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Diagnostic and management strategies for lateral pelvic lymph nodes in low rectal cancer—a review of the evidence

Dedrick Kok Hong Chan[1,2], Ker-Kan Tan[1,2], Takashi Akiyoshi[3]

[1]Division of Colorectal Surgery, University Surgical Cluster, National University Health System, Singapore, Singapore; [2]Department of Surgery, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore; [3]Gastroenterological Centre, Department of Gastroenterological Surgery, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

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Correspondence to: Dedrick Kok Hong Chan. Division of Colorectal Surgery, University Surgical Cluster, National University Health System, 1E Kent Ridge Road, Singapore 119228, Singapore. Email: dedrick_kh_chan@nuhs.edu.sg; Takashi Akiyoshi. Gastroenterological Centre, Department of Gastroenterological Surgery, Cancer Institute Hospital, Japanese Foundation for Cancer Research, 3-8-31 Ariake, Koto-ku, Tokyo 135-8550, Japan. Email: takashi.akiyoshi@jfcr.or.jp.

Abstract: Patients with low rectal cancer who have enlarged lateral pelvic lymph nodes are known to have a worse prognosis. There is however uncertainty over what constitutes a lateral pelvic lymph node of clinical significance. As the main modality for the detection of such lymph nodes is magnetic resonance imaging (MRI), characteristics of these lateral lymph nodes identified may have prognostic value and assist with guiding treatment. Options to manage such lateral lymph nodes includes neoadjuvant chemoradiotherapy as well as lateral lymph node dissection. Surgery is extensive and may lead to significant morbidity to the patient. This review article evaluates diagnostic and management strategies in patients with lateral pelvic lymph nodes in low rectal cancer.

Keywords: Lateral pelvic lymph node; neoadjuvant chemoradiotherapy; low rectal cancer; lateral pelvic lymph node dissection

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Introduction

The presence of metastatic lateral pelvic lymph nodes has been shown to portend a worse prognosis for patients with low rectal cancer (1). In patients with low rectal cancer, the lymphatic drainage does not only flow along the inferior mesenteric artery, but also along the internal iliac artery, therefore its propensity to metastasize to the lateral pelvic lymph nodes. Dissection of these nodes was standard treatment in the 1980s, with literature from that period suggesting a reduction in local recurrence as well as prolonged overall survival (2,3). The advent of neoadjuvant chemoradiation therapy has however changed Western paradigms, such that there is ongoing debate about the effectiveness of lateral pelvic lymph node dissection in the era of neoadjuvant chemoradiation therapy. In contrast, the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines continue to advocate lateral pelvic lymph node dissection for all patients who have tumours below the peritoneal reflection (4).

Treatment strategies in patients with lateral pelvic lymph nodes are not without complications. Lateral pelvic lymph node dissection has been associated with autonomic neuropathy, affecting urinary continence as well as leading to sexual dysfunction (5-8). Even among Japanese studies, urinary incontinence occurs between 10–20% and sexual dysfunction 10–30%. As such, lateral pelvic lymph node dissection should not be undertaken without clear advantage

to the patient.

Till date, with the paucity of data comparing neoadjuvant chemoradiotherapy versus lateral pelvic node dissection in low rectal cancers. We therefore performed a review of the literature to understand contemporary diagnostic techniques for lateral pelvic lymph nodes detection, as well as the latest evidence regarding the management of positive lateral pelvic lymph nodes.

Results

Nodal detection using magnetic resonance imaging (MRI)

The mainstay of lateral pelvic lymph node detection is by MRI (9). The European Society of Medical Oncology (ESMO) guidelines recommend MRI as first-line imaging due to its ability to evaluate both within and outside of the mesorectum (10). In a population in which 19.9% of patients had positive lateral pelvic lymph nodes, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of MRI were 75%, 69.1%, 36.4%, 92.2% and 70.2% respectively (11).

One of the key factors which alters the test characteristics of MRI in detecting lateral pelvic lymph node positivity has been the size cut-off for which a pathologic lymph node is considered. At the traditional cut-off of 10 mm, MRI suffers from a lack of sensitivity. Instead, some authors have utilised 5 mm as the cut-off for radiologic lateral pelvic lymph node positivity (12). Ogawa *et al.* demonstrated the diagnostic performance of MRI using 10 mm as the cut-off being 85.4%, 27.5%, 99.1%, 87.5% and 8.3% for accuracy, sensitivity, specificity, PPV, NPV respectively (13). Using 5 mm as the cut-off, the test characteristics were 77.6%, 68.6%, 79.7%, 44.3% and 91.5% respectively. This demonstrated a statistically significant improvement in the area under curve (AUC) value from 0.6326 for 10 mm and 0.7418 for 5 mm (P=0.0034).

Risk factors which portend a higher likelihood of truly metastatic lateral lymph node have been evaluated by many authors. This ability to predict truly metastatic positive lymph nodes on MRI prior to surgery can have an impact on multidisciplinary rectal cancer management. For the radiation oncologist, the neoadjuvant treatment plan in terms of dose, schedule and radiation field may be altered. For the surgeon, the aggressiveness of dissection and resection may also be changed according to MRI findings. Engelen *et al.* have described from a series of sixteen patients with 40 lateral pelvic lymph nodes who were evaluated by MRI that the majority of such nodes are located at tumour height or above (14). There was a statistically significant decrease in positive nodes below the tumour height compared with negative nodes, and no nodes were located more than 14 mm below the inferior edge of the tumour.

It is hence not surprising that a combination of MRI findings as well as patient risk factors have been put together as a logistic model to predict the presence of lateral pelvic lymph node positivity. A prediction model utilising MRI lateral pelvic lymph node status, histopathological grade of the tumor, and pathological mesorectal lymph node positivity was shown to predict for pathological lateral pelvic lymph node positivity better than MRI lateral pelvic lymph node status alone (right-side AUC 0.8923 *vs.* 0.7904, P=0.0002; left-side AUC 0.8505 *vs.* 0.7484, P=0.0001) (15,16). Although the obvious drawback of this model is that pathological mesorectal lymph node positivity can only be obtained post-operatively, nonetheless, this model strongly shows that positive mesorectal lymph nodes increases the likelihood of positive lateral pelvic lymph nodes. In fact, in a retrospective analysis, lateral pelvic lymph node dissection has been shown to be ineffective in improving five-year relapse free survival among patients who had pathologically negative mesorectal lymph nodes (17).

Nodal detection in patients following neoadjuvant chemoradiotherapy

Nodal detection is often more complex in patients who have received neoadjuvant chemoradiotherapy as the administration of the neoadjuvant therapy itself can lead to shrinkage of the lateral pelvic lymph nodes. Given this shrinkage, there also exists controversy regarding whether MRI findings before or after neoadjuvant treatment should be considered as the marker of lymph node metastases. A recent study by Kim *et al.* has evaluated predictive factors for lymph node metastasis, and have shown that pre-neoadjuvant therapy MRI lateral lymph node short-axis diameter of >8 mm, a size reduction of <33% between pre-neoadjuvant and post-neoadjuvant MRI, and heterogeneous signal intensity were independently associated with lateral pelvic lymph node metastasis on multivariate analysis (18). Another study by Akiyoshi *et al.* also demonstrated that pre-neoadjuvant short-axis diameter of lateral pelvic lymph node >8 mm was significantly associated with lateral pelvic lymph node metastasis (19). In contrast, post-neoadjuvant MRI findings did not seem to be useful.

The above findings were further supported by Kim *et al.*, who divided 84 patients into three groups (20). Group A and B comprised of patients who had good response to neoadjuvant chemoradiotherapy defined as post-treatment MRI with lateral pelvic node short-axis diameter <5 mm, whereas group C consisted of patients with persistently enlarged lateral pelvic lymph nodes. Group A patients underwent TME only, whereas group B patients underwent both TME as well as lateral pelvic lymph node dissection. Notably, local recurrence was highest in group A (22.6%), which was even high than group C patients (17.4%). There was no local recurrence in group B. Furthermore, 3-year disease free survival was best in group B (74.2%) patients compared with group A (53.7%) or C (46.9%).

Novel concepts for nodal detection using a sentinel node approach

Yanagita *et al.* has proposed utilising a sentinel node approach towards detecting lateral pelvic lymph nodes instead of the traditional approach via radiologic imaging (21). In this novel approach, 99m-technetium was injected either to the submucosa of cT1 or muscularis propria of cT2–4 tumours, with subsequent harvesting of the lateral pelvic sentinel nodes containing the radioisotope. The authors were able to identify isolated tumour cells on immunohistochemistry in three out of sixteen patients who had the sentinel lymph nodes harvested. The authors therefore concluded that a sentinel node approach towards lateral pelvic lymph nodes may be feasible, though further studies will need to be performed in order to determine if detecting sentinel nodes by such means translates to oncologic survival amongst patients.

Prophylactic lateral pelvic lymph node dissection

There is a lack of high-level evidence for prophylactic lateral lymph node dissection to be performed in low rectal cancer patients who have undetectable enlarged lateral lymph nodes. The JCOG0212 represents the only randomised controlled trial which has compared mesorectal excision versus mesorectal excision with lateral lymph node dissection in patients with low rectal cancer. Even so, this was a non-inferiority trial (22). This trial showed that 5-year relapse free survival in patients who underwent mesorectal excision and lateral lymph node dissection was non-significant when compared with patients who had undergone mesorectal excision only (73.4% *vs.* 73.3% respectively; hazard ratio 1.07, 95% CI , 0.84–1.36, P=0.0547). Similarly, 5-year overall survival (92.6% *vs.* 90.2%) and 5-year local recurrence free survival (87.7% *vs.* 82.4%) was also non-significant. The authors therefore concluded that the non-inferiority of mesorectal excision alone was not proven. They had noted reduced local recurrence in patients who had undergone both mesorectal excision as well as lateral pelvic lymph node dissection (7.4% *vs.* 12.6%, P=0.024).

Retrospective evidence regarding prophylactic lymph node dissection supports prophylactic lateral lymph node dissection. Ozawa *et al.* performed a retrospective matched cohort study comprising 499 pairs (23). The demonstrated improved 5-year overall survival in patients who had undergone lateral lymph node dissection compared to those who had not (68.9% *vs.* 62.0% respectively; hazard ratio 0.755, 95% CI , 0.604–0.944, P=0.013). Another study performed in Japan attempted to demonstrate the impact of lateral lymph node dissection on prognosis, whilst taking into account other prognostic factors such as age, sex, tumour diameter, tumour differentiation, T-stage and N-stage (24). The authors demonstrated that lateral lymph node dissection accounted for about 4–5% of the survival benefit in patients who have undergone it. They also demonstrated that there was increased benefit in performing bilateral lateral lymph node dissection versus unilateral lateral lymph node dissection, based on an increased hazard ratio of 2.02 (95% CI , 1.05–3.66, P=0.026) in patients who had unilateral compared with bilateral dissection.

Neoadjuvant chemoradiotherapy for lateral pelvic lymph nodes without dissection

The evidence surrounding the necessity of lateral pelvic lymph node dissection following neoadjuvant chemoradiotherapy continues to be debated in the literature. One of the first articles to have been published which disputed the necessity of lateral pelvic lymph node dissection was written by Dharmarajan *et al.* (25). In this study of 53 patients, all of whom received total mesorectal excision and neoadjuvant chemoradiotherapy, the authors observed no difference in local recurrence, overall as well as disease-free survival among patients who had and did not have enlarged lateral pelvic lymph nodes. This led the authors to conclude that lateral pelvic lymph node dissection was not necessary following chemoradiation therapy pre-operatively. Notably, these findings have been debated in the literature, owing to criticisms about the definition of low

rectal cancer, the considerably high number of patients with lateral pelvic lymph node metastases which may have skewed results, as well as the unusual pattern of lateral pelvic lymph node metastases when compared with other results (26). In the paper by Dharmarajan *et al.*, approximately 15% of patients had tumours which would not have satisfied the Japanese guidelines for a low rectal cancer. The authors also had a very high number of patients with lateral pelvic lymph node metastases (57%) compared with other studies where the incidence in their populations was between 15–20% (13,27-29). Finally, Kobayashi *et al.* published their results showing a large number of lateral pelvic wall metastases to the external iliac (53.5%) and presacral (53.3%) regions, whereas another large study of 1,272 patients showed that metastases predominantly arises along the internal iliac artery (73%) and the obturator (38%) regions (30).

Results from a study from Kim *et al.* also questioned the necessity of lateral pelvic lymph node dissection in all patients with enlarged lateral pelvic lymph nodes (31). The authors in this study from South Korea stratified the short axis diameter of the lateral pelvic lymph nodes to <5, between 5–10 and >10 mm. All patients had undergone neoadjuvant chemoradiotherapy and total mesorectal excision. The authors observed a statistically significant reduction in lateral pelvic node recurrence free survival rate between the <5, 5–10 and >10 mm groups of 98.2%, 91.7% and 40.1% (P<0.05) respectively. Local recurrence free survival rate (95.5% *vs.* 87.6% *vs.* 40.1%; P<0.05), disease free survival (76.8% *vs.* 72.5% *vs.* 30.3%; P<0.05) and overall survival (86.3% *vs.* 83.0% *vs.* 57.5%; P<0.05) were also reduced significantly. The authors concluded that lateral pelvic lymph node dissection might only be necessary in patients who have enlarged lateral pelvic lymph nodes of >10 mm.

Combined neoadjuvant chemoradiotherapy and lateral pelvic lymph node dissection for lateral pelvic lymph nodes

In contrast to the above, other authors have proposed that neoadjuvant chemoradiotherapy and lateral pelvic lymph node dissection is indeed synergistic and improves oncologic survival. Nagasaki *et al.* demonstrated that patients who underwent lateral pelvic side wall dissection alone without neoadjuvant chemoradiotherapy fared worse than similar patients who had neoadjuvant chemoradiotherapy alone without surgical dissection (32). The surgery alone group had worse 5-year overall survival (78.2% *vs.* 41.1%; P=0.02), 5-year disease free survival (72.1% *vs.* 25.4%, P<0.01) and 5-year local recurrence rate (3.5% *vs.* 39.6%; P<0.01). These findings led the authors to conclude that surgical dissection and neoadjuvant chemoradiotherapy might be synergistic with each other.

In one of the earliest papers advocating both neoadjuvant therapy as well as lateral pelvic lymph node dissection in radiologically suspicious lateral pelvic lymph nodes on MRI prior to neoadjuvant therapy, Akiyoshi *et al.* have published their results involving patients who received neoadjuvant chemoradiotherapy and underwent surgical resection (33). Comparing 38 patients who had TME as well as lateral pelvic lymph node dissection due to enlarged lateral pelvic lymph nodes during pre-neoadjuvant MRI imaging, and 89 patients who underwent TME alone, local recurrence was noted in 3 patients (3.4%) in the TME alone group compared with none in the group which had undergone both TME and lateral pelvic lymph node dissection, suggesting that lateral pelvic lymph node should be undertaken to improve local control and survival of patient with lymph node metastasis in patients with neoadjuvant chemoradiotherapy.

Similarly, in a paper described above, the combination of neoadjuvant chemoradiotherapy together with lateral pelvic lymph node dissection even in patients who developed a good response to neoadjuvant chemoradiotherapy on post-treatment MRI produced the best overall 3-year survival rate (20).

Finally, the importance of combined neoadjuvant chemoradiotherapy and surgery was reiterated by Kim *et al.* who reported a 6.6% lateral lymph node recurrence rate in patients who underwent only neoadjuvant chemoradiotherapy and total mesorectal excision alone (12). Moreover, they noted that an increase in the size of the lateral pelvic lymph nodes also increased the rate of lateral pelvic lymph node recurrence with lateral lymph node size of ≥5 mm having a recurrence rate of 26.6%, increasing to 68.8% when the lateral pelvic lymph node size was ≥10 mm. This finding shows that neoadjuvant chemoradiotherapy alone is insufficient in preventing lateral pelvic lymph node recurrence.

Open, laparoscopic and robotic lateral pelvic lymph node dissection

In spite of the lack of conclusive evidence in the literature regarding lateral pelvic lymph node dissection, authors have published data regarding differing surgical approaches towards the procedure. Ogura *et al.* also showed that

laparoscopic lateral pelvic lymph node dissection to low rectal cancer patients who had undergone neoadjuvant chemoradiotherapy and total mesorectal excision in patients with enlarged lateral pelvic lymph nodes was feasible. In this study, the authors achieved similar major complication rates between patients who underwent laparoscopic lateral pelvic lymph node dissection and TME compared with TME alone (9.3% *vs.* 5.5%; P=0.188). There were also no conversions to open surgery (34).

Yamaguchi *et al.* demonstrated similar safety as well as oncologic efficacy in patients who underwent laparoscopic lateral lymph node dissection compared with an open approach (35). Although not statistically significant, postoperative complication rate was reduced in patients who had laparoscopic versus open dissection (35.8% *vs.* 43.6%, P=0.10) and improved 3-year disease-free survival (80.3% *vs.* 72.6%, P=0.07).

Kagawa *et al.* has also published his experience performing robotic lateral pelvic lymph node dissection in 50 consecutive patients, describing this approach as safe and feasible (27). Although he did not make any comparison with either the laparoscopic or the open approach, he noted a median operative time of 476 min (range, 320–683 min) and median lateral lymph node dissection time of 165 min (range, 85–257 min). None of the patients in this series suffered from an anastomotic leak, and no patients were converted to either the open or the laparoscopic approach. Yamaguchi *et al.* compared the robotic approach against the open approach, and showed that although robotic lateral lymph node dissection resulted in longer operative times (455 *vs.* 410 min; P=0.007), complications including wound infection, small bowel obstruction, anastomotic leakage, and urinary retention were significantly lower in the robotic group than in the open group (28).

Complications associated with lateral lymph node dissection

The extensive dissection required during lateral lymph node dissection has traditionally been associated with concerns of urinary as well as sexual dysfunction. Authors from the JCOG0212 trial published complication rates from their trial comparing rates of urinary dysfunction (29) and sexual dysfunction (36) among patients who underwent total mesorectal excision alone versus total mesorectal excision and lateral pelvic lymph node dissection. The authors found that there was no statistically significant increase in urinary dysfunction (58% *vs.* 59% respectively; P=0.76) or sexual dysfunction (68% *vs.* 79%; P=0.37). The authors therefore concluded that lateral lymph node dissection may not increase either urinary or sexual dysfunction.

Conclusions

Contemporary management of low rectal cancer involves neoadjuvant chemoradiotherapy. The addition of lateral pelvic lymph node dissection in either a prophylactic or therapeutic manner continues to be debated in the literature. This is partly dependent on our current ability to detect lateral pelvic lymph nodes with the aid of MRI. In addition, MRI findings can help us prognosticate which patients require additional therapy to their lateral pelvic lymph nodes. With only one non-inferiority trial investigating oncologic outcomes with the addition of lateral pelvic lymph node dissection, the impetus is on further trials to be performed to determine the efficacy of lateral pelvic lymph node dissection. Thus far, retrospective studies have suggested conflicting results regarding its efficacy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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