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Abstract

Nodal dissemination in locally advanced rectal cancer occurs mainly in two directions: upward and lateral. Lateral node involvement has been demonstrated; however, lateral lymph node dissection (LLND) is not routinely performed in Western countries and the focus is more on neoadjuvant treatment regimens. The main reasons for this are the high morbidity associated with the operation and the uncertain oncological benefit. There is, however, recent evidence that in selected cases, neoadjuvant treatment combined with total mesorectal excision only might not be sufficient. In this article, the historical developments in the East and the West, the current evidence regarding lateral nodal disease, and the surgical steps in the LLND are discussed.

Keywords
- rectal cancer
- lateral nodes
- local recurrence

The lateral lymph node dissection (LLND) is a controversial operation, that is mainly performed in the East, while in the West, the main focus is on (neo)adjuvant treatment regimens in combination with standard total mesorectal excision (TME). In this article, we will discuss the history of LLND, the evidence regarding the indications, and finally the techniques.

From anatomic studies dating from 1895, it has been shown that lymph node drainage occurs retrograde along the arterial vessels from the rectum.[1] The complex network of lymphatic channels can be divided into three lymphatic flow routes. The upper route is along the superior rectal artery to the inferior mesenteric artery. The lateral route reaches from the middle rectal artery to the internal iliac and obturator basins. And the third, downward, route extends to the inguinal lymph nodes. The downward route is only involved when tumor growth has infiltrated into the anal canal. The upper route is enveloped in the mesorectum and is thus removed in standard TME. The lateral route has shown to be involved especially in low and more advanced rectal cancers and is left in situ with TME surgery alone.

History

Treatment of lymph node metastases in the lateral lymph flow route has undergone different developments in the East and the West, which will be described separately.

West

The division of the rectum in two main lymphatic zones, upper and lateral routes, was known since 1895 when Gerota described these from anatomic studies.[1] Nevertheless, the description of Miles,[2] of solely up- and downward spread, was accepted generally. He stated that the zones of "lateral spread" were located between the levators ani and the pelvic fascia, thus promoting a wide abdominoperineal resection as the method to resect these lymphatic networks.

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However, results after surgery differed between lower and higher rectal carcinomas, with 5-year survival rates between 25 and 45% in lesions up to 6 cm from the anal verge and 30 to 80% in lesions at least 6 cm from the anal verge.[3,4] This difference between high and low lesions was also present when lesions were only treated by abdominoperineal resection. A similar worse outcome was seen in local recurrence rates between high and low lesions.[5] Meanwhile, the significance of the peritoneal reflection and the middle valve of Houston as a landmark in low and high lesions was described by Villemin and Oliveira.[6,7] According to these authors, this level was the limitation between two lymphatic areas of the rectum.

In 1941, Coller et al described that in 7 out of 19 very low lying rectal cancers, there was nodal involvement up to the margin of the excision of the levator ani muscle.[8] Dukes in 1944 suggested that growth might be laterally along the lymphatics accompanying the middle rectal vessels.[9] Sauer and Bacon[10] in 1951 stated that the "lateral spread" suggested by Miles was an anatomic misinterpretation. They quoted previous studies in which it was described that not all nodes are located over the levators ani, but rather on the pelvic walls and within the lateral ligaments. Lateral spread into these lateral lymph nodes would be responsible for the worse results in low rectal cancers as compared with higher disease. Waugh and Kirklin had a similar argument.[3] Sauer and Bacon reported on 17 patients with low rectal carcinoma, on which extended dissection of the iliac and sacral nodes was performed, 2 cases had metastases in the lateral nodes. In high cancer, no lateral metastases were found. LLND was not associated with lower mortality or higher morbidity rate.

Stearns and Deddish[11] examined the role of abdominopelvic lymphadenectomy in the management of rectal cancer in 1959. Total 122 patients with high and low rectal carcinomas were operated, but lateral lymph node metastases occurred only in tumors located less than 10 cm from the anal verge. In Dukes C patients, the 5-year survival for the extended operation was 40%, while it was 23% in conventional surgery. Due to a lack of difference in survival, and as morbidity was significantly different, the authors suggested that LLND had no beneficial effect.

Enker et al[12] reported on LLND in 1986 to set objective definitions for LLND surgery. Of 412 patients, 192 underwent en bloc pelvic lymphadenectomy mainly for low and middle rectal tumors, combined with abdominoperineal resection or low anterior resection. A difference with the method of Stears and Deddish was that obturator compartment stayed untouched, only dissecting the parailiac nodes. Enker et al observed a superior survival after extended dissections, when compared with conventional resections (63.8 vs. 54.3%), particularly in Dukes C patients. There was no added operative mortality and in terms of morbidity, only urinary function was mentioned as being temporarily compromised. Enker et al suggested LLND as the therapy of choice when preoperative examination suggests that the rectal cancer penetrates the bowel wall.

A group of patients having undergone LLND was retrospectively reviewed by Glass et al in 1985.[13] Based on vague indications, namely, local extension or unfavorable histologic grade, 75 patients underwent LLND. These were compared with 2,266 patients who underwent conventional resection. No improvement in 5-year survival or local recurrence rate was observed in patients within the extended resection group, and concluded that no patients would benefit from LLND.

In 1992, Michelassi and Block reported on 73 patients who had conventional surgery and 64 who had wide pelvic lymphadenectomy.[14] The indications were dependent on the surgeons' preference. There was a reduction in local recurrence rate from 16.4 to 9.4%, but this was not significant. No numbers were given on survival or morbidity.

After this, only a few reports described outcomes of LLND in Western patients. Since the 1990s, the focus was mainly on TME and (neo)adjuvant regimens in the treatment of rectal cancer.

East

Reports on LLND come mainly from Japan. Senba[15] conducted a study of lymphatic system of the rectum in more than 200 fetuses. He found the same routes as Gerota in 1908,[1] but also found an additional route running along the inferior rectal artery, passing through the ischiorectal fossa, to the internal iliac artery.

Kuru[16] applied the knowledge of the lateral lymph flow route directly in a clinical setting and reported on this in 1940. Total 126 patients underwent LLND, of which overall lymph node involvement was 42% and lateral lymph node involvement was around 9%. In low rectal cancer, the involvement was observed in 4 of 13 cases (31%). In 1977, Koyama reported the 5-year survival rate of 45% in patients after LLND versus 30% after conventional surgery.[17]

The first English report on LLND surgery from 1962 to 1976 came from Hojo and Koyama in 1982.[18] Better survival rates were observed in the National Cancer Center Hospital (NCCH) since the introduction of LLND in 1969 (5-year survival rate of 71 vs. 59%). Local recurrence rate was reduced significantly in Dukes B lesions, from 25 to 7%. The metastatic rate of lateral nodes was 20% in low rectal cancer and 6% in higher ones. In 1989, Hojo et al reported on urinary and sexual dysfunctions, respectively, of 39 and 76% after LLND.[19] They concluded that pelvic nerves should be preserved in patients with lower rectal cancer without lymph node spreading.

In 1991, Sato and Sato described that the lateral ligament could be divided into a medial part, containing mainly middle rectal artery, and a lateral part in which the pelvic plexus was located.[20] To reduce urinary and sexual dysfunctions, Hojo et al reported how injury to this plexus could be avoided through nerve-sparing techniques.[21] Moriya, the successor of Hojo, then described several nerve-sparing techniques in 1995.[22,23] Dependent on tumor extent, total or partial nerve preserving techniques were applied. In total nerve preservation, urinary function was preserved in 98% of the cases and erection was preserved in 90%, although ejaculation was possible in only 68%. Operative time was 90 minutes longer as compared with limited operations. Oncologic outcomes did not seem to be compromised by autonomic preservation.[24]

In 1998, Mori et al[25] reported on 25.5% lateral lymph node metastases in 157 patients with Dukes C stage low rectal carcinoma. The mean 5-year survival rate of patients with

lateral lymph node metastases was 37.5%. Sexual function was poor in unilateral autonomic nerve preservation. In bilateral preservation, erection could be achieved in 75% and ejaculation in ~50%.

In 2005, Matsumoto et al[26] analyzed 387 lymph nodes after bilateral LLND and found that 15.5% of histologically negative lymph nodes were shown to harbor micrometastases. The possible survival benefit in resecting micrometastases by LLND was described by Sugihara et al,[27] who reviewed 2,916 patients from various centers. In stage II disease, patients with a LLND had a better (87.1%) 5-year survival than patients without LLND (78.0%). They concluded that survival benefit could be explained by the resection of micrometastases by LLND, which were not considered involved in standard histopathology.

After 2000, more studies appeared in which neoadjuvant treatment regimens with TME were compared with LLND, or were combined with LLND. This will be discussed later.

Two Different Entities: "Prophylactic LLND" and "Indicated LLND"

To describe the indications for a LLND, it is useful to discern two different sorts of LLND: the "prophylactic LLND" and the "indicated LLND," which are both always in combination with standard TME. These can be performed with or without nerve-sparing techniques.

The "prophylactic LLND" is a LLND in all low locally advanced rectal cancers, irrespective of lateral lymph node size. All studies in the historical perspectives described in the previous article concerned the prophylactic LLND, as there were no good preoperative imaging techniques during that time. The prophylactic LLND has been practiced in the East since the 1990s, when it was found that lateral node metastases were mainly found in tumors below the peritoneal reflection. A bilateral prophylactic LLND was the standard, but in later years, unilateral prophylactic LLNDs were also performed if the tumor was located on a certain side.

The "indicated LLND" is performed only when lateral lymph nodes are enlarged on preoperative imaging, for example, when the nodes are larger than 10 mm. There are a few Japanese centers who have adopted this method in the last decade, but the Japanese national guidelines still say that a prophylactic LLND should be performed in all locally advanced rectal cancers below the peritoneal reflection.

We will discuss the results of the prophylactic LLND versus neoadjuvant treatment first and then continue with current evidence regarding the indicated LLND.

"Prophylactic LLND" versus (Neo)Adjuvant Treatment with TME

Eastern Studies

While in Japan in the 1990s in some centers, the focus was on performing the LLND with specialized nerve-sparing techniques to improve functional outcomes, some other centers questioned whether these would be feasible enough and whether the prophylactic LLND could not be replaced by neoadjuvant treatment regimens to reduce morbidity.

In 2001, Nagawa et al[28] published a randomized study in which 51 patients with low locally advanced rectal cancer were treated with neoadjuvant 50 Gy radiotherapy from 1993 to 1995 and were randomized between standard rectal resection (with nerve sparing) versus LLND without nerve-sparing techniques. Disease-free survival and overall survival were similar, while urinary and sexual function was significantly worse in the LLND group. Preoperative imaging at the time consisted of computed tomography and/or endorectal ultrasound. No data were given on the rate of lateral lymph node involvement in the LLND group, but patients with peroperative evidently enlarged lateral lymph nodes were excluded from the study; therefore, probably, this must have been very low. The authors concluded that LLND can be omitted in patients with advanced rectal cancer who receive preoperative radiotherapy, but this study only suggests that radiotherapy can replace a LLND if the nodes are not enlarged.

The same group of authors published another study 1 year later[29] in which 115 patients were retrospectively divided into four subgroups: radiotherapy (Rad) + LLND − , Rad + LLND + , Rad − LLND + , and Rad − LLND − . Local recurrence rates, disease-free survival, and overall survival were not significantly different between Rad + LLND− and Rad − LLND + . The authors suggested that preoperative radiotherapy could be an alternative for LLND in patients with low rectal carcinoma.

The third Eastern study comparing prophylactic LLND to TME was published in 2007 by Kim et al[30] and compared 176 patients with TME and postoperative chemoradiotherapy (CRT) with TME combined with a LLND in a retrospective manner. The 5-year overall survival and disease-free survival rates did not differ significantly. In patients in the LLND group with stage III low rectal cancer, local recurrence rate was 16.7%, higher than 7.5% in the postoperative CRT group ($p = 0.044$). However, the LLND group might possibly have consisted of "very low" rectal cancers.[31]

There are no Western studies comparing prophylactic LLND with standardized TME combined with (neo)adjuvant treatment. We performed a comparative study between Japanese and Dutch patients with low rectal cancer, which will be described later. However, we have to discuss a few factors that make comparison between the East and the West difficult.

Difficulties in Comparing the East and the West

The following differences between the East and the West hinder reliable comparison.

First, the definition of rectum and low rectal cancer differs between the continents. In the West, distance from the anal verge is often measured by rigid endoscopy and the rectum is mostly defined as 15 to 16 cm from the anal verge.[32,33] The distance of a rectal carcinoma from the anal verge is the distance between the lower edge of the tumor and the anal verge. The definition of low rectal carcinoma differs per publication, varying from 5 to 6 cm from the anus, as measured by endoscopy. In the East, in particular in Japan,

definitions are related to anatomy rather than endoscopic measurement. The rectum is located below the lower border of the second sacral vertebra and the rectosigmoid is located more proximal up to the level of the promontory.[34] "Low" rectal cancer is defined as a tumor of which the major part is located at or below the peritoneal reflection, as seen on preoperative imaging or as palpated intraoperatively. Due to anatomic variations and differences in sex, the distance of the peritoneal reflection to the anal verge can differ from 6 to 9 cm.[35] Thus, cohorts of patients with low rectal carcinoma in Japan probably also contain tumors which would be defined as "middle" in Western terms.

Second, pathologic techniques differ between the East and the West. In the West, the resected specimen is first fixated and then sliced to perform circumferential resection margin (CRM) measurement according to the method of Quirke.[36] During this process, the amount of resected lymph nodes is counted. In Japan, lymph nodes are harvested from the fresh specimen by the surgeons, directly after surgery.[34] This immediate harvesting of lymph nodes precludes assessment of the CRM at a later stage. Thus, the focus of pathology is on CRM management in the West and lymph node harvesting in the East. The difference in average amount of lymph nodes harvest might be a result of these differences in techniques, as the amount of mesorectal lymph nodes (without lateral) is at least 20 in Japan, and rarely reaches that amount in the West. Further, removal of lymph nodes might be more difficult in Western patients, as only a low amount of lymph nodes could be removed from Dutch patients by Japanese clearing methods.[37] It is well known that higher lymph node removal results in better staging, or maybe even upstaging, referred to as the Will Rogers phenomenon.[38] This automatically changes prognostic outcomes and therefore can be responsible for differences between various groups.

Finally, especially important in comparing the feasibility of LLND in Japanese and Western patients, difference in body mass index is crucial. Japanese patients, especially males, are significantly thinner than Western patients.[39] Obesity makes LLND with nerve-sparing techniques considerably difficult, which might result in more complications and morbidity. These might overshadow oncologic outcomes and worsen results of LLND in Western patients, as compared with Japanese patients.

Study Comparing East and West

In a comparative study between Japan and the Netherlands in the treatment of low rectal cancer, the patterns of local recurrence were analyzed.[40] The Dutch group consisted of patients of the TME trial; 376 patients were operated by TME for low rectal cancer, and 379 received preoperative radiotherapy (RT + TME). In the Japanese group, 324 patients who underwent extended surgery consisting of a prophylactic LLND were analyzed. The majority received no (neo)adjuvant therapy. The Dutch and Japanese patients were matched as closely as possible, by selecting only tumors up to 7 cm from the anal verge, which was considered as the level of the peritoneal reflection. Five-year local recurrence rates were 6.9% for the Japanese NCCH group, 5.8% in the Dutch RT + TME group, and 12.1% in the Dutch TME group. It could be concluded that Japanese extended surgery and RT + TME result in good local control, as compared with TME alone. Interestingly, lateral local recurrences could not be prevented by a prophylactic LLND, but the presacral local recurrence rate was much lower in the LLND patients, compared with the TME patients. Preoperative radiotherapy could reduce lateral local recurrence significantly (0.8% 5-year rate), compared with TME alone (2.7% 5-year rate). It could, however, not prevent presacral local recurrences.

Japanese Trial

In the randomized phase 3 JCOG0212 noninferiority multicenter trial, TME with or without LLND was studied. The preoperative work-up consisted of endoscopic ultrasonography and magnetic resonance imaging (MRI). Patients with histologically confirmed adenocarcinoma below the peritoneal reflection and clinical stage II or III disease were included. When lymph nodes were larger than 10 mm or there was invasion into other organs, the patients were not included in the trial. None of the patients had neoadjuvant (chemo)radiotherapy. The inclusion of 701 patients was completed in 2009. In an initial report regarding short-term outcomes, it was described that operative time and blood loss was greater in the LLND group, but that postoperative complications were not significantly different from standard TME.[41]

Fujita et al published the oncologic results[42] and showed that the 5-year recurrence-free survival (RFS) was similar: 73.4% in the LLND arm and 73.3% in the TME arm, meaning that the noninferiority of TME without LLND could not be confirmed ($p = 0.055$). Local RFS was not significantly different between the arms (87.7% in the LLND arm vs. 82.4% in the TME arm; hazard ratio: 1.37, 95% confidence interval: 0.97–1.93). The amount of lateral recurrences was however much lower in the LLND arm (4 of 351 patients), compared with the TME arm (23 of 350 patients), but 5-year lateral local recurrence rates were not given.

The main message for the West from this trial is that not "treating" the lateral compartment will result in high local recurrence rates (17.6% 5-year rate). It would have been interesting if TME + LLND had been compared with CRT + TME, but unfortunately, we can only learn from this study that lateral local recurrence can be prevented by a prophylactic LLND.

What to Do in the West if Lateral Lymph Nodes Are Not Enlarged?

Although evidence is scarce, we can conclude from abovementioned data that there is no value of performing a prophylactic LLND in Western patients when lateral lymph nodes are not enlarged. The operative morbidity will be high, especially because in obese Western patients, nerve-sparing techniques are difficult. Evidence suggests that neoadjuvant therapy can sterilize microscopic lateral node particles which may cause recurrence and can result in similar outcomes than a prophylactic lateral node dissection in Eastern patients.

However, an indicated LLND may need to be considered in Western patients if lateral lymph nodes are enlarged. We will review the literature about this later.

Important in the West is that the lateral compartment should not be ignored in the prophylactic setting: in the case of low, lymph node positive or locally advanced tumors, the lateral compartment should be included in the radiation target volume, especially in intensity modulated radiotherapy techniques. Without radiotherapy in low rectal cancers in the Dutch TME trial, local recurrence rate was 12%, which is probably even higher if only locally advanced cancers are included.[40] As suggested earlier, the Japanese trial has the same message; the lateral compartment should be "treated."

The Role of the "Indicated" LLND

Is Neoadjuvant Chemoradiotherapy with TME Sufficient in Enlarged Lateral Lymph Nodes?

There are several recent, mainly Korean studies in which patients who had neoadjuvant CRT followed by standard TME (without LLND) were analyzed to see whether they developed local recurrence in the lateral lymph node compartment.

Kim et al[43] studied 366 patients with low locally advanced (>cT3/N +) rectal cancer who underwent standard TME after neoadjuvant CRT; the lateral lymph nodes were included in the radiation target. Local recurrence developed in 29 patients (7.9%), of which 23 were isolated lateral local recurrences. After multivariate analysis, a larger size of the lateral nodes before neoadjuvant treatment was associated with an increased chance of lateral recurrence. The estimated probability of lateral recurrence increased as lateral lymph node size on MRI increased: ~10% in nodes of 5 mm, ~45% in nodes of 10 mm, and up to more than 80% in nodes of 15 mm. In this study, 42% of the patients with a lateral recurrence had no distant metastases, suggesting it was still localized disease. Decrease of lymph node size on MRI after neoadjuvant treatment did not affect the chance of lateral local recurrence.

In another Korean study from 2014,[44] 443 patients with stage II or III cancers up till 15 cm of the anal verge who had CRT with TME were studied; 53 (11.9%) had local recurrence, of which 20 had isolated lateral recurrences. Again, pre CRT lateral lymph node size predicted the rate of lateral local recurrence (size < 10 mm: 4.0%, > 10 mm: 11.7% lateral local recurrence rate, $p = 0.024$). A similar probability graph was shown, although the chances of lateral local regrowth were lower than the previous study (up to 35% in size of 20 mm). After multivariate analysis, the number of enlarged lateral lymph nodes and the proportion of positive mesorectal nodes were significantly associated with lateral pelvic recurrence.

In a very recent study,[45] 900 patients who underwent CRT and TME for locally advanced tumors up to 10 cm of the anal verge were described. Sixty-five patients had local recurrence (7.2%), of which 42 had lateral regrowth. Short-axis diameter was significantly associated with lateral pelvic recurrence after multivariate analysis. A size smaller than 5 mm results in a 5-year lateral pelvic recurrence rate of 1.8%, while this is 8.3% for nodes between 5 and 10 mm and 59.9% for nodes larger than 10 mm ($p < 0.001$); 47% of the patients with lateral local regrowth had no distant metastases.

Concluding from these studies, we can say that in locally advanced rectal cancer, there is around 5% chance of lateral pelvic recurrence after CRT with TME. However, if lateral nodes are enlarged on imaging, there is a highly increased risk of lateral regrowth, with a probability which is suggested to be between 10 and 80%. It seems that neoadjuvant CRT with TME alone might not be sufficient to prevent lateral regrowth in the case of obvious lateral lymph node metastases. Also, around 40% of these patients who had a recurrence had no distant spread, suggesting that even the recurrence was still localized disease.

Results of Neoadjuvant Chemoradiotherapy Combined with an "Indicated LLND"

As mentioned earlier, the Japanese guidelines still advise that a LLND should be performed in all low locally advanced rectal cancers. However, there are a few Eastern hospitals, where an indicated LLND is performed, based on the size of the lymph nodes on MRI before neoadjuvant CRT.

A Korean study from 2013 by Lim et al[46] describes a cohort of 1,068 with locally advanced cancers up till 10 cm of the anal verge who underwent CRT. Sixty-seven patients (6.3%) had suspected lateral lymph nodes, defined as larger than 5 mm on MRI, for which 82 LLNDs were performed. Of the 82, 32 LLNDs resulted in pathologically positive lateral nodes (40%). In these patients, the average lateral lymph node size was significantly larger before and after CRT (before: 16.5 mm and after: 13.4 mm) than in the patients who had pathologically negative lateral nodes (before: 10.6 mm and after: 7.9 mm). Disease-free survival was significantly lower (31.4%) in the patients who had positive nodes than the patients who had negative nodes (70.5%). Of 67, 2 (3.0%) patients who underwent LLND experienced urinary dysfunction, and 3 (4.5%) had sexual dysfunction.

Another Korean study[47] published in 2014 studied a total of 2,263 patients from three hospitals who underwent CRT for cancers up till 9 cm of the anal verge; 77 (3.4%) had lateral nodes larger than 5 mm and underwent LLND; 66 of these were studied, 11 were excluded because the patients had other pelvic malignancies, previous radiation, or no post-CRT MRI. In the case of persistent nodes (remaining > 5 mm after neoadjuvant CRT, in 22 of 36 patients), in 61.1% pathologically positive lymph nodes were found. In the 30 patients who had responsive nodes, shrinking to smaller than 5 mm, no positive lymph nodes were found. In the patients with positive lateral nodes, the average lateral lymph node size was significantly larger before and after CRT (before: 10.0 mm and after: 8.5 mm) than in the patients who had pathologically negative lateral nodes (before: 7.0 mm and after: 4.4 mm). Five-year disease-free survival was significantly lower (40.9%) in the patients who had positive nodes than the patients who had negative nodes (77.3%). Focusing on the disease-free survival according to persistence of nodes, this was 52.8% in the patients with persistent nodes, significantly lower than in the ones with responsive nodes (80%).

In a Japanese study from 2014 by the group of Akiyoshi et al,[48] 127 patients with locally advanced tumors up till 8 cm were studied. Of the 127, 38 patients had suspected lateral lymph nodes, defined as larger than a 7-mm long axis on MDCT and MRI, and underwent a LLND. Of these, 25 (66%)

had lateral node metastases, despite of CRT; half of which had no positive mesorectal lymph nodes. Disease-free survival was 83.8% in the patients who underwent a LLND, similar to the patients who had no enlarged nodes and thus underwent TME only (74.6%).

In a later study[49] by the same authors, the MRI findings were described in 77 patients who had undergone CRT and LLND for enlarged lymph nodes as indicated before. Of the 77, 31 LLNDs resulted in pathologically positive lateral nodes (40%). In these patients, the average lateral lymph node size was significantly larger before and after CRT (before: 8 mm and after: 7 mm) than in the patients who had pathologically negative lateral nodes (before: 6 mm and after: 4 mm). Patients with a pre-CRT short-axis diameter of the nodes $>$ 8 mm had significantly higher percentages of metastases than those with a pre-CRT short-axis diameter of the nodes $<$ 8 mm (75 vs. 20%, $p < 0.001$). Patients with persistent lateral nodes had a significantly higher percentage of metastases than patients with responsive lateral nodes (75 vs. 20%, $p < 0.001$). In this study, responsiveness did not affect disease-free survival significantly. Patients with lateral node metastases however had a worse disease-free survival (3-year 75%) than patients without metastases (95%).

Concluding from these studies, we can say that between 5 and 30% of the patients with low locally advanced rectal cancers seem to have enlarged lateral lymph nodes. If an indicated LLND is performed in these patients after neoadjuvant CRT still in 40 to 66% of the cases metastases can be found in the nodes, showing these cannot be sterilized totally. Interestingly, in one[48] of these studies, 5-year disease-free survival rates after nCRT + LLND (showing 66% metastases) was similar (84%) to patients who had unsuspected nodes and thus only had nCRT + TME (75%). This is the only study that actually shows that patients can have a good survival after a LLND with positive nodes; in the other studies, only the prognosis is shown for pathologically positive or negative lateral lymph nodes separately, which is, of course, worse in the ones with positive lymph nodes. However, it would be interesting to know the survival in all patients who underwent a LLND in these studies, compared with patients who had no enlarged lateral lymph nodes. There are no uniform conclusions to be made from these few studies about the role of responsiveness of the lateral nodes on CRT; in one study,[47] they are completely sterile, while in the other,[49] still 20% contained metastases.

What Should We Do in the West in the Case of Enlarged Lateral Lymph Nodes?

Western surgeons have always learned that lateral nodal disease is metastasized disease and that these patients cannot be cured with a LLND anyway. Contradictory to this is also the idea that CRT is enough to prevent lateral nodal recurrence. Recent evidence, described earlier, however, suggests we should reconsider our ideas. Times have changed and now in the era where neoadjuvant treatment regimens are used, there might be some patients who need these in combination with more extensive surgery than TME alone.

The studies show that if lateral nodes are enlarged on imaging, there is a highly increased risk of lateral regrowth after CRT and TME, with a probability which is suggested to be between 10 and 80%. Also, around 40% of these patients who have a lateral recurrence have no distant spread, suggesting that even the recurrence is still localized disease. Further, if patients who have enlarged lateral lymph nodes and undergo a LLND (showing 66% metastases), their disease-free survival might go up to 84%, absolutely contradicting the idea that these patients cannot be cured anyway.

More evidence is needed to confirm these findings in Western patients. Currently, a retrospective multicenter analysis is being performed in Western patients with low locally advanced rectal cancer who underwent CRT with TME to analyze what the percentage of lateral nodal regrowth is, according to lateral lymph node characteristics on primary MRI, looking at not only size but also other nodal characteristics, such as border irregularities and internal heterogeneity (http://www.essoweb.org/eursso/about-esso/40-quality-assurance.html). If this is alarmingly high, a future prospective study might have to be considered to analyze the role of an indicated LLND in these selected (few) patients. Considering the high morbidity associated with this procedure patients who need it should be treated in national referral centers that treat locally advanced rectal cancers and have enough exposure to this procedure.

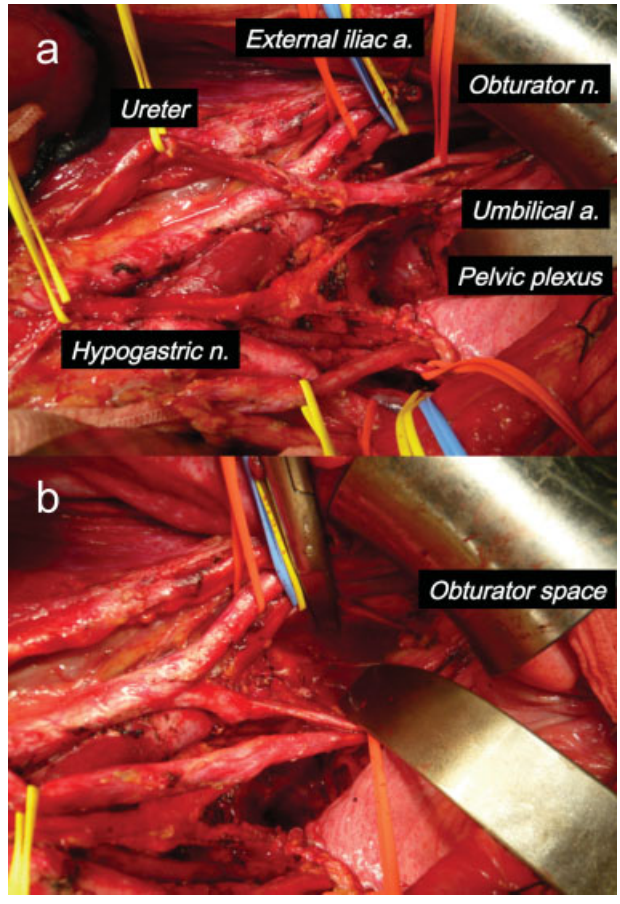

Fig. 1 Pictures after LLND by traditional open approach. LLND, lateral lymph node dissection.

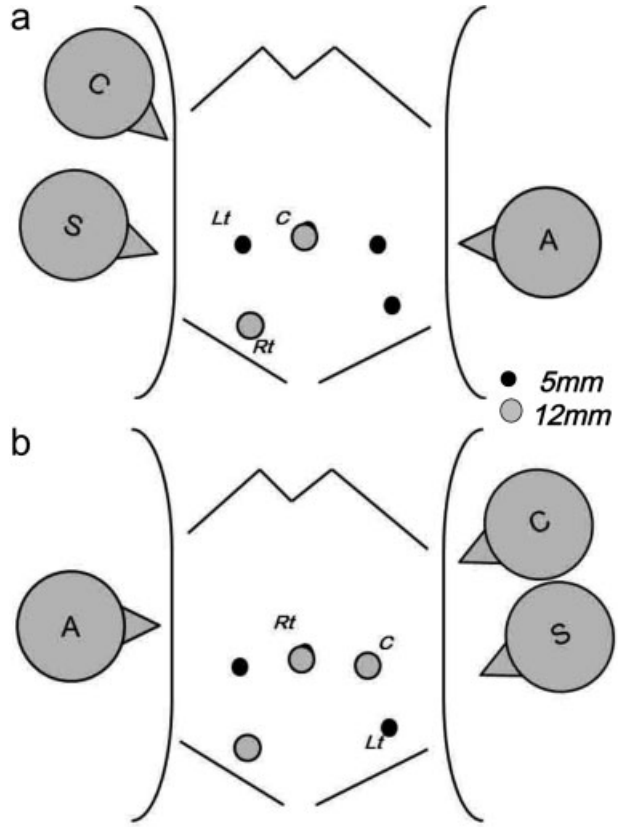

Fig. 2 (a) The operating surgeon stands on the right side of the patient during the left-sided LLND. (b) The surgeon moves to the left side when the right-sided LLND is performed. At that time, the camera should be inserted from the left upper port. (C) Assistant holding camera; (S) surgeon; (A) assisting surgeon; LLND, lateral lymph node dissection.

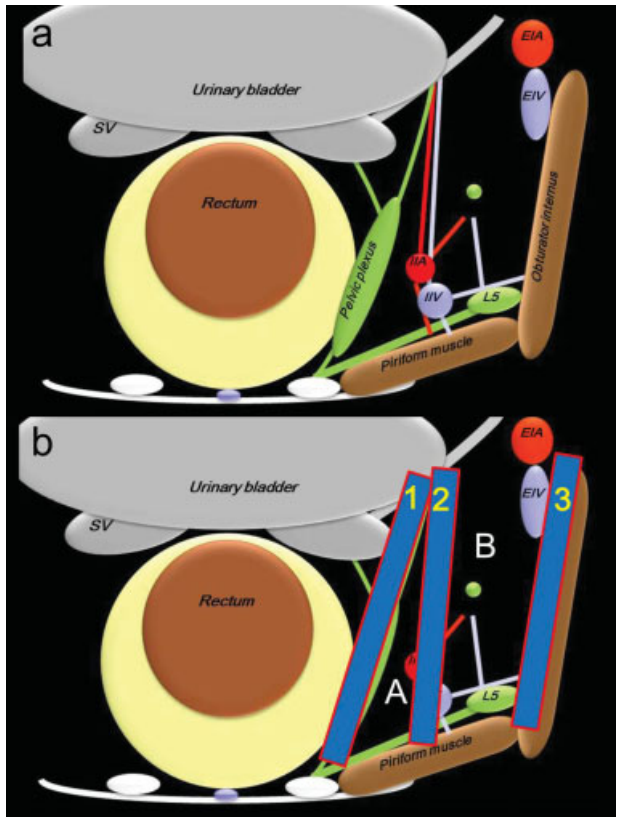

Fig. 3 (a) A scheme of lateral pelvis. (b) Three partitions are shown. 1, hypogastric nerve to the pelvic plexus; 2, main trunk of the internal iliac vessels and several branches to the urinary bladder, prostate, and neurovascular bundle; 3, internal obturator muscle.

Technique LLND

When the rectum is removed after low anterior resection or abdominoperineal resection, TME is followed by a LLND. ►**Fig. 1** shows intraoperative pictures of the traditional open LLND, but currently, it is mostly performed laparoscopically.

Port Placement

The port placement for LLND is similar to that for usual laparoscopic rectal resections. A total of five trocars are used as shown in ►**Fig. 2a**. Port A is a 12-mm camera port placed through the umbilical incision; further three 5-mm ports and one 12-mm port are inserted. The operating surgeon stands on the right side of the patient during the left-sided LLND (►**Fig. 2a**) and moves to the left side when performing the right-sided LLND (►**Fig. 2b**). At that time, the left upper port should be changed to a 12-mm port and can thus be used as a camera port. The surgeon then uses both the umbilical and left lower port for his instruments.

LLND with Totally Autonomic Nerve Preservation

This method is the basic procedure in LLND to avoid urinary and sexual dysfunction. ►**Fig. 3** shows the lateral pelvis in which we can recognize three partitions, which have to be preserved during LLND with autonomic nerve preservation. The medial partition is the autonomic nerve system, in which the hypogastric nerve connects to the pelvic plexus (partition 1). The middle partition contains the internal iliac vessels, with several branches to the urinary bladder, prostate, and the neurovascular bundle (partition 2). The lateral partition is the pelvic side wall, which includes the internal obturator muscle (partition 3). These three partitions have to be carefully exposed and preserved while resecting the lymph nodes between them. As a result, lymph nodes are dissected out of two compartments: the inner (A) along to the proper and internal iliac vessels and the lateral compartment (B), the obturator space. We will now describe the procedure step by step.

First, the ureter should be fully mobilized (►**Fig. 4a**). Then, lymph nodes are resected off the common and internal iliac area (area A). The medial border is the hypogastric nerve (partition 1) and the lateral borders are the common and internal iliac vessels (partition 2) (►**Fig. 4b**, **c**). Dorsally, the sacral periosteum is exposed (►**Fig. 4d**). Dissection is proceeded down along to the iliac vessels. The distal end of the area A is around the first branch of the inferior vesicle vessel in males (►**Fig. 4e**). Going beyond this area is likely to cause postoperative urinary and sexual dysfunction.

Next is the dissection of the obturator space (area B). The umbilical artery is pulled medially and the medial border of the obturator space is opened (partition 2) (►**Fig. 4f**). The dorsal edge of the external iliac vein is exposed (►**Fig. 4g**) and

the lymph node dissection is proceeded down along to the internal obturator muscle (partition 3) (►**Fig. 4h**). Caudally, the lymphatic vessels are divided where they continue further to the inguinal canal at the ventral side of the pectineal ligament. Then, the distal end of the obturator nerve and vessels can be seen. The obturator nerve is preserved, but the obturator vessels are resected (►**Fig. 4i**). Proximally, the roots of the obturator vessels are found out and divided (►**Fig. 4j**). Fat tissue of the obturator space is lifted up and dissected from the bottom, dividing some branches of the internal iliac vein. Finally, the fat tissue of obturator space is completely removed (►**Fig. 4k**). ►**Fig. 4l** is a picture after LLND with total autonomic nerve preservation.

Extended LLND Combined with Resection of the Autonomic Nerves and Internal Iliac Vessels

For patients with massive lateral lymph node metastases which involve the nerves and/or internal iliac vessels, extended LLND with en bloc resection of nerves and vessels is sometimes indicated, depending on what is involved. The most difficult technique is the combined resection of the main trunk of the internal iliac vein (►**Fig. 5a**). This vein is stuck to the bottom of the pelvic floor, and moreover, there are numerous branches to the pelvis. These branches have a very short neck; therefore, the division of these branches should be performed with great care: massive bleeding from such veins brings major trouble. Therefore, we usually

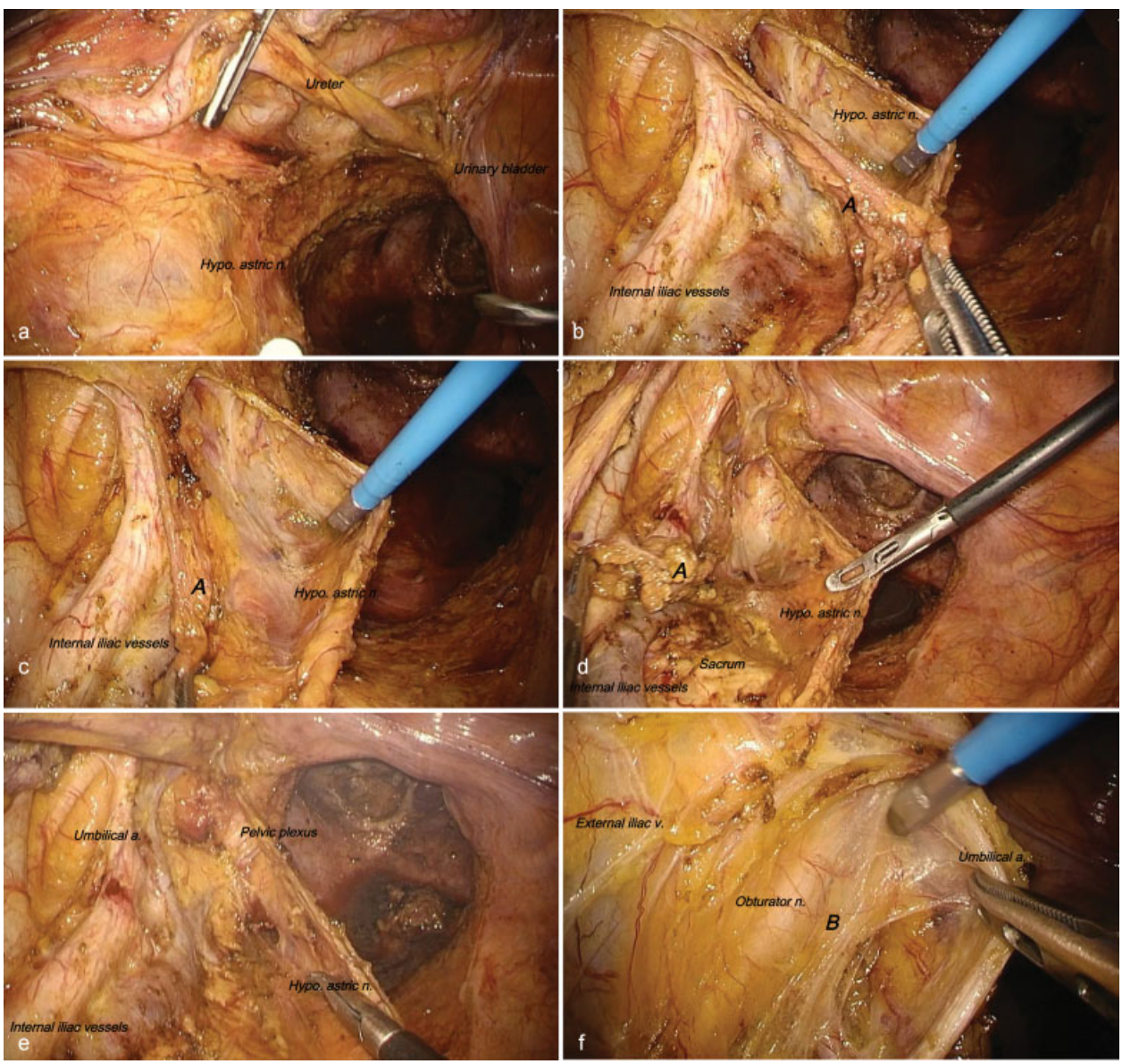

Fig. 4 (a) The ureter should be fully mobilized. (b) The medial border is the hypogastric nerve. (c) The lateral borders are the common and internal iliac vessels. (d) Dorsally, the sacral periosteum is exposed. (e) The distal end of the area A is around the first branch of the inferior vesicle vessel. (f) The medial border of the obturator space is opened. (g) The dorsal edge of the external iliac vein is exposed. (h) Dissection is proceeded down along to the internal obturator muscle. (i) The obturator nerve is preserved, but the obturator vessels are dissected. (j) The roots of the obturator vessels are divided. (k) The fat tissue of obturator space is completely removed. (l) The view after LLND with total autonomic nerve preservation. LLND, lateral lymph node dissection.

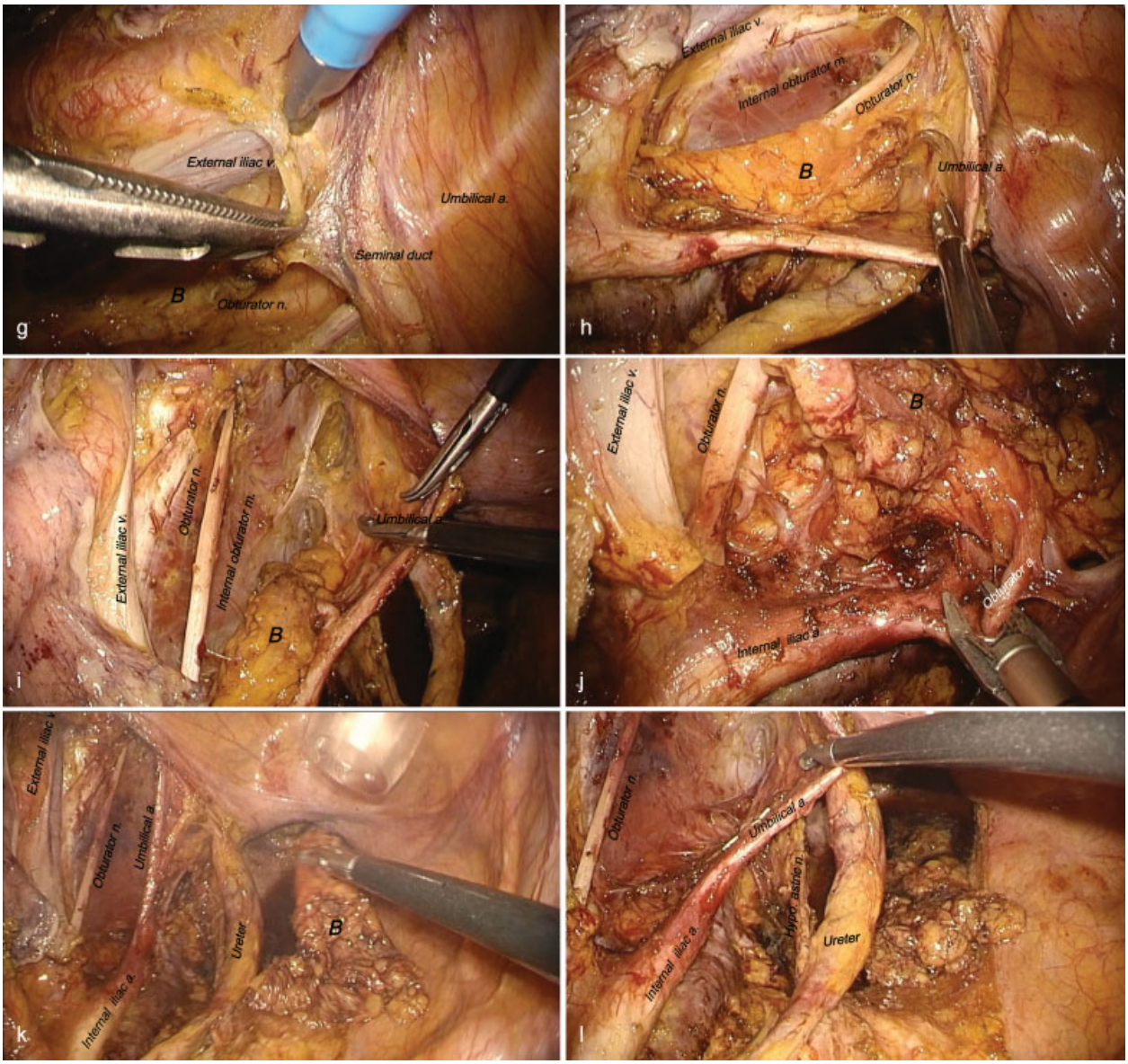

Fig. 4 (*Continued*)

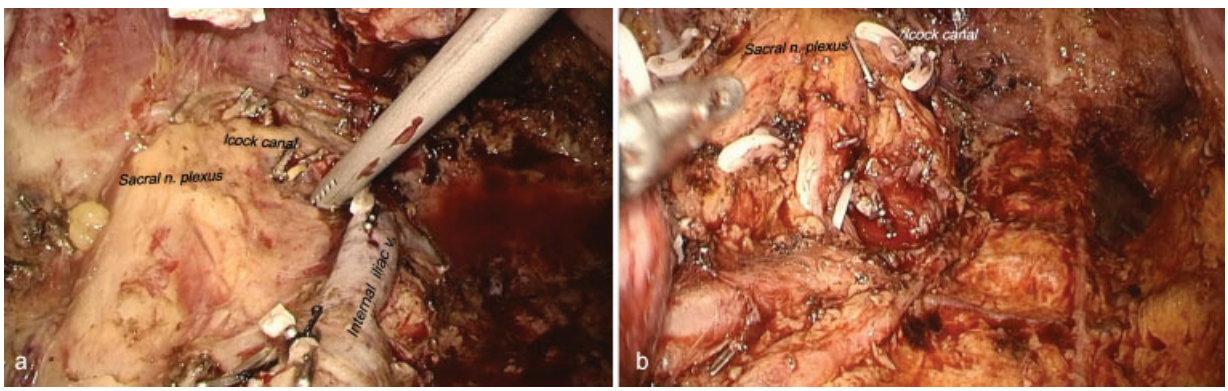

Fig. 5 (a) View after combined resection of the main trunk of the internal iliac artery and vein. The sacral nerve plexus is fully exposed at the bottom. (b) The main trunk of the internal iliac vein is usually preserved and only the trunk of the artery is divided.

preserve the main trunk of the internal iliac vein and divide only the trunk of the artery (►**Fig. 5b**).

Conflict of interest
None.

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