

Lateral lymph node dissection for low rectal cancer: Is it necessary?

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Abstract

Rectal cancer constitutes a major public health issue. Total mesorectal excision has remained the gold standard treatment for mid and low rectal tumors since its introduction in the late 1980s. Removal of all lymph nodes located in the mesorectum has indeed improved pathological and oncological outcomes. However, when cancer spreads to the lateral lymph nodes (located along the iliac and obturator arteries) Western and Japanese practices differ. Where the Western guidelines consider this condition as an advanced form of the disease and use neoadjuvant radiochemotherapy liberally, the Japanese guidelines define it as a local disease and proceed to lateral lymph node dissection with or without neoadjuvant treatment. Herein, we review the current literature regarding both therapeutic strategies, with the aim of contributing to potential improvements in treatment and outcome for patients with low and mid rectal cancer.

Key words: Total mesorectum excision; Mesorectal resection; Lateral node metastasis; Extended lymphadenectomy

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Core tip: Total mesorectal excision has remained the gold standard treatment for mid and low rectal tumors since its introduction in the late 1980s. However, where the Western guidelines consider spread to the lateral lymph nodes as an advanced form of the disease and use neoadjuvant radiochemotherapy liberally, the Japanese guidelines define it as a local disease and proceed to lateral lymph node dissection with or without neoadjuvant treatment. We review the current literature for therapeutic strategies, enhancing knowledge for treatment of patients with low and mid rectal cancer.

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INTRODUCTION

Rectal cancer is ranked 8th among all cancers worldwide in terms of both incidence (3.9%) and mortality (3.2%), according to the latest data from GLOBOCAN 2018^[1]. Although introduction of the total mesorectal excision (TME) treatment method^[2] led to improved pathological and oncological outcomes-emerging as the gold standard surgical procedure-the treatment of mid and low rectal cancers remains challenging^[3].

TME allows for the removal of perirectal lymph nodes, reducing the local recurrence rate from the pre-TME rates of 14%-40% down to 6.5%^[4]; however, low and mid rectal cancer cells have the tendency to spread to lateral nodes, such as the internal iliac nodes, common iliac nodes, obturator nodes, and external iliac nodes^[5]. Cases of metastases in these nodes reportedly range between 10.6% and 25.5% when the lateral lymph node dissection (LLND) has been performed for advanced rectal cancers (stages II-III)^[6]. One of the main issues nowadays is what to do with these lateral nodes? While they are considered as regional metastatic nodes and surgically removed in Japan^[7], they are defined as advanced disease in the West and lead to the use of neoadjuvant treatment^[8].

LYMPHATIC DRAINAGE OF THE RECTUM

Lymphatic vessels of the rectum are formed from the lymphatic plexuses located in the rectal wall under the mucosa. Then, they reach the perirectal ganglia located in the mesorectum. After crossing the mesorectum, they form three trunks with nodal groups: the superior trunk drains into the rectosigmoid and forms the inferior mesenteric nodal groups; the middle trunk drains into the internal, external and common iliac lymph nodes and sacral nodes; and the inferior trunk drains into the superficial inguinal and external iliac lymph nodes, but also into the pelvic, sacral and internal iliac nodal groups. In case of cancer, its level of localization correlates to the risk of lymph node metastasis^[9]. Moreover, rates of lymph node metastasis follow the depth of invasion and consequently the T stage^[10,11].

The rectum is considered as a digestive segment, measuring around 15 cm in length and consisting of two parts: One covered by the peritoneum and one without peritoneum. However, there is no consensus regarding the definition of low rectum and, as a consequence, none for the localization of low rectal cancers. Traditionally, the rectum has been considered to be 15 cm long, as measured from the anal verge; however, Germany and the United States have defined the length as 16 cm and 12 cm, respectively^[12]. Recently, the LOREC program of the United Kingdom (designed with the aim of improving low rectal cancer management^[13]), proposed a magnetic resonance imaging (commonly known as MRI)-based anatomical definition. In such, low rectum is defined as the place "where the mesorectum tapers at the origin of the levators, at the pelvic sidewall" (around 6 cm from the anal verge).

On the other hand, in Japan, the classification depends on location of the tumor in relation to the peritoneal reflection, being either above (Ra) or below (Rb)^[14]. However, it is most often an operative findings' based-classification. It may be indeed difficult to achieve a correct preoperative assessment of the peritoneal reflection with the current imaging modalities.

LATERAL LYMPH NODE METASTASIS CONSTITUTES AN ONCOLOGICAL PREDICTOR

The latest tumor-node-metastasis classification (AJCC 8th edition)^[15] considers lateral lymph node (LLN) involvement as indicating distant disease status. However, Japanese surgeons still acknowledge the presence of LLN involvement as a local disease, and consequently as a resectable disease^[16]. Thus, in addition to TME, Japanese guidelines recommend performing systematic LLND when positive LLN(s) are suspected or in cases of stages II-III^[16].

In addition, the presence of positive LLN(s) seems to be a prognostic factor not only for local recurrence but for overall survival as well. Indeed, in a retrospective study of 66 patients with stage I-III low rectal cancer treated with TME and LLND (without any neoadjuvant treatment), the presence of micro-metastatic LLN(s) was found to be significantly associated with reduced 10-year overall survival and recurrence-free survival^[17].

In recent Japanese publications reporting on patients who underwent LLND for advanced low rectal cancer, the prevalence of LLN metastasis has ranged from 6%^[18] to 50%^[19]. This high heterogeneity in reported prevalence is in part due to bias in patient selection, with some of the research groups having performed systematic LLND^[20] and others selective LLND based on preoperative imaging^[21]. Recently, a systematic review and meta-analysis showed that MRI was accurate for the identification of LLN metastasis, with a pooled sensitivity of 0.72 and a pooled specificity of 0.80^[22].

TREATMENT OF METASTATIC LLNS

Considering both prevalence of LLN metastasis and its negative impact on oncological outcomes, therapies should aim at treating LLN(s), especially in advanced cancer stages. In the 1950s, LLND was performed systematically for all rectal cancer cases but survival rates were not those expected and many complications, such as bleeding, were observed^[23]. A 5-year survival rate of 54% was reported in patients treated with LLND *vs* 46% of those who did not undergo systematic dissection; moreover, complications were more frequent and serious after LLND, including increased transfusion rate, prolonged hospital stay, and major urinary complications. A more recent Turkish cohort study showed an increase of 19% in urinary incontinence and 12% in urinary retention in patients with extended LLND compared to patients without^[24]. Of note, similar findings were reported after preoperative radiotherapy alone^[25]. From a sexual function point of view, this was confirmed in a Dutch cohort study, from which a decrease in sexual function was found to have occurred after preoperative radiotherapy^[26]. These results are in accordance with Japanese data, which also showed worse sexual function after LLND^[27].

Globally, the debate continues regarding the best management of patients with suspected LLN. Very recently, in a large multicenter study, Ogura *et al*^[28] found that standard neoadjuvant treatment might be insufficient for preventing local recurrence in patients with advanced low rectal cancer (cT3/T4) and enlarged LLNs (defined as having a short axis of at least 7 mm). The authors reported that neoadjuvant radiochemotherapy plus TME plus LLND led to a 5-year lateral local recurrence rate of 5.7% (*vs* 19.5% without LLND). These results have to be taken cautiously as 19.5% local recurrence rate is unusual after randomized clinical trial (RCT) and TME. Also, the role of LLND in combination with neoadjuvant treatment could have been further explored. Also, the role of LLND in combination with neoadjuvant treatment should have been further explored. A recent Korean study^[29] in which patients who had neoadjuvant CRT followed by standard TME (without LLND) were analysed to see whether they developed local recurrence in the lateral lymph node compartment. Out of 366 patients having benefited from neoadjuvant chemoradiotherapy and TME, 24 had lateral pelvic recurrence (6.6%); multivariate analysis showed that lateral pelvic recurrence was significantly associated with ypN and size of lateral lymph node. It has been suggested that the association of neoadjuvant RCT and TME might not be sufficient to prevent lateral recurrence in the case of obvious lateral lymph node metastases. Yet, the overall survival advantage of LLND is still under debate. In a recent systematic review and meta-analysis including 5502 patients, LLND did not improve the 5-year overall survival rate but instead led to higher rates of sexual and urinary dysfunctions, as compared to TME without LLND (odds ratio of 3.7)^[30].

Based on these contradictory facts, Japanese surgeons continue performing LLND for advanced rectal cancers^[31]. On the other hand, over the last 10 years, Japanese teams have tried to improve their results, not only by attempting to decrease the number of sexual and urinary complications through use of a nerve-sparing technique^[32] but also by limiting the indications of LLND^[33]. Since the 2000s, Japanese guidelines have recommended limiting LLND to tumors with a lower edge lying at or below the peritoneal reflection^[33] and classified as cT3-4 with or without lymphatic node metastasis^[34]. These adjustments have been shown beneficial in terms of both functional^[35] and oncological outcomes^[36]. A recent Japanese randomized controlled trial comparing TME with and without LLND for clinical stage II or III low rectal cancer demonstrated the two groups to have similar incidence for early urinary dysfunction (59% and 58% respectively)^[35]. Considering oncological outcomes, Fujita

et al^[36] found 7.4% of patients treated with TME and LLND had local recurrences compared to 12.6% of the patients treated with TME without LLND ($P = 0.024$). Overall, both approaches have advantages and drawbacks. Specific strategies are needed when dealing with low rectal cancer, especially when a significant risk of LLN involvement is present.

PERSPECTIVES

Further research in this field is definitely needed, to precisely determine the prevalence of metastatic LLN^[37] and to identify the candidates for LLND. Subgroups of patients should be identified based on preoperative workup^[38,39], to offer targeted therapies, including neoadjuvant radiochemotherapy and/or LLND, according to the risk of metastatic LLN. It is conceivable that a multistep treatment, including both of these therapeutic strategies, could be adopted consensually.

Imaging seems to constitute a key element in determining the aggressiveness of LLN. Thus, by combining radiologic, histologic and proteomic/genomic findings and using deep learning-machine (radiomics), we might develop a better prognostic model, leading to personalized therapeutic strategy^[40].

As a result, the best strategy to be chosen remains an open debate. It is necessary to underline that computed tomography and MRI methods in detecting nodal involvement in this lateral region^[41] proved to be efficient in only 80%-90%. Moreover, in western countries, people have more often higher body mass index than in Asia resulting in more difficulties for surgery. Despite these elements, good surgical technique seems to be a key factor^[42]. As a consequence, it is fundamental to have an expert colorectal unit being able to perform LLND with preservation of nerves.

CONCLUSION

To conclude, despite therapeutic improvements, rectal cancers remain a major health issue. TME is the gold standard to treat mid and low rectal tumors. However, Japan and Western guidelines differ as to the definition of when the cancer cells reach the LLN(s), applying LLND for the former and neoadjuvant treatment for the latter. With the Japanese approach, functional complications can occur but have been lessened by the recent emergence of the nerve-sparing technique, whereas it appears that neoadjuvant treatment exposes patients to long-term functional complications. Furthermore, local recurrence can occur after radiochemotherapy, especially when enlarged LLN(s) are found preoperatively in advanced low rectal cancers. Of note, the survival advantage of LLND remains to be demonstrated. Thus, considering both Western and Japanese strategies, it is necessary to focus more attention on the preoperative findings in order to better identify LLN involvement and offer LLND to the most appropriate, selected group of patients. Routine application of LLND is still a matter of debate, at least in Western countries, where liberal use of neoadjuvant radiochemotherapy remains the gold standard.

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