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ORIGINAL ARTICLE

# Incidence and Predictive Model for Lateral Pelvic Lymph Node Metastasis in Lower Rectal Cancer

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## Abstract

The lateral pelvic lymph node recurrence after curative resection in rectal cancer has been reported in more than 20% of cases and the lateral pelvic lymph node (LPLN) metastasis is an independent risk factor for local recurrence. A prospective cohort study with diagnosis of lower rectal cancer stages II and III performed to identify the factors with significant correlation with LPLN metastasis was categorised based on the number of positive factors and proposed a risk stratification model to uncover a possible benefit of LPLD in specific patient subgroups. Forty-three patients with lower rectal cancer underwent curative surgery, total mesorectal excision with bilateral lateral pelvic lymph node dissection. Pre-operative, female gender, raised serum CEA (> 5 ng/mL), cT4, enlarged mesorectal lymph nodes, borderline enlarged LPLN on MRI, lower location (< 5 cm from anal verge), large size (> 5 cm) and non-circumferential lesion were significant predictors for LPLN metastasis. Histopathological, higher tumour grade, higher pT and pN stage, and the presence of LVI were significant factors. On cox-proportional hazard model analysis, female gender, large tumour, cT4, enlarged mesorectal lymph nodes, borderline enlarged LPLN, pN1 and positive LVI were associated with significant hazard. In conclusion, a specific group of patients with lower rectal cancer of stages II and III might be have treated with LPND in spite of concurrent chemo-radiation to achieve satisfactory oncological outcome. The proposed stratification grouping is strongly guiding the patient for lateral pelvic lymph node dissection. Further study to prove the oncological advantage of LPND is warranted at large scale.

**Keywords** Lower rectal cancer · Lateral pelvic lymph node dissection · Predictive factors · Risk stratification score

## Introduction

The prognostic importance of lymph node metastasis in rectal cancer has been proven based on multiple statistically robust published trials and is generally used in patient management. Lateral pelvic lymph node (LPLN) metastasis in rectal cancer is considered as a systemic disease. Minimum of 12 lymph nodes should be examined in order to confirm the node negativity in rectal cancer. Conclusions of a four-arm trial (INT-0089) has indicated that overall survival and cancer specific survival is significantly higher as the number of reported lymph nodes increases even with negative nodes [1].

In rectal cancers, the incidence of lateral lymph node involvement in patients who received treatment without chemo-radiation has been reported as 10 to 25% [2–12, 4–9, 2–8/Ishihara]. This "vulnerable field" has oncological significance as well due to close proximity to circumferential margin of the primary tumour. UICC staging has also included the internal iliac artery region lymph nodes as the regional lymph nodes in rectal cancer. There is a theory for metastasis to the LPLN that the lymphatic drainage from lower rectum passes beyond mesorectum through the lateral ligament and then along the internal iliac artery and obturator space. Among lateral pelvic lymph node regions, the obturator region has the highest rate of nodal involvement, so it should be considered as an important region of cancer spread in cases of lower rectal cancer [13]. However, the importance of lymphadenectomy respective to these lateral pelvic areas is of prognostic benefit both in survival as well as local control of the disease and also it

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determines the optimal extent of lymphadenectomy [14, 15]. A significant local recurrence rate in rectal cancer compared to colon cancer is a challenging issue even with advancement in surgical and non-surgical treatments [16].

It is very difficult to generalise the indications of lateral pelvic lymphadenectomy because the parameters related to malignant potential of the tumour are not adequate to decide the selection criteria for prophylactic lateral pelvic lymphadenectomy. Existence of clinically suspected lateral pelvic lymph nodes is of greatest value to lymph node dissection. In the western world, surgeons are in favour of lateral lymph node dissection in a group of the patients with diverse prognostic factors [3, 9, 17]. The Colon and Rectal Surgery Guidelines 2000 have also mentioned that the lateral pelvic lymph node dissection should be done in clinically suspected lateral pelvic disease [18].

The clinical parameters of the malignant potential in lower rectal cancer are level of distal tumour edge, annularity, depth of invasion, number of metastatic nodes other than LPLN, involvement of superior rectal artery region nodes, pre-operative serum CEA level and histologic differentiation of tumour. Among all these features, only some risk factors including tumour aggressiveness as the status of mesorectal nodes and tumour grade have been reported in previous studies [14]. For performing lymph node dissection, it is important to have pre-operative diagnosis of LPLN metastasis, but the available imaging including CECT or MRI has low accuracy in diagnosing metastatic LPLN in about 85% cases [19, 20]. The combined use of clinico-pathological factors with these modalities can achieve more precise diagnosis. However, the evidence level to justify prophylactic lateral pelvic lymphadenectomy is still low [19]. There are few drawbacks of the prophylactic lateral pelvic lymphadenectomy as well. These include longer operative time, higher intraoperative blood loss and higher rate of post-operative complications including urinary and sexual dysfunction especially in non-metastatic lateral lymphadenectomy cases [21, 22].

The 5-year survival of patients with lateral pelvic lymph node metastasis has been found to be comparable to patients with resectable liver or lung metastasis, as about 40% and recurrence free survival is about 55% [14, 15]. The possibility of advantage in survival and local disease control has been proposed by several authors in different patients' population but definitive evidences are awaited [6, 23]. These data are based on the reports from Japan and China. The overall recurrence rate after curative resection in rectal cancer is more than 20% has been reported in various studies and the LPLNs metastasis is an independent risk factor for local recurrence [3, 23]. Few reports favour the role of pre-operative chemo-radiotherapy in locally advanced rectal cancer in improving the local recurrence rate but survival benefit is still not clear [24, 25]. We hypothesised that the lateral pelvic lymph node involvement is a regional disease in lower rectal cancer patients and LPND may be beneficial in selective group of lower rectal cancer patients with higher risk of LPLN metastasis.

## Material and Methods

### Patients

It was a prospective cohort study of patients with diagnosis of rectal cancer admitted in the Department of Surgical Oncology for surgical treatment at Kidwai Memorial Institute of Oncology, Bangalore, over the period from July 2015 to December 2016. We included patients with diagnosis of carcinoma rectum based on digital rectal examination, colonoscopy and histopathology of rectal biopsy. All patients underwent pre-operative imaging with oral and intravenous contrast enhanced computerised tomography (CECT) of the abdomen and pelvis to assess the characteristics of tumour including level of lower edge of the tumour, transmural depth (T2/T3/T4), annularity ($< 3/4$ or $\geq 3/4$), involvement of mesorectal lymph nodes, nodal involvement in upward direction including superior rectal artery region, inferior mesenteric artery region and para-aortic area and to rule out distant metastasis. All patients underwent biopsy of rectal lesion to confirm the diagnosis and to grade the tumour. Required demographic parameters were considered into account for all the patients. All patients assessed for fitness for the anaesthesia under ASA II or less. All patients had haematological and biochemical work-up including liver function tests, renal function tests, cardiac assessment, chest radiogram and serum CEA.

Patients with histo-pathologically proven diagnosis of rectal cancer with lower edge of the tumour at or below the peritoneal reflection and clinical stage on pre-operative imaging T3, T4,or T2 N+ were included. Patient with distant metastasis such as hepatic or lung metastasis or malignant ascites, patients who had received neo-adjuvant radiotherapy or chemotherapy, and circumferential margin positive for tumour on histopathological examination were excluded.

All patients underwent curative resection either anterior resection or abdominal perineal resection with total mesorectal excision followed by bilateral lateral pelvic lymph node dissection in internal pudendal artery area, internal iliac artery area and obturator region. In case of enlarged lateral pelvic lymph nodes picked up during surgery, extended lymph node dissection along external and common iliac artery area and presecral area was done.

We noted the presence of metastasis in lateral pelvic lymph nodes separately in different groups. On histopathological examination, the total number of dissected lymph nodes, number of positive nodes in total and in "vulnerable field", diameter (average of long axis and short axis) of largest involved lymph nodes among different regions noted. The incidence of

involvement of lateral pelvic lymph nodes evaluated in relation to tumour characteristics such as the level of lower edge of tumour, trans-mural depth (T2/T3/T4), annularity (< 3/4 or ≥ 3/4), involvement of mesorectal lymph nodes (0, 1–3 or ≥ 4), nodal involvement in upward direction, biopsy grade (well, moderate, and poor/mucinous differentiation) and serum CEA level (≤ 5 or > 5 ng/mL). The factors with significant correlation with LPLN metastasis, were categorised based of the number of positive factors and proposed a risk stratification to uncover a possible benefit of LPLD in specific patients group. It was the primary end point of our study.

### Statistical Analysis

All parameters were analysed and the differences compared statistically by the log-rank test among various risk factors. For multivariate analysis Cox's proportional hazards model was used. The differences between groups were considered statistically significant at $p < 0.05$.

## Results

### Patient Characteristic

Forty-three patients with lower rectal cancer underwent curative surgery, total mesorectal excision with bilateral lateral pelvic lymph node dissection during the period from July 2015 to December 2016 at our institute. At the end of framed time period, all patients were divided into two cohorts, first cohort was positive LPLN and second was non-metastatic LPLN. Demographic profile of both cohorts detailed in Table 1. Age at the time of diagnosis was comparable between two groups. Female gender had significantly higher LPLN metastasis ($p = 0.004$). No significant differences were seen in BMI and ASA grade of the patients between these groups (Table 1).

### Tumour Characteristics

The clinical characteristics and staging of tumour are shown in Table 1. Group with positive LPLN had higher number of patients with epicentre of tumour located below the peritoneal reflection but statistical non-significant ($p = 0.1$). Serum CEA level (< 5 ng/mL) was significantly higher with positive LPLN ($p = 0.01$). Among radiological imaging features, higher T stage (cT4 vs cT3), enlarged mesorectal lymph nodes and non-significant enlarged LPLN were significantly correlated with LPLN metastasis. Non-circumferential lesions were significantly associated with higher incidence of ipsilateral LPLN metastasis [Table 1].

### Pathological Characteristics

Although majority of patients with LPLN metastasis had pT3 or pT4 (89%), but the pT stage distribution was not significantly different between both groups. Lower rectal cancer had higher LPLN metastasis compared to Middle-rectum. Large tumour size, higher histological grade, pathological positive mesorectal lymph nodes and the presence of LVI were significantly associated with higher rate of LPLN metastasis [Table 2].

### Risk Stratification for LPLN Metastasis

All clinical and pathological factors with significant correlation with LPLN metastasis were analysed with cox-proportional hazard model [Table 3]. Among pre-operative features, female gender, large tumour size (≥ 5 cm), higher clinical T stage (cT4 vs cT3), enlarged mesorectal lymph nodes and non-significant enlarged LPLN (< 8 mm on MRI) were associated with significant hazard ratio for LPLN metastasis. Pathological N stage and the presence of LVI also had significant hazard. Based on those factors, the proposed stratification (group I to IV) showed the cumulative incidence of LPLN metastasis in group I to IV as 7.14, 11.10, 33.3 and 80%, respectively [Table 4].

## Discussion

The extent of lymphatic spread in rectal cancer can be divided into mesorectal and extra-mesorectal lateral pelvic lymph node metastasis and it is the most important parameter regarding post-operative survival. The regional lymphatic areas of lower rectum are classified among four areas, i.e., mesorectal area, superior rectal artery (SRA) area, inferior mesenteric artery (IMA) area, and lateral area. The lateral area, outside of the mesorectum is further divided into six regions based on the named vessels: (1) the internal pudendal (outside of the pelvic plexus), (2) the internal iliac (proximal to the superior vesical artery), (3) the common iliac, (4) the external iliac, (5) the obturator, and (6) the presacral regions [2]. Among these lateral regions, the internal pudendal artery region, the internal iliac artery and obturator region have the highest rate of nodal involvement, which is called as "vulnerable field" in the lower rectal cancers [13].

After curative resection in rectal cancer, LPLN metastasis is the major cause of pelvic recurrence that imposes high morbidity and ruins the patient's quality of life [24]. For the mesorectum, total mesorectal excision (TME) is the standard procedure for surgically resectable low rectal cancer and has been accepted due to good prognosis and low morbidity. The available strategy to treat the extra-mesorectal disease is TME followed by adjuvant radiotherapy. The Korean study

**Table 1** Pre-operative clinico-radiological factors and incidence of LPLN metastasis

| Characteristics | | LPLN metastasis positive ($N = 9$) | LPLN metastasis negative ($n = 34$) | $p$ value |
|---|---|---|---|---|
| Age | < 50 years | 5 (55.5%) | 15 (44.1%) | 0.11 |
| | ≥ 50 years | 4 (45.5%) | 19 (55.9%) | |
| Gender | Male | 3 (33.3%) | 18 (52.9%) | 0.004 |
| | Female | 6 (67.7%) | 16 (47.1%) | |
| Serum CEA | ≤ 5 ng/mL | 2 (22.2%) | 13 (38.2%) | 0.01 |
| | > 5 ng/mL | 7 (77.8%) | 21 (61.8%) | |
| Tumour location | R | 6 (66.7%) | 19 (55.9%) | 0.1 |
| | r | 3 (33.3%) | 15 (44.1%) | |
| Clinical T stage (MRI) | T3 | 3 (33.3%) | 21 (61.8%) | 0.0001 |
| | T4 | 6 (66.7%) | 13 (38.2%) | |
| Regional lymph nodes | N0 | 3 (33.3%) | 19 (55.9%) | 0.004 |
| | N1 | 5 (55.5%) | 13 (38.2%) | |
| | N2 | 1 (11.2%) | 2 (5.9%) | |
| LPLN on MRI | Not enlarged | 5 (55.5%) | 31 (91.2%) | 0.0001 |
| | Enlarged < 8 mm short axis | 4 (44.5%) | 3 (8.8%) | |
| Annularity | ≤ 2/3 | 5 (55.5%) | 13 (38.2%) | 0.01 |
| | > 2/3 | 4 (44.5%) | 21 (61.8%) | |

*R*—tumour left below peritoneal reflation, *r*—tumour left above peritoneal reflection

demonstrated that adjuvant radiotherapy without lateral lymph node dissection was not enough to control the local recurrence and LPLN metastasis [24]. On the other side, the lateral pelvic lymph node dissection has been demonstrated to have the survival benefit with pathologically proven metastatic LPLN, which is why it is routine practice in Japan but not in Western and Indian subcontinent. Contrary to this, in Dutch TME trial, TME plus radiotherapy showed that most frequent site of recurrence was presacral area rather than lateral pelvic wall [26]. In its support, Swedish study also concluded that LPLN metastasis is not an important cause of local recurrence in lower rectal cancer patients [27].

The most important matter in this regard is to diagnose metastatic LPNL pre-operatively. The sensitivity of cross sectional imaging either trans-abdominal or trans-rectal is not satisfactory. However, available data indicates that the incidence of metastatic lateral pelvic lymph nodes should be correctly assessed in lower rectal cancers for which pathological proof of lymph node metastasis is necessary in a large prospective study. On the other hand, it is important to identify the tumour characteristics such as those having the risk of the metastasis to lateral pelvic lymph nodes. The available studies in literature are mainly from Japan, Korea and China and the clinical results published on lateral lymphadenectomy in the literature are conflicting.

We found that female gender significantly correlated with higher LPLN metastasis, also supported by a recent multicentre study from Japan by Ishihara et al.; females

**Table 2** Post-operative pathological factors and LPLN metastasis

| Characteristics | | LPLN metastasis positive ($N = 9$) | LPLN metastasis negative ($N = 34$) | $p$ value |
|---|---|---|---|---|
| Pathological T stage | T1,T2 | 1 (11.2%) | 6 (17.6%) | 0.14 |
| | T3 | 4 (44.5%) | 17 (50%) | |
| | T4 | 4 (44.4%) | 11 (32.4%) | |
| Mesorectal nodes | Metastasis positive | 4 (44.5%) | 9 (26.5%) | 0.0008 |
| | Metastasis negative | 5 (55.5%) | 25 (73.5%) | |
| Tumour differentiation | Well | 2 (22.2%) | 12 (35.3%) | 0.01 |
| | Moderate | 3 (33.3%) | 13 (38.2%) | |
| | Poor | 4 (44.5%) | 9 (26.5%) | |
| LVI | Present | 6 (66.7%) | 11 (32.4%) | 0.0001 |
| | Absent | 3 (33.3%) | 23 (67.6%) | |
| Size of tumour | ≥ 5 cm | 7 (77.8%) | 19 (55.9%) | 0.009 |
| | < 5 cm | 2 (22.2%) | 15 (44.1%) | |
| Distance from anal verge | < 5 cm | 5 (55.5%) | 14 (41.2%) | 0.03 |
| | ≥ 5 cm | 4 (44.5%) | 20 (58.8%) | |

**Table 3** Cox proportional hazard model analysis of clinico-pathological factors associated with LPLN metastasis

| Factor | Odd ratio (95% C.I.) | *p* value |
|---|---|---|
| Gender (female/male) | 2.25 (0.48–10.5) | 0.02 |
| Serum CEA ng/mL (> 5/≤ 5) | 2.17 (0.39–12.6) | 0.06 |
| Clinical T stage (T4/T3) | 3.23 (0.69–15.21) | 0.04 |
| Regional nodes on MRI (positive/negative) | 2.53 (0.54–11.85) | 0.01 |
| LPLN (enlarged/negative) | 8.27 (1.41–48.53) | 0.0001 |
| Annularity (> 2/3/≥ 2/3) | 0.5 (0.11–2.19) | 0.9 |
| pT stage (T4/T2-T3) | 1.67 (0.37–7.48) | 0.07 |
| pN stage (N+/N-) | 2.22 (0.49–10.16) | 0.02 |
| Tumour differentiation (moderate or poor/well) | 1.91 (0.34–10.68) | 0.09 |
| LVI (present/absent) | 4.18 (0.88–19.92) | 0.001 |
| Size (≥ 5 cm/< 5 cm) | 2.76 (0.5–15.29) | 0.01 |
| Distance from anal verge (< 5 cm/≥ 5 cm) | 1.79 (0.41–7.86) | 0.08 |

having higher incidence of LPLN metastasis than males (4.2 vs 3.8%) among patients who had undergone LPND. Incidence rates were correlated with improved cancer specific survival with LPND. Several hypotheses have been postulated including the short stature in Japanese population increases, the possibilities of lateral spread and that is why they are supporting this extensive dissection. Western colorectal surgeons assume that higher fatty tissue in pelvic cavity precluded the dissection and supported pelvic radiotherapy to cover the vulnerable lymph node field. Indian females have average stature and obesity; thus we recommend for LPND [28].

Clinical T stage on imaging may guide to perform LPND in individual case irrespective of adjuvant treatment. Sugihara et al. observed the survival advantage of LPND in patients with stage II rather than stage III. Although we noted the higher LPLN metastasis in patients with cT4 compared to cT3, but the association between the prognosis and LPND is equivocal [6]. Previous large studies, contradicting the survival advantage of LPND with respect to cT stage, might be due to the inclusion of the patients with early stage tumours (cT1, cT2), and patients treated over a long period of time up to 40 years. Our results are more clear due to inclusion of patients with cT2–4, underwent surgery with complete upward node dissection during a short period of time [25, 29, 30]. The pathological metastatic mesorectal lymph node is a strong predictor for LPLN metastasis, specially patients with N1 status resulting improved survival with LPND [31]. The association of size of primary lesion, pre-operative serum CEA level with LPLN metastasis is not supported by recent multicentre study; however, patients with metastatic LPLN had higher mean size of primary lesion and higher mean serum CEA levels [28]. We observed the significant higher incidence of LPLN metastasis with large tumour size of more than 5 cm.

Pre-operative imaging specially MRI pelvis can play a pivotal role to identify the patient groups, vulnerable to LPLN metastasis. There are several limitations including, enlarged nodes can be inflammatory and the normal-sized nodes could harbour micro-metastasis. Although, the accuracy of MRI for metastatic LPLN is below the mark, but smaller size up to 5 mm lymph node in lateral pelvic group also reported with metastasis in up to 60% in reported series [32]. In our study, patients with enlarged LPLN (size < 8 mm) had higher LPLN metastasis with odd ratio 8.27 (95% CI 1.41–48.53; $p = 0.0001$). Thus, we recommend prophylactic LPLND in selected patients with borderline enlarged LPLN. Other than pN stage, the presence of LVI on histological examination is also a strong predictor of LPLN metastasis.

Collectively, we propose a risk stratification classification based on significant predictors for LPLN metastasis. We noted that patients with four or more than four risk factors have 80% risk of LPLN metastasis, and patients with two and three risk factors have 33% risk of LPLN metastasis. Our institute is a Regional Cancer Centre in South India that receives a large number of referrals of rectal cancer patients for treatment. Hence, the risk factors for lateral pelvic lymph node metastasis in patients with rectal cancer effectively studied in our set up.

**Table 4** LPLN metastasis predictive model based on risk stratification score

| Group | No. of patients | No. of patients LPLN metastasis | Incidence of LPLN metastasis (%) |
|---|---|---|---|
| I (no risk factors) | 14 | 1 | 7.14 |
| II (single risk factor) | 18 | 2 | 11.10 |
| III (2 or 3 risk factors) | 6 | 2 | 33.33 |
| IV (4 or more risk factors) | 5 | 4 | 80 |

The secondary end point of our study as the survival outcome in selected cohort will be analysed with patients of stage II and III rectal cancer who underwent treatment without LPND.

## Conclusion

In conclusion, a specific group of patients with lower rectal cancer of stages II and III might be have advantage of LPND in spite of concurrent chemo-radiation to achieve satisfactory oncological outcome. The proposed stratification grouping is strongly guiding the patient for lateral pelvic lymph node dissection. Further study to prove the oncological advantage of LPND is warranted at large scale.

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## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflicts of interest.

**Ethical Clearance** The study was approved in meeting held by Scientific Review Board of our institute and followed by Ethical clearance which has been taken in meeting held by Medial Ethics Committee on 26-03-2015 with Justice Balakrishna as chairperson.

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