

# Clinical Implications of Lymph Node Metastasis in Colorectal Cancer: Current Status and Future Perspectives

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Lymph node metastasis is regarded as an indubitable prognostic factor for predicting disease recurrence and survival in patients with colorectal cancer. Lymph node status based on examination of a resected specimen is a key element of the current staging system and is also a crucial factor to determine use of adjuvant chemotherapy after surgical resection. However, the current tumor-node-metastasis (TNM) staging system only incorporates the number of metastatic lymph nodes in the N category. Numerous attempts have been made to supplement this simplified N staging including lymph node ratio, distribution of metastatic lymph nodes, tumor deposits, or extracapsular invasion. In addition, several attempts have been made to identify more specific prognostic factors in resected colorectal specimens than lymph node status. In this review, we will discuss controversies in lymph node staging and factors that may influence survival beyond lymph node status.

**Keywords:** *Lymph node metastasis; TNM staging; Lymph node ratio; Colorectal neoplasms; Survival*

## INTRODUCTION

Complete resection of the primary tumor and regional lymph nodes has been accepted as the most important task in the treatment of colorectal cancer. In addition, evaluation of the surgical resection specimen is considered an essential step in identifying prognostic factors for predicting disease recurrence after surgery. The American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC) suggested the tumor-node-metastasis (TNM) staging system, which assesses primary tumor (T), lymph node metastasis (N), and distant metastasis (M) to predict disease recurrence and survival [1, 2].

Lymph nodes are a key element of the TNM staging system and

are considered a significant factor for predicting disease-free survival (DFS) and overall survival (OS) in patients with colorectal cancer without distant metastasis. Lymph node status is also a crucial factor for determining the use of adjuvant chemotherapy after surgical resection [1-3]. Although the underlying mechanism is not clear, it is suggested that tumor cells spread from the primary tumor site to the lymph nodes via lymphatic vessels and consequently, to the next distant organ. Therefore, regional lymph node metastasis is believed an essential step in tumor cell dissemination in colorectal cancer [4].

The N category in the TNM staging system is categorized by the number of metastatic lymph nodes as N1 (1-3 metastatic nodes) and N2 ( $\geq 4$  metastatic nodes). Several attempts have been made to supplement the prognostic ability of this simplified N staging, including lymph node ratio (LNR), distribution of metastatic lymph nodes (LND), tumor deposits (TDs), and extracapsular invasion (ECI) [5-8]. In addition, several attempts have been made to identify more implacable prognostic factors in resected specimens beyond lymph node status, including venous invasion (VI) [9-11]. In this review, we will discuss these attempts against the N category of the TNM staging system reported in recent literature.

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## UPDATE TO THE N CATEGORY IN THE 8TH EDITION OF THE TNM STAGING SYSTEM

The N category was divided according to the number of metastatic lymph nodes into N1, which was subdivided into N1a, N1b, and N1c, and N2, which was subdivided into N2a and N2b. This classification is similar to that given in the 7th edition (Table 1) [12, 13]. N1c was described more clearly in the 8th edition. In the 7th edition, N1c was considered TDs identified in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissue without any regional nodal metastasis. In the 8th edition, presence of an identifiable vessel wall or neural tissue around a TD was categorized into lymphovascular invasion or perineural invasion, respectively.

## MINIMUM NUMBER OF EXAMINED LYMPH NODES

Evaluation of an abundant number of lymph nodes had been emphasized for accurate evaluation of lymph node status in colorectal cancer [1-3, 12-15]. Fielding et al. [14] suggested an adequate minimum of 12 lymph nodes because evaluation of less than 12 lymph nodes led to a high rate of false-negative rate of lymph node metastasis, i.e. under-staging. The current TNM staging system also recommended evaluation of at least 12 nodes for proper staging. In addition, evaluation of less than 12 nodes is included as a high-risk feature of stage II colorectal cancer and leads to the use of adjuvant chemotherapy after surgical resection [16, 17].

Several studies have suggested examination of as many lymph nodes as possible with no fixed minimal requirement because number of examined lymph nodes is positively associated with increased survival [17-19]. These findings became the basis for introduction of LNR in stage III colorectal cancer. The positive correlation between survival and number of lymph nodes might result in the staging migration and therapeutic benefit caused by removal of a high number of regional lymph nodes.

However, wide variability has been reported in the number of examined lymph nodes. Furthermore, one population-based

analysis pointed out that an adequate number of lymph nodes were examined in only 37% of patients [20]. The number of examined lymph nodes has been reported to be influenced by extent of surgical resection, diligence of pathologic examination, patient-related factors such as body mass index, right or left-sided tumor location, tumor staging, and use of neoadjuvant treatment [21-23]. When the TNM staging system began considering the concept of TD, some previously considered lymph nodes were reclassified as TDs; consequently, the total number of lymph nodes decreased [12, 13].

Different methods of node harvesting have been reported to increase lymph node yield from specimens for pathologic evaluation. Lisovsky et al. [24] suggested a second-look protocol that involved re-evaluation of lymph nodes in the entire mesocolon if peritumoral lymph nodes are negative, even after evaluation within 5 cm from both sides of the tumor edge. They reported that this method improved correlation between lymph node staging and survival. Another attempt to increase the total number of examined lymph nodes involved the use of specific dyes, such as indocyanine green or methylene blue, during operation. This technique contributed to easy identification of lymph nodes from surrounding lymphoadipose tissue. However, a more convenient method with proven efficacy is warranted for routine use in daily practice.

## LYMPH NODE RATIO

LNR is defined as the ratio of the number of positive nodes to the total number of harvested nodes; the strength of this indicator is the value of these 2 parameters combined. LNR has been regarded as a good predictor of survival in stage III colon cancer, and its reliability was already demonstrated in other types of solid tumors [25, 26]. Results from recent studies have indicated that high LNR is associated with poor DFS and OS, and that the prognostic value of LNR is better than that of N staging (suggested by the AJCC/UICC) [5, 27-29]. A systemic review of 16 studies that included a total of 33,984 patients with stage III colorectal cancer also demonstrated that LNR had superior prognostic value compared to N

**Table 1.** N category in the TNM staging system

6th edition		7th edition		8th edition	
N stage					
Nx		Nx		Nx	
N0		N0		N0	
N1	1-3 metastatic nodes	N1a	1 metastatic node	N1a	1 metastatic node
N2	4 or more metastatic nodes	N1b	2-3 metastatic nodes	N1b	2-3 metastatic nodes
		N1c	TDs	N1c	TDs
		N2a	4-6 metastatic nodes	N2a	4-6 metastatic nodes
		N2b	7 or more metastatic nodes	N2b	7 or more metastatic nodes

TD, tumor deposit.

staging and that the pooled hazard ratios (HRs) of LNR for DFS and OS were 3.71 (95% confidence interval [CI], 2.56–5.38) and 2.36 (95% CI, 2.14–2.61), respectively [5]. Interestingly, Peng et al. [27] suggested that integrated LNR and N staging had higher prognostic value for predicting survival than each individual parameter.

Some studies reported that LNR only had a significant influence on survival in patients with adequate number of examined lymph nodes ( $\geq 10$ –12) [30, 31]; however, a few studies have reported that N staging was superior to LNR in predicting patient survival with a high number of examined lymph nodes [32]. Antithetically, some studies have reported that LNR was an independent prognostic factor for survival, regardless of the total number of examined lymph nodes [33–38]. Recent meta-analysis of 33 studies that included a total of 75,839 patients with node-positive colorectal cancer supported these findings. In this study, high LNR was significantly associated with low DFS (HR, 2.75; 95% CI, 2.14–3.53;  $P < 0.001$ ) and OS (HR, 1.91; 95% CI, 1.71–2.14;  $P < 0.001$ ). In addition, LNR remained a significant prognostic factor regardless of the number of harvested LNs;  $\geq 12$  and  $< 12$  of harvested LNs (HR, 1.97; 95% CI, 1.71–2.26;  $P < 0.001$  and HR, 1.74; 95% CI, 1.40–2.17;  $P < 0.001$ , respectively) [33].

A standard reference value of LNR is required for universal use of LNR for predicting prognosis; however, there is no consensus on what this value should be. In previous studies, LNR was presented as a categorical variable rather than a continuous one. Although the number of categories ranged from 2 to 10, the majority of studies divided all patients into 3 or 4 categories for better correlation to survival. In addition, the intervals between cutoff values of LNR in each category, which ranged from 5% to 25%, varied in each study. A previous review article suggested 10% of median LNR as a cutoff value after evaluating 16 studies; however, this cutoff requires validation [5].

## DISTRIBUTION OF METASTATIC LYMPH NODES

The Japanese classification of colorectal carcinoma has suggested different lymph node staging classified by the location of metastatic lymph nodes rather than the number of metastatic lymph nodes. In this system, metastatic lymph nodes in the pericolic region, along major vessels (intermediate), and around the roots of involved major vessels (apical) were classified as N1, N2, and N3, respectively [39]. Many studies named the stages of this grading system as LND 1, LND 2, and LND 3 to avoid confusion with the TNM staging system. This method of N staging was included in the 4th edition of the TNM staging system, and lymph node metastasis around the roots of major vessels was classified as N3 regardless of the number of metastatic nodes. However, this version of N3 was deleted from the 5th edition because of the complexity of dividing lymph node zones for pathologic evaluation. However, it remains controversial whether LND provides improved prog-

nostic ability in node-positive colorectal cancer.

One study analyzed the utility of LND as a tool for further subdivision of stage III patients compared to N staging. This study classified 164 patients with colon cancer according to the LND grading system: 41.5% negative-node, 29.3% LND 1, 18.3% LND 2, and 11.0% LND 3. With TNM staging, 23.8% and 34.8% of patients were classified as having N1 and N2 disease, respectively. In this study, the LND grading system also showed a wider range of survival rates than TNM staging [40].

Many studies supported that proximal LND was associated with poor survival, which reinforced incorporation of LND into the TNM staging system. Furthermore, some studies analyzed the clinical implications of LND according to tumor location. One study that evaluated 187 patients with stage III right-sided colon cancer showed that both proximal LND and N2 significantly influenced poor survival; however, they reported that LND had better prognostic ability than the TNM staging system [41]. Huh et al. [42] evaluated 1,205 patients with sigmoid colon or rectal cancer. In a total of 590 patients with stage III colorectal cancer, LND was an independent prognostic factor for both OS and DFS by multivariate analysis.

Despite evidence supporting the use of LND as a classification for metastatic lymph nodes, it has not been generally applied in clinical practice compared to the TNM system because of its laborious nature and conflicting results from several retrospective studies suggesting that pathologic N staging was more significantly associated with survival than LND [43]. Suzuki et al. [43] also demonstrated that N staging was only an independent factor for predicting 5-year OS compared to LND, which was divided patients into only two groups (LND 1 vs. LND 2 and 3) in patients with node-positive colon cancer.

Although some studies have emphasized the prognostic value of LND in patients with rectal cancer, the significance remains unclear. Kobayashi et al. [44] compared the prognostic implications between LND and N staging and showed that proximal LND was significantly associated with poor survival only in colon cancer whereas N staging was significantly associated with poor survival in rectal cancer. In contrast, a study evaluating 1,188 patients with rectal cancer showed that 5- and 10-year survival rates were significantly lower in patients diagnosed with proximal lymph node metastases around the origin of the inferior mesenteric artery (40% and 21%, respectively) compared to those who did not have proximal lymph node metastases [45]. Furthermore, Leibold et al. [46] showed the predictive ability of LND by assessing 121 patients with rectal cancer who received preoperative chemoradiotherapy (CRT) followed by resection. Lymph node metastases in the proximal area around the major feeding vessels resulted in significantly lower DFS; therefore, they strongly suggested that LND should be considered in rectal cancer treated by CRT. They also recommended intensified adjuvant chemotherapy in patients with rectal cancer with proximal lymph node metastases.

Several studies have evaluated the association between survival

and apical lymph node metastases around the main feeding artery (LND 3); they showed that patients with LND 3 had significantly poorer survival rates than patients without apical node metastases. In addition, this specific subgroup of patients with LND 3 had similar survival rates as those with stage IV disease that achieved R0 resection [42, 47]. Consequently, they suggested that lymph node metastases located around the main vessel should be categorized as systemic metastasis rather than as regional node metastasis based on the survival data and anatomic background.

Some studies evaluated the metastatic patterns of lymph nodes, which were grouped according to tumor location based on the Japanese classification of colorectal carcinoma [39]. They evaluated lymph node metastatic patterns in detail and attempted to determine adequate surgical extent based on tumor location. Park et al. [48] evaluated 419 patients who underwent curative resection for right-sided colon cancer and lymph nodes were immediately grouped after surgery. They reported that ileocolic lymph node metastases were the most common in cecal and ascending colon cancer; however, 6.1% of patients with cecal cancer had lymph node metastases along the right-branch of the middle colon artery. Conversely, middle colic lymph node metastases were the most common in patients with transverse colon cancer while 10% showed right colic node metastases. They also evaluated the value of sigmoid mesenteric lymph node metastases in 347 patients with rectal cancer and showed that 23.2% of patients had metastases to the sigmoid mesenteric lymph node with or without metastases to the superior rectal or inferior mesenteric lymph nodes [49]. Although these aberrant lymph node metastases did not influence survival in either study, the findings emphasize that removal of these nodes is required for proper staging, but not for cure.

## SITE SPECIFIC CONSIDERATIONS

The treatment of lateral pelvic node (LPN) metastasis is still controversial. In Japan, prophylactic or therapeutic lateral pelvic node dissection (LPND) have been routinely recommended for advanced lower rectal cancer to reduce local and even systemic failure [50, 51]. The recently published JCOG0212 trial evaluated 701 patients with stage II or III rectal cancer showed lower local recurrence rates when total mesorectal excision (TME) was combined with routine LPND than TME alone. However, they did not perform preoperative CRT in these rectal cancer patients [52]. On the other hand, in western countries, preoperative CRT and TME are regarded as the standard treatment in locally advanced rectal cancer [53, 54]. It is primarily due to effective local control by preoperative CRT, higher morbidity rates of LPND without improving oncologic results, therefore implying systemic disease [55, 56]. Recent studies suggested TME with selective LPND for suspected LPN metastasis in patients with rectal cancer who have undergone preoperative CRT [57, 58]. However, preoperative CRT may sterilize lymph nodes in the pelvic sidewall. Therefore,

the indication criteria for LPND, especially size criteria ( $\geq 5$  mm,  $\geq 7$  mm, or  $\geq 10$  mm) and the timing of imaging studies (preoperative or postoperative) are still controversial [57-60].

Recently, some collaborative studies between western and eastern countries were published for evaluating the significance of metastatic LPN on survival rates. Ogura et al. [61] analyzed 1,216 patients with cT3/T4 rectal cancer including 142 patients who underwent TME with LPND and used MRI to assess LPN features. Patients having LPN with a short-axis diameter  $\geq 7$  mm had a significantly lower local recurrence rate of 5.7% with TME plus LPND compared to a local recurrence rate of 19.5% with TME alone. The mandatoriness of LPND in patients who are suspected to have metastatic LPNs should be further evaluated.

Para-aortic lymph node (PALN) metastasis is uncommon in colorectal cancer with a reported incidence rate of less than 2% but is categorized as M1 in the TNM staging system with poor survival outcomes [13, 62, 63]. However, the Japanese classification of colorectal carcinoma considers it a regional, stage III disease [39]. Therefore, optimal management for PALN metastasis is still not clearly defined based on these different views.

Several case series have reported favorable survival rates by performing para-aortic lymph node dissection (PALND) in selected patients [63-65]. The outcomes featured tolerable morbidity rates ranged from 7.8% to 33%. Choi et al. [63] analyzed 24 patients who underwent PALND for isolated PALN metastasis and compared them with those who did not receive surgery. Five-year OS rate was 53.4% in the PALND group versus 12.0% in the non-surgery group ( $P = 0.045$ ). In addition, the presence of two or less PALN metastases was the only prognostic factor for better survival. Therefore, they suggested that the two or less PALN metastases can be a good indication of PALND. Gagnière et al. [65] compared the oncologic outcomes of 15 patients with isolated PALN metastasis and 10 with concurrent extra-PALN metastases. By performing PALND, patients with isolated PALN metastasis showed 56% and 51% of 5-year OS and DFS rates, respectively while those with extra-PALN metastasis showed 51% and 13%, respectively. However, further study for indications of PALND is needed. Chemotherapy with or without radiation therapy has been used as a form of salvage therapy for patients with PALN metastasis [66-68]. One meta-analysis reported that the complete response rate ranged from 43% to 100% and partial response rate ranged from 27 to 57%. Recurrence rates were reported from 60% to 68% and median OS was from 37 to 41 months [62]. However, Min et al. [64] reported significantly worse survival rate after CRT when compared to patients who underwent PALND. There was no multi-center, randomized study for these two different approaches to treat PALN metastasis. Further study is needed to conclude these controversies.

## TUMOR DEPOSIT

TD was included in the 7th edition of the TNM staging system as



a new category, N1c [12]. TDs were described as separate tumor nodules identified in the pericolic or perirectal adipose tissue without evidence of lymph node. The concept of TD has been undergoing changes in the past several decades, especially since it was included in the TNM staging system. TD was included in the 5th edition of the TNM staging system and was classified according to TD size: >3 mm, regional lymph node metastasis and  $\leq$ 3 mm, extension of T staging [69]. The current concept of TD was introduced in the 7th edition of the TNM staging system [12]. In the 8th edition, TD was defined in further detail [13]. The definition stated that in the presence of an identifiable vessel wall or neural structure, a nodule was classified as lymphovascular invasion or perineural invasion, respectively (Table 1). To help detect vessel walls, the use of special stains may be considered in addition to routine hematoxylin-eosin stains. These changes were introduced with the concept of TD in the TNM staging system because many studies suggest that TDs are associated with advanced tumor growth and decreased survival [70-73]. In addition, Ueno et al. [74] demonstrated that a high number of TDs ( $\geq$ 5) was correlated with poor survival. They also suggested that TDs showed similar survival rates as node-positive disease. Therefore, the 8th edition recommended evaluation of the number of TDs, specifically 1-4 TDs or  $\geq$ 5 TDs.

However, large interobserver variability has persisted in interpretation of TDs and differentiation from discontinuous tumor spread, totally replaced lymph node, and VI. Therefore, further studies are needed to increase interobserver pathologist agreement in diagnosis of TDs.

### EXTRACAPSULAR INVASION

ECI has been reported as a valuable prognostic factor related to inferior survival [75-77]. This finding was based on the morphologic features of lymph nodes rather than on the number or location of metastatic lymph nodes. ECI is defined as penetration of tumor cells from the nodal capsule into the perinodal fatty tissue. Therefore, ECI might reflect the aggressiveness of tumor biology and supplement the current lymph node staging system [78]. ECI has also emerged as a predictive factor in various solid tumors [79, 80]. In a recent meta-analysis that analyzed 1,336 patients with colorectal cancer from 13 studies, ECI was strongly correlated with advanced tumor staging and differentiation and was associated with significantly worse OS (HR, 1.75; 95% CI, 1.42-2.16;  $P < 0.0001$ ) and DFS (HR, 2.07; 95% CI, 1.54-23.44;  $P < 0.0001$ ) [8]. However, four studies included in this meta-analysis used an alternative definition of ECI, and one study used a different definition of ECI as extension of metastatic cells through the nodal capsule into perinodal adipose tissue and/or extranodal tumor cells [81]. Universal interobserver agreement is required to evaluate ECI in colorectal cancer. During isolation of lymph node, pathologists should include adipose tissue around lymph nodes. ECI and TDs exist in the adipose tissue surrounding lymph nodes.

Therefore, analysis of this tissue is important for appropriate evaluation of these factors.

### OTHER PROGNOSTIC FACTORS BEYOND LYMPH NODES

Although TNM staging is one of most important prognostic factors for survival in colorectal cancer, a few studies have demonstrated the intriguing features of stage IIIA, which involves identification of lymph node metastasis in early T staging [82-84]. Most patients with stage IIIA disease showed excellent survival even in the presence of lymph node metastases; survival was similar to that observed in stage I and better than that observed in stage II. However, although most patients showed good survival, patients with VI and undifferentiated grade showed worse survival, similar to that of stage IIIB or stage IIIC colon cancer. Therefore, there are some exceptions to the current TNM staging system. There might be additional factors more closely related to survival than lymph node status.

Numerous studies reported that the presence of VI in a resected specimen was the most reliable risk factor for hematogenous metastases in colorectal cancer [85-87]. A hypothesis suggested to explain these findings that VI in peritumoral areas might allow entrance to systemic circulation more easily than lymph node metastases [4, 88].

However, one of the main reasons VI has been emphasized less than lymph node status to predict survival is because of the considerable discrepancy observed in reporting rates between pathologists compared to well-established evaluation of lymph node metastasis. Therefore, many attempts have been made to increase the detection rate of VI using special stains; some studies have demonstrated the superiority of elastin stain for detecting VI compared to the standard hematoxylin-eosin stain [89-91]. However, more evidence for the clinical implications of VI detected by special stains and comparisons with lymph node status is needed.

### CONCLUSION

Since lymphatic flow from a primary tumor site was first identified, numerous studies have attempted to classify metastatic lymph nodes to accurately predict survival in colorectal cancer. The TNM staging system has been generally adopted in daily practice due to the prognostic ability and simplicity of N staging. However, numerous attempts have been made to improve the prognostic value of metastatic lymph nodes in colorectal cancer.

High LNR is closely associated with poor survival, although some conflicting findings are noted with respect to tumor location, preoperative treatment, and total number of lymph nodes. However, a standardized reference cutoff value of LNR is still not available. Further studies are needed to select a standardized cutoff value in the future.

Proximal LND is significantly associated with poor survival, al-

though conflicting results are also reported with respect to tumor location, preoperative treatment, and clinical impact of apical lymph node metastasis. However, proximal LND is not used extensively because of its laborious nature. In addition, there are some conflicting results about the lymph node metastasis on specific sites including paraaortic or pelvic sidewall. Further studies are also needed for evaluating clinical significance of lymph node dissections in these specific areas.

Both TD and ECI are emerging prognostic factors for evaluation of lymph node metastases. For appropriate evaluation of these factors, pathologists should include the adipose tissue around lymph nodes identified during lymph node isolation. In addition, further interobserver agreement for identifying both TD and ECI is needed for routine use of these factors.

The intriguing oncologic outcomes of stage IIIA resulted in investigation of other prognostic factors in resected specimens, and VI is one convincing factor that potentially predicts survival. However, standardized detection of VI is still needed to evaluate its influence on survival.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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