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Lymphadenectomy in Colorectal Cancer: Therapeutic Role and How Many Nodes Are Needed for Appropriate Staging?

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Abstract Surgical resection with adequate lymphadenectomy is the treatment of choice for accurate diagnosis and proper treatment in colorectal cancer. Lymph node (LN) staging is an important prognostic factor in colorectal cancer and remains to be the most main criteria to select patients for adjuvant treatment. In colorectal cancer, a focus of treatment has been to collect as many LNs as possible to improve staging and increase survival. However, the scientific evidence for a minimum LN harvest remains controversial and the use of international cut-off values should be considered again. In practice, a thorough pursuit of a set high number of LNs may not be appropriate, but the best practice should be to collect as many LNs as possible.

Keywords Colorectal cancer · Lymph node count · Lymph node harvest · Lymphadenectomy

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Introduction

Colorectal cancer is one of the most common cancers worldwide. In the USA, approximately 95,270 patients with colon cancer and 39,220 rectal cancer patients were estimated in 2015. For the same time period, 49,190 deaths in colorectal cancer accounted for about 12% of all cancer deaths [1].

The prognosis for colorectal cancer is primarily determined by the tumor–node–metastasis (TNM) stage of the disease. The currently most widely accepted staging system for colorectal cancer—the 7th American Joint Committee on Cancer staging system (AJCC)—is based on the number of metastatic lymph nodes (LNs) present as well as the pathologic T stage [2]. Surgical resection with adequate lymphadenectomy is the treatment of choice for patients with colorectal cancer, for accurate diagnosis and treatment. All surgeons agree on the following principles of surgical tumor management: removal of the primary site, its lymphatic drainage structures, and invaded organs and prevention of tumor cell spillage. Although colon and rectal cancer are different probably due to the different biological behavior and secondly due to the different operations performed, lymphadenectomy in colonic and rectal cancers is performed for the same reasons.

In fact, as resection of LNs in colorectal cancer has proven to be an important treatment, over the past decade the focus of LN has shifted to the total number of LNs that are primarily removed from the actual size of the LN. Although there are precise indications in this area, there are actually many variables that can interfere with LN retrieval and are not always respected practically.

Role of Lymphadenectomy

It seemed quite reasonable that locoregional recurrence, distant metastasis, and poor survival after cancer surgery were at

least partly related to the presence of occult residual tumor or undetectable micrometastasis within the lymphatic systems in the mesocolon, the mesorectum, and the para-aortic nodes [3–5]. At least 85% of patients with lateral resection margin involvement by either the tumor itself or by lymphatic metastasis developed local recurrence [6]. Resection of all potentially involved lymphatic tissue therefore resulted in improved locoregional control, decreased overall recurrence rate, and ultimately in improved long-term survival [5, 7, 8]. Resection of lymphatic tissue is the treatment of choice since the intra-operative assessment of malignant involvement versus inflammatory changes by the surgeon is accurate in only 50% of the cases [9, 10] and preoperative assessment has an accuracy yield of only 83% [11•].

According to the American Joint Committee on Cancer (AJCC) 7th edition [2], all histologic stages are considered to be a determinant of colorectal cancer stage by sufficient number of LNs to ensure the prognosis of the patient [12–37]. In the discussion that follows, we argue that this is not the case. The lack of reliable staging data makes the current system insufficiently accurate. This deficiency leads to stage migration, which may be responsible for the observed 20–25% recurrence in node-negative patients [38–43], as well as for the documented superior prognosis for stage IIIa compared to stage IIb tumors [40–43].

The precise staging of patients treated with colorectal cancer is also important in planning adjuvant therapies to ensure that oncologic outcomes are optimal, especially in stage III and patients with a favorable stage that may be judged to be understated [12, 17, 19, 20, 24, 26, 28, 31–33, 36, 40, 42, 44–46]. Clinical practitioners and organizations, such as the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN), recommend adjuvant chemotherapy for patients who do not have sufficient LN at the time of surgical resection [16, 30, 34, 44, 47, 48].

Lymph Node Staging

LN assessment is the basis of a substantial pathologic staging system for colorectal cancer. The most commonly used staging system is the AJCC TNM system, which describes stages from I to IV based on depth of tumor invasion (T), status of metastatic lymph nodes (N), and presence of distant metastasis (M). In particular, the absolute number of metastatic LNs has been shown to be an effective predictor of adverse prognosis [2, 49]. Thus, the prognostic stratification of LN disease in the AJCC staging system is based on the absolute number of metastatic LNs.

The major differences between editions of the AJCC TNM system for LN staging are as follows: The 5th edition of the TNM system introduced a 3-mm rule for classification and provided a tool based on the size of LN. The 6th edition ignored the size criteria and referred to the contour of LN. The 7th edition focused on the differentiation of LN metastasis in tumor deposits, including the latter in the pN category; pN1c. The potential value of the 7th edition should be evaluated in larger prospective studies. The fact that patients with tumor deposits will be classified in the metastatic group (pN1c) has raised major concerns. This is especially important in the evaluation of tumor regression and residual tumor foci after preoperative therapy [50]. In the patients who had not undergone preoperative treatment, nevertheless, staging according to the 7th edition showed to provide superior prognosis compared to the 5th and 6th edition [50].

Lymph Node and Prognosis

In addition to its accuracy in staging, quantitative LN assessment has been repeatedly identified as a strong prognostic factor in patients with colorectal cancer. Data from the United States Surveillance, Epidemiology and End Results (SEER) cancer registry database shows a decrease in 5-year crude overall survival with increasing LN invasion for each T stage [51, 52]. Furthermore, many case-study reviews [12, 14, 19, 20, 23, 28, 29, 33–37, 44, 53••, 54–62], especially in patients with stage II, report a directly proportional relationship between the number of LNs harvested and survival rate. Chang et al. [33] have demonstrated that increased survival of patients with stage II was associated with increased numbers of LNs harvested. The most likely explanation is that the greater the number of LNs examined led to a superior assessment of more nodes that might actually be negative to harbor metastatic deposits. Other authors [30, 53••, 63, 64], on the other hands, believe that lymphadenectomy is more therapeutic in advanced stages of patients by improving surgical removal of tumors and by reducing metastatic spread through lymphatic drainage. This is not a uniformly agreed upon concept in colorectal cancer [14, 20].

Lymph Node Counts and Survival

Regardless of whether stage II colorectal cancer is considered together or divided into colon and rectal cancer, there is a significantly reduced overall survival (OS) and disease-free survival (DFS) in patients with lower LN examined. However, the cut-off points in these studies are highly data-centric demonstrating substantial variability from a low of 6 LN to as high 21 LN [34, 36, 65–71, 72••].

Although several studies have not demonstrated a similar association between survival and LN counts in stage III patients [44, 65, 66, 68, 72••], others have shown results analogous to stage II subjects. For instance, Le Voyer et al. [36]

demonstrated that for colon cancer patients with one to three positive LNs, OS in the case of >40 LN analyzed was improved by an absolute 23%, compared to ≤10 LN ($P < 0.0001$); moreover, in patients with more than four metastatic LNs, OS analyzed by>35 vs. <35 LNs was 71 and 51%, respectively ($P = 0.002$). Similarly, Chen et al. [61] showed that when 1–7, 8–14, and ≥15 LN were harvested from colon cancer, the increased median survival were 46, 52, and 67 months, respectively ($P < 0.001$). Additionally, Vather et al. [70] showed that the mean number of LNs retrieval in stage III patients who died within 5 years was 13.1 vs. 14.8 in survivors ($P < 0.0001$).

Sentinel Lymph Node for Colorectal Cancer

The sentinel LN, defined as the first lymph node within the lymph drainage zone, is considered important in oncologic management. In colorectal cancer, the potential benefit of sentinel LN biopsy differs from that of other malignancies such as melanoma and breast cancer. Sentinel LN biopsy for colorectal cancer does not reduce the scope of the surgery but aims to identify conditions that require more extensive lymphadenectomy. Another goal is to establish more accurate LN staging to identify the risk of recurrence or progression of the disease [73].

According to a meta-analysis, the pooled sentinel LN identification rate and the pooled sensitivity of the procedure are approximately 90 and 70% in colorectal cancer, respectively [74]. Subgroups with significantly higher sensitivity were identified. These subgroups include individuals with ≥4 sentinel nodes identified (vs. individuals <4 nodes, 85.2 vs. 66.3%, $P = 0.003$), colonic location (vs. rectal location, 77.6 vs. 65.7%, $P = 0.04$), and pT1/2 carcinomas (vs. pT3/4 carcinomas, 93.4 vs. 58.8%, $P = 0.01$).

Saha et al. [75•] demonstrated how sentinel LN biopsy may be successfully integrated into general practice. The authors investigated 192 patients undergoing surgery for colon cancer and identified aberrant drainage; drainage against the standard resection margin requiring change of the scope of operation, in 22% of patients. Remarkably, nodal positivity was higher in patients who underwent change of operation (62%) than those who underwent standard resection (43%).

Significant problems with SNL biopsy persist, primarily related to incomplete detection rates and relatively low sensitivity for the identification of nodal status. The detection rate is strongly influenced by several patient- and disease-specific factors, the most important of which are body mass index, experience of the surgeon with the technique, and a steep learning curve [76]. The significantly high false negative rate to confirm node positivity might be the results of abnormal drainage sites and skipped lesions. It is known that skip lesions occur when lymphatics are occluded by tumor cells. Retter et al. [77] reported that in 63% of their false negative tumors, there was lymphatic and venous invasion by cancer cells.

Factors Associated Lymph Nodes Harvest

Even though surgery and pathological evaluation have been well performed, there is a general agreement among oncologist, pathologists, and surgeons that there are patient-related factors that affect LN retrieval. Some of these are modifiable and some are unmodifiable. All modifiable and unmodifiable variables that can affect LN sampling should be examined to provide the best clinical decisions regarding oncologic outcomes.

Modifiable Factors

Surgical Factors

In colorectal cancer, compliance with Total Mesorectal Excision (TME) and Complete Mesocolic Excision (CME) principles is required to ensure a proper removal of the mesenteric package [78, 79]. The extent to which the surgeon's experience and expertise affects the quality of the surgery performed has often been considered as a factor that can affect the number of LN removed [12, 20, 30, 32, 54]. Although surgical variables are considered as independent factors, there is no clear difference between more and less experienced surgeons with regards to the number of LNs harvested.

There currently is no statistical difference related to surgeon expertise or between colorectal surgeons and general surgeons regarding the number of LN retrieved following surgical intervention [17, 28, 31, 80–84]. In spite of this, there are proponents of a training program for all surgeons involved in colorectal cancer that enable more accurate surgical techniques [18, 79, 85]. There is wide disagreement in the relationship of the length of intestinal resection and the ability to retrieve LN [28, 30, 81, 86]. Currently, the literature fails to provide conclusive data on whether emergency surgery is responsible for limited operation and the small number of LNs collected [28, 53••, 84, 87].

With the rapid development of laparoscopic surgery (LS) for cancer treatment, one concern about LS is this new technology may limit the removal of LN [88, 89]. After reviewing the 24 RCTs, Wu Z et al. [90••] reported the amount of lymph node harvested, there was no difference in the number of lymph nodes harvested in these two approaches (weighted mean difference = −0.25; 95% confidence interval, −0.57 to 0.08; $P = 0.542$), as well as in subgroups of colon cancer and of rectal cancer. On the other hand, Lujan et al. [91] have reported advantages of laparoscopic surgery in relation to the number of LNs taken from rectal cancer patients (13.63 vs. 11.57, $P = 0.026$). It is reasonable to remove as many lymph nodes as possible during curative resections for colorectal cancer [92],

as surgeons should have paid more attention to removal of the lymphatic drainage of the colon and the rectum.

Pathologic Factors

While conflicting arguments in pathological examination of LN exists [31, 54, 82], the diligence of a pathology staff: pathologists, assistants of pathology, residents of pathology, technicians of pathology, could influence the number of LNs count [19, 20, 30, 44, 63, 80, 84, 93, 94]. The lack of working time, more than the lack of educational training, seems to be a more important factor [15, 17, 36, 93, 95•].

An appropriately trained staff with sufficient time to perform a thorough LN harvest should dissect the specimen if accurate staging is to be achieved [96]. Manual dissection through routine histological evaluation based on hematoxylin and eosin (HE) stained slides routinely is the standard approach in the examination of LN in cancer specimens [97]. However, some authors have argued that examination based on HE-stained slides are lacking for proper evaluation [98]. Because the recommended number of LNs is often not reached by conventional manual dissection, pathologists have introduced a new technical method to facilitate the harvesting of LN in adipose tissue. These include fat removal methods, methylene blue-assisted LN dissection, and subsequent compression of adipose tissue with acetone elution (acetone compression). It is known that the methylene blue-assisted LN dissection technique significantly increases the number of LNs compared to manual dissection [99]. This effect is especially evident in rectal cancer patients after preoperative therapy and ensures adequate LN harvest in these patients. However, according to a recently study [100], the application of this technique appears to be unrelated to the increased detection of metastatic LN. It is known that a reduction of about 90% of the mesorectal fat volume is achieved by the acetone compression method [101]. Acetone compression facilitates the detection of all tumor deposits of mesorectal and mesenteric adipose tissue and provides a reliable investigation of tumor cell deposits including perineural cancer infiltration, especially after preoperative therapy [102].

A concern with a set number of nodes to be retrieved for staging purposes according to guidelines (i.e., 12) is that once this number is met, the examination for LN harvest might be terminated independent of the number of metastatic LNs left in the sample [103]. This further highlights the need to question the current dependence on specific LN cut-off numbers.

Unmodifiable Factors

Patients-Related Factors

Patient-related variables are less controversial. For instance, there is a general consensus that aging can have a negative impact on LN sampling [19, 53••, 54, 58, 61, 63, 80, 93, 104, 105], decreasing by 9% for every 10 years of age [105]. With regards to gender, most authors do not report different content of LN numbers [28, 31, 45, 83, 86, 105] but some refer to larger sampling in women [93, 106].

The impact of obesity during lymphadenectomy is currently a debatable topic. Some authors report high LN harvest in obese patients and lower LN harvest in high body mass index (BMI) patients, this is probably due to a more difficult surgical dissection [18, 53••, 82, 107]. However, the relationship between BMI and LN sampling remains a controversial issue. Indeed, there are not sufficient studies that actually demonstrate such a correlation [18, 31, 82, 94].

Patient's disease-related variables and tumor location are important in the number of LN that can be obtained for pathological analysis. For instance, despite the high proportion of metastatic LN harvested, the size of the LN is smaller when the tumor is in the rectum, making it more difficult to achieve the set goal of LNs [12, 80]. In the colon, the number of harvested LN is significantly higher in the right colon due to the longer length of the mesentery root [14, 86] or more embryological differences in the number of LNs [81]. Tumor characteristics have often been thought to affect LN harvest; the larger the size and progression of the tumor (T and grading), the greater the number of LNs retrieved [18, 19, 30, 31, 34, 105]. This is probably due to a larger immune response [81] or to more aggressive surgery [18, 19].

Effects of Preoperative Treatment on Lymph Node Harvest

In rectal cancer, the increase of preoperative chemoradiotherapy (pCRT) is another important factor affecting the yield of LN. In pCRT, LNs undergo a process of regression. Thus, in a large international clinical trial investigating the benefits of pCRT in rectal cancer, only 12 of the recommended LN were achieved in 20% of the patients. These results raise questions as to whether the insufficient of LN is due to the loss of LN or whether it reflects a decrease in LN size accompanied by progressive atrophy and fibrosis [102].

Doll et al. [108], Govindarajan et al. [109], and Rullier et al. [110] report a significant difference between patients treated with pCRT and surgery alone (respectively 12.9 vs. 21.4, $P<0.001$; 10.8 vs. 15.5, $P<0.001$; 13 vs. 17, $P<0.001$). Rullier et al. [110] report that for every Gray of radiation, the harvested LNs number will be less than 0.21% and Norwood et al. [28] show that this reduction is evident especially when preoperative radiation therapy is used in conjunction with chemotherapy. Interestingly, reducing the number of harvested LNs is considered a positive response to pCRT, even though it does not affect survival [108–110]. This has led some authors [26, 72••] to suggest that 12

recommendations for LN in patients with rectal cancer treated with pCRT were unrealistic. However, even though pCRT for current rectal cancer has been shown to reduce total number of harvested LNs; 8–13 [72••, 108–110], the goal of surgeons and pathologists should still be to ensure adequate LN retrieval as many LNs as possible.

Optimal Number of Harvested Lymph Nodes

Appropriate assessment of LN status depends on the total number of harvested LNs available for histological evaluation. However, there is still controversy about the optimal number of LNs required for proper staging. The number of LNs harvested has been discussed for over 20 years, but there are still many opinions. In fact, since 1990, at the World Congress of Gastroenterology in Sydney, this figure was set to 12 LNs as the minimum standard of the LN to be examined since 90% of the cases allowed the accurate diagnosis of N0 [15, 30, 93, 107]. This recommendation was adopted by the AJCC TNM system and has been included in various clinical practice guidelines [111, 112]. Because affected LN is a major determinant of adjuvant chemotherapy, the minimum number of LNs to be assessed ensures accurate staging, prognosis, and appropriate treatment.

In this regard, Stocchi et al. [54] reported that, considering only patients treated with stage II colon cancer, harvesting of at least 12 LNs is associated with improved outcomes. This improvement reduces if a smaller yield of LNs is examined, but it does not increase with a larger yield of LNs. Other data reported by Nelson et al. [107], Norwood et al. [28], Han et al. [72••], and Lee et al. [113] have corroborated the findings of Stocchi. Nelson et al. [107] reported that the metastatic LN is correctly identified in 90% of patients by examining 12 LNs; Norwood et al. [28] and Han et al. [72••] demonstrated that only when the number of LNs is <12 there is a reduction in the survival; finally, Lee et al. [113] reported that the examination of a number of LNs ≥12 increases the probability of diagnosing metastatic LNs by 30%.

Considering these data, it seems that more than 12 LN harvests are adequate. However, more 12 LN of harvests are certainly controversial, given that the limit of 12 LN harvests is still not the gold standard because this is not a scientific biological figure and is a grade C recommendation based on level of III or IV evidence [53••, 107, 114, 115].

It is not surprising that there is a significant change in the actual number of LNs examined internationally after colorectal surgery. McDonald et al. [15] point out that there is no consensus on the number of LN cut-offs, and that the actual cut-off point varies widely (between 6 and 21). This range is similar to the one reported by Valsecchi et al. [30] (between 6 and 17) and lower than the one reported by Noura et al. [55] (between 6 and 40). Data from a US study for 116,995 patients undergoing resection for colorectal cancer (without neo-adjuvant chemotherapy) was reported by Baxter et al. [116]. The median number of LNs examined was 9. Only 37% of patients harvested more than 12 LNs, although this increased over time (1988, 32%; 2001, 44%). However, the United Kingdom National Bowel Cancer Audit (2009) [117] showed that a median number of 15.1 LNs were examined in resection specimens for the period 2006/8, with 78.6% of UK providers achieving the guideline of 12. US data from Baxter et al. [116] was population-based, with only limited information on patient and tumor factors. In addition, they had no information regarding surgical and pathologic factors such as procedure volume, specimen adequacy, or the use of specialized techniques (such as xylene or alcohol fat clearance), all of which affect lymph node retrieval. Therefore, for these reasons, the median number of LNs examined might be lower compared to other studies.

It is clear that there is a need to attempt to harvest as many LNs as possible in clinical practice [23]. However, a ceiling effect can be reached. Baxter et al. [103] reported a significant increase in the odds ratio of metastatic node deposits with increasing node count up to six LNs. However, there is only a slight increase between the range 7–11 LN and the range 12–17 LN, and when >17 LN were evaluated, the odds ratio of finding a metastatic LN actually decreases. The authors conclude that increasing the LN yield improves the staging of pT3 cancer when the LN yield is low, but that the increased LN yield has a marginal effect on the staging when the LN retrieval is larger.

Thus, LN yield is significantly affected by many factors related to patient demographics, surgeon's experience, pathologists, tumor location, and tumor biology. Therefore, setting arbitrary numbers for the appropriate LN is not clinically sound and does not seem to improve individual outcomes. In practice, a thorough pursuit of a very high number of LNs may not be appropriate, but it should be best to collect as many LNs as possible. Standard practices for LN retrieval during surgical resection, LN handling, and pathological analysis may assist in providing better information in this area and would allow to derive further conclusions on this subject.

Conclusions

LN staging is an important prognostic factor in colorectal cancer and is the most valuable criteria for selecting patients for adjuvant chemotherapy. The practical focus of treatment in colorectal cancer was to harvest as many LNs as possible to improve staging and survival. However, as the lack of scientific evidence on the minimum number of LNs is controversial, the use of international cut-off values should be considered again. This is particularly evident in subgroups of patients with pCRT, suggesting a response to treatment with a low number of LNs and may be more favorable oncologically. Research that

indicates that LN harvesting serves as a marker of quality should continue to be investigated since the quality of surgical technique or pathology examination as well as tumor biology can also affect differences in LN count. Understanding modifiable and unmodifiable factor leading to LN retrieval is advantageous such that clinicians can bank of all the modifiable factors and set guidelines for practitioners.

Compliance with Ethical Standards

Conflict of Interest Jeonghee Han, Kyung Tae Noh, and Byung Soh Min declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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