RESEARCH ARTICLE

Current understanding and management of positive lateral lymph nodes in rectal cancer patients.

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Abstract
In the context of minimizing local recurrence rates after surgical treatment of rectal cancer, the issue of lateral pelvic lymph node (LPLN) dissection has remained as a controversial issue between West and East surgeons. The aim of the present paper was to review the incidence of lateral nodes, the associated risk factors and all the controversies regarding their management. While in Japan a prophylactic LPLN removal with autonomic nerve preservation (without neoadjuvancy) is considered the standard management of extra-peritoneal advanced rectal cancers, Western patients are usually treated with preoperative chemoradiotherapy (CRT) followed by total mesorectal excision. This choice is based on the effective reduction of local recurrences induced by CRT, culminating with similar outcomes when compared with LPN dissection. On the other side, this procedure is currently performed in Japan where LPN involvement is considered regional disease, so LPLN dissection is considered essential to improve outcomes. There exist suggestions that a selective approach to lateral nodes could be safely adopted in patients exhibiting radiological response after neoadjuvancy. However, others think that a more extended procedure is necessary even after CRT. Thus, the source and the risks of local recurrence must be individually assessed, and further high quality investigations must be developed to evaluate the efficacy of LPLN dissection with or without CRT.

Keywords: rectal cancer; chemoradiation; lateral pelvic nodes; survival.

Introduction

During the last three decades, the evolution of rectal cancer treatment allowed a reduction in local recurrence rates from 20% to 4-7%. In Western countries, a combination therapy with neoadjuvant chemo and radiotherapy (CRT) followed by Total Mesorectal Excision (TME) is the standard of care for high-risk T3, T4 or node-positive tumors (1 - 3). Besides this progress, local recurrence is still a great concern during the follow-up period. In this context, metastasis to lateral pelvic lymphnodes (LPLN) has been incriminated as an important mechanism leading to local recurrence [4. 5].

Classical and more recent anatomical studies [6 – 9] have demonstrated that locally advanced rectal tumors bellow the peritoneal reflection drain in a retrograde way via lymphnodes along the arterial vessels. Spread may occur through the upper lymphatic route (via superior rectal artery to the inferior mesenteric artery) or lateral lymphatic drainage (via middle rectal artery to the internal iliac and obturator basins). Involvement of downward route occurs only when a distal rectal tumor invades the anal canal, leading to inguinal lymphnode metastasis. Thus, LPLN in the extra-mesenteric space are affected mainly in association with distal tumors, and are not included within the TME.

For years, the role of LPLN dissection in rectal cancer management has remained a matter of intense debate between East and West surgeons, and there is no general consensus about this issue so far. In Western countries, LPLN are not usually removed because lateral dissemination is considered distant metastases, there is insufficient evidence regarding the impact of lateral dissection on outcomes when compared to CRT and LPLN dissection may lead to worst results concerning hemorrhaging, sexual and urinary dysfunction and longer operative time [10-12].

According to these ideas, LPLN are not considered targets for surgical resection, being either ignored or left to CRT control. Being located outside the TME surgical field, their dissection is not routinely performed. Two recent meta-analyses [13, 14] demonstrated that LPLN dissection does not improve survival or recurrence rates, but these conclusions derived mostly from small-scale single-institution retrospective studies.

In Japan, lateral extra-mesorectal metastases are considered locoregional disease based on the better survival when compared to stage IV patients [15]. Thus, Japanese surgeons have historically adopted an extended surgery including TME and prophylactic LPLN removal with autonomic nerve preservation (without CRT) as the standard therapy for extra-peritoneal advanced rectal cancers [16, 17]. A procedure with prophylactic intention turned to be a routine in the East (mainly Japan) since the 90's, initially bilateral and subsequently unilateral. With the evolution of imaging techniques, LPLN dissection began to be performed if size was bigger than 10 mm, although the majority of Japanese surgeons still preferred to follow their Society guidelines.

Although physical differences of body weight may have favored the acceptance of lymphadenectomy in the East along the years, this choice is supported by reports suggesting that lateral LPLN dissection may effectively reduce local recurrence, with improved survival rates [18 – 20]. Another important difference is that eastern surgeons usually define low rectal cancer

those bellow the peritoneal reflection, lesions that in the West would be called middle rectal tumors.

Besides a suggestion that LPLN dissection and CRT have similar effects [21], others believe that complete eradication of LPLN is not accomplished with CRT, and that lateral dissection may improve results even after neoadjuvant CRT [22]. In a balance of ideas, CRT has not been considered a trade-off of LPND as therapeutic modality for LPN metastasis, and vice versa (23). In a different view, LPLN dissection could be selectively performed.

Prophylactic dissection of the lateral compartment has been advocated even for patients with clinically negative lateral nodes. Results deriving from the JCOG0212 trial [17], a randomized study that compared TME with or without LPLN dissection for stages II/III low rectal cancers, showed no difference in relapse-free survival rates and significantly greater recurrence in the TME group (12.6% *vs.* 7.4%).

Management of locally advanced rectal cancer with lateral lymphnode metastasis is far from consensus. For this reason, the present paper aims to discuss the incidence of LPLN and to confront ideas and outcomes regarding the current trends in this setting. The literature was carefully analyzed in order to review historical data, current understanding of the issue and future perspectives.

Positive LPLN: Incidence and risk factors

Lateral pelvic metastasis has been reported to occur in 11.3% to 27% of patients with locally advanced rectal cancers before neoadjuvancy, mainly in the area surrounding the internal iliac vessels (63%) [4, 15, 18, 19, 24, 25].

Incidence increases in low rectal tumors [18, 26, 24, 27] and also varies with deeper transmural invasion, showing incidences of 5.4% (pT1), 8.2% (pT2), 16.5% (pT3) and 37.2% (pT4) [19]. In addition, young age, female sex, mesorectal nodes, enlarged nodes before CRT and angio-lymphatic invasion were also been implicated as risk factors [24]. Ishihara et al 2016 also suggested that LPND should be considered for female patients even if considered clinically negative. However, risk factors after CRT have not been well established.

In Japan, lateral nodes size is considered the most important criteria rather than other features in the radiological evaluation. Patients with greater nodes are thus considered to be at higher risk. Kim et al [28] reported 1.8%, 8.3% and 59.9% recurrence rates in patients with nodes measuring less than 5 mm, 5-10 mm and larger than 10 mm ($p<0,001$), respectively. In another paper, Kusters et al [20] reported a 33.3% recurrence rate in nodes greater than 10 mm against 10.1% in smaller ones, despite radiotherapy. Even after neoadjuvant CRT, the risk of lateral regrowth may vary between 10% and 80% depending on size [3, 28].

Radiological assessment of rectal cancer patients plays an important role in the preoperative staging planning, including identification of lateral involvement [17]. Ultrasonographic-guided biopsy identified lateral positive nodes in 13% (30), similar to the Mercury study that found an 11.7% rate, thus conferring a poorer disease-free survival (42% versus 70.7%) to those with suspicious pelvic sidewall nodes, unless the patients had received CRT [31]. However, reported rates of positive predictive values have varied from 36% to 100% [32, 33].

Considered the first-line radiological method (34), magnetic resonance imaging (MRI) has helped to define other important features of LPLN metastasis. The MRI in Rectal Cancer European Equivalence Study Group used the presence of mixed signal intensity or a irregular border rather than the size, a criteria that could identify 11.7% of patients with worst survival [35].

Thus, criteria and experience in radiological imaging certainly help to establish prognosis and define treatment. In an opposite direction to the standard guidelines of the Japanese Society recommending prophylactic LPLN dissection [16], others think that evidence is insufficient to perform dissection in patients without enlarged nodes [36, 37]. However, others believe that LPLN dissection may remove micrometastases not detected by usual methods [18, 38, 39]. Micrometastasis have been detected in 15.5% of 387 LPLN histologically negative [38]. Moreover, in a multicenter review of stage II patients (18), LPLN dissection led to better survival (87.1% vs. 78%), an advantage attributed to the removal of micrometastasis not detected in standard histopathology.

The lymphnode response after CRT is considered another important risk factor. Inoue et al [40] described poorer oncological results (73 vs. 84% survival and 32 vs. 78% relapse) in patients who remained with positive nodes (diameter > 7 mm) after CRT after 52 months of follow-up. Moreover, patients exhibiting downsize to < 7 mm didn't have recurrence. The authors suggest using LPLN downsizing to < 7 mm as a prognostic marker to avoid lateral dissection after neoadjuvant CRT.

Clinical significance of positive LPLN

The issue of LPLN involvement and resection still raises important questions and doubts. What is the real significance of an enlarged LPLN before treatment? When they should be prophylactic resected? Do neoadjuvant CRT and LPLN dissection provide the same oncological benefits?

Metastasis in LPLN correlate with more advanced lesions and a worst prognosis, as survival rates fall from 55% in negative LPLN to 29%-45% when they are involved [15]. Furthermore, Japanese studies in stage III rectal cancer demonstrated that LPLN dissection improves survival in 8% and reduce pelvic recurrence in 50% [3, 18, 37, 41].

However, previous studies have reported similar incidences of local recurrence after TME with or without LPLN dissection [1, 42-44]. But in a recent Randomized Clinical Trial with clinical stage II/III rectal tumors, Fujita el al [17] compared 351 TME + LPLN dissection against 350 TME. This latter group presented a greater recurrence rate (12.6% *vs*. 7.4%, p=0.02), suggesting that a prophylactic LPLN dissection is effective in preventing recurrence when patients don't receive CRT.

Most Japanese surgeons believe that regional LPLN do not represent systemic disease, thus its removal is essential to reduce local recurrence [24]. A 45% survival rate among patients undergoing LPND for metastasis has been reported [4, 18]. Moreover, reduced survival rates were described among patients not submitted to LPLN dissection without CRT (45.8% vs. 71.2%) [18].

However, others think that clinically enlarged nodes don't affect prognosis of stage III rectal cancer

patients who received neoadjuvant CRT and TME [45]. This suggests that lateral dissection omission may be acceptable in patients not suspected of having metastasis [24]. Also, selective lymph node dissection may be indicated when response was positively assessed with radiological evaluation [24]. This group reported that prognosis of resected LPLN metastasis is comparable to that observed in patients having only mesorectal spread [15].

What is the role of LPLN dissection in comparison to neoadjuvant CRT?

Neoadjuvant therapy has proven to reduce the number of involved lymph nodes and promote tissue regression, even in the lateral ones. Studies from the group of Watanabe and Muto in the earlies 2000 demonstrated that radiotherapy may be a good alternative to LPLN dissection when lateral nodes are not enlarged [38]. On the other hand, a revision of studies in which patients underwent LPLN dissection for enlarged nodes showed that 40-66% will still present positive nodes even after preoperative CRT [29].

In order to assess the validity of LPLN dissection, Otowa et al [46] found no differences in survival between patients undergoing CRT and radical surgery only compared to those treated by unilateral (determined by pretreatment imaging) or bilateral LPLN dissection. These authors showed that preoperative CRT was able to lower clinical lymph node status in 50% of patients.

Similarly, Ishihara et al [24] also found a 50% reduction from 14% positive nodes (before neoadjuvancy) to only 8% found in the surgical specimen. In a multivariate analysis of LPND after preoperative CRT in 580 rectal cancer patients, Kim et al [47] observed a poorer outcome among patients not exhibiting response to CRT, but the group responding partially to treatment performed similarly to those with no suspected lymphnode before treatment. In this study, the authors considered that half of patients assumed to have positive nodes (in the pretreatment phase) were effectively controlled by CRT. Similar results were reported in a retrospective analysis of 66 patients with lateral metastasis [48].

Kusters et al [12] published an interesting comparison among matched groups of Dutch (376 TME, 379 RT+TME) and Japanese patients (324 TME+LPLN dissection) with low rectal cancers (up to 7 cm from the anal verge). They observed that Japanese and Dutch RT+TME groups presented similar and lower recurrence rates (6.9% vs. 5.8%) when compared to Dutch TME patients. Interestingly, lateral dissection was also associated with much lower rates of presacral recurrence.

The response to CRT may also serve as a guide to indicate lateral node dissection selectively. Inoue et al (40) demonstrated that none of 7 out of 19 positive patients (36.8%) who presented a downsizing to < 7mm developed recurrence, while those who remained LPLN positive after CRT had poorer oncological outcomes. In addition, a correlation between T downstaging of the primary tumor with lateral nodes response has been described [24]. And a multivariate analysis demonstrated that CRT was an independent predictor for better overall survival (78.2 x 41.1%), and 5-year local recurrence rates (3.5% x 39.6%), respectively. In this study, the presence of more than 4 metastatic LN was also considered a predictor of poorer survival and recurrence.

Advanced rectal cancer with positive LPLN is not associated with a good prognosis, the reason why LPLN dissection may improve results even after CRT [3, 37, 49]. In a recent retrospective analysis of patients diagnosed with lateral nodes metastasis, Nagasaki et al [50] compared the results of those undergoing CRT and LPLN dissection (n=30) with others who didn't receive preoperative CRT (n=43). This study showed that oncological outcomes concerning survival, local recurrence and LPLN metastasis were significantly better in the CRT group, demonstrating the prognostic impact of a combined therapy for patients with lateral involvement. An interesting study by Kim et al [49] showed that decrease of LN size in response to CRT didn't affect the risk of lateral recurrence, even though the probability of recurrence varied according to the LN size before CRT.

Considering the good oncological outcomes after LPN dissection without CRT [17], an alternative option of avoiding chemoradiation and its related consequences should be balanced against the high rates of urinary and sexual dysfunction historically associated with LPLN dissection. Moreover, a powered randomized study eventually designed to compare the benefits of CRT or LPLN dissection would probably face problems such as weight differences and technical standardization.

Lateral pelvic dissection: technical details

Dissection of LPLN has been traditionally accomplished with an open approach. Progressively, advances in minimally invasive techniques have convinced skilled surgeons to perform LPN dissection during laparoscopic resection of rectal cancer stages II and III.

The laparoscopic approach has been associated with better short-term outcomes represented by reduced blood loss, less morbidity and faster recovery 51-54). Moreover, recent evidence of similar oncological outcomes will certainly encourage a greater number of surgeons to adopt this feasible and safe alternative [50].

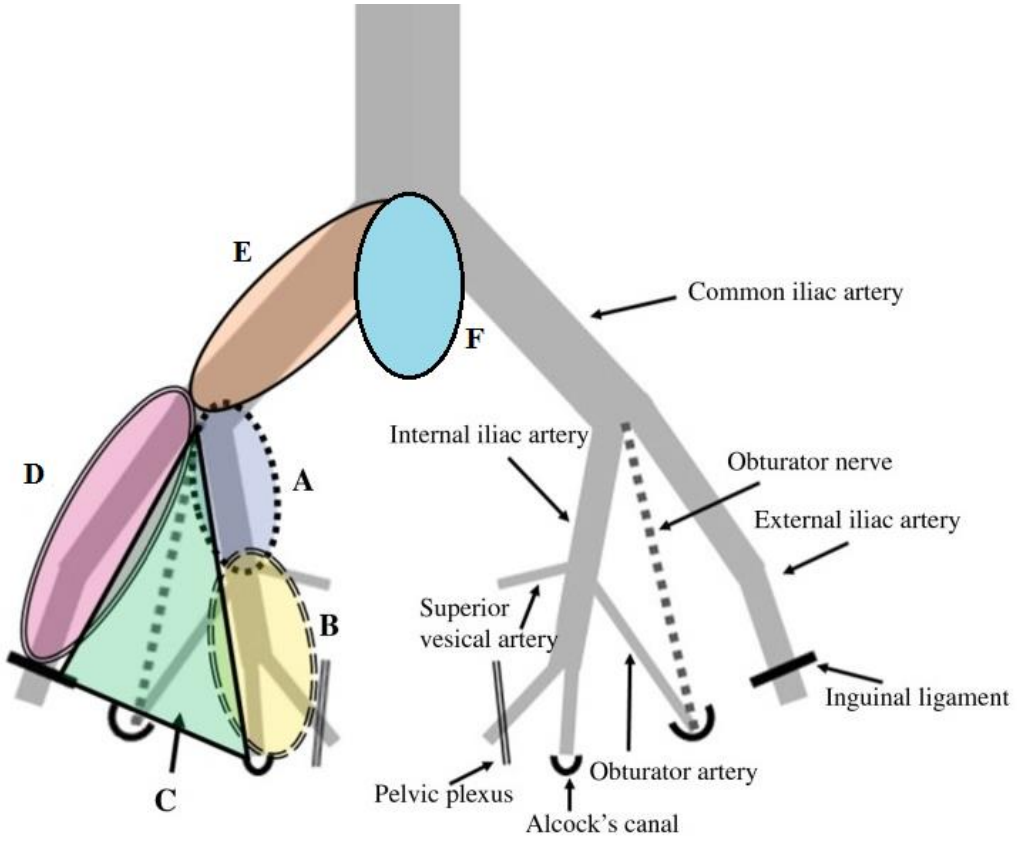
In a nationwide retrospective study recruiting data from 69 specialized centers in Japan, Yamaguchi et al [55] compared short-term and oncological results of open and laparoscopic patients undergoing LPLN dissection. The authors demonstrated complications advantages favoring the laparoscopic group and no compromise of oncological outcomes.

According the Japanese Society for Cancer of the Colon and Rectum (JSCCR), the pelvic area containing the lateral lymph nodes was subdivided into six regions: A) internal iliac area cranial to the superior vesical artery; B) intern iliac area caudal to the superior vesical artery; C) obturator area; D) external iliac artery area; E) common iliac artery, and F) aortic bifurcation, and median sacral regions (Figure 1) [16].

Our group standardized either open or laparoscopic LPLN dissection in a similar way to that proposed by Japanese surgeons [16, 56, 57]. We prefer to perform rectal resection and TME as the first step in order to improve visualization of all LPLN six regions and to decrease the risk of vascular or nerve damage. This choice is especially safer in obese patients, as it allows easier and faster access to the pelvic arteries and veins when injury occurs. At the beginning, lateral traction of both ureters near the anterior surface of the common iliac artery is performed, together with the hypogastric nerves identification at

the aorta bifurcation. We prefer not to traction these nerves to avoid involuntary damage.

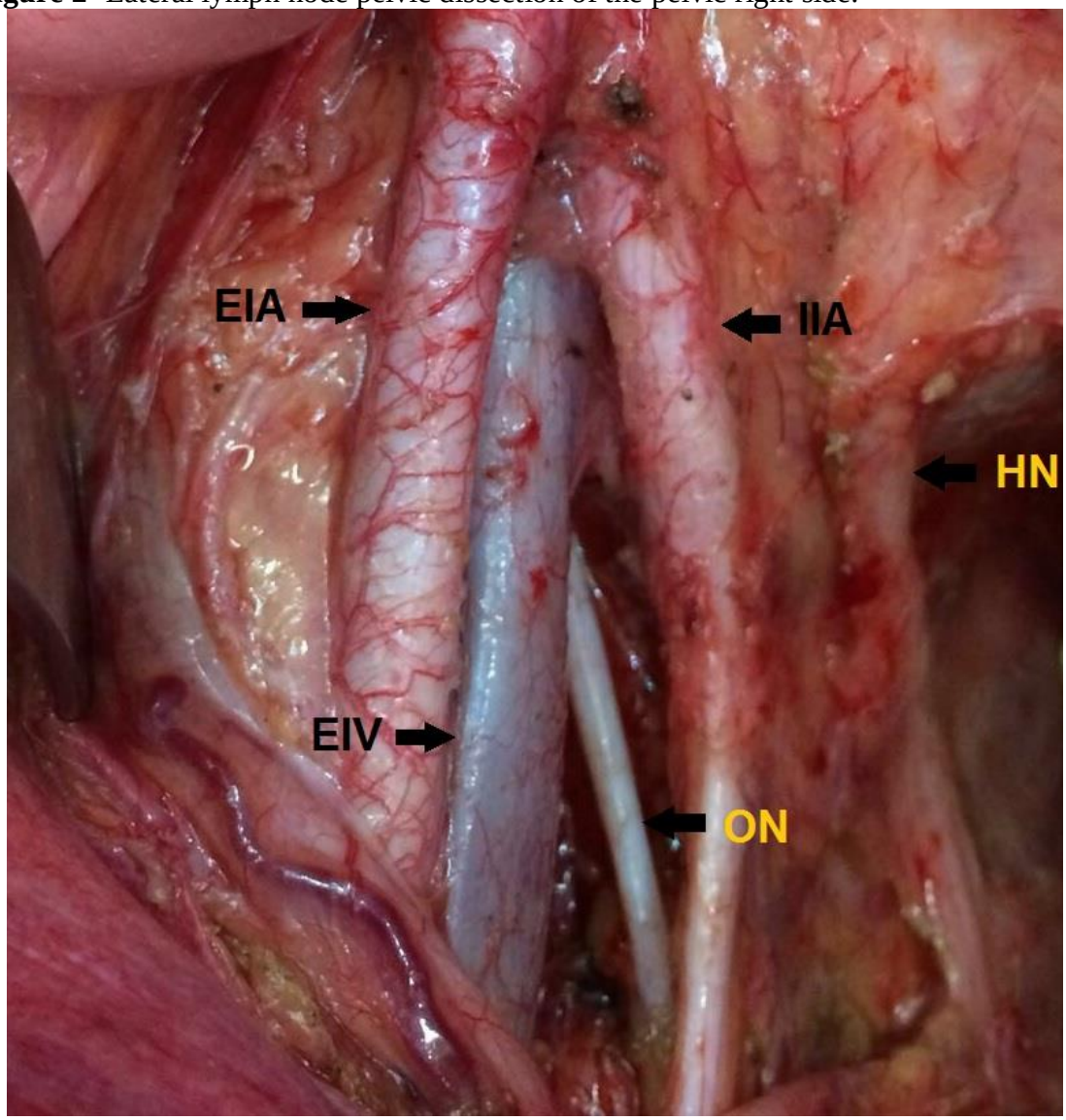
Fig. 1 - Lateral pelvic lymph nodes regions (A-F)



(A) internal iliac area cranial to superior vesical artery, (B) caudal to superior vesical artery, (C) obturator area, (D) external iliac area, (E) common iliac area, and (F) aortic bifurcation and median sacral areas.

The lymph nodes located anteriorly to the common iliac artery (in the region extending from the aorta bifurcation to the division of internal and external iliac arteries) are removed together with the adipose tissue. Dissection is extended into the lateral wall pelvic and the posterior sciatic nerve. Finally, the obturator nerve and vessels are clearly observed, and regional lymph nodes are resected (Figure 2). identification and complete dissection of all obturator fossa structures is essential, because approximately 80% of the lateral lymph nodes are located in the region between the internal iliac vessels and the obturator fossa. Like others, we only resect the internal iliac artery or its branches (umbilical artery, superior or inferior vesical arteries or obturator artery) *en bloc* when metastatic invasion is suspected [37].

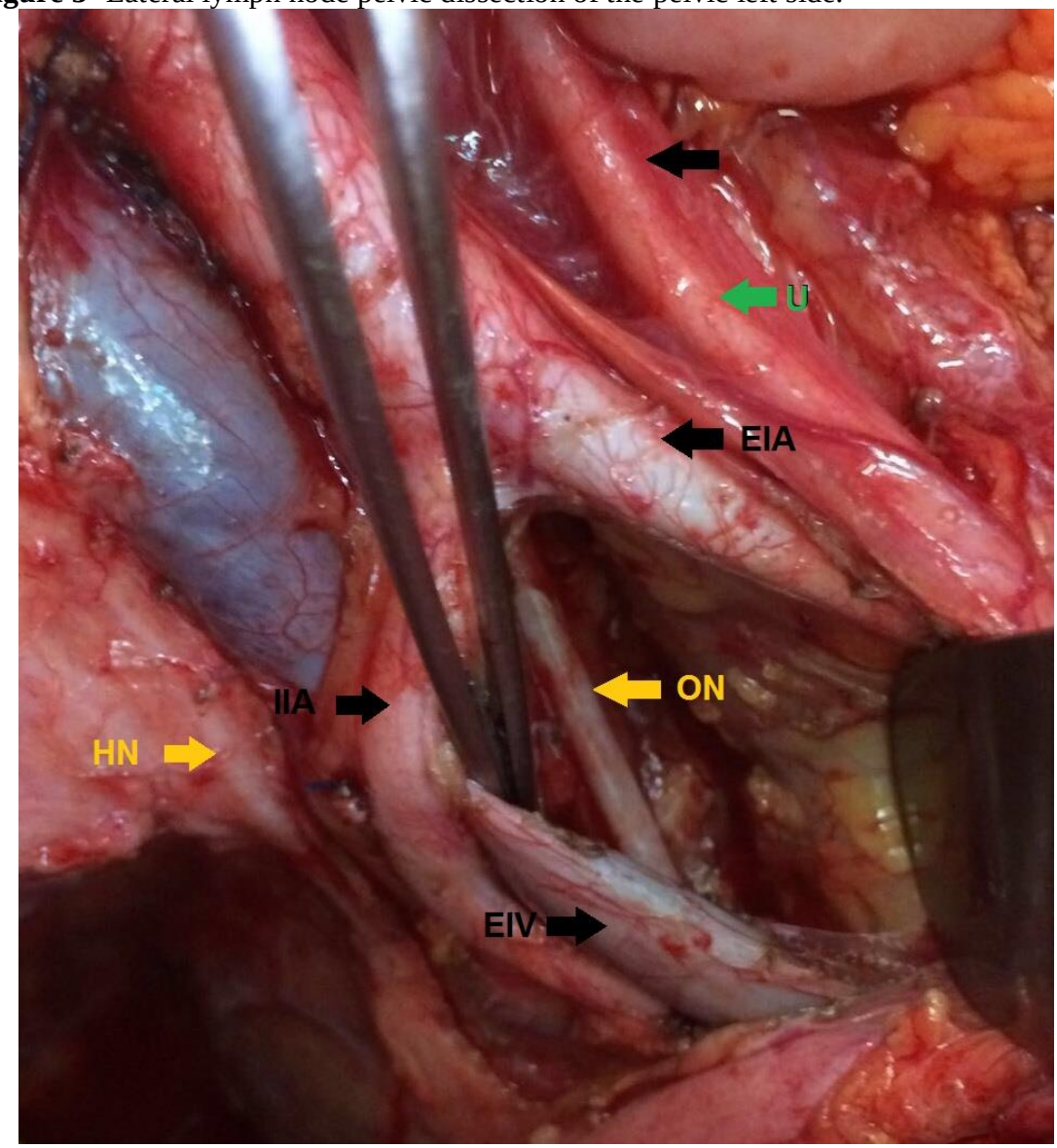
Figure 2- Lateral lymph node pelvic dissection of the pelvic right side.



EIA= External iliac artery; EIV= External iliac vein; IIA= Internal iliac artery; HN= right hypogastric nerve; ON= Obturator nerve

After dissection of the surrounding tissue along the internal iliac artery, the superior vesical artery is identified with gentle movements because the pelvic nerve plexus is located medially and inferiorly. Peripherally, the obturator artery arising from the internal iliac artery, the inferior vesical vein, and the pelvic nerve (S3 and S4) plexus are preserved, and the surrounding adipose tissue is resected. This step completes the LPLN dissection (Figure 3).

Figure 3- Lateral lymph node pelvic dissection of the pelvic left side.



EIA= External iliac artery; EIV= External iliac vein; IIA= Internal iliac artery; HN=left hypogastric nerve; ON= Obturator nerve; U= Ureter

Morbidity associated with LPLN dissection

Regardless the potential oncological benefit of lateral node dissection, this choice is centrally based on technical demands and may be associated with morbidity. During the initial phase in Japan, LPLN dissection was not performed with autonomic preservation, leading to high rates of bladder (30-70%) and sexual (80-100%) disturbances. Subsequently, the evolution of autonomic preservation allowed a reduction in urinary (10-20%) and sexual (10-30%) complications [58].

As LPN removal requires a more extensive area of dissection, it should be expected a longer duration, greater blood loss and risks. The influence of extended LPLN resection seems more limited to

ejaculatory function than on erectile function [59]. Certainly, all these motives limited the indication of LPLN dissection in Western countries.

However, in recent years, the routine adoption of total or partial nervous preservation techniques during LPND and the dissemination of minimally invasive techniques helped to improve postoperative outcomes. Moreover, the use of the laparoscopic technique to perform LPLN dissection is considered safe and feasible [60]. This approach has the potential to facilitate identification of the fine nerve branches from the autonomic plexus at the lateral pelvic wall. However, initial reports didn't reveal significant differences regarding functional outcomes after laparoscopic or even robotic LNPD [61].

Final comments

Regardless of the numerous clinical studies dedicated to understanding the role of LPLN in the development of local recurrence and the best way to manage them, LPLN metastasis should be considered as a regional disease with potential to be cured. But many questions have not been answered so far. Some of them are what to do with negative LPLN and what are the selection criteria to diagnose and perform resection of positive nodes. More than that, western surgeons would surely like to discover when LPLN dissection would improve oncological results beyond preoperative CRT.

Probably, omission of prophylactic lateral dissection is clearly acceptable when lymph nodes are not enlarged in preoperative assessment. In the West, lack of technical standardization and patient's obesity would potentially increase morbidity in a patient that could be adequately controlled with neoadjuvant CRT including the lateral compartment as a target.

Thus, a consensus regarding the management of LPLN is still lacking. There is a suggestion that neoadjuvant CRT may not replace LPLN dissection in some cases, although an unknown proportion of patients may succeed only with TME following CRT. But one remaining question is how much neoadjuvant therapy can control extra-mesenteric tumor deposits, and what are the prognostic parameters to identify risk patients before and after CRT [62].

In this concern, a short-axis LNs diameter of 7 mm seems to be an optimal cut-off value before CRT for predicting pathological metastasis and prognosis. As LNs may shrink after CRT, a smaller size is expected to be found in those who respond (64). A 5mm node size ≥5 mm after neoadjuvant chemoradiation has been strongly associated with pathologic positivity [65].

Thus, it appears that a proper decision based on perioperative findings and a change of ideas about this issue among Western surgeons is definitively required from now on [66]. Within this context, a global approach combining CRT and LPLN dissection would probably help to answer some questions regarding indications, benefits and risks of prophylactic or therapeutic treatment, since retrospective studies haven't yet demonstrated its real efficacy [63, 67, 68].

References

1. Heald RJ, Moran BJ, Ryall RD, et al. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978 – 1997. Arch Surg. 1998;133:894 – 899.
2. Kodeda K, Johansson R, Zar n, et al. Time trends, improvements and national auditing of rectal cancer management over an 18-year period. *Colorectal Dis*. 2015;17:o168–o179.
3. Kim TG, Park W, Choi DH, Park HC, Kim SH, Cho YB, Yun SH, Kim HC, Lee WY, Lee J, Park JO, Park YS, Lim HY, Kang WK, Chun HK. Factors associated with lateral pelvic recurrence after curative resection following neoadjuvant chemoradiotherapy in rectal cancer patients. Int J Colorectal Dis. 2014 ;29(2):193-200.
4. Ueno H, Mochizuki H, Hashiguchi Y, Ishiguro M, Miyoshi M, Kajiwara Y, et al. Potential prognostic benefit of lateral pelvic node dissection for rectal cancer located below the peritoneal reflection. Ann Surg 2007;245:80-7.
5. Sato H, Maeda K, Maruta M, Masumori K, Koide Y. Who can get the beneficial effect from lateral lymph node dissection for Dukes C rectal carcinoma below the peritoneal reflection? Dis Colon Rectum 2006;49:S3-12 .
6. Villemin F, Huard P, Montagn'e M. Recherches anatomiques sur les lymphatiques du rectum et de l'anus: leur applications dans le traitement chirurgical du cancer. Rev Chir. 1925;63:39–80.
7. Sauer I, Bacon HE (1952) A new approach for excision of carcinoma of the lower portion of the rectum and anal canal. Surg Gynecol Obstet 95:229–242 .
8. Stearns MWJr, Deddish MR. Five-year results of abdominopelvic lymph node dissection for carcinoma of the rec- tum. Dis Colon Rectum 1959;2:169-172.
9. Takahashi T, Ueno M, Azekura K et al (2000) Lateral node dissection and total mesorectal excision for rectal cancer. Dis Colon Rectum 43:S59–S68 .
10. Wang Z, Loh KY, Tan KY, Woo EC (2012) The role of lateral lymph node dissection in the management of lower rectal cancer. Langenbeck's Arch Surg 397:353–361.
11. Kim JC, Takahashi K, Yu CS, et al. Comparative outcome between chemoradiotherapy and lateral pelvic lymph node dissection following total mesorectal excision in rectal cancer. Ann Surg. 2007;246(5): 754–762.
12. Kusters M, Beets GL, vandeVelde CJ et al. A comparison between the treatment of low rectal cancer in Japan and the Netherlands, focusing on the patterns of local recurrence. *Ann Surg*. 2009;249(2):229–235.
13. Georgiou P, Tan E, Gouvas N, Antoniou A, Brown G, Nicholls RJ, Tekkis P (2009) Extended lymphadenectomy versus conventional surgery for rectal cancer: a meta-analysis. Lancet Oncol 2009;10: 1053-1062.
14. Cheng H, Deng Z, Wang ZJ et al (2011) Lateral lymph node dissection with radical surgery versus single radical surgery for rectal cancer: a meta-analysis.

Asian Pac J Cancer Prev 12:2517–2521.

15. Akiyoshi T, Watanabe T, Miyata S, Kotake K, Muto T and Sugihara K; Japanese Society for Cancer of the Colon and Rectum: Results of a Japanese nationwide multi-institutional study on lateral pelvic lymph node metastasis in low rectal cancer: Is it regional or distant disease? Ann Surg 2012; 255: 1129-1134.
16. Watanabe T, Itabashi M, Shimada Y et al. Japanese society for cancer of the colon and rectum (JSCCR) Guidelines 2014 for treatment of colorectal cancer. Int J Clin Oncol 2015; 20:207–239
17. Fujita S, Mizusawa J, Kanemitsu Y, Ito M, Kinugasa Y, Komori K, Ohue M, Ota M, Akazai Y, Shiozawa M, Yamaguchi T, Bandou H, Katsumata K, Murata K, Akagi Y, Takiguchi N, Saida Y, Nakamura K, Fukuda H, Akasu T, Moriya Y; Colorectal Cancer Study Group of Japan Clinical Oncology Group. Mesorectal Excision With or Without Lateral Lymph Node Dissection for Clinical Stage II/III Lower Rectal Cancer (JCOG0212): A Multicenter, Randomized Controlled, Noninferiority Trial. Ann Surg. 2017; 266(2):201-207.
18. Sugihara K, Kobayashi H, Kato T, et al. Indication and benefit of pelvic sidewall dissection for rectal cancer. Dis Colon Rectum. 2006; 49:1663–1672.
19. Kobayashi H, Mochizuki H, Kato T, et al. Outcomes of surgery alone for lower rectal cancer with and without pelvic sidewall dissection. Dis Colon Rectum. 2009;52:567–576.
20. Ozawa H, Kotake K, Hosaka M, Hirata A, Sigihara K. Impact of Lateral Pelvic Lymph N ode Dissection on the Survival of Patients with T3 and T4 Low Rectal Cancer. World J Surg. 2016;40(6):1492-9.
21. Watanabe T, Tsurita G, Muto T, Sawada T, Sunouchi K, Higuchi Y, Komuro Y, Kanazawa T, Iijima T, Miyaki M and Nagawa H: Extended lymphadenectomy and preoperative radiotherapy for lower rectal cancers. Surgery 2002; 132: 27-33.
22. Ishihara S, Watanabe T, fukushima Y, et al. safety and factors contributing to the dificulty of laparoscopic surgery for rectal cancer treated with preoperative chemoradiotherapy. Tech Coloproctol. 2014;18:247–255.
23. Ishihara S, Kanemitsu Y, Murono K, Otani K, Koji Y, Nishikawa T, Tanaka T, Tanaka J, Kiyomatsu T, Kawai K, Hata K, Nozawa H, Kazama S, Yamaguchi H, Sunami E, Sugihara K, Watanabe T. Oncological benefit of lateral pelvic lymph node dissection for rectal cancer treated without preoperative chemoradiotherapy: a multicenter retrospective study using propensity score analysis. Int J Colorectal Dis 2016; 31:1315–1321.
24. Ishihara S, Kawai K, tanaka T, Kiyomatsu T, Hata K, Nozawa H, Morikawa T, Watanabe T. Oncological Outcomes of Lateral Pelvic Lymph Node Metastasis in Rectal Cancer Treated With Preoperative Chemoradiotherapy . Dis Colon Rectum 2017; 60: 469–476.
25. Nagayoshi K, Ueki T, Manabe T, Moriyama T, Yanai K, Oda Y,

Tanaka M. Laparoscopic lateral pelvic lymph node dissection is achievable and offers advantages as a minimally invasive surgery over the open approach. Surg Endosc 2015; 30 (5): 1938-47.

26. Watanabe T, Itabashi M, Shimada Y, Tanaka S, Ito Y, Ajioka Y, Hamaguchi T, Hyodo I, Igarashi M, Ishida H, Ishiguro M, Kanemitsu Y, Kokudo N, Muro K, Ochiai A, Oguchi M, Ohkura Y, Saito Y, Sakai Y, Ueno H, Yoshino T, Fujimori T, Koinuma N, Morita T, Nishimura G, Sakata Y, Takahashi K, Takiuchi H, Tsuruta O, Yamaguchi T, Yoshida M, Yamaguchi N, Kotake K, Sugihara K; Japanese Society for Cancer of the Colon and Rectum. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2010 for the treatment of colorectal cancer. Int J Clin Oncol. 2012 Feb;17(1):1-29.
27. Fujita S. Incidence and prognosis of lower rectal cancer with limited extramesorectal lymph node metastasis. Int J Colorectal Dis. 2014 ; 29(9):1077-80.
28. Kim MJ, Kim TH, Kim DY, et al. Can chemoradiation allow for omission of lateral pelvic node dissection for locally advanced rectal cancer? J Surg Oncol. 2015;111:459–464.
29. Kusters M, Slater A, Muirhead R, Hompes R, Guy RJ, Jones OM, George BD, Lindsey I, Mortensen NJ, Cunningham C. What To Do With Lateral Nodal Disease in Low Locally Advanced Rectal Cancer? A Call for Further Reflection and Research. Dis Colon Rectum. 2017 ; 60(6):577-585.
30. Gleeson FC, Clain JE, Rajan E, Topazian MD, Wang KK, Levy MJ. EUS-FNA assessment of extramesenteric lymph node status in primary rectal cancer. Gastrointest Endosc. 2011;74(4):897-905
31. Shihab OC, Taylor F, Bees N, Blake H, Jeyadevan N, Bleehen R, Blomqvist L, Creagh M, George C, Guthrie A, Massouh H, Peppercorn D, Moran BJ, Heald RJ, Quirke P, Tekkis P, Brown G. MERCURY Study Group. Relevance of magnetic resonance imaging-detected pelvic sidewall lymph node involvement in rectal cancer. Br J Surg. 2011 ;98(12):1798-804.
32. Kobayashi H, Kikuchi A, Okazaki S, et al. Diagnostic performance of multidetector row computed tomography for assessment of lymph node metastasis in patients with distal rectal cancer. Ann Surg Oncol. 2015;22:203–208.
33. Ishibe A, Ota M, Watanabe J, et al. Prediction of lateral pelvic lymph-node metastasis in low rectal cancer by magnetic resonance imaging. World J Surg. 2016;40:995–1001.
34. Ogawa S, Hida JI, Ike H, Kinugasa T, Ota M, Shinto E, Itabashi M, Okamoto T, Yamamoto M, Sugihara K, Watanabe T. Prediction of lateral pelvic lymph node metastasis from lower rectal cancer using magnetic resonance imaging and risk factors for metastasis: Multicenter study of the Lymph Node Committee of the Japanese Society for Cancer of the Colon and Rectum. Int J Colorectal Dis. 2017 Oct;32(10):1479-1487.
35. Shihab OC, Taylor F, Bees N et al. Relevance of magnetic resonance

imaging-detected pelvic sidewall lymph node involvement in rectal cancer. Br J Surg. 2011;98:1798–1804.

36. Nelson H, Petrelli N, Carlin A, et al. Guidelines 2000 for colon and rectal cancer surgery. J Natl Cancer Inst. 2001;93:583–596.
37. Akiyoshi T, Ueno M, Matsueda K, Konishi T, Fujimoto Y, Nagayama S, Fukunaga Y, Unno T, Kano A, Kuroyanagi H, *et al*: Selective lateral pelvic lymph node dissection in patients with advanced low rectal cancer treated with preoperative chemoradiotherapy based on pretreatment imaging. Ann Surg Oncol 21: 189-196, 2014.
38. Matsumoto T, Ohue M, Sekimoto M, Yamamoto H, Ikeda M, Monden M. Feasibility of autonomic nerve-preserving surgery for advanced rectal cancer based on analysis of micrometastases. Br J Surg. 2005 ;92(11):1444-8..
39. Coy CS, Meirelles LR, Leal RF et al. Evaluation of lateral lymph node metastases in advanced distal rectal cancer. Hepatogastroenterology 2010; 57:1363–1366
40. Inoue Y, Saigusa S, Hiro J, Toiyama Y, Araki T, Tanaka K, Mohri Y, Kusunoki M. Clinical significance of enlarged lateral pelvic lymph node s before and after preoperative chemoradiotherapy for rectal cancer. Mol Clin Oncol. 2016 ;4(6):994-1002.
41. Ishihara S, Kawai K, Tanaka T, Kiyomatsu T, Hata K, Nozawa H, Morikawa T, Watanabe T. Oncological Outcomes of Lateral Pelvic Lymph Node Metastasis in Rectal Cancer Treated With Preoperative Chemoradiotherapy. Dis Colon Rectum. 2017; 60(5):469-476
42. Moriya Y, Sugihara K, Akasu T, et al. Importance of extended lymphadenectomy with lateral node dissection for advanced lower rectal cancer. World J Surg. 1997;21:728 – 732.
43. Lopez-Kostner F, Lavery IC, Hool GR, et al. Total mesorectal excision is not necessary for cancers of the upper rectum. Surgery. 1998;124:612–617.
44. Zaheer S, Pemberton JH, Farouk R, et al. Surgical treatment of adenocarcinoma of the rectum. Ann Surg. 1998;227:800–811.
45. Dharmarajan S, Shuai D, Fajardo AD, Birnbaum EH, Hunt SR, Mutch MG, Fleshman JW and Lin AY: Clinically enlarged lateral pelvic lymph nodes do not influence prognosis after neoadjuvant therapy and TME in stage III rectal cancer. J Gastrointest Surg 15: 1368-1374, 2011.
46. Otowa Y, Yamashita K, Kanemitsu K, Sumi Y, Yamamoto M, Kanaji S, Imanishi T, Nakamura T, Suzuki S, Tanaka K, Kakeji Y. Treating patients with advanced rectal cancer and lateral pelvic lymph nodes with preoperative chemoradiotherapy based on pretreatment imaging. Onco Targets Ther. 2015 ; 8:3169-73.
47. Kim MJ, Chan Park S, Kim TH, Kim DY, Kim SY, Baek JY, Chang HJ, Park JW, Oh JH. Is lateral pelvic node dissection necessary after preoperative chemoradiotherapy for rectal

cancer patients with initially suspected lateral pelvic node? Surgery. 2016 ;160(2):366-76.

48. Oh HK, Kang SB, Lee SM, Lee SY, Ihn MH, Kim DW, et al. Neoadjuvant chemoradiotherapy affects the indications for lateral pelvic node dissection in mid/low rectal cancer with clinically suspected lateral node involvement: A multicenter retrospective cohort study. Ann Surg Oncol 2014;21:2280-7.
49. Kim TH, Jeong SY, Choi DH, et al. Lateral lymph node metastasis is a major cause of locoregional recurrence in rectal cancer [SEP] treated with preoperative chemoradiotherapy and curative resection. *Ann Surg Oncol*. 2008;15:729–737.[SEP]19.
50. Nagasaki T, Akiyoshi T, Fujimoto Y, Konishi T, Nagayama S, Fukunaga Y, Ueno M. Preoperative Chemoradiotherapy Might Improve the Prognosis of Patients with Locally Advanced Low Rectal Cancer and Lateral Pelvic Lymph Node Metastases. WJSurg 2017; 41 (3): 876-883.
51. Park JS, Choi GS, Lim KH, Jang YS, Kim HJ, Park SY, Jun SH. Laparoscopic extended lateral pelvic node dissection following total mesorectal excision for advanced rectal cancer: initial clinical experience. Surg Endosc 2011; 25:3322–3329.
52. Liang JT. Technical feasibility of laparoscopic lateral pelvic lymph node dissection for patients with low rectal cancer after concurrent chemoradiation therapy. Ann Surg Oncol 2011; 18:153–159
53. Furuhata T, Okita K, Nishidate T, Ito T, Yamaguchi H, Ueki T, Akizuki E, Meguro M, Ogawa T, Kukita K, Kimura Y, Mizuguchi T, Hirata K (2014) Clinical feasibility of laparoscopic lateral pelvic lymph node dissection following total mesorectal excision for advanced rectal cancer. Surg Today 45:310–314
54. Mukai T, Akiyoshi T, Ueno M, Fukunaga Y, Nagayama S, Fujimoto Y, Konishi T, Ikeda A, Yamaguchi T (2013) Laparoscopic total pelvic exenteration with en bloc lateral lymph node dissection after neoadjuvant chemoradiotherapy for advanced primary rectal cancer. Asian J Endosc Surg 6:314–317
55. Yamaguchi T, Konishi T, Kinugasa Y, Yamamoto S, Akiyoshi T, Okamura R, Ito M, Nishimura Y, Shiozawa M, Yamaguchi S, Hida K, Sakai Y, Watanabe M. Laparoscopic Versus Open Lateral Lymph Node Dissection for Locally Advanced Low Rectal Cancer: A Subgroup Analysis of a Large Multicenter Cohort Study in Japan. Dis Colon Rectum. 2017 ;60(9):954-964
56. Ueno M, Oya M, Azekura K, et al. Incidence and prognostic significance of lateral lymph node metastasis in patients with advanced low rectal cancer. Br J Surg. 2005;92:756–63.
57. Konishi T, Kuroyanagi H, Oya M, et al. Multimedia article. Lateral lymph node dissection with preoperative chemoradiation for locally advanced lower rectal cancer through a laparoscopic approach. Surg Endosc. 2011;25:2358–9.
58. Moriya Y, Sugihara K, Akasu T, et al. Nerve-sparing surgery with

lateral node dissection for advanced lower rectal cancer. Eur J Cancer. 1995;31A:1229–1232.
59. Matsuoka H, Masaki T, Sugiyama M. et al. Impact of lateral pelvic lymph node dissection on evacuatory and urinary functions following low anterior resection for advanced rectal carcinoma. Langenbecks Arch Surg (2005) 390: 517–522.2005
60. Akiyoshi T, Nagata J, Nagasaki T, et al. Laparoscopic salvage lateral pelvic lymph node dissection for locally recurrent rectal cancer. Colorectal Dis. 2015;17(10):O213-216 2015
61. Kim HJ, Choi GS, Park JS, et al. Selective lateral pelvic lymph node dissection: a comparative study of the robotic versus laparoscopic approach. Surg Endosc. 2017; 32(5):2466-2473
62. Moriya Y. Treatment of lateral pelvic nodes metastases from rectal cancer: the future prospective. G Chir. 2013; 34(9-10):245-8.
63. Sammour T, Chang GJ. Lateral Node Dissection in Low Rectal Cancer: Time for a Global Approach? Ann Surg 2017; 20: 1-2.
64. Lee D, Matsuda T, Yamashita K, Hasegawa H, Yamamoto M, Kanaji S, Oshikiri T, Nakamura T et al. Significance of Lateral Pelvic Lymph Node Size in Predicting Metastasis and Prognosis in Rectal Cancer. Anticancer Res 2019; 39: 003-998.
65. Malakorn S, Yang Y, Bednarski BK, Kaur H, You YN, Holliday EB et al. Who Should Get Lateral Pelvic Lymph Node Dissection After Neoadjuvant Chemoradiation? Dis Colon Rectum 2019; 62: 1158–1166
66. Christou N, Meyer J, Toso C, Ris F, Buchs NC. Lateral lymph node dissection for low rectal cancer: Is it necessary? World J Gastroenterol 2019; 25(31): 4294-4299
67. Chan DK, Tan KK, Akiyoshi T. Diagnostic and management strategies for lateral pelvic lymph nodes in low rectal cancer—a review of the evidence. J Gastrointest Oncol 2019;10(6):1200-1206.
68. Kusters M, Uehara K, Cornelis J. H. van de Velde, Moriya Y. Is There Any Reason to Still Consider Lateral Lymph Node Dissection in Rectal Cancer? Rationale and Technique. Clin Colon Rectal Surg 2017; 30: 346–356.

