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REVIEW ARTICLE

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Lateral pelvic lymph node dissection and radiation treatment for rectal cancer: Mutually exclusive or mutually beneficial?

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Abstract

Lateral pelvic lymph nodes (LPLN) in mid-/low rectal cancer pose a theoretical and practical challenge for the clinician and the patient, with geographical differences in management based on historical competing priorities. Although there has been a tendency to think of neoadjuvant radiation versus intraoperative LPLN dissection as a binary choice, they should be more constructively seen as complementary options in the personalized management of patients with rectal cancer. Herein we propose one potential algorithm for using these treatment options in this way based on local preoperative staging and the current evidence available. We also outline future research priorities in this area with the aim of answering several residual questions that remain.

KEYWORDS

chemoradiotherapy for rectal cancer, lateral pelvic lymph node, lateral pelvic lymph node dissection, multidisciplinary treatment for rectal cancer, rectal cancer

Management of lateral pelvic lymph nodes (LPLN) in rectal cancer poses theoretical and practical challenges, with ongoing debate and interest regarding the respective roles of dissection and neoadjuvant radiation treatment in this setting.[1] In the West, the paradigm for rectal cancer management is well established. Broadly speaking, early disease is treated with total mesorectal excision (TME) alone, but for more advanced disease (with significant adenopathy or a threatened radial margin) neoadjuvant therapy is used. In selected cases, induction chemotherapy or consolidation chemotherapy may also be used, all before carrying out surgery.[2,3] The paradigm in some Eastern countries differs somewhat. In Japan, according to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines, Ra (above the peritoneal reflection) rectal cancer is treated by surgery and adjuvant chemotherapy for node-positive disease and, for Rb (below the peritoneal reflection) tumors, lateral pelvic lymph node dissection is carried out as part of the routine surgical treatment.[4] Western centers do not routinely remove the LPLN for early or advanced disease, instead focusing on neoadjuvant treatment as the mainstay of treatment for the lateral compartment.

These differing paradigms have developed out of competing priorities. In the West, the main focus has been oncological surgical clearance of the resection margin. The circumferential resection margin (CRM) is one of the most important prognostic factors in rectal cancer surgery with respect to local control and therefore deserves considerable attention. This is particularly true considering the high local recurrence rates reported in early surgical series.[5] This focus has, to some extent, however, taken the attention away from the importance of surgical clearance of pelvic lymph node metastases, so much so that many surgeons in the West still consider positive lateral nodes to be systemic/distant disease, rather than locoregional disease. Anatomically and biologically, it is more appropriate to consider lateral nodes for a tumor in the mid- and low rectum as locoregional, rather than as distant disease. In the East, the evolution in gastrointestinal cancer surgery in general has been toward lymph

node clearance and, as a result, lateral pelvic nodes have been considered local-regional disease from the outset. The treatment has thus evolved to include surgical therapy of this compartment for patients with rectal cancer. Conversely, neoadjuvant chemoradiation to improve margin control has received relatively less attention.

Multiple randomized trials in the West have confirmed that neoadjuvant treatment improves local control.[6–8] Conversely, several studies from Japan have also demonstrated good local control with LPLN dissection without neoadjuvant treatment.[9] The recently published JCOG0212 trial compared routine LPLN dissection versus TME alone in patients without clinical evidence of LPLN metastasis.[10] The rate of local recurrence with LPLN dissection was lower than without routine dissection and, therefore, the non-inferiority of TME alone in patients without clinical evidence of LPLN metastasis was not proven. This suggests that, at least in the Japanese population, lateral node dissection can be used to reduce local recurrence in the absence of neoadjuvant radiation. Several years ago, data from the Dutch TME trial were compared directly with data from the National Cancer Center Hospital.[11] The rates of local control were again not different between TME preceded by radiotherapy versus TME with lateral pelvic lymph node dissection (with the caveat that in the Dutch TME trial, the rate of radial margin positivity for distal disease was unacceptably high at more than 20%). A 2009 meta-analysis also showed no difference in local recurrence, overall or disease-free survival between "extended lymphadenectomy" including the lateral compartment versus neoadjuvant treatment without extended lymphadenectomy.[12] Increased rates of male sexual and urinary dysfunction were noted in the lymphadenectomy group, but this was not supported by the more recent JCOG0212 data.[12,13]

Despite ongoing attempts to compare radiation with LPLN dissection, in the authors' opinion, it is not correct (nor constructive) to think about lateral compartment management as a simplified binary choice.[14] In fact, there exist multiple populations of patients and the actual situation is somewhat more complex. There are patients with mid-/low rectal cancer who have macroscopically positive nodes (clinically abnormal on magnetic resonance imaging [MRI] staging) and those with negative nodes (some of whom will ultimately have microscopic disease), and they represent completely different populations with varied risk profiles. When one then considers the independent impact of T staging on neoadjuvant treatment decision-making, as well as the impact of N and M staging on choice of induction chemotherapy, and the inherent lateral compartment response profiles that may eventuate, it becomes clear that one size does not fit all. Rather than an approach of mutual exclusivity, an approach where all available modalities are considered and used to optimize treatment outcomes should be adopted.

It is clear that even in the context of neoadjuvant treatment, LPLN abnormalities detected on pretreatment imaging do still matter.[15] Data from a Korean study which included patients who underwent chemoradiation therapy and then TME without lateral lymph node dissection showed on multivariate analysis that LPLN short-axis diameter (<5, 5-10, and ≥10 mm) was significantly associated with locoregional recurrence-free survival, relapse-free survival, and overall survival.[16] Japanese data would suggest a cutoff of 8 mm is independently predictive of residual nodal disease after chemoradiation.[17] Response to neoadjuvant treatment also has a role to play, with poor responders in the lateral compartment having demonstrably worse oncological outcomes and potentially more to gain from dissection after neoadjuvant treatment.[18–20] Recurrence and survival benefit from posttreatment dissection has yet to be confirmed in this context, however.[14]

Based on the available information, we would suggest that patients with mid-/low rectal cancer being treated with curative intent could be classified into three categories for the purposes of the lateral compartment management:

1. Low risk of LPLN disease, defined as: cT1/T2/early T3 (and Ra) with clinically negative LPLN on MRI.
2. Moderate risk of LPLN disease, defined as: cT3 + /T4 with clinically negative LPLN on MRI (potential microscopic disease) (or Rb).
3. High risk of LPLN disease, defined as clinically abnormal LPLN on MRI (macroscopic disease) (Ra or Rb).

Broadly speaking and pending further evidence, the authors would argue that patients in group 1 could be managed with TME surgery alone, patients in group 2 with neoadjuvant treatment + TME or TME + LPLN dissection, and group 3 with neoadjuvant treatment + TME and LPLN dissection (particularly if the abnormal nodes do not respond to neoadjuvant treatment based on interval imaging). In addition, those patients with CRM at risk or with high-risk features such as Extramural Vascular Invasion based on MRI staging should undergo neoadjuvant treatment.

Looking to the future, additional data to further refine treatment decisions are needed with some urgency. First, comparative data regarding lateral node dissection are required from a Western population of patients to mitigate potential biases pertaining to geographical differences in patient body habitus and disease biology. In addition, it remains unclear whether dissecting the lateral compartment after neoadjuvant treatment alters the patient's survival and recurrence trajectory, or whether it only provides further staging and prognostication. Whether LPLN metastases represent locoregional or systemic disease, there should be little debate about the potential role of surgical management, in much the same way that the management of resectable distant metastasis to the liver or the lungs should include surgery. Finally, the role of induction preoperative chemotherapy (in isolation or in the context of total neoadjuvant treatment regimens) remains undefined for locally advanced rectal cancer. There are several ongoing studies attempting to answer these questions, and we look forward to the results with extreme interest.[21–24] However, at the present time, debating between neoadjuvant radiotherapy and lateral pelvic lymph node dissection misses the mark of optimal treatment. The way forward should be based on detailed pretreatment workup and an individualized approach that considers and can include all available modalities to

optimize the treatment of patients with rectal cancer in the West or the East.

DISCLOSURE

Conflicts of Interest: Dr George J Chang is a consultant for J&J and MORE Health.

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