DOI: 10.4274/tjcd.83435
Turk J Colorectal Dis 2017;27:76-83

RESEARCH ARTICLE

The Prognostic Value of Lymph Node Ratio in Patients with Node-Positive Colorectal Cancer

Nod-Pozitif Kolorektal Kanser Hastalarında Lenf Nodu Oranının Prognostik Önemi

Nüvit Duraker[1], Zeynep Civelek Çaynak[2], Semih Hot[1]

[1]Okmeydanı Training and Research Hospital, Clinic of General Surgery, İstanbul, Turkey
[2]Bayındır Hospital, Clinic of General Surgery, İstanbul, Turkey

ABSTRACT

Aim: Lymph node metastasis is one of the most important prognostic factors in colorectal cancer. We investigated the prognostic value of lymph node ratio (LNR); (the ratio of the number of metastatic lymph nodes to the number of removed lymph nodes) in node-positive colorectal cancer patients.

Method: We assessed 321 node-positive colorectal cancer patients. To determine the LNR threshold value that will separate patients in two prognostic groups with significantly different cancer-specific survival (CSS) rates, survival analyses were conducted with LNR threshold values between 0.05 and 0.95, at increments of 0.05.

Results: In the whole series, the most significant LNR threshold value separating patients in low-risk (213 patients) and high-risk (108 patients) groups in terms of CSS was 0.40 (p<0.001) and LNR grouping had independent prognostic significance in multivariate Cox analysis (p<0.001). CSS of patients with tumor-node-metastasis (TNM) N1 and N2 disease was significantly different (p<0.001) and TNM nodal classification had independent prognostic significance in Cox analysis (p<0.001). When LNR and TNM nodal groupings were included together in the Cox analysis, LNR grouping maintained its independent prognostic significance (p<0.001), while TNM nodal grouping lost its prognostic significance (p=0.095).

Conclusion: LNR is a stronger prognostic parameter than TNM nodal grouping in separating node-positive colorectal cancer patients into prognostic groups.

Keywords: Colorectal carcinoma, prognosis, lymph node metastasis, lymph node ratio, tumor-node-metastasis classification

ÖZ

Amaç: Kolorektal kanserli hastalarda lenf nodu metastazı en önemli prognostik faktörlerden biridir. Biz nod-pozitif kolorektal kanserli hastalarda lenf nodu oranının (LNO); (metastatik lenf nodu sayısının çıkarılan lenf nodu sayısına oranı) prognostik değerini araştırdık.

Yöntem: Biz 321 nod-pozitif kolorektal kanserli hastayı değerlendirdik. Hastaları anlamlı derecede farklı kansere özgü sağkalım (KÖS) oranlarına göre iki prognostik gruba ayıracak LNO eşik değerini belirlemek için, sağkalım analizleri LNO eşik değeri 0,05 arttırılarak 0,05 ve 0,95 arasında yapıldı.

Bulgular: Tüm serilerde, hastaları KÖS açısından düşük risk (213 hasta) ve yüksek risk (108 hasta) gruplarına ayıran en anlamlı LNO eşik değeri 0,40 (p<0,001) idi ve çok değişkenli Cox analizlerinde LNO gruplama bağımsız prognostik öneme sahipti (p<0,001). Tümör-nod-metastaz (TNM) N1 ve N2 hastalığı olan hastaların KÖS'si anlamlı derecede farklıydı (p<0,001) ve Cox analizinde TNM nodal sınıflandırma bağımsız prognostik öneme sahipti (p<0,001). LNO ve TNM nodal gruplama Cox analizinde birlikte alındığında, LNO gruplama bağımsız prognostik önemini korurken (p<0,001), TNM nodal gruplama prognostik önemini kaybetmekteydi (p=0,095).

Sonuç: Nod-pozitif kolorektal kanserli hastaları prognostik gruplara ayırmada LNO TNM nodal gruplamadan daha güçlü bir prognostik parametredir.

Anahtar Kelimeler: Kolorektal karsinoma, prognoz, lenf nodu metastazı, lenf nodu oranı, tümör-nod-metastaz sınıflama

Address for Correspondence/Yazışma Adresi: Semih Hot MD
Okmeydanı Training and Research Hospital, Clinic of General Surgery, İstanbul, Turkey
Phone: +90 212 221 77 77 **E-mail:** semihhot@hotmail.com **ORCID ID:** orcid.org/0000-0001-9623-356X
Received/Geliş Tarihi: 18.06.2017 **Accepted/Kabul Tarihi:** 11.08.2017

©Copyright 2017 by Turkish Society of Colon and Rectal Surgery
Turkish Journal of Colorectal Disease published by Galenos Publishing House.

Introduction

Lymph node metastasis is one of the most important prognostic factors for colorectal cancer patients with no distant metastasis who have undergone curative resection. According to the American Joint Cancer Commission/Union for International Cancer Control tumor-node-metastasis (TNM) classification, nodal disease is divided into two prognostic risk groups depending on the number of metastatic regional lymph nodes: N1 indicates 1-3 metastatic lymph nodes and N2 indicates 4 or more metastatic lymph nodes.[1] Various studies have shown that the number of metastatic lymph nodes increases with the number of lymph nodes removed.[2,3,4,5,6] The number of lymph nodes removed is associated with the width of the surgical dissection, the extent of pathological examination, and the characteristics of the tumor and patient.[3,4,5,7,8,9,10,11,12,13] The minimum number of excised lymph nodes required to stage nodal disease is specified as 7-14 in the 6th edition of the TNM classification and as 10-14 in the 7th edition; however, the number of lymph nodes recommended for removal is not taken into account when determining node-negative disease or in grouping based on the number of metastatic lymph nodes, and classification can be done even when fewer lymph nodes are removed.[1,14,15] Several studies accept the minimum lymph nodes harvest as 12.[8,9,12,16,17,18,19,20] Lymph node ratio (LNR), (the ratio of metastatic lymph nodes to total lymph nodes removed) is a parameter that does not take into account the minimum number of lymph nodes that need to be removed, and numerous studies using a wide range of threshold values have reported its prognostic significance in colon and rectum cancers.

In the present study, we investigated the prognostic value of LNR in node-positive (stage III) colorectal cancer patients and whether it could contribute to the TNM classification.

Materials and Methods

Patients

Stage III colorectal cancer patients who were operated between January 1993 and December 2004 in our surgery unit, had no history of other malignancies, and underwent curative resection were evaluated. Nineteen patients who received neoadjuvant therapy, 10 patients with synchronous colorectal cancer, 11 patients with familial adenomatous polyposis, and 19 patients who died of complications in the early post-operative period were not included in the study. A total of 321 patients met the inclusion criteria for this study. Histological stage was grouped as low-grade (well or moderately differentiated) and high-grade (poorly differentiated, undifferentiated, mucinous, signet ring cell). All patients who received chemotherapy were given a 5-fluorouracil based regimen; chemotherapy was not administered to 35 patients whose general condition was poor or who rejected medical treatment. The clinicopathological data of all patients were collected prospectively.

Survival data of the patients were obtained from the oncology unit of our hospital or via phone calls to the patients or their relatives. The end point of the study was patient death. Cancer-specific survival (CSS) was defined as the time interval between surgery and mortality due to disease recurrence.[15,21] For 6 patients who developed a second malignancy, the date on which the second malignancy was diagnosed was accepted as the final follow-up date. For the 40 patients who died of causes unrelated to cancer, date of death was accepted as the final follow-up date.

This study was conducted in accordance with the principles of the Declaration of Helsinki and written informed consent was obtained from all patients prior to participation.

Statistical Analysis

In order to determine the LNR threshold value that would divide patients into two prognostic groups based on significantly different CSS rates, survival analyses were made with LNR values between 0.05 and 0.95 at increments of 0.05. Analyzes were performed on the entire series and subgroups including patients with <12 lymph nodes removed, ≥12 lymph nodes removed, TNM N1 disease, and TNM N2 disease.

CSS curves of the patient groups were calculated and rendered using the Kaplan-Meier method, and compared with the log-rank test. The relative significance of prognostic features was investigated using the Cox proportional hazards model. All comparisons were two-tailed. P values less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 17.0 (SPSS, Inc., Chicago, Illinois, USA).

Results

The clinicopathological characteristics and treatment specifications of the patients are shown in Table 1. One hundred fifty-one patients (47.1%) had fewer than 12 lymph nodes removed and 170 patients (52.9%) had 12 or more lymph nodes removed. TNM node class was stage N1 in 191 patients and N2 in 130 patients. One hundred ninety patients died of colorectal cancer by the end of the study in June 2013. The average follow-up time for surviving patients was 120.1 months.

Among the entire patient population, the most significant LNR threshold value that divided patients into low-risk (213 patients) and high-risk (108 patients) groups based on CSS was 0.40 (log-rank χ^2=66.216, p<0.001) (Figure 1), and LNR grouping had independent prognostic significance in multivariate Cox analyses (p<0.001) (Table 2). CSS was

Table 1. Clinicopathological and treatment features of the patients

Feature	n	%
Gender		
Female	157	48.9
Male	164	51.1
Age, years		
Mean	58.1	
Median	60.0	
Range	19.0-87.0	
Age, years		
<65	211	65.7
≥65	110	34.3
Tumor site		
Colon	172	53.6
Rectum	149	46.4
Tumor size, cm		
≤5	102	31.8
>5	219	68.2
Histological grade		
Low grade	252	78.5
High grade	69	21.5
T stage		
T1-T2	35	10.9
T3-T4	286	89.1
No. of LN† removed		
Mean	12.9	
Median	12	
Range	1-43	
Number of LN removed		
<12	151	47.0
≥12	170	53.0
Number of metastatic LN		
Mean	4.1	
Median	3	
Range	1-24	
N stage		
N1	191	59.5
N2	130	40.5
LNR‡		
Mean	35.9	
Median	27.2	
Range	2.3-100	
LNR		
≤0.40	213	66.4
>0.40	108	33.6
Surgery		
Elective	271	84.4
Urgent	50	15.6
Iatrogenic tumor perforation		
No	296	92.2
Yes	25	7.8
Adjuvant chemotherapy		
Yes	286	89.1
No	35	10.9

†LN: Lymph node, ‡LNR: Lymph node ratio

Table 2. Cox proportional hazards model analysis of the clinicopathological and treatment features, and lymph node ratio†

Feature	Relative risk	95% CI‡	p
Gender			
Female	1.00	0.59-1.07	0.140
Male	0.79		
Age, years			
<65	1.00	1.10-2.15	0.010
≥65	1.54		
Tumor site			
Colon	1.00	0.92-1.75	0.139
Rectum	1.27		
Tumor size, cm			
≤5	1.00	0.62-1.21	0.412
>5	0.86		
Histological grade			
Low grade	1.00	1.09-2.20	0.014
High grade	1.55		
T stage			
T1-T2	1.00	1.51-5.77	0.001
T3-T4	2.95		
Number of LN§ removed			
<12	1.00	0.77-1.43	0.731
≥12	1.05		
LNR			
≤0.40	1.00	2.14-3.97	<0.001
>0.40	2.91		
Surgery			
Elective	1.00	0.75-1.87	0.467
Urgent	1.18		
Iatrogenic tumor perforation			
No	1.00	1.12-3.07	0.016
Yes	1.85		
Adjuvant chemotherapy			
Yes	1.00	0.54-1.68	0.868
No	0.95		

†LNR: Lymph node ratio, ‡CI: Confidence interval, §LN: Lymph node

significantly different in patients with TNM N1 and N2 disease (log-rank χ^2=29.854, p<0.001) (Figure 2) and TNM node status had independent prognostic significance in the Cox analysis (p<0.001) (Table 3). When the LNR and TNM node grouping were combined in the Cox analysis, LNR maintained its independent prognostic significance (p<0.001), while TNM node grouping lost its prognostic significance (p=0.095) (Table 4).

In the patient group with <12 nodes removed, the most significant LNR threshold value discriminating low-risk (96 patients) and high-risk (55 patients) groups based on CSS was 0.40 (log-rank χ^2=42.911, p<0.001) (Figure 3). Including both LNR and TNM node class in the Cox analysis revealed that LNR maintained its independent prognostic significance (p<0.001), while TNM node class, which had prognostic significance in the univariate analysis, lost its prognostic significance (p=0.209). Among patients with ≥12 lymph nodes removed, the most significant LNR threshold value that divided patients into low-risk (117 patients) and high-risk (53 patients) groups was also 0.40 (log-rank χ^2=24.816, p<0.001) (Figure 4). When the LNR and TNM node class were both included in the Cox analysis, LNR grouping maintained its independent prognostic significance (relative risk=2.10, 95% confidence interval=1.23-3.57, p=0.006), while TNM node class, which had prognostic significance in the univariate analysis (log-rank χ^2=14.014, p=0.001) lost its prognostic significance (relative risk=1.48, 95% confidence interval=0.84-2.61, p=0.175).

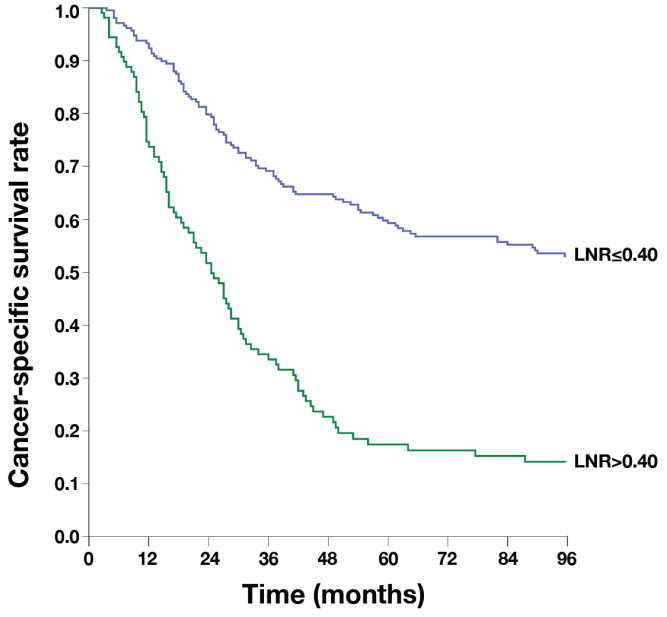


Figure 1. Cancer-specific survival rates of the patients according to lymph node ratio (LNR) in the whole series (log-rank χ^2=66.216, p<0.001); LNR ≤0.40 (low-risk, 213 patients) vs. LNR >0.40 (high-risk, 108 patients)
LNR: Lymph node ratio

In both the N1 and N2 patient groups, the most significant LNR threshold value separating low-risk (167 and 46 patients, respectively) and high-risk patients (24 and 84 patients, respectively) groups was 0.40 (log-rank χ^2=14.357 and log-rank χ^2=17.530 respectively, p<0.001).

In the group of patients with LNR ≤0.40, there was no significant difference (p=0.330) between the CSS rates of

Table 3. Cox proportional hazards model analysis of the clinicopathological and treatment features, and tumor-node-metastasis N stage

Feature	Relative risk	95% CI‡	p
Gender			
Female	1.00	0.71-1.29	0.817
Male	0.96		
Age, years			
<65	1.00	1.06-2.06	0.019
≥65	1.48		
Tumor site			
Colon	1.00	1.03-1.93	0.030
Rectum	1.41		
Tumor size, cm			
≤5	1.00	0.55-1.08	0.141
>5	0.77		
Histological grade			
Low grade	1.00	1.13-2.28	0.007
High grade	1.61		
T stage			
T1-T2	1.00	1.50-5.68	0.002
T3-T4	2.92		
Number of LN‡ removed			
<12	1.00	0.54-1.04	0.085
≥12	0.75		
N stage			
N1	1.00	1.67-3.20	<0.001
N2	2.31		
Surgery			
Elective	1.00	0.78-1.89	0.380
Urgent	1.22		
Iatrogenic tumor perforation			
No	1.00	1.22-3.31	0.006
Yes	2.01		
Adjuvant chemotherapy			
Yes	1.00	0.54-1.63	0.826
No	0.94		

†CI: Confidence interval, ‡LN: Lymph node

patients with N1 (167 patients) and N2 (46 patients) disease. There was also no significant difference in CSS between N1 (24 patients) and N2 (84 patients) patients with LNR >0.40 (p=0.132).

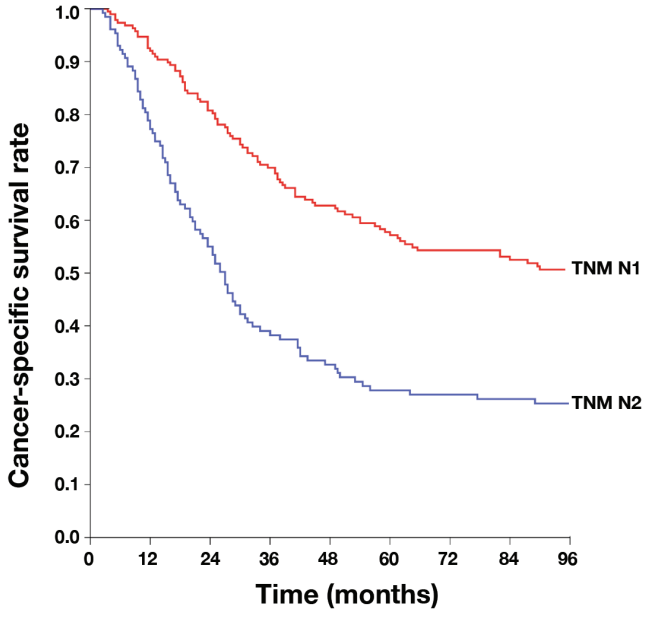


Figure 2. Cancer-specific survival rates of the patients according to tumor-node-metastasis nodal disease in the whole series (log-rank χ^2=29.854, p<0.001); N1 disease (191 patients) vs. N2 disease (130 patients)
TNM: Tumor-node-metastasis

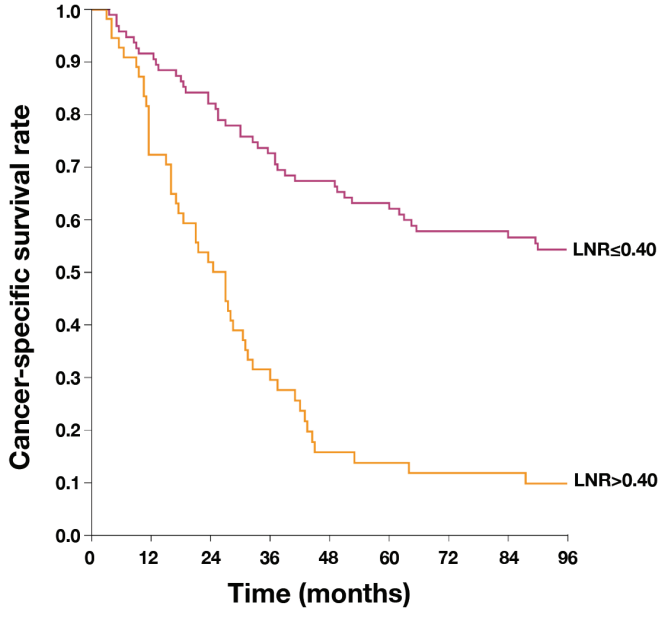


Figure 3. Cancer-specific survival rates of the patients according to lymph node ratio (LNR) in the patient group with the number of lymph nodes removed <12 (log-rank χ^2=42.911, p<0.001); LNR ≤0.40 (low-risk, 96 patients) vs. LNR >0.40 (high-risk, 55 patients)
LNR: Lymph node ratio

Discussion

The first study to investigate the prognostic significance of LNR in colon cancer was published in 2005. In that study, multivariate Cox analysis including both LNR and TNM node class in patients with ≥10 lymph nodes removed showed that TNM node class had no prognostic significance, while LNR was found to be the most significant prognostic factor.[22] In a review of 16 studies, it was noted that LNR was superior to positive node number in the prognostic classification in stage III colon and rectal cancer patients who were not receiving neoadjuvant therapy.[23] LNR was also found to be a stronger prognostic factor than TNM node class in three population-based studies including large numbers of colon and colorectal cancer patients. In another population-based study involving colon cancer patients, LNR and TNM node class were each found to be independent prognostic factors.[24,25,26,27]

In our series consisting of node-positive (stage III) colorectal cancer patients not receiving neoadjuvant therapy, an LNR of 0.40 had the highest discriminatory power between CSS prognostic groups in analyses of the entire series as well as subgroups of patients with <12 and ≥12 lymph nodes removed. In all three of these patient groups, TNM node class had prognostic significance in univariate analysis, but when the LNR and node class were both included in the Cox analysis, LNR continued to be a significant prognostic indicator while node class lost its prognostic significance. An LNR of 0.40 also divided patients into two prognostic

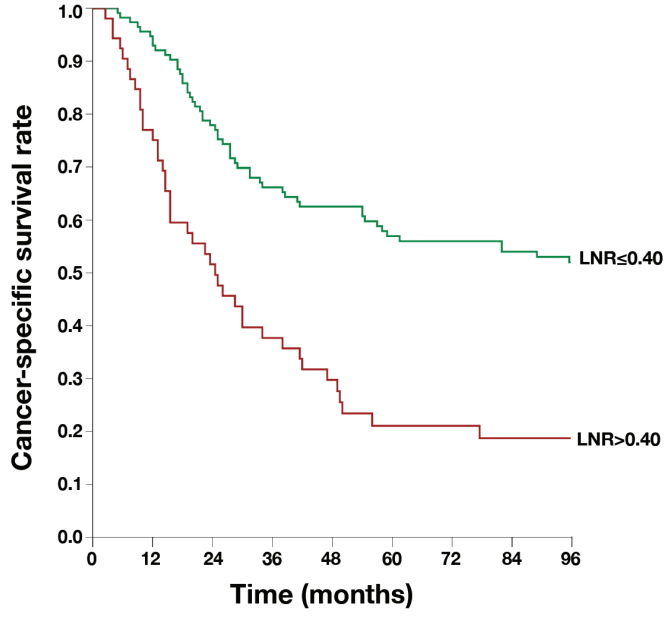


Figure 4. Cancer-specific survival rates of the patients according to lymph node ratio (LNR) in the patient group with the number of lymph nodes removed ≥12 (log-rank χ^2=24.816, p<0.001); LNR ≤0.40 (low-risk, 117 patients) vs. LNR >0.40 (high-risk, 53 patients)
LNR: Lymph node ratio

groups with significantly different CSS rates in both the TNM N1 and N2 patient groups. On the other hand, there was no significant difference between the prognoses of N1 and N2 patients in both the group of patients with LNR ≤0.40 and those with LNR >0.40. These findings indicate that the LNR is a stronger prognostic parameter than TNM node class in colorectal cancer.

Table 4. Cox proportional hazards model analysis of the clinicopathological and treatment features, tumor-node-metastasis N stage and lymph node ratio†

Feature	Relative risk	95% CI‡	p
Gender			
Female	1.00	0.61-1.13	0.240
Male	0.83		
Age, years			
<65	1.00	1.10-2.15	0.011
≥65	1.54		
Tumor site			
Colon	1.00	0.93-1.77	0.116
Rectum	1.29		
Tumor size, cm			
≤5	1.00	0.59-1.16	0.274
>5	0.82		
Histological grade			
Low grade	1.00	1.07-2.15	0.018
High grade	1.52		
T stage			
T1-T2	1.00	1.47-5.61	0.002
T3-T4	2.87		
Number of LN§ removed			
<12	1.00	0.67-1.31	0.720
≥12	0.94		
N stage			
N1	1.00	0.94-2.07	0.095
N2	1.40		
LNR			
≤0.40	1.00	1.67-3.53	<0.001
>0.40	2.43		
Surgery			
Elective	1.00	0.74-1.85	0.482
Urgent	1.17		
Iatrogenic tumor perforation			
No	1.00	1.10-3.03	0.018
Yes	1.83		
Adjuvant chemotherapy			
Yes	1.00	0.57-1.77	0.982
No	1.01		

†LNR: Lymph node ratio, ‡CI: Confidence interval, §LN: Lymph node

To date, studies have reported varying LNR categories to divide node-positive colon and rectal cancer patients into prognostic groups. LNR categories have been used to separate patients into five, three, or two prognostic gr oups.[6,12,16,18,19,20,21,22,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42] All of these studies determined that LNR has independent prognostic significance. Studies which separated patients into 2 prognostic groups, as in our study, used LNR threshold values of 0.16, 0.17, 0.18, 0.20, 0.25, 0.30, and 0.60.[6,20,37,38,39,40,41,42]

Some studies have evaluated the prognostic significance of LNR within patient subgroups created based on number of lymph nodes removed. LNR was shown to have prognostic significance in groups with <10 and ≥10 nodes removed and with <12 and ≥12 nodes removed.[12,16,18,19,20,24] Different authors have reported that LNR had no prognostic significance below but did show prognostic value above lymph node harvest thresholds of 10, 12, and 13.[22,36,42]

In some studies, the LNR has distinguished patients with TNM N1 and N2 disease into groups with significantly different prognoses.[19,24,33,37,38] Another study showed that the LNR separated N2 patients into prognostic groups with significantly different survival rates, but could not do the same for N1 patients.[22] Some studies reported no difference in survival rates between patients with N1 and N2 disease in patient subgroups created according to LNR.[19,33]

As in our study, numerous authors have reported that in multivariate Cox analysis including LNR and TNM node class, only LNR maintained its independent prognostic significance.[6,12,19,30,33,34,35,36,37,38,39,40,41,42] In one study, node class also maintained its independent prognostic significance in the Cox analysis, but LNR was found to be a stronger prognostic factor.[29]

LNR is superior to TNM node class in separating node-positive colorectal cancer patients into prognostic groups, and may be useful in planning adjuvant therapy. However, there is a need for prospective clinical studies including sufficient numbers of patients to determine whether LNR can be used in place of or in combination with TNM node class, as well as to determine a standard LNR threshold value instead of the wide range of LNR threshold values that have been used previously.

Ethics

Ethics Committee Approval: Ethics Committee approval was not obtained because there was no ethics committee at that time. This study was conducted in accordance with the principles of the "Declaration of Helsinki".

Informed Consent: Consent form was filled out by all participants.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.D., Concept: N.D., Design: N.D., Data Collection or Processing: Z.C.Ç., S.H., Analysis or Interpretation: N.D., Literature Search: Z.C.Ç., S.H., Writing: N.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC Cancer Staging Handbook. 7th ed. New York; Springer-Verlag. 2010.
2. Le Voyer TE, Sigurdson ER, Hanlon AL, Mayer RJ, Macdonald JS, Catalano PJ, Haller DG. Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. J Clin Oncol 2003;21:2912-2919.
3. Kelder W, Inberg B, Schaapveld M, Karrenbeld A, Grond J, Wiggers T, Plukker JT. Impact of the number of histologically examined lymph nodes on prognosis in colon cancer: a population-based study in the Netherlands. Dis Colon Rectum 2009;52:260-267.
4. Hashiguchi Y, Hase K, Ueno H, Mochizuki H, Kajiwara Y, Ichikura T, Yamamoto J. Prognostic significance of the number of lymph nodes examined in colon cancer surgery: clinical application beyond simple measurement. Ann Surg 2010;251:872-881.
5. Kotake K, Honjo S, Sugihara K, Hashiguchi Y, Kato T, Kodaira S, Muto S, Koyama Y. Number of lymph nodes retrieved is an important determinant of survival of patients with stage II and stage III colorectal cancer. Jpn J Clin Oncol 2012;42:29-35.
6. Lu YJ, Lin PC, Lin CC, Wang HS, Yang SH, Jiang JK, Lan YT, Lin TC, Liang WY, Chen WS, Lin JK, Chang SC. The impact of the lymph node ratio is greater than traditional lymph node status in stage III colorectal cancer patients. World J Surg 2013;37:1927-1933.
7. Mekenkamp LJ, van Krieken JH, Marijnen CA, van de Velde CJ, Nagtegaal ID; Pathology Review Committee and the Co-operative Clinical Investigators. Lymph node retrieval in rectal cancer is dependent on many factors- the role of the tumor, the patient, the surgeon, the radiotherapist, and pathologist. Am J Surg Pathol 2009;33:1547-1553.
8. Dillman RO, Aaron K, Heinemann FS, McClure SE. Identification of 12 or more lymph nodes in resected colon cancer specimens as an indicator of quality performance. Cancer 2009;115:1840-1848.
9. Chou JF, Row D, Gonen M, Liu YH, Schrag D, Weiser MR. Clinical and pathologic factors that predict lymph node yield from surgical specimens in colorectal cancer: a population-based study. Cancer 2010;116:2560-2570.
10. Elferink MA, Siesling S, Visser O, Rutten HJ, van Krieken JH, Tollenaar RA, Lemmens VE. Large variation between hospitals and pathology laboratories in lymph node evaluation in colon cancer and its impact on survival, a nationwide population-based study in the Netherlands. Ann Oncol 2011;22:110-117.
11. Nash GM, Row D, Weiss A, Shia J, Guillem JG, Paty PB, Gonen M, Weiser MR, Temple LK, Fitzmaurice G, Wong WD. A predictive model for lymph node yield in colon cancer resection specimens. Ann Surg 2011;253:318-322.
12. Wong KP, Poon JT, Fan JK, Law WL. Prognostic value of lymph node ratio in stage III colorectal cancer. Colorectal Dis 2011;13:1116-1122.
13. Duraker N, Bati B, Çaynak ZC, Demir D. Lymph node ratio may be supplementary to TNM nodal classification in node-positive breast carcinoma based on the results of 2,151 patients. World J Surg 2013;37:1241-1248.
14. Greene FL, Page DL, Fleming ID, Fritz AG, Balch CM, Haller DG, Morrow M. AJCC Cancer Staging Handbook. 6th ed. New York; Springer-Verlag. 2002.
15. Duraker N, Civelek Çaynak Z, Hot S. The prognostic value of the number of lymph nodes removed in patients with node-negative colorectal cancer. Int J Surg 2014;12:1324-1327.
16. Rosenberg R, Friederichs J, Schuster T, Gertler R, Maak M, Becker K, Grebner A, Ulm K, Höfler H, Nekarda H, Siewert JR. Prognosis of patients with colorectal cancer is associated with lymph node ratio: a single - center analysis of 3026 patients over a 25-year time period. Ann Surg 2008;248:968-978.
17. Chen HH, Chakravarty KD, Wang JY, Changchien CR, Reiping T. Pathological examination of 12 regional lymph nodes and long-term survival in stages I-III colon cancer patients: an analysis of 2,056 consecutive patients in two branches of same institution. Int J Colorectal Dis 2010;25:1333-1341.
18. Qiu HB, Zhang LY, Li YF, Zhou ZW, Keshari RP, Xu RH. Ratio of metastatic to resected lymph nodes enhances to predict survival in patients with stage III colorectal cancer. Ann Surg Oncol 2011;18:1568-1574.
19. Tong LL, Gao P, Wang ZN, Song YX, Xu YY, Sun Z, Xing CZ, Wang X, Xu HM. Can lymph node ratio take the place of pN categories in the UICC/AJCC TNM classification system for colorectal cancer? Ann Surg Oncol 2011;18:2453-2460.
20. Wang LP, Wang HY, Cao R, Zhu C, Wu XZ. Proposal of a new classification for stage III colorectal cancer based on the number and ratio of metastatic lymph nodes. World J Surg 2013;37:1094-1102.
21. Duraker N, Çaynak ZC, Trabulus DC. Free/Total Serum Prostate-Specific Antigen Ratio in Women with Colorectal Cancer Has Prognostic Significance. J Gastrointest Cancer 2017;48:8-12.
22. Berger AC, Sigurdson ER, LeVoyer T, Hanlon A, Mayer RJ, Macdonald JS, Catalano PJ, Haller DG. Colon cancer survival is associated with decreasing ratio of metastatic to examined lymph nodes. J Clin Oncol 2005;23:8706-8712.
23. Ceelen W, Van Nieuwenhove Y, Pattyn P. Prognostic value of the lymph node ratio in stage III colorectal cancer: a systematic review. Ann Surg Oncol 2010;17:2847-2855.
24. Wang J, Hasset JM, Dayton MT, Kulaylat MN. Lymph node ratio: role in the staging of node-positive colon cancer. Ann Surg Oncol 2008;15:1600-1608.
25. Lykke J, Roikjær O, Jess P; Danish Colorectal Cancer Group. The relation between lymph node status and survival in stage I-III colon cancer: results from a prospective nationwide cohort study. Colorectal Dis 2012;15:559-565.
26. Rosenberg R, Engel J, Bruns C, Heitland W, Hermes N, Jauch KW, Kopp R, Pütterich E, Ruppert R, Schuster T, Friess H, Hölzel D. The prognostic value of lymph node ratio in a population-based collective of colorectal cancer patients. Ann Surg 2010;251:1070-1078.
27. Chen SL, Steele SR, Eberhardt J, Zhu K, Bilchik A, Stojadinovic A. Lymph node ratio as a quality and prognostic indicator in stage III colon cancer. Ann Surg 2011;253:82-87.
28. Thomas M, Biswas S, Mohamed F, Chandrakumaran K, Jha M, Wilson R. Dukes C colorectal cancer: is the metastatic lymph node ratio important? Int J Colorectal Dis 2012;27:309-317.
29. Derwinger K, Carlsson G, Gustavsson B. A study of lymph node ratio as a prognostic marker in colon cancer. Eur J Surg Oncol 2008;34:771-775.
30. Moug SJ, Saldanha JD, McGregor JR, Balsitis M, Diament RH. Positive lymph node retrieval ratio optimises patient staging in colorectal cancer. Br J Cancer 2009;100:1530-1533.
31. Kobayashi H, Mochizuki H, Kato T, Mori T, Kameoka S, Shirouzu K, Saito Y, Watanabe M, Morita T, Hida J, Ueno M, Ono M, Yasuno M, Sugihara K; Study Group for Rectal Cancer Surgery of the Japanese Society for Cancer of the Colon and Rectum. Lymph node ratio is a powerful prognostic index in patients with stage III distal rectal cancer: a Japanese multicenter study. Int J Colorectal Dis 2011;26:891-896.

32. Sjo OH, Merok MA, Svinland A, Nesbakken A. Prognostic impact of lymph node harvest and lymph node ratio in patients with colon cancer. Dis Colon Rectum 2012;55:307-315.
33. Lee HY, Choi HJ, Park KJ, Shin JS, Kwon HC, Roh MS, Kim C. Prognostic significance of metastatic lymph node ratio in node-positive colon carcinoma. Ann Surg Oncol 2007;14:1712-1717.
34. Peng J, Xu Y, Guang Z, Zhu J, Wang M, Cai G, Sheng W, Cai S. Prognostic significance of the metastatic lymph node ratio in node-positive rectal cancer. Ann Surg Oncol 2008;15:3118-3123.
35. Park IJ, Choi GS, Jun SH. Nodal stage of stage III colon cancer: the impact of metastatic lymph node ratio. J Surg Oncol 2009;100:240-243.
36. Chin CC, Wang JY, Yeh CY, Kuo YH, Huang WS, Yeh CH. Metastatic lymph node ratio is a more precise predictor of prognosis than number of lymph node metastases in stage III colon cancer. Int J Colorectal Dis 2009;24:1297-1302.
37. Vaccaro CA, Im V, Rossi GL, Quintana GO, Benati ML, Perez de Arenaza D, Bonadeo FA. Lymph node ratio as prognosis factor for colon cancer treated by colorectal surgeons. Dis Colon Rectum 2009;52:1244-1250.
38. Galizia G, Orditura M, Ferraraccio F, Castellano P, Pinto M, Zamboli A, Cecere S, De Vita F, Pignatelli C, Lieto E. The lymph node ratio is a powerful prognostic factor of node-positive colon cancers undergoing potentially curative surgery. World J Surg 2009;33:2704-2713.
39. Dekker JW, Peeters KC, Putter H, Vahrmeijer AL, van de Velde CJ. Metastatic lymph node ratio in stage III rectal cancer; prognostic significance in addition to the 7th edition of the TNM classification. Eur J Surg Oncol 2010;36:1180-1186.
40. Ainsworth PD, Johnson MA. The prognostic siginificance of the metastatic lymph node ratio in Dukes stage C colorectal cancer in a district general hospital. Colorectal Dis 2010;12:1219-1222.
41. Hong KD, Lee SI, Moon HY. Lymph node ratio as determined by the 7th edition of the American Joint Committe on Cancer staging system predicts survival in stage III colon cancer. J Surg Oncol 2011;103:406-410.
42. Shimomura M, Ikeda S, Takakura Y, Kawaguchi Y, Tokunaga M, Egi H, Hinoi T, Okajima M, Ohdan H. Adequate lymph node examination is essential to ensure the prognostic value of the lymph node ratio in patients with stage III colorectal cancer. Surg Today 2011;41:1370-1379.