

Treatment of lateral pelvic nodes metastases from rectal cancer: the future prospective

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SUMMARY: Treatment of lateral pelvic nodes metastases from rectal cancer: the future prospective.

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One feature of rectal cancer that remains controversial is the significance of lateral lymph node, because TME does not remove these nodes. We discussed the brief history of lateral nodes dissection and some problems in performing the extended surgery.

In Japan, an ongoing prospective multicenter randomized trial comparing TME alone and TME with clearance of lateral node is progress. In the West, MERCURY study showed 11.7% of patients with rectal cancer had MRI-identified suspicious pelvic side wall nodes. Judging from incidence and prognosis, pelvic side wall nodes in the west are

almost similar meaning as lateral nodes in Japan. There is long-standing controversy as to whether lateral lymph nodes metastasis represent systemic or localized disease. Though there has been reports suggesting effect of RT on lateral nodes metastases, the question remains whether preoperative CRT can fully sterilize lateral nodes deposits. Is it appropriate inspection assuming that positive CRM and bowel perforation is major cause of local recurrence after abdominoperineal resection? Some reports say that lateral node metastasis is major cause of local recurrence.

We must share following views that the east and the west should join forces to improve selection criteria for lateral node dissection and neoadjuvant treatment to prevent overtreatment, and ultimately aim to improve quality of life and oncological outcome for patients with low rectal cancer.

KEY WORDS: Low rectal cancer - Lateral pelvic lymph nodes metastases - Lateral pelvic lymph nodes dissection - Preoperative chemoradiotherapy.

The role of surgery is central for the treatment of rectal cancer. The search for decades has been continuing to minimize local recurrence after surgical resection. One feature of rectal cancer that remains controversial is the significance of lateral pelvic lymph nodes (LPN), because total mesorectal excision (TME) does not remove these nodes.

Gerota, in 1895, described the lateral and the upward lymphatic flow of the rectum as shown by a dye injection method (1). Poirier and colleagues described three lymphatic vessels for lateral lymphatics. The significance of the peritoneal reflection as a landmark in low and high lesion was described by Villemain et al. in 1925 (2). In Japan, in 1927, Senba conducted an anatomic study on lymphatics of the rectum by injecting a dye into fetus cadavers and concluded that the lateral lymphatic vessels are distributed around the internal iliac arteries and inside the obturator spaces (3). Today it is generally understood that some lymphatics, mostly from the lower rectum, easily penetrate into extra-mesenteric lymphatics through the lateral ligament and ascend along the internal iliac arteries. These lymphatics are called LPNs. Based on these historical researches, since 1970's, a clearance of LPNs on both sides has become a routine procedure for low-lying rectal cancer in leading hospitals in Japan. In Japanese guideline, the tumor is described according to anatomical relationships, defining the low rectal cancer as tumor located below the peritoneal reflection (4).

Due to anatomic variation and differences in sex, the distance of the peritoneal reflection to the anal verge can differ from 6 to 9cm. Thus, cohorts of patients with low rectal cancer in Japan probably also contain tumors which would be defined as “middle” in Western terms. Although the terminology for clearance of LPNs has varied considerably, LPN dissection (LPND) is thought to be appropriate to encompass surgical excision of LPNs.

Here, we would like to look back on the brief history of LPND. In 1951, Sauer and Bacon published their initial results with LPND for rectal cancer in 32 patients (5). In 1959, Stearns and Deddish reported results on 122 patients who performed LPND. The authors suggested that LPND might have no beneficial effects on survival, or local control, based on the increased number of postoperative complications (6). Subsequently in the West, LPND has been generally abandoned until today. Taking into consideration of the 1950's unfavorable outcomes, it is not presumptuous to say that the differences in results occurred if there was no true concept about the extent of surgery, especially with LPND. An additional problem when performing extended surgery is the difference in physique between Japanese and Western patients. Obesity and perivasculitis are handicaps during surgical procedures in either gender, especially lymphadenectomy along the adventitial layer of vessels. We may therefore suppose that these two factors influence the surgery in question. In Japan, on the other hand, LPND has been pursued with enthusiasm for decades. LPND in Japan, in the 1980's, was associated with significant morbidity, longer operating time, greater blood loss and functional impairment. Subsequently, to obtain good local control with an acceptable quality of life it was recognized among Japanese surgeons that the technique of LPND with autonomic nerve-preservation is essential (7).

It is speculated that LPND may remove micrometastasis not detected by routine histopathological examination. In 2005, Matsumoto analyzed 387 lymph nodes after bilateral LPND and found that 15.5% of histologically negative lymph nodes were shown by RT-PCR to harbor micrometastases (8). In Japan, an ongoing prospective multicenter randomized trial comparing TME alone and TME with LPND is in progress. The study is designed for patients with clinical stage II/III low rectal cancer considered to have uninvolved LPN judged by CT or MRI. Nonetheless, the first report said that the 7% of patients in TME with LPND group were found to have LPN metastases histopathologically. Therefore, a similar proportion of patients undergoing TME alone probably have such metastasis. If all patients with LPN metastasis have local or systemic recurrence, then the relapse rate will be about 7% higher in patients who undergo TME alone than in those who also have LPND. The final results will help to elucidate the role of prophylactic LPND in low rectal cancer (9).

Ueo et al. demonstrated that the rate of LPN metastases in T3/4 low rectal tumours below 8 cm was 17 per cent, but this varied from 42 per cent if located at 0-2.0 cm, to 10.5 per cent for tumours at 6.1 to 8.0 cm from the anal verge (10). Recently several authors reported that LPN metastasis was associated with tumor location, number of positive mesorectal nodes, grade of differentiation and lymphovascular invasion, tumour size of 4 cm or more.

In the West, MERCURY study showed 11.7% of patients with rectal cancer had MRI-identified suspicious pelvic side-wall nodes on baseline scans. Such nodes were associated with poor five-year disease-free survival showing 42 and 70.7 per cent respectively for patients with, and without suspicious pelvic side-wall nodes (11). Judging from incidence and prognosis, pelvic side-wall nodes in the west are almost similar meaning as LPNs in Japan (12).

There is long-standing controversy as to whether LPN metastases represent systemic or localized disease. LPND is considered a major part in reducing local recurrence and improving survival in Japan. In patients with low rectal cancer without overt metastasis to distant organs or to LPN, the current treatment in Japan is that TME with prophylactic LPND based on the indication criteria, which includes low rectal cancer with T3 and more or any involved mesorectal nodes is the standard. On the other hand, the approach to LPNs in the west has been either to ignore them, or to treat only obvious LPN metastasis with chemoradiation (CRT), reflecting to be systemic spread rather than regional disease (13). Overall, patients with LPN metastasis seem to constitute a heterogeneous population. The reported 5-year survival rates of patients range from 25 to 80 per cent, suggesting that some have a poor prognosis, and selected patients achieve favorable outcomes with LPND, particularly in Japan (14).

Preoperative CRT has proven its role in rectal cancer treatment (15). In Dutch TME Trial, the difference in lateral recurrence in the radiotherapy (RT)+TME group (0.8%) vs. the TME group (2.7%) was significant, suggesting that RT plays a significant role in the reduction of local recur-

rence in the lateral subsite (16). And MERCURY study also reported that patients with suspicious pelvic side-wall nodes on MRI had significantly worse disease-free survival that appeared improved with the use of preoperative RT. Though there have been these reports suggesting effect of RT on LPN metastases, the question remains whether preoperative CRT can fully sterilize lateral extra-mesenteric tumor particle. In addition to issues of cost, convenience, and short-term complications, pelvic irradiation for rectal cancer is associated with such long-term adverse outcomes as sexual dysfunction, impaired continence, and small-bowel obstruction. These considerations suggest that a selective approach to preoperative radiation might be the best way forward.

It is now accepted that high-quality surgery on the basis of anatomical principles such TME is a key component in avoiding local recurrence. However, even the pioneer of TME surgery, professor Heald, reported local recurrence in only 5% of cases 10 years after LAR, but in his patients who underwent an abdominoperineal resection, the local recurrence rate was as high as 36% (17). This is ascribed to the difficulty to obtain a wide circumferential resection margin and the higher rate of bowel perforations, especially in the case of abdominoperineal resection. This is partly owing to an anatomical volume reduction in the distal mesorectum, which is associated with local recurrence. Therefore, answer to the problem whether we should perform coning resection or cylindrical resection is that we should perform cylindrical resection (18, 19). Is it an appropriate inspection assuming that positive circumferential resection margin and inadvertent bowel perforation are a major cause of local recurrences in patients with low rectal cancer? In terms of causes of local recurrence, is it permitted even if we do not consider LPN metastasis? More recent work has outlined that the lower the tumor and the deeper its penetration, the higher the incidence of LPN metastasis. Kim and colleagues showed that LPN metastasis is a major cause of local recurrence of low rectal cancer (20). With serial sections from human fetuses and three-dimensional reconstruction, Kusters et al. demonstrated that tumour recurrence might arise from LPN (21).

In the choice between more extensive surgery and preoperative radiotherapy as a means to sterilize LPN metastasis or to improve the local recurrence rate, the morbidity associated with the treatment plays a major role.

Japanese surgeons currently advocate LPND with pelvic autonomic nerve preservation, aiming to maintain postoperative genitourinary function without compromising oncological benefits.

More accurate imaging diagnosis for LPN metastasis may facilitate a further individualization of therapy allowing the selection of patients who would gain prognostic and therapeutic benefit both from LPND and preoperative CRT. In these cases, LPND is probably not enough and it is uncertain where the LPN metastases can be fully sterilized by pre-operative CRT. Therefore the surgeons who are able to perform proper LPND must conduct randomized studies comparing preoperative CRT with TME and TME with LPND. Additionally, the risk of disseminated disease is high and prognosis is unfavorable for LPN-positive patients. For these patients, it may be wise to consider a combination of treatments: neoadjuvant CRT, LPND and possibly adjuvant systemic chemotherapy. We must share following views that the east and the west should join forces to improve selection criteria for LPND and neoadjuvant treatment to prevent overtreatment, and ultimately aim to improve quality of life and oncological outcome for patients with low rectal cancer (22).

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