

## Surgical Management of Colorectal Cancer

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### Abstract

**Introduction:** CRC is the fourth most frequently diagnosed malignancy in both genders, with one million cases annually. CRC is the third most common cause of cancer-related death in the world, accounting for 630,000 deaths annually and over 30,000 new cases per year in South Korea.

**Aim of Work:** In this review, we will discuss Surgical management of colorectal cancer.

**Methodology:** We did a systematic search for recent advances in the surgical management of colorectal cancer using PubMed search engine (<http://www.ncbi.nlm.nih.gov/>) and Google Scholar search engine (<https://scholar.google.com>). All relevant studies were retrieved and discussed. We only included full articles.

**Conclusions:** The lack of clearly defined guidelines for the appropriate extent of lymph-adenectomy in colorectal cancer has led to various ways in staging and treatment. The lack of strong evidence for the benefits of extra-regional lymph node dissections in colorectal cancer makes it challenging to recommend a universal approach. This review indicates that pelvic LN dissection treatment for rectal cancer remains under debate. Approaches to PALN metastasis have also not been addressed thoroughly enough in the literature to determine the best treatment strategies. In PALN metastasis, chemotherapy might play a role in evaluating tumor response, which then enables the surgeon to decide whether to proceed with surgery or to continue palliative chemotherapy.

**Keywords:** Colorectal Cancer; Cancer Metastasis; Surgical Management

### Introduction

CRC is the fourth most frequently diagnosed malignancy in both genders, with one million cases annually. CRC is the third most common cause of cancer-related death in the world, accounting for 630,000 deaths annually and over 30,000 new cases per year in South Korea [1]. The majority of CRC morbidity is due to local recurrence, which has been reported at a rate of 21 to 46%. Enhancements in surgical techniques and the invention of TME principles have significantly decreased the local recurrence rate to an average of 4-8%. Despite this improvement, CRC recurrence is still a major cause of morbidity and mortality. In addition, existence of scarring and fibrosis

at the tumor bed contributes to further difficulty in eliminating metastatic deposits, which are a possible cause of local failure. Moreover, extra-mesenteric metastases such as LPLN or PALN are not excised by the TME technique. Therefore, extensive lymph-adenectomy may be indicated to eliminate the source of the disease or TME combined with radiotherapy [2]. However, treatment strategies vary among countries and institutes due to the lack of supporting randomized clinical trials. Incidence of ERLN metastasis is rarely seen in cases of CRC, which has also contributed to the lack of literature regarding treatment strategies and procedures. The most common site of ERLN metastasis in CRC is either PALN, with an estimated risk of 1.2% to 2.1% [3] or LPLN, which is linked to T-stage status. Definition, staging and treatment of ERLN metastasis differ in various countries. For instance, isolated para-aortic lymph node recurrence (IPLR) is a rare type of CRC metastasis which was previously identified as a retroperitoneal recurrence [4]. Currently, PALN metastasis is defined as the presence of an unequivocally enlarged lymph node adjacent to the abdominal aorta in the absence of distal metastasis at any other site. PALN has been classified according to location to the renal vein and referred to 16A (above the renal vessels) or 16B (below the renal vessels), in accordance with the classification by the Japanese Society of Clinical Oncology [5]. On the other hand, LPLN metastasis is defined as a dissection of a pelvic tumor to a lymph node outside the defined regional nodes. LPLN is named along with anatomical location of these nodes; presacral, common iliac vessels, proximal and distal part of the internal iliac vessels and obturator canal. In our practice, LPLN dissection starts at the common iliac vessel bifurcation and extends down to the level of obturator canal (Alcock's canal) in order to ensure lymph node clearance as it counts the site of the highest incidence among LPLN metastasis group. This procedure is facilitated by removing all fat and areolar tissue attached along the course of internal iliac vessels as well as to swipe all lymph nodes adherent and around obturator vessels in a given effort to preserve obturator nerve. Furthermore, PALN dissection, however, must extend to the level of the renal vessels superiorly to obtain sufficient information for diagnosis and possible therapeutic options.

### Methodology

We did a systematic search for recent advances in the surgical management of colorectal cancer using PubMed search engine (<http://www.ncbi.nlm.nih.gov/>) and Google Scholar search engine (<https://scholar.google.com>). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: colorectal cancer, cancer metastasis, surgical management.

### Surgical management of metastatic disease

According to the staging system of the American Joint Committee on Cancer (AJCC), PALN metastasis is considered as M1 disease [6], while in the LPLN metastasis staging it is considered as a regional lymph node to rectum cancer as long as it is confined to the proximal group of the internal iliac lymph node. LPLN metastasis are considered to be of a better prognosis than stage 4 diseases although it has a very poor prognosis. A multi-centric study by Akiyoshi, *et al.* [7] reported on the prognosis and metastasis to the lateral pelvic lymph node in low rectal in Japan. 11,567 patients diagnosed with stage I to III low rectal cancer were included, of which 5789 (50%) had LPLN dissection. The metastasis in the lymph node was classified according to the metastatic site into groups; mesorectal-lymph node group, internal lateral pelvic lymph node metastasis (which are localized to or extending beyond the internal iliac area) and external-LPLN group respectively. The overall survival (OS) and cancer-specific survival (CSS) in the external-LPLN group were significantly better than in patients with stage IV disease who underwent curative resection (OS: 29% vs 24%,  $P = 0.0240$ ; CSS: 34% vs 27%,  $P = 0.0117$ ).

The presence of Lymphatic Spread in cases of colorectal cancer is considered to be a sign of a disease outside its area of origin which is the pelvic cavity, meaning that further treatment methods other than radical resection. Understanding the anatomy and the routes of lymphatic spread in CRC is important in order to monitor and progress of the disease and the lymphatic draining of the tumor in cases where CRT or surgical resection are under consideration. The risk of LPLN metastasis is found to be higher in patients with cases of advanced CRC, the risk PALN metastasis was also found to be higher as it follows the inferior or superior mesenteric artery. Recently, the overall survival rates in CRC patients has increased due to the medical attention on ERLN metastasis and the recent surgical techniques that eradicate the tumor with no residual cancer cells and decreasing the incidence of local recurrence, which currently is considered to be the best line of treatment in cases of ERLN metastasis in CRC.

The overall incidence of LPLN metastasis In Japan and Korea varies between 10.6% to 25.5%, with an average risk of 15% [8] with higher incidence in cases with advanced rectal tumor, especially in the sub-peritoneal reflection tumors. A study by Kobayashi, *et al.* [9] studied the relation between the depth of the tumor and the incidence of LPLN metastasis, reporting that the risk of LPLN metastasis to be 5.4% in pT1 cancers, 8.2% in pT2 cancers, 16.5% in pT3 cancers and 37.2% in T4 cancers. Furthermore, in cases of sub-peritoneal reflection tumor, the average risk of LPLN metastasis increases to 13.9%. However, in a Japanese multi-center study [10] Sugihara, *et al.* found that the rate of LPLN metastasis is only 1.7 % in cases of tumors above the peritoneal reflection [11]. Therefore, due to the high chance of metastasis, Japanese surgeons recommend the dissection of LPLN in cases of advanced sub-peritoneal rectal cancer (T3, T4). In the other hand, the literature in western countries regarding LPLN metastasis is insufficient as the previous studies had low survival rates. Since then, Enhanced CRT targeted agents has been preferred to dissection surgery, which improved the survival rates and helped in the local control in CRC patients. The overall incidence of Isolated PALN is 1.7%, which considered relatively rare. A multi centric Japanese study observed the incidence of synchronous PALN metastasis during surgery in both sigmoid and rectal cancer and it was 2.1% and 1.9% respectively.

The number and location of metastatic lymph nodes are the most important prognostic features of ERLN metastatic lymphatic spread in CRC. These nodes are a primary factor in determining the overall survival and outcome of CRC patients [12]. The involvement of Lymph node is associated with a very poor prognosis, which becomes even worse in case of ERLN metastasis. In rectal cancer, the depth of the tumor is considered a prognostic factor for estimating the risk of LPLN metastasis, which could rise up to 37.2% in cases of pT4 cancers [9]. Sugihara, *et al.* [11] reported a 58% increase in the incidence of LPLN metastasis associated with cases in females, lower rectal cancers, non-well-differentiated adenocarcinoma, tumor sizes greater than or equal to 4 cm and T3-T4 tumors. Furthermore, the prognostic values of LPLN metastasis was studied by Wu, *et al.* [13] in 96 patients diagnosed with low rectal cancer who underwent TME and LPLN dissection. LPLN metastasis was found in 14.6% of the cases. Furthermore, it reported that the incidence of metastasis increased with poorly differentiated tumors and in T4 lesion in which the LPLN is larger than 5 mm in short axis diameter. Such conditions increased the local recurrence to 64.3% while it is only 11% in negative LPLN cases. There is no enough studies addressing the risk factors of PALN metastasis in CRC patients. However, many studies reported a higher risk of PALN metastasis in cases of colon tumors rather than rectal tumors. Min, *et al.* reported that the histological grade, PALN location and surgical resection were associated with improved overall survival and recurrence rates. The location of the IPALN below the renal vessels (B region) was also associated with better survival rates rather than above to renal vessels (A region). Lu, *et al.* [14] analyzed 3388 CRC patients with no distant metastases divided into two groups, those with visible PALN or not visible. This study predicted poor prognoses in cases of visible PALNs equal or greater than 10 mm, an even worse prognosis was predicted in cases with lympho-vascular invasion, higher grade disease or if more regional lymph node metastasis were present. Another study reported an increased risk of regional or extra-mesenteric lymph node metastasis in CRC cases that invades the muscular layer or extend deeper in the bowel wall areas [15].

Adequate imaging and interpretation of CRC cases is essential to avoid the complications of unnecessary dissection and chemotherapy. Regarding rectal cancer, MRI is considered to be more accurate than a CT in the evaluation of the tumor depth, adjacent organ invasion and LPLN metastasis involvement, where the accuracy of MRI images is 83%, compared to 77% accuracy of CTs. Recently, a retrospective study by Ogawa, *et al.* [16] of 449 patients diagnosed with low rectal cancer in six institutions. Only 324 of them underwent TME plus LPLN dissection, proceeded by preoperative MRI to estimate the risk of LPLN metastasis however not all of the patients had undertaken LPLN dissection], MRI sensitivity was 72.6 %, specificity was 54.7%, PPV was 61.9% and NPV was 66.3%. Kim, *et al.* [17] also found a high sensitivity for high-resolution pelvic MRIs in detecting metastatic LPLN but high specificity for PET/CT. Generally, MRI is considered to be a key diagnostic tool in rectal cancer for assessing tumor depth, tumor invasion and regional lymph node metastasis as well as predicting features of LPLN metastasis. In addition, if an MRI leads to a suspicion of LPLN metastasis, a PET is favorable and may be combined with the MRI to support or discard these findings. For example, if the shape is round or irregular, the node is likely metastatic. If there is signal intensity heterogeneity on a T2-weighted MRI or central necrosis on a CT, evidence of metastasis may be expected. In other era of

the research, PALN metastasis was indicated in our institute by suspicious finding in CT scan and confirmed by PET scan uptake. Lee, *et al.* [18] studied 66 patients with different abdominal malignancies who underwent both CT and PET scans to diagnose PALN metastasis and suggested that the CT was more sensitive while the PET was more specific. The overall accuracy was slightly higher in the PET scan.

Several methods of treatment have been developed to improve the survival rates in metastatic CRC patients. There is a huge debate regarding the definition, staging and approach of treatment in cases of ERLN metastasis. For instance, in Japan, ERLN is defined differently from western countries. In the west, it is considered as a systemic disease, LPLN metastasis is usually treated with radiotherapy or chemotherapy followed by TME, with rates of local recurrence less than 10% [19]. In Japan, however, LPLN is considered to be a regional disease and usually treated with extensive lymph node dissection in cases with locally advanced rectal cancer in order to reduce local recurrence and improve the overall survival rate [20]. However, in Japan CRC cases with PALN involvement are considered an M1 disease, it is believed that cases managed by surgery before chemotherapy will probably have better outcomes and overall survival. Moreover, the NCCN guidelines recommend to perform a biopsy or excision of suspicious nodes outside the resection field, and in the absence of clinically suspicious nodes extended resection will not be indicated due to the possible complications of surgery, including urinary and sexual impairment, long operative times and intra operative blood loss. In cases with an advanced rectal tumor located below the peritoneal reflection. If ERLN metastasis was suspected, the patient is advised to proceed with 6 - 12 cycles of chemotherapy upfront followed by reassessment, after which either resection or palliative care is advised. The standardization of the TME technique and advances in chemo-radiotherapy agents have participated in decreasing the rate of local recurrence and improving survival rates [21]. In the west, CRT followed by TME and adjuvant chemotherapy is considered to be the standard treatment for LPLN metastatic rectal cancer. However, in Japan, TME and LPLN dissection with adjuvant chemotherapy is considered the standard treatment in Japan [22]. A recent study by Akasu, *et al.* [23] evaluated the function of the male genitourinary tract in 69 patients undergoing LPLN dissection. 29 patients underwent TME alone and 40 patients operated by TME and LPLN dissection, a worse sexual and urinary function were observed after LPLN dissection. In addition to the risk of preoperative radiotherapy which impairs the sexual and urinary functions. Generally, an Upfront CRT is preferred to be done before surgery as it is associated with lower morbidity and genitourinary dysfunction when compared to surgery alone [24]. While LPLN dissection is not preferred in Europe and North America as it is associated with increased complications with no improvement in the overall survival [25]. Otowa, *et al.* [26] studied the effect of preoperative CRT on LPLN metastasis in 32 patients, he reported that CRT reduced the clinical lymph node in 50% of the cases. In Japan, prophylactic pelvic dissection has been recommended, particularly in cases of T3 or T4 low rectal cancer below the peritoneal reflection. Many studies reported that LPLN dissection in rectal cancer is associated with decreased recurrence rate and improvement of the overall survival rate [27]. Recently, Kim, *et al.* [28] investigated the association between overall survival rates and short axis diameters in LPLN. 10 mm LPLNs was significantly associated with a worse survival rate even after CRT. Several recently published reports have studied LPLN metastasis outcome based on images with or without LPLN dissection. However, the largest comparative study was performed by Kobayashi, *et al.* [9] where he compared LPLN and non-LPLN dissection for low rectal cancer recurrence rate and overall survival. 1,272 patients were gathered from across Japan. 784 underwent LPLN dissection, of them, 117 patients (14.9%) had lateral pelvic lymph node metastasis. Surprisingly, they concluded in no significant differences between patients with and those without LPLN dissection in terms of local recurrence rate (10.5% vs. 7.4%) or 5-year overall survival (75.8% vs. 79.5%). However, patients with stage II lower rectal cancer who underwent LPLN dissection had a significantly better prognosis reached up to 87.0% 5-year survival. Georgiou, *et al.* [19] showed similar survival rates in both categories. In addition, Watanabe, *et al.* [24] compared outcomes of preoperative radiotherapy without LPLN dissection and LPLN dissection without radiotherapy and found no significant difference in survival or local recurrence in two groups. Thus, indication and selection criteria are crucial; whether the treatment is LPLN dissection or preoperative CRT, to prevent unnecessary intervention. However, there is a lack of evidence and a well-structured standard regarding the best methods of management of LPLN metastasis in CRC.

Modulated radiotherapy (IMRT) and tomotherapy and robotic linear accelerators (CyberKnife, Accuray Inc., Sunnyvale, CA) have made it possible to deliver a carefully calculated high-dose radiation accurately to certain areas without damaging any near normal structures [29]. The use of both Radiotherapy in addition to surgery has been used widely in the treatment of rectal cancer. However, radiotherapy

have a very little role in the treatment of PALN recurrence in CRC, and its survival benefits remain unknown. Kim., *et al.* [30] have studied the recurrence PALN metastasis in the rectal cancer after the surgery in seven patients. The initial report suggested that selected PALN recurrence could potentially be treated by radiotherapy. Masaki., *et al.* compared the efficacy of IORT to standard treatment (TME + bilateral LPLN dissection + partial sacral nerve preservation) in 41 patients. He reported that the IORT group had a better voiding function and a shorter duration of urinary catheter usage (8 vs.13 days,  $P = 0.055$ ), this can mean that IORT provides a better nerve preservation to the standard treatment. Future randomized clinical trials are required to determine the effects of radiotherapy in ERLN metastasis in CRC.

Recently, a minimally invasive approach has been used in the treatment of rectal cancer. Laparoscopic TME has been found to be associated with less surgical trauma and better short term outcomes, in addition to faster recovery times and shorter hospital stays. However, the use of minimally invasive surgery in the treatment of ERLN dissection have not been studied yet. Liang., *et al.* [31] reported that the use of laparoscopic surgery in LPLN dissection to be safe and feasible and does not compromise oncology safety. Akiyoshi., *et al.* [27] found similar results. Furthermore, Konishi., *et al.* [32] reported laparoscopic LPLN dissections to have in less postoperative complications, shorter hospital stays and faster recovery times than open surgeries. The role of robotic LPLN dissection in lower rectal cancer has been studied by Park and Bae., *et al.* [33] they reported that robotic surgery is safe and feasible and does not normally result in dissection-related morbidity.

## Conclusion

The lack of clearly defined guidelines for the appropriate extent of lymph-adenectomy in colorectal cancer has led to various ways in in staging and treatment. The lack of strong evidence for the benefits of extra-regional lymph node dissections in colorectal cancer makes it challenging to recommend a universal approach. This review indicates that pelvic LN dissection treatment for rectal cancer remains under debate. Approaches to PALN metastasis have also not been addressed thoroughly enough in the literature to determine the best treatment strategies. In PALN metastasis, chemotherapy might play a role in evaluating tumor response, which then enables the surgeon to decide whether to proceed with surgery or to continue palliative chemotherapy. In the future, randomized multicenter studies may be required to conclude the ongoing debates, but it is clear that accurate risk stratification and careful patient selection are central to disease management.

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