Review

Lymph Node Evaluation and Survival in Colorectal Cancer: Review of Population-based, Prospective Studies

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Abstract. *Aim: The total number of lymph nodes retrieved, the number of positive nodes, and/or their ratio are used to evaluate the degree of progression of colorectal cancer. The aim of the present study is to review the relevant literature in order to improve lymph node evaluation and the quality of clinical practice. Materials and Methods: The English language literature on large, population-based, prospective clinical studies of the evaluation of lymph nodes in colorectal cancer was reviewed. This review focuses on the lymph node harvest (LNH) and the lymph node ratio (LNR), and the survival was also assessed. Results: The LNH was influenced by patient age, tumor size, Dukes' stage, preoperative radiotherapy, operative urgency, specimen length, pathology template, and academic status of the hospital. Many prospective studies demonstrated a significant correlation between high LNH and increased survival. LNR is an independent prognostic indicator for stage III colorectal cancer. However, there were many different cut-off values allowing for the optimal separation of subgroups according to survival. Conclusion: To improve lymph node evaluation and the quality of clinical practice, daily collaboration between surgeons and pathologists is important. Scientific evidence for reasonable and practical LNH and LNR values should be identified based on large, well-controlled, prospective studies.*

Colorectal cancer is the second or third leading cause of cancer death in many countries, but survival after surgery still varies among countries (1-3). From the time of Dukes, the depth of wall invasion and the status of lymph node metastasis have been the major factors predicting survival. Accurate diagnosis of the presence or absence, and level or number of metastatic nodes based on properly examined lymph nodes is important for assessing the stage of disease, estimating the probability of recurrence, and planning for postoperative adjuvant chemotherapy (4-6).

Studies on the status of lymph node metastasis have been reported from many countries and facilities. The aim of this study is to identify recent clinical studies that evaluated lymph nodes in colorectal cancer.

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Key Words: Colorectal cancer, lymph node metastasis, lymph node harvest, lymph node ratio, survival, population-based study, prospective study, review.

Materials and Methods

The English language literature of primarily the past 10 years was searched on PubMed using the key words of "colorectal cancer", "lymph node metastasis", "lymph node harvest" (LNH), "lymph node ratio" (LNR) and "survival". After checking all abstracts and reviewing the available articles, 100 articles, especially of large, population-based, prospective studies published in well-known medical journals, were selected, focusing on the following items: Factors affecting LNH; LNH and survival; Dukes' B or rectal cancer; LNR and survival.

Results

Factors affecting LNH. Based on single-institution, retrospective studies, many authors found that the LNH number was affected by patient, tumor, surgical, and pathological factors, including age, sex, and body/mass index (BMI) of patients, site, size, and grade of tumors, stage of disease, length of specimen, extent of lymph node dissection, skill level of pathology technicians, type of hospital, and year of diagnosis (7-12).

Based on large, population-based, prospective studies, Wright *et al.* examined 8,848 cases of colorectal cancer using the Ontario Cancer Registry and showed that the LNH number was affected by patient age, tumor size, specimen length, pathology template, and academic status of the hospital (13). Tekkis *et al.* examined 5,164 cases of colorectal cancer using a database of 79 hospitals in Great Britain and Ireland and showed that independent predictors

of LNH were age, American Society of Anesthesiology (ASA) grade, Dukes' stage, operative urgency, type of resection, and preoperative radiotherapy (14). Morris *et al*. examined 7,062 cases of colorectal cancer using the Northern and Yorkshire Cancer Registry and Information Service (NYCRIS) and showed that the median LNH number was higher when the tumor was advanced and the surgery and pathology were undertaken by specialists (15).

Using the Surveillance, Epidemiology, and End Results (SEER) database, Baxter *et al*. examined 116,995 colorectal cancer cases and showed that patients older than 70 years (Hazard Ratio, HR=0.45), these with left-sided colon cancer (HR=0.45), and these with rectal cancer (HR=0.52) were less likely to undergo adequate LNH (16). Chou *et al*. examined 153,483 cases of colorectal cancer and showed that the LNH number was affected by age, tumor size, and year of diagnosis, with an increased frequency of 2% to 3% annually (17). Gonen *et al*. examined 131,953 cases of colonic cancer and showed that the probability of missing positive nodes was 30% if five nodes were examined, 20% if eight nodes were examined, and dropped to 14% if 12 nodes were examined (18).

Using the National Cancer Data Base (NCDB), Bilimoria *et al*. examined 156,789 colonic cancer cases and showed that 12-node measure-compliant hospitals increased from 15% in 1996-1997 to 38% in 2004-2005, and National Cancer Institute-designated hospitals were more frequently compliant with the 12-node measure than were other academic hospitals, Veterans' Administration hospitals, and community hospitals (78% *versus* 52%, 53%, and 34%, respectively), even after adjustment for differences in patients' characteristics (19).

One randomized trial evaluated the effect of direction by opinion leaders on optimizing LNH after colonic cancer surgery. All 42 hospitals in Ontario received a standardized lecture about LNH by an expert opinion leader, and the 21 intervention hospitals also received academic detailing by a local opinion leader with a toolkit containing a pathology template and a poster that emphasized that at least 12 lymph nodes should be assessed. LNH improved after the lecture both at control (from 11 to 13 nodes) and intervention (from 13 to 16 nodes) hospitals, but academic detailing showed no additional benefit (20).

In 1990, the Working Party Report to the World Congresses of Gastroenterology recommended evaluation of 12 or more nodes for adequate nodal staging of colorectal cancer (21). For TNM classification by the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) criteria, at least 12 lymph nodes must be examined by pathologists for accurate nodal staging of colorectal cancer (22). The greater the LNH, the better the nodal staging; however, exhaustive pursuit of many more nodes is impractical, and other cut-off values may be more realistic or reasonable (23). Examining 11,044 cases of T3 colonic cancer from the SEER database, Baxter *et al*. recently reported that there was a dramatic increase in node positivity with increasing count to five nodes, but when more than seven nodes were evaluated, there was little increase in the rate of node positivity; he concluded that when five to seven nodes were identified, up-staging did not occur with increasing LNH (24).

LNH and Survival

Based on single-institution, retrospective studies, many authors found that the LNH number was associated with the survival of patients with colorectal cancer, particularly in those with stage II tumors (25-30) (Table I).

There were two secondary analyses of clinical trials. Prandi *et al*. examined 3,648 cases of colonic cancer enrolled in the National Intergroup for Adjuvant Therapy on Colon Cancer (INTACC) trials and showed that patients with an LNH of 18 or more had lower recurrence (HR=0.75), and patients with stage II disease with an LNH of less than seven had shorter survival (31). Le Voyer *et al*. examined 3,411 cases with colonic cancer enrolled in an intergroup trial (INT0089) and showed that the survival increased as more nodes were examined after controlling for the number of involved nodes, even when no nodes were involved (32). Joseph NE *et al*. mentioned that the number of nodes retrieved at resection influence the accuracy of determining nodal status in colon cancer from a secondary analysis of INT0089 (33).

Based on large, population-based, prospective studies, Bui *et al*. examined 960 cases with colonic cancer using the Ontario Cancer Registry and showed that among patients with stage II tumors, cancer mortality was lower for these with an LNH of 10 or more compared to those with an LNH of one to three (HR=0.6) (34). Vather *et al*. examined 4,309 cases with colonic cancer using the New Zealand Cancer Registry database and showed that the LNH number was an independent predictor of 5-year survival, and that survival improved consistently between nodal strata up to 16 nodes (35).

Using the SEER database, Chen *et al*. showed that when compared with patients with an LNH of one to seven, those with an LNH of 8 to 14 experienced an 11% reduction in mortality (HR=0.89) and those with an LNH of 15 or more experienced a 21% reduction in mortality (odds ratio, OR=0.79) (36). Moore *et al*. showed that compared with patients with an LNH of less than seven, those with an LNH of 7 to 11 had a 13% lower risk of death (HR=0.87), and those with an LNH of 12 or more had a 17% lower risk of death (HR=0.83) (37). Parsons *et al*. showed that although patients with a high LNH were only slightly more likely to be node-positive, the patients had a lower chance of death

Table I. *Lymph node harvest (LNH) and survival.*

Author	Years (Ref.)	Tumor	Cases	LNH category	Survival rate	Hazard ratio
Prandi *et al*.	2002 (31)	Colon	3,648	1-7/8-12/13-17/>17	66%/74%/77%/83%	1.0/0.94/0.75/0.75
Csemi *et al*.	2002 (51)	Colorec*	8,574	1/2/3/4/5/6/7/8/9/etc.		0.979 per node
Le Voyer *et al*.	2003 (32)	Colon	3,411	1-10/11-20/>20	73%/80%/87%	
Swanson *et al*.	2003 (52)	Colon*	35,787	1-7/8-12/>12	50%/56%/63% (II)	
Bui *et al*.	2006 (34)	Colon	960	1-3/4-6/7-9/>9		1.0/0.9/0.9/0.6
Chen *et al*.	2006 (36)	Colon	82,896	1-7/8-14/>14		1.0/0.89/0.79
Billimoria *et al*.	2008 (58)	Colon*	142,009	1-11/>11		1.0/0.75 (R) 1.0/0.80 (L)
Vather *et al*.	2009 (35)	Colon	4,309	1-12/>12	NA	
Moore *et al*.	2010 (37)	Colon	11,399	1-6/7-11/>11		1.0/0.87/0.83
Parsons *et al*.	2011 (38)	Colon	86,394	1-8/9-11/12-15/16-19/ 20-29/30-39/39<	1.0/0.87/0.83/0.74/	0.73/0.66/0.64
Wong *et al*.	2011 (39)	Colorec	8,521	1-6/7-9/>9**	73%/74%/77% (II/III) 79%/82%/85% (II)	
Kotake *et al*.	2012 (40)	Colorec	16,865	1-9/10-16/17-26/>26		1.0/0.63/0.59/0.46 (II) 1.0/0.91/0.92/0.75 (III)

Ref., Reference; Colorec, colon and rectum; NA, not available; II/III, TNM stages II and III; R/L, right/left colectomy; *Dukes' B tumor; **median LNH number per hospital.

compared with those having 1-8 nodes, with the HR being 0.87 for 9 to 11 nodes, 0.83 for 12 to 15 nodes, 0.74 for 16 to 19 nodes, 0.73 for 20 to 29 nodes, 0.66 for 30 to 39 nodes, and 0.64 for 40 or more nodes (38).

Wong *et al*. examined 8,521 cases of colorectal cancer using the California Cancer Registry and showed that when hospitals were stratified into three groups according to the median LNH number (<7, 7-9 and, >9), 5-year disease-specific survival was different among the three hospital groups (73%, 74% and, 77%respectively), especially in the treatment of node-negative tumors (79%, 82% and, 85% respectively) (39). Kotake *et al*. examined 16,865 cases with T3 or T4 colorectal cancer using the Japanese Society for Cancer of the Colon and Rectum (JSCCR) registry and showed that 5-year survival was associated with the LNH number; with an increase of one in the LNH number, the mortality rate decreased by 2.1% for patients with stage II and 0.8% for these with stage III disease (40).

One meta-analysis evaluated the studies on the relationship between the LNH number and survival after colorectal cancer surgery. Chang *et al*. performed electronic database searches and reviewed 17 studies involving 61,371 patients from nine countries, including five large, population-based, prospective studies, two secondary analyses of clinical trials, and 10 single-institution, retrospective case series, and showed that despite a wide variation of LNH cut-off values (6 to 40), 16 out of 17 studies involving patients with stage II disease reported an increased survival associated with increased LNH number, and four out of six studies involving patients with stage III disease also reported a positive association between LNH number and survival (41).

Although a causal relationship has not been established, it is easy to accept that a greater LNH is associated with better prognosis, since the LNH number is high when the patients are young and female, the tumors are right-sided and well-differentiated, the resection is wide, lymph node dissection is aggressive, and hospitals are specialized and high-volume, which are all associated with higher survival. Furthermore, when more lymph nodes are examined, the chance of metastatic nodes detection increases, and more patients receive adjuvant chemotherapy, more patients receive detailed follow-up examination, and more patients undergo curative resection of recurrence, which all result in a higher survival rate and longer survival period. Thus, the favorable effect of LNH on the prognosis of patients with both node-negative and node-positive tumors is partly associated with stage migration or the Will Rogers effect (42-46).

Dukes' B and Rectal Cancer

Dukes' B tumors have a low risk for recurrence, and most patients with Dukes' B tumors are not candidates for postoperative chemotherapy. Although several prognostic factors, including depth of wall invasion and lymphatic invasion, are reported in patients with Dukes' B colonic cancer (47-50), the LNH number is another important prognostic factor after colectomy.

Based on large, population-based, prospective studies, Csemi *et al*. examined 8,574 cases with T3N0 colorectal cancer using the SEER database and showed that 5-year survival improved with an increased LNH number, with a reduction in risk of death by 2.1% for each examined

lymph node (51). Using the NCDB registry, Swanson *et al*. examined 35,787 cases with T3N0 colonic cancer and showed that the three categories of LNH (1-7, 8-12 and, >12) were associated with different 5-year survival (50%, 56%and, 63% respectively) (52). Bilimoria *et al*. also examined 142,009 cases with N0 colonic cancer and showed that when adjusted for patient age and hospital volume, patients with an LNH of 12 or more had lower cancer mortality than those with an LNH fewer than 12 after right colectomy (HR=0.75) and left colectomy (HR=0.80) (53, 54).

For patients with locally advanced rectal cancer, neoadjuvant therapy is useful for tumor down-staging, and preoperative chemoradiotherapy often results in decreases in tumor and lymph node size. The decrease in lymph node size and number is recognized irrespective of the presence or absence of metastasis. Consequently, the LNH number decreases, and pathological evaluation of lymph nodes becomes insufficient in patients with rectal cancer who receive neoadjuvant therapy (55-59).

Based on single-institution, retrospective studies, Taflampas *et al*. examined 168 cases with rectal cancer and showed that when the patients were divided into three groups (chemoradiotherapy, short course of chemoradiotherapy, and long course of chemoradiotherapy), the percentage of patients with LNH fewer than 12 was higher in patients with a long course of chemoradiotherapy (34%, 30%, and 57%, respectively) (60). Marks *et al*. examined 176 cases with rectal cancer treated with neoadjuvant chemoradiotherapy and showed that only 28% had an LNH of 12 or more, 32% had an LNH of fewer than six, and the LNH number was not affected by radiation dosage or tumor response (61). Klos *et al*. examined 390 cases with rectal cancer and showed that although patients with positive nodes had a shorter survival and earlier recurrence, survival and recurrence were not different between patients with an LNH of less than 12 and those with an LNH of 12 or more (62).

Ha *et al*. examined 615 cases with rectal cancer, including 399 with preoperative chemoradiotherapy for T3 or T4 tumors, and showed that age, BMI, chemoradiotherapy, and stage were independent factors affecting LNH number, and the mean LNH number was lower in patients treated with chemoradiotherapy than in those without chemoradiotherapy (15 *vs*. 22), with a 33% reduction rate (63). Kim *et al*. examined 900 cases with rectal cancer treated with adjuvant chemoradiotherapy and showed that cancer-specific survival of patients with stage II disease with an LNH of less than 15 was worse than that of these with stage II disease with an LNH of more than 15 and not different from that of these with stage III disease (64). Tsai *et al*. examined 372 cases with rectal cancer, treated with preoperative chemoradiotherapy, and pathologically node-negative tumors and showed that compared with patients with an LNH of less than eight, those with an LNH of eight or more had higher 5-year relapse-free survival (86% *vs*. 72%) and cancer-specific survival (95% *vs*. 86%), with lower risks for relapse (HR=0.39) and death from cancer (HR=0.45) (65).

There was one large, population-based, prospective study. Chang *et al*. examined 23,809 cases with rectal cancer using the SEER database and showed that the median numbers of retrieved nodes (6 *vs*. 10) and positive nodes (2 *vs*. 3) were lower in patients treated with preoperative radiotherapy than in those treated with postoperative radiotherapy, but when lymph node metastasis was present, there was an increased risk for cancer-specific death for patients treated with preoperative radiotherapy (HR=1.23) (66).

LNR and Survival

In patients with lymph node metastasis of colorectal cancer, both the level and number of positive nodes affect survival (67-74). The TNM classification divides patients into three lymph node groups: N0 for these with negative nodes, N1 for these with one to three positive nodes, and N2 for these with four or more positive nodes (Table II)

Recently, the prognostic value of LNR, *i.e*. the ratio of the number of positive nodes to the total number of examined nodes, which combines two survival parameters, has been evaluated. Based on single-institution, retrospective studies, many authors found that the LNR is an independent prognostic indicator for stage III colorectal cancer, and the number of positive nodes either lost its prognostic value or had a less significant value (75-86).

There were two secondary analyses of clinical trials. Stocchi *et al*. examined 673 cases with rectal cancer and showed that the number of positive nodes and LNR (<0.25, 0.25-0.50, 0.50-0.75 and 0.75-1.0) were associated with survival (70%, 55%, 39% and 37%, respectively), and only the LNR was independently correlated with local recurrence (87). Edler *et al*. examined 1,025 cases of colorectal cancers and showed that LNR (<0.2, 0.2-0.49, 0.5-0.69 and 0.7-1.0) was an independent prognostic factor for overall survival (77%, 56%, 51% and 44%, respectively) (88).

Based on large, population-based, prospective studies, Jestin *et al*. examined 3,735 cases with colonic cancer using the Uppsala/Orebro health care database and showed that overall survival was higher for those with a median LNR of 0.32 or less compared to those with a median LNR of 0.33 or more, and the survival difference was larger when categorized by LNR than by the number of positive nodes (89). Berger *et al*. examined 3,557 cases with colonic cancer using an intergroup trial (INT-0089) and showed that LNR was an independent factor for survival, and LNR divided by quartiles (<0.05, 0.05-0.19, 0.2-0.39 and 0.4-1.0) maintained its significance for overall, cancer-specific, and disease-free survival (90).

Table II. *Lymph node ratio (LNR) and survival.*

Author	Years (Ref.)	Tumor	Cases	LNR category	Survival rate (Hazard ratio)
Stocchi *et al*.	2001 (87)	Rectum	673	<0.25/0.25-0.5/0.5-0.75/0.75-1.0	70%/55%/39%/37%
Jestin *et al*.	2005 (89)	Colon	3,735	<0.33/0.33-1.0	51%/32%
Berger *et al*.	2005 (90)	Colon	3,557	<0.05/0.05-0.19/0.2-0.39/0.4-1.0	79%/73%/63%/52% 77%/70%/62%/50% (DFS)
Ridder *et al*.	2006 (91)	Colorec	26,181	<0.4/0.4-1.0	56%/25%
Edler *et al*.	2007 (88)	Colorec	1,025	<0.2/0.2-0.49/0.5-0.69/0.7-1.0	77%/56%/51%/44%
Mammen *et al*.	2007 (92)	Colon	5,823	<0.1/0.1-0.21/0.22-0.43/0.44-1.0	44%/49%/30%/27%
Rosenberg *et al*.	2008 (93)	Colon	3,026	0/0.01-0.17/0.18-0.41/0.42-0.69/0.7-1.0	87%/61%/34%/18%/5% (1/1.98/3.16/3.95/4.44)
Wang *et al*.	2009 (96)	Colon	24,477	<0.07/0.07-0.24/0.25-0.49/0.5-1.0	75%/72%/70%/65% (IIIA) 64%/55%/44%/34% (IIIB)
Rosenberg *et al*.	2010 (94)	Colorec	27,803	<0.17/0.18-0.41/0.42-0.69/0.7-1.0	52%/33%/20%/8%
Chen *et al*.	2011 (97)	Colon	36,712	<0.1 /0.1-0.24/0.25-0.49/0.5-1.0	(1/1.32/1.65/2.88) (≥12)* (1/1.24/1.47/1.82) (<12)*
Chang *et al*.	2012 (101)	Colon	9,644	<0.09/0.09-0.17/0.18-0.33/0.34-1.0	NA

Ref., Reference; Colorec, colon and rectum; DFS, disease-free survival; IIIA/IIIB, TNM stages IIIA and IIIB; NA, not available; *LNH number.

Ridder *et al*. examined 26,181 stage III colorectal cancer cases using the SEER database and showed that LNR was an independent risk factor; 5-year cancer-specific survival of patients with an LNR of less than 0.4 and that of these with an LNR of 0.4 or more was 56% and 25%, respectively, and the prognostic separation obtained by the LNR was superior to that by the number of positive nodes (64% and 28%) (91). Mammen *et al*. examined 5,823 colonic cancer cases using the Veterans Affairs Central Cancer Registry database and showed that the LNR divided by quartiles (<0.1, 0.1-0.21, 0.22-0.43 and 0.44-1.0) affected survival more significantly than the number of positive nodes, with 5-year overall survival being 27% for the highest quartile *versus* 44% for the lowest (92).

Rosenberg *et al*. examined 3,026 cases with colorectal cancer using a surgical center database and showed that the LNR had a better prognostic value than the number of positive nodes, and the optimal cut-off values of LNR for prognostic differentiation were calculated as 0.17, 0.41 and 0.69, with 5-year survival rates for the four categories of 61%, 34%, 18% and 5%, respectively (93). They also examined 27,803 cases with colorectal cancer using the Munich Cancer Registry and showed that when categorized by the same cut-off values, LNR was an independent prognostic factor, with 5-year survival rates for the four categories being 52%, 33%, 20% and 8%, respectively (94).

Using the SEER database, Wang *et al*. examined 24,477 stage III colonic cancer cases and showed that when divided according to cut-off points of 1/14 (0.07), 1/4 (0.25), and 1/2 (0.50), 5-year survival rates for the four categories were 75%, 72%, 70% and 65%, respectively, in stage IIIA, and 64%, 55%, 44% and 34%, respectively, in stage IIIB (95), although patients with a higher LNH had a worse survival than those with a lower LNH among patients with LNR 0.25 to 0.5 (41% *vs*. 47%) and those with LNR 0.5 or more (22% *vs*. 32%) (96). Chen *et al*., therefore, examined 36,712 stage III colonic cancer cases and showed that when divided according to cut-off points of 1/10 (0.1), 1/4 (0.25), and 1/2 (0.50), the chance of death increased with higher LNR, both in patients with a higher LNH and those with a lower LNH (97).

One meta-analysis evaluated studies on the prognostic value of the LNR in stage III colorectal cancer. Ceelen *et al*. performed electronic database searches and reviewed 16 studies on 33,984 patients, including two population-based, prospective studies, four secondary analyses of clinical trials, and 10 single-institution, retrospective case series, and showed that LNR was an independent prognostic factor, and the prognostic separation obtained by the LNR was superior to that by the number of positive nodes, with a pooled HR of 2.36 for overall survival and 3.71 for disease-free survival (98).

Using prospective databases, some authors evaluated the prognostic significance of the number of negative nodes and showed that a greater number of negative nodes was associated with higher survival in patients with colorectal cancer (99, 100). However, Chang *et al*. recently examined 9,644 cases with colonic cancer using the Taiwan Cancer Database and showed that among LNH number, number of positive nodes, number of negative nodes, LNR, and log odds of positive nodes, LNR had the best discriminating capability to predict overall, disease-free, and disease-specific survival for patients with stage III colonic cancer (101).

Discussion

In patients with colorectal cancer, the status of lymph node metastasis is a significant prognostic factor, and lymph node evaluation is important for staging the disease, evaluating the prognosis, deciding on adjuvant therapy, and planning follow-up. To improve lymph node evaluation and the quality of clinical practice, daily collaboration between surgeons and pathologists is important through clinicopathological conferences and multidisciplinary meetings.

Many prospective studies have demonstrated a significant correlation between high LNH and increased survival. Although this correlation may represent an effect of lymph node dissection, it is difficult to determine whether high LNH is an indicator of improved surgical procedure, pathological assessment, patient care or hospital level. The scientific evidence for a minimum LNH number of 12 is questionable, and the use of a more reasonable and practical LNH number should be determined based on large, well-controlled, prospective studies.

Since LNR is a combination of the numbers of positive nodes and LNH, LNR provides stronger and superior prognostic power than the number of positive nodes alone. However, it remains unclear how we should categorize patients based on the LNR, and future prospective studies are needed to define the cut-off values that allow for optimal separation between subgroups of stage III tumors, for example, 0.25 or 0.5, and to verify whether the LNR can be used in decision making for adjuvant chemotherapy.

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