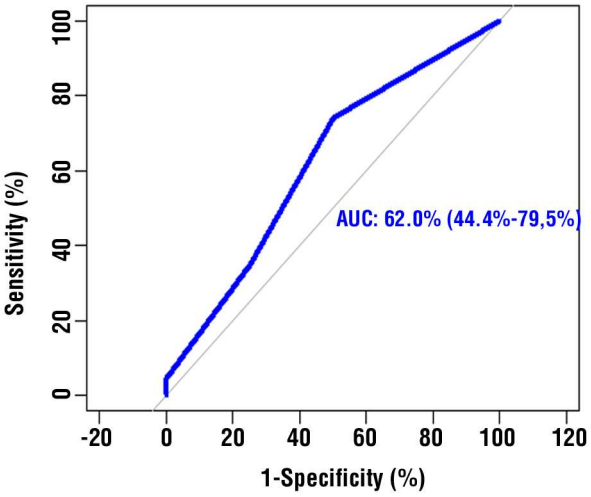

Figure 4 - ROC Curve of Node size (post nCRT) to detect LN positivity (metastases)

DISCUSSION

The probability of lateral compartment recurrence is significantly increased in rectal cancer diagnosed patients with clinical evidence of LLN metastases if they get TME without LLND, even if they undergo combined-modality chemoradiation therapy with TME (5) Even after a curative proctectomy and preoperative CRT, 83% of patients experienced locoregional recurrence with lateral pelvic related recurrence (6) In the Western population, the rate of lateral local recurrence at five years was about 11.8%; patients with lateral nodes that seemed to be malignant had a rate that was twice as high (20.9%) as those without them (7). The lateral wall involved pelvic LN metastases prevalence in advanced local rectal cancer taking into account all pertinent research that has recently been published. It varies between 7 and 24% (8).

There was no significant difference in regard to the patients' demographic data including "age in years, gender, BMI kg/m^2 and performance status ECOG scale" among the two groups of LLN positivity/ negativity as regard of age at (p= 0.773), gender at (p=0.869), BMI difference at (p=0.135) and ECOG at (p=0.508) as shown in *table 1*. Similarly Malakorn et al. (9) and Ogawa et al. (8) reported identical outcomes. On the other hand Ueno et al. research (10) reported gender was a significant predictor of positive LLNs and Sugihara et al. (11) study's multivariate analysis displayed a significant relationship among the female gender and a higher incidence of lateral pelvic lymph node metastases., while Kinugasa et al. (12) indicated that male gender was a significant predictor of positive LLNs at (p=0.009). Participants in the LLND group were younger than those in the non-LLND group; according to Peilan Ma et al. who conducted that age may be an influencing factor. However, this has to be further investigated and verified (13). Regarding ypT classification;

Table 2 - Diagnostic performance (sensitivity, specificity) of Node Size (post nCRT) to detect positivity of lateral pelvic lymph node

AUC	P	95% C. I	Cut off Node Size (Post nCRT):	Sensitivity	Specificity	PPV	NPV
62%	0.184	(0.44-0.80)	8 mm	73.9%	50%	68%	57.1%

AUC: Area under a curve; P-value: Probability value; PPV: positive predictive value; NPV: negative predictive value

our study found a difference of no statistical significance in the depth of tumor invasion (T) between the histologically positive and negative groups at (p=0.268) as shown in *table 1*. Also Malakorn et al. (9) and Ogawa et al. (8) reported the same at (p= 0.15), (p= 0.094) respectively. Kinugasa et al. (12) noted the same results that the depth of tumor invasion (T) was not a significant predictor of positive LLNs at (p= 0.3459). While, Otero de Pablos, Mayol J ; (14) Tan et al. (15) and Fujita et al. (16) reported that T3-T4 rectal tumors were significantly associated with an increased risk of LLN metastasis, and that low rectal cancer and T3-T4 stage cancer had the highest hazard ratios. Our investigation indicated that perirectal involved LN metastasis and mesenteric node metastasis (ypN) were a significant determinant among the histologically positive and negative groups at (p 0.001) as reported in *table 1*. The identical outcomes were also reported by Malakorn et al. (9) and Ogawa et al. (8) at (p 0.001) and (p=0.0423, respectively. Kinugasa et al. (12) verified that perirectal lymph node metastasis had a higher hazard ratio and was related with a higher occurrence in positive LLNs. Regarding lymphovascular invasion; our study found that lymphovascular invasion among the histologically positive and negative groups was highly significant statistically at (p=0.001) and the rate of lymphovascular invasion was considerably higher in the group with positive LPLNs (95.7% vs. 50%, p = 0.001) as shown in *table 1*. Malakorn et al. (9), Ogawa et al. (8), Tan et al. (15), Fujita et al. (16) and Kinugasa et al. (12) reported the same results. According to the findings of our investigation, patients with post-nCRT LLN diameters of more than 5 mm had significantly more advanced stages of disease at (p 0.001) and Malakorn et al. (9) reported also the same at (p < 0.001). Regarding the cutoff for the lateral pelvic lymph nodes included size used to choose suitable individuals for the combined nCRT, TME, and LLND strategy; Our study results reported that LLN size (post nCRT) ranged between (5-10) mm with median 6.5 mm and mean 7.0 ± 2.2 in negative LN group while ranged between (5-12) mm with median 8 mm and mean 8.0 ± 2.1 in positive LN group with statistically insignificant difference at (p=0.184) as displayed in *table 1*. Therefore, as shown in *table 2*, *fig. 4*, the optimal cut-off value for LLN size (post nCRT) when identifying positivity of LLN was 8 mm. Another study by Shiratori et al. (17) showed that LLN metastasis was substantially linked with pre-neoadjuvant long-axis diameter of LPLN >6 mm and Akiyoshi et al. (18) similarly showed that LLN metastasis was substantially linked with pre-neoadjuvant short-axis diameter of LPLN >8 mm.. Malakorn et al. (9) similarly reached the conclusion those patients with post-nCRT LLN sizes 5 mm were 100% sensitive for identifying patients with positive LLNs. These results support nCRT-related treatment for patients with chronically enlarged LLN at 5 mm or greater, in addition to TME and LLND. Cribb et al. 2021 (19), Ogura et al. 2019 (20) and Malakorn et al. 2019 (9) have stated that after chemoradiotherapy, lateral pelvic lymph nodes with SA diameters more than 5 mm on MRI are at a high metastatic risk.

Our study is a prospective observational cohort study with accurate data collection, and its main advantages are that it facilitates the study of uncommon exposures, permits the examination of multiple effects, avoids selection bias because it uses a single population group, and permits the collection of data from various sources.

We must also address this study's weaknesses. Because of the small sample size, it may be difficult to get a firm conclusion about the proposed nodal size threshold that would need lateral pelvic LN dissection. The various perspectives of expertise in laparoscopic LPLN dissection among the surgeons participating in this investigation are another factor.

CONCLUSION

As far as we are concerned, this is one of the few prospective studies in the Middle East and Northern Africa region targeting LLN in rectal cancer surgery. Our preliminary findings indicate that residual lateral pelvic lymph nodes larger than 8 mm after nCRT in rectal cancer are suspicious of being metastasized, and we do recommend ipsilateral pelvic LN dissection for this group of patients. The current study seeks to promote multidisciplinary collaboration and broaden global consensus by available current data presentation and recommendations provision per specialty. Finally, LLNs-involved systematic research is required, paying close attention to the anatomical placements, primary- and restaging sizes, and LLNs themselves.

Competing interests

The authors declare that they have no competing interests.

Source of Fund

This study didn’t receive any fund.

Ethics declarations

This study was approved by the Institutional Review Board and Ethical Research Committee of the National Cancer Institute of Cairo University, Egypt with Institutional Review Board (IRB) approval number (IRB Review Number: 201920017.3). The authors confirm that all steps of scientific research were performed in accordance with relevant guidelines and regulations. Informed written consent to participate in the study was provided by all participants.

Author's contributions

All Authors shared in this research work, read and approved the final manuscript.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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