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Management of lateral pelvic lymph nodes in rectal cancer: Is it time to reach an Agreement?

Sigfredo E Romero-Zoghbi, Fernando López-Campos, Felipe Couñago

Abstract

In this editorial, we proceed to comment on the article by Chua JYJ *et al* published in the recent issue of the *World Journal of Clinical Oncology* 2023; 14: 584-592, addressing the management of metastatic lateral pelvic lymph nodes (mLLN) in stage II/III rectal cancer patients below the peritoneal reflection. The treatment of this nodal area sparks significant controversy due to the strategic differences followed by Eastern and Western physicians, albeit with a higher degree of convergence in recent years. The dissection of lateral pelvic lymph nodes (LPLND) without neoadjuvant therapy is a standard practice in Eastern countries. In contrast, in the West, preference leans towards opting for neoadjuvant therapy with chemoradiotherapy or radiotherapy, that would cover the treatment of this area without the need to add the dissection of these nodes to the total mesorectal excision (TME). In the presence of high-risk nodal characteristics for mLLN related to radiological imaging and lack of response to neoadjuvant therapy, the risk of lateral local recurrence increases, suggesting the appropriate selection of strategies to reduce the risk of recurrence in each patient profile. Despite the heterogeneous and retrospective nature of studies addressing this area, an international consensus is necessary to approach this clinical scenario uniformly.

INTRODUCTION

Localized and locally advanced rectal adenocarcinomas below the peritoneal reflection in stages II/III present locoregional recurrence rates of approximately 6.5% following the introduction of total mesorectal excision (TME) [1], with improved outcomes seen through the introduction of multimodal treatments such as radiotherapy and chemotherapy [2-5]. However, recurrence in the lateral compartments of the pelvis is reported in 10% to 25% of patients with locally advanced rectal cancer [6, 7], remaining a concern for those with rectal tumors located below the peritoneal reflection as these tend to drain along the middle and inferior rectal arteries towards the obturators, internal iliac, and external iliac, reaching the common iliac artery. These lateral nodes are precisely not encompassed in TME [8]. Some studies from Eastern countries advocate for lateral pelvic lymph node dissection (LPLND) for patients with clinical or radiological involvement and prophylactical [9,10,11]. Conversely, in Western countries, neoadjuvant treatment with radiotherapy (RT) with or without chemotherapy (CT) followed by TME remains the standard treatment for these patients [2-4]. Other studies recommend selective LPLND if there are high-risk factors for nodal metastasis after neoadjuvant treatment [12-15]. In the era of total neoadjuvant therapy (TNT), a significant reduction in lateral nodal metastasis is expected, favoring selective dissection only in selected cases with limited or absent response to neoadjuvant treatment. In this sense, we discuss the article by Chua JYJ *et al*, evaluating the available clinical evidence from various perspectives [16].

DIFFERENCES IN THE MANAGEMENT OF LPLND BETWEEN EASTERN AND WESTERN VIEWS

Prophylactic Management of Lateral Pelvic Lymph Nodes (LPLN):

The randomized controlled trial 0212 by the Japanese Clinical Oncology Group (JCOG) [9], a multicenter, non-inferiority trial, enrolled 701 patients diagnosed with lower third rectal cancer, stage II or III, without enlarged lymph nodes (short-axis diameter ≥ 10 mm on primary pelvic CT or MRI). Patients were randomized between TME with

LPLND (n = 351) and TME alone (n = 350) without neoadjuvant treatment. The local recurrence rate was significantly lower in the TME plus LPLND group (7.4% vs. 12.6%; P = 0.024), with no significant differences in median follow-up of 7 years in relapse-free survival and overall survival curves between both groups. Subgroup analysis demonstrated improved relapse-free survival in clinically stage III patients undergoing TME with LPLND compared to TME alone [10]. These findings led the Japanese Society for Cancer of the Colon and Rectum (JSCCR) to recommend LPLND, even when LPLNs with a short-axis diameter ≥10 mm are not detected by imaging [10]. However, the trial did not include patients with LPLNs ≥10 mm on initial radiological imaging, and only 7.3% of patients in the TME + LPLND group had pathological LPLNs [11]. Thus, these results indicate that prophylactic LPLND in patients without pathological LPLNs might be overtreatment for this patient subset. Additionally, this study demonstrates that the short-axis diameter (>5 mm) of LPLNs is a predictive factor for positivity in pathological anatomy.

Regarding Western management in this disease scenario, neoadjuvant treatment includes radiotherapy in this area, which could effectively encompass the pelvic nodes. In this regard, the American Society for Radiation Oncology (ASTRO) positioned itself in 2021, stating that in clinical stage II-III, there is strong evidence to recommend neoadjuvant radiotherapy. Multiple clinical trials have shown that neoadjuvant radiotherapy decreases the risk of local recurrence, even in the era of total mesorectal excision (TME) [19-21], and the European Society for Medical Oncology (ESMO) guidelines [22] recommend neoadjuvant treatment with chemoradiotherapy (CRT) as superior to LPLND in terms of efficacy and morbidity. Lastly, the 2020 guideline by the American Society of Colon and Rectal Surgeons considers that in the absence of clinically positive lymph nodes in the lateral pelvic compartment, routine dissection of LPLNs is generally not required, with a strong recommendation based on low-quality evidence [23].

Selective Management of Lateral Pelvic Lymph Nodes (LPLN) and the Role of Imaging Studies:

Detecting suspicious lateral pelvic lymph nodes in rectal cancer patients using imaging studies such as computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography/computed tomography (PET/CT) with 18F-fluorodeoxyglucose poses a challenge given the heterogeneity of available studies and discrepancies between imaging diagnosis and pathological diagnosis [24]. Assessing not only the size of the nodes but also their morphological characteristics like shape, heterogeneous intensity, and borders is helpful in the initial diagnosis [25]. However, after neoadjuvant treatment with chemoradiotherapy (CRT)/radiotherapy (RT), it's advisable to evaluate node size in the short axis and their absence on MRI. A nodal size ≤2.5 mm in the short axis or a reduction of ≥70% in size are predictors of a good response post-surgery [26]. Nevertheless, there's no uniform international consensus on what specific sizes of lateral pelvic lymph nodes could be considered suspicious for malignancy, both at the initial diagnosis and post-neoadjuvant treatment before surgery. The presence of metastatic lateral pelvic lymph nodes in nodes ≤5mm might remain hidden in up to 20% of nodes after neoadjuvant treatment [27]. A study by Ogura A *et al* [28], involving 741 rectal cancer patients, revealed that lymph node size impacts locoregional recurrence rates (LRR). Nodes >7mm on primary MRI showed a 17.9% LRR after treatment. At 3 years, those with nodes <4mm had no recurrences. On the other hand, nodes >7mm on primary MRI and internal iliac nodes had a 52.3% LRR, considerably higher than those of similar size in the obturator compartment (9.5%). CRT with TME and LPLND in these nodes reduced LRR to 8.7% (hazard ratio, 6.2; 95%CI, 1.4-28.5; P = 0.007), proving significantly more effective than CRT and TME alone treatment. In this regard, the 2023 version of The Society of Abdominal Radiology's Colorectal and Anal Cancer Disease-Focused Panel (DFP) [29] updated the rectal cancer lexicon, highlighting a new suggested size threshold for lateral lymph nodes. It suggests nodes with short-axis diameter (SAD) >7mm at the internal iliac and obturator levels as suspicious at initial staging, while post-CRT treatment considers SAD >4mm for

internal iliac nodes and >6mm for obturator nodes as suspicious. However, other features should be considered, such as heterogeneity, abnormal parenchymal signal, irregular borders, and tumor deposit, with the latter being the strongest indicator of poor prognosis in lymph node involvement. Therefore, the MERCURY study considers heterogeneity and irregular borders as suspicious features of preoperative MRI [30].

ADVANTAGES OF SURGICAL TECHNIQUES AND ASSOCIATED COMORBIDITIES

LPLND is considered a relatively complex surgery in colorectal cancer, associated with longer surgical times, more significant blood loss, and a moderate risk of sexual and urinary dysfunction, although it doesn't appear to increase these risks inherent to surgery alone [7]. Studies indicate that preserving autonomic nerves during LPLND can enhance functional outcomes, especially in reducing urinary retention [31]. Comparisons among open, laparoscopic, and robotic surgery suggest the advantages of laparoscopy and robotic surgery. Robotic surgery involves less blood loss (25 mL vs. 637 mL; $p < 0.0001$) and fewer complications, albeit with longer operating times (455 vs. 410 min; $p < 0.007$) compared to open surgery [32]. Robotic surgery can offer improved visualization in the deep pelvis and enhanced precision in identifying vessels and nerves [32]. Despite these advancements, oncological outcomes do not differ among surgical approaches, demonstrating that both laparoscopy and robotic surgery can be equally effective in the short term for treating colorectal cancer with LPLND [33].

CURRENT CHALLENGES AND FUTURE PERSPECTIVES

The surgical approach for advanced rectal cancer with TME and LLND is common in Eastern medical societies, while the Western focus prioritizes neoadjuvant with CRT or TNT followed by TME. A Western study compared patients treated with CRT followed by TME and LPLND with those treated only with CRT and TME, reporting a local recurrence rate of 3% with LPLND *vs* 11% without LPLND ($P = 0.13$), with similar survival figures and identifying LPLND as a significant independent factor for local

recurrences in multivariable analysis (P = 0.01). In patients with long-duration neoadjuvant and adjuvant chemotherapy, LPLND showed a lower LRR (3% vs. 16% without LPLND; P = 0.04), although disease-free survival and overall survival were similar between groups (P = 0.10 and P = 0.11, respectively) [34]. These results suggest a potential shift in the therapeutic approach, assessing the role of systemic treatment in this therapeutic strategy. Indeed, the presence of mLLN should be considered locally advanced disease and treated with CRT or TNT within the Western approach. The OPRA trial [34] evaluated 324 stage II/III rectal cancer patients. After TNT treatment, those achieving complete or near-complete clinical response could adopt a wait-and-watch protocol (W&W), while others underwent total mesorectal excision (TME). At 5 years, the TME-free survival was 39% vs. 54% (P = 0.01), distant metastasis-free survival was 82% vs. 79% (P = 0.66), and local recurrence-free survival was 94% vs. 90% (P = 0.27), respectively, with similar 5-year overall survival data. These results support the safety of the W&W strategy for patients with complete or near-complete clinical responses and the use of TNT as a treatment approach in these patients. This W&W approach has gained more acceptance due, in part, to improvements/intensification in neoadjuvant treatments, where neoadjuvant systemic treatment alongside radiotherapy contributes to optimizing outcomes in these patients. Regarding radiotherapy treatment, proper coverage of the posterior compartment volume in all high-risk patients is crucial. If there are suspicions of affected lateral lymph nodes, the upper border of the mesorectal clinical target volume (CTV) should be at the S1-S2 Level, raising doubts about whether the radiotherapy dose coverage is adequate in routine clinical practice. In this regard, a Dutch study analyzed the coverage of internal iliac and obturator lymph nodes in standard radiotherapy treatment for rectal cancer according to volumes set by major international clinical guidelines. They observed that out of 223 patients with nodes ≥5 mm, 80.7% were within the treatment area, but only 33.3% were included as macroscopic tumor volume (GTV). Despite receiving adequate doses, notable local recurrence rates at 4 years were observed, especially when nodes

were outside the treatment area or received lower doses. These findings suggest the need for improved techniques to locally control affected nodes [36].

For this purpose, the predictive capability of radiomic features in pre-CRT MRI images to forecast the treatment response of lymph nodes in locally advanced rectal cancer is another area of research. In a recently published study involving 78 patients who received neoadjuvant radiotherapy, five radiomic characteristics accurately discriminated responses in the training (AUC 0.908) and validation (AUC 0.865) cohorts were identified. A nomogram combining these features and morphological aspects of lymph nodes exhibited good calibration and discrimination (AUC 0.925 in training, AUC 0.918 in validation). The authors suggest that this model could personalize treatment plans and guide W&W strategies in locally advanced rectal cancer patients, offering a promising tool to enhance care and therapeutic approach [37].

Several studies explore immunotherapies such as nivolumab or toripalimab in locally advanced rectal cancer, showing high complete responses [38,39]. KRAS mutation and circulating tumor DNA (ctDNA) are biomarkers predicting recurrence and prognosis [40,41]. The GALAXY study [42] indicates that molecular residual disease detected by ctDNA is a robust indicator of recurrence. However, prospective clinical trials evaluating molecular and radiomic determinations in predicting the recurrence of LPLN are needed.

CONCLUSION

The difficulty in achieving a global consensus on the ideal treatment of lateral pelvic lymph nodes (LPLN) in rectal cancer due to the variability of available data requires adopting an Intermediate Agreement between Western and Eastern approaches. In a context involving CRT treatment, the selective dissection of lateral pelvic lymph nodes seems to be more beneficial as part of an optimal strategy. The size of LPLN evaluated by MRI with a short-axis diameter (SAD) of ≥7mm, or the presence of suspicious characteristics, could be a crucial predictor of recurrence and should be considered in selective lymph node dissection. It's noteworthy that laparoscopic and robotic surgeries

entail less bleeding and reduced need for transfusions, emphasizing nerve preservation to lower dysfunction risks. CRT, TNT, and surgery with selective lymph node dissection should be considered, but establishing optimal selection criteria for each therapeutic approach is necessary.

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