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Brief communication (Original)

Pathologically-based positive lymph node ratio (pLNR) for stage III colorectal cancer patients: prognostic impact on cases with fewer than 12 lymph node retrievals

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Background: The pathologically-based positive lymph node ratio (pLNR) has been proposed as alternative lymph node (LN) parameters to the conventional TNM staging.
Objective: We evaluated the prognostic value of the pLNR for patients with stage III colorectal after curative surgery with adequate and inadequate LN retrieval (<12).
Materials and Method: A total of 258 patients with stage III colorectal adenocarcinoma who underwent curative resection performed in Phramongkutklao Hospital from January 1, 2003 through December 31, 2010 were given a regular follow-up according to established guidelines with routine physical examination, serum carcinoembryonic antigen (CEA), and colonoscopic surveillance. Imaging studies for detecting organ metastases were computed tomography (CT), magnetic resonance imaging, positron emission tomography (PET) CT scan, and ultrasonography. Patients were categorized into four groups according to the pathologically-based positive lymph node ratio (pLNR) (pLNR1: 0.1 to 0.25, pLNR2: 0.26 to 0.50, pLNR3: 0.51 to 0.75, and pLNR4: 0.76 to 1.0). Tumor-free survival was calculated from the date of primary colorectal tumor resection to the date of appearance of local recurrence or metastatic disease. The prognostic impact of pLNR was determined in the evaluated cohort and in a subgroup of patients with fewer than 12 LN retrievals who were examined.
Results: The number of LN examined ranged from 2 to 50 with a mean (SD) of 15.8 (8.7). In all, 93 (36%) patients with fewer than 12 LN were examined. Local recurrence or distant site metastases were found in 123 (47.7%) patients during the surveillance period with a median tumor-free survival of 41 months (95% CI, 28.7–53.3). Median tumor-free survival was categorized according to pLNR as follows: pLNR1 = 56 (95% CI, 36.3–75.7), pLNR2 = 22 (95% CI, 18.5–25.5), pLNR3 = 26 (95% CI, 10.5–70.9), and pLNR4 = 8 (95% CI, 1.1–5.8) months. Serum carcinoembryonic antigen (CEA) > 10 ng/dl, AJCC tumor stage 3C, and higher pLNR were found significantly associated with shorter tumor-free survival with univariate analysis. Potentially associated variables were then tested using multivariate analysis with a Cox regression model. This study found that the pLNR was the independent factor that was significantly associated with a risk of local recurrence or distant site metastases. In the evaluated cohort, the adjusted hazard ratio (HR) compared pLNR1 for pLNR2 = 2.27 (95% CI, 1.058–4.875; $p < 0.01$), pLNR3 = 4.365 (95% CI, 1.447–13.166; $p < 0.05$) and pLNR4 = 4.897 (95% CI, 1.546–15.518; $p < 0.01$). In the subgroup of patients with fewer than 12 LN retrievals who were examined, multivariate analysis was not consistently significant for all ranges of the adjusted hazard ration (HR) compared with pLN1 for pLNR3 = 10.552 (95% CI, 1.911–58.277; $p < 0.05$)
Conclusion: This study revealed pLNR was a significant independent prognostic factor that was associated with a risk of local recurrence or distant site metastases in patients with stage III colorectal cancer after curative surgery. A higher pLNR had a negative impact on tumor-free survival irrespective of the adequacy of LN retrieval.

Keywords: Colorectal cancer, lymph node, lymph node ratio, prognostic factor

The tumor node metastasis (TNM) staging system proposed by the American Joint Committee on Cancer (AJCC) [1] and the International Union Against Cancer (UICC) [2] remains the most reliable staging system used for predicting long-term outcomes of colorectal cancer patients. The "N" stands for nodal metastasis, the total number of lymph node (LN) metastases (N stage) is known as an important

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prognostic factor for survival in colorectal cancer patients. In 2000, the College of American Pathologists consensus stated a minimum harvest of 12 lymph nodes was an optimal number of lymph nodes that should be examined [3, 4]. However, many factors can influence the number of LN harvested and examined. The heterogeneity in LN numbers being harvested and examined can affect the accuracy of the N categories of this system. Patients with inadequate LN sampling can inappropriately be classified as having node–negative disease.

pLNR estimated by dividing the number of positive LN by the total number of LN harvested, has been reported as a prognostic factor on various kinds of solid tumors including colon cancer [5-13]. For the study in rectal cancer [14], LN ratios were possibly a better staging method than absolute positive LN counts because frequently fewer than 12 LN were examined due to the effect of neoadjuvant chemoradiation. However, chemoradiation per se could affect pLNR and confound the result. In the present study, clinicopathological characteristics and follow-up data of stage III colon and rectal cancer patients were collected prospectively. This study aimed to evaluate the prognostic value of the pLNR for patients with stage III colorectal cancer after curative surgery with adequate and inadequate LN retrieval (<12).

Material and method

The study was reviewed and approved by the Institutional Review Board of Phramongkutklao Hospital prior to initiation. The study was conducted on a cohort of 258 patients with stage III colorectal adenocarcinoma who underwent curative resection performed in Phramongkutklao Hospital from January 1, 2003 through December 31, 2010. Patients' department-based electronic medical records were reviewed to determine the impact of pLNR on tumor-free survival. All operations were performed or supervised by board-certified colon and rectal surgeons in the Division of Coloproctology (SA, CB, BC, PCh). All rectal cancer patients were treated by standard mesorectal excision technique. Total mesorectal excision (TME) was used for mid and distal rectal cancer, while partial mesorectal excision (PME) was performed for patients with higher rectal tumor. Only rectal cancer patients who underwent standard mesorectal excision without preoperative chemoradiation were eligible for recruitment into this study. The standard de Gramont regimen or oxaliplatin/ de Gramont regimen was used in combination as standard adjuvant treatment. Standard pathological analysis was performed on all resection specimens. Each colorectal tumor specimen was staged according to the AJCC Cancer Staging Manual [15]. The records of each patient were reviewed and documented for age, sex, type of surgery, tumor location, tumor stage, histopathological features (tumor differentiation, mucinous component, and lymphovascular invasion) of primary colorectal cancer specimens. The pLNR is defined as the ratio of the number of positive LN divided by the total number of examined nodes within one specimen. All patients were given regular follow-up every three months for the first two years, every six months during the third and fifth years, and annually, thereafter. After accomplishing R0 resection and completion of adjuvant treatment, patients were given regular follow-up according to established guidelines with routine physical examination, serum carcinoembryonic antigen (CEA), and colonoscopic surveillance. Imaging studies for detecting organ metastases were computed tomography (CT), magnetic resonance imaging, positron emission tomography (PET) CT scan, and ultrasonography.

A total of 258 patients were categorized into four groups according to pLNR, pLNR1: 0.1 to 0.25, pLNR2: 0.26 to 0.50, pLNR3: 0.51 to 0.75 and pLNR4: 0.76 to 1.0. All local recurrence or distant site metastases detected during postoperative surveillance were identified as clinical, radiologic, and/or pathological evidence of disease recurrence. The tumor-free survival was defined as the interval between primary colorectal tumor resection and appearance of local recurrence or metastatic disease.

Statistical analysis

All statistical analyses used Stata 12. The tumor-free interval was calculated from the date of primary colorectal tumor resection surgery to the date of appearance of local recurrence or metastatic disease. Tumor-free survival was calculated using the Kaplan–Meier method. The log–rank test was performed to evaluate the prognostic value of pLNR and covariate analysis was performed with Cox regression analysis to determine those independent variables significantly associated with recurrence. A *p*-value less than 0.05 was considered statistically significant.

Results

The clinicopathological features of patients can be seen in **Table 1**. A total of 258 patients with a mean (SD) age of 61.4 years (12.3 years), there were 232 (89.9%) patients that were diagnosed with colon cancer while 26 (10.1%) were diagnosed with rectal cancer. Local recurrence and/or distant site metastases were found in 123 (47.7%) patients during surveillance period with a median tumor-free survival of 41 months (95% CI, 28.7–53.3). Median tumor free-survival was categorized according to pLNR as follows: pLNR1 = 56 (95% CI, 36.3–75.7) months, pLNR2 = 22 (95% CI, 18.5–25.5) months, pLNR3 = 26 (95% CI, 10.5–70.9) months, and pLNR4 = 8 (95% CI, 1.1–5.8) months.

The total number of LN examined ranged from 2 to 50 with a mean (SD) of 15.8 (8.7). Univariate survival analysis of time to local recurrence/distant site metastasis comparison between groups using a log rank test, serum carcinoembryonic antigen (CEA) > 10 ng/dl, AJCC tumor stage 3C, and higher pLNR found significant associations with shorter tumor-free survival (**Table 2**). According to multivariate analysis, with Cox regression, for the risk of local recurrence/distant site metastasis, pLNR was the only independent factor that was significantly associated with risk of local recurrence or distant site metastases with adjusted hazard ration (HR) comparing to pLNR1 for pLNR2 = 2.27(95% CI, 1.058–4.875; $p < 0.01$), pLNR3 = 4.365 (95% CI, 1.447–13.166; $p < 0.05$), and pLNR4 = 4.897 (95% CI, 1.546–15.518; $p < 0.01$)

In all, 93(36%) patients with fewer than 12 LN examined. Comparison to patients with a total LN examined of 12 or more, no clinical differences were found in demographic information between these two subgroups (**Table 3**). Median tumor-free survival categorized according to pLNR for these two subgroups is shown (**Table 4**). Number of fewer than 12 lymph nodes retrieved did not affect tumor-free survival in this study. With respect to the subgroup of fewer than 12 LN were examined, pLNR but not N stage was found significantly associated with a risk of local recurrence or distant site metastases in a univariate (log–rank) test. As shown in **Table 5**, pLNR did not consistently demonstrate significantly negative impact on tumor-free survival for all range possible from insufficient numbers of patient in each range. However, this result showed that pLNR is the only significant factor for this subgroup.

Meanwhile, serum CEA, lymphovascular invasion, and cell differentiation were not found significantly associated with risk of local recurrence or distant site metastases in this subgroup.

Table 1. Clinicopathological features of patients (n = 258)

	Number of patients (%)
Age (mean □ SD = 61.4 □ 12.3)	
Gender	
Male	140 (54.3)
Female	118 (45.7)
Tumor location	
Colon	232 (89.9)
Rectum	26 (10.1)
Histological differentiation	
Well	24 (9.3)
Moderate	195 (75.6)
Poor	39 (15.1)
AJCC stage	
IIIA	110 (86.3)
IIIB	16 (13.7)
IIIC	96 (76.2)
Lymphovascular invasion	
No	137 (53.1)
Yes	121 (46.9)
Total number of lymph node retrieval	
Less than 12	93 (36)
12 or more	165 (64)
Recurrence (local/distant)	
No	135 (52.3)
Yes	123 (47.7)

Table 2. Univariate and multivariate analysis of risk factors for tumor-free survival (n = 258)

All cases	*p*	HR	95%CI	*p*	Adjusted HR	95%CI
pLNR range						
0.01–0.25		1			1	
0.26–0.50	<0.001	2.302	(1.509–3.512)	0.035	2.270	(1.058–4.875)
0.51–0.75	0.044	1.890	(1.017–3.511)	0.009	4.365	(1.447–13.166)
0.76–1.00	<0.001	6.087	(3.248–11.408)	0.007	4.897	(1.546–15.518)
AJCC stage						
3A		1			1	
3B	0.148	2.824	(0.693–11.51)	0.561	1.816	(0.243–13.596)
3C	0.004	7.968	(1.93–32.898)	0.356	2.714	(0.326–22.592)
Differentiation						
Well		1			1	
Moderate	0.266	0.718	(0.401–1.286)	0.678	0.791	(0.263–2.386)
Poor	0.588	0.819	(0.398–1.687)	0.358	0.520	(0.129–2.098)
Serum CEA						
<10 ng/dl		1			1	
≥10 ng/dl	0.012	2.043	(1.173–3.558)	0.293	1.414	(0.741–2.699)
LVI						
Negative		1			1	
Positive	0.089	1.366	(0.953–1.957)	0.613	0.845	(0.440–1.623)

Table 3. Patients' clinicopathological characteristics categorized according to number of LN examined (n = 258)

Variables	Number of patients (%)	
	<12 (n = 93)	≥12 (n = 165)
Age (mean)	62 (13.9)	61 (11.3)
Gender		
Male	50 (53.8)	90 (54.5)
Female	43 (46.2)	75 (45.5)
Recurrence (local/distant)		
No	47 (50.5)	88 (53.5)
Yes	46 (49.5)	77 (46.5)
Tumor location		
Colon	79 (84.9)	153 (92.7)
Rectum	14 (15.1)	12 (7.3)
Histological differentiation		
Well	4 (4.5)	21 (13)
Moderate	83 (93.3)	113 (82.1)
Poor	2 (2.2)	8 (4.9)
AJCC stage		
IIIA	6 (6.5)	6 (3.6)
IIIB	73 (78.5)	115 (69.7)
IIIC	14 (15)	74 (26.7)
Lymphovascular invasion		
No	51 (54.8)	70 (42.4)
Yes	42 (45.2)	95 (57.6)
Pathologically-based pLNR		
0.1–0.25	50 (53.8)	121 (73.3)
0.26–0.50	25 (26.9)	29 (17.6)
0.51–0.75	11 (11.8)	9 (5.5)
0.76–1.00	7 (7.5)	6 (3.6)

Table 4. Tumor-free survival categorized according to number of LN examined

Variables	Tumor Free Survival (months) median (95%CI)	
Number of LN examined	<12	≥12
Tumor-free survival	30 (17.0–42.9)	47 (33.0–60.9)
Histological differentiation		
Well	47 (0–106)	42 (0.76–83.2)
Moderate	30 (17.5–42.4)	47 (33.7–60.3)
Poor	8	77 (0–210.1)
AJCC stage		
IIIA	76 (16.5–170.4)	96 (56.4–135.6)
IIIB	33 (10.9–55.0)	68 (42.1–93.8)
IIIC	19 (14.3–23.6)	19 (12.0–25.9)
Lymphovascular invasion		
No	56 (25.2–86.8)	52 (26.9–77.0)
Yes	20 (16.2–23.7)	25 (0–53.2)
Pathologically-based pLNR		
0.1–0.25	47 (7.3–86.7)	67 (41.4–92.6)
0.26–0.50	22 (14.7–29.3)	22 (13.7–30.3)
0.51–0.75	16 (2.3–29.7)	48 (10.8–85.2)
0.76–1.00	21 (18.8–23.1)	6 (2.8–9.2)

Table 5. Univariate and multivariate analysis of risk factors for tumor-free survival in subgroup of patients that fewer than 12 LN were examined

LN <12	*p*	HR	95%CI	*p*	Adjusted HR	95%CI
pLNR range						
0.01–0.25		1			1	
0.26–0.50	0.039	2.02	(1.038–3.93)	0.158	2.759	(0.675–11.273)
0.51–0.75	0.035	2.411	(1.063–5.467)	0.007	10.552	(1.911–58.277)
0.76–1.00	0.009	3.388	(1.353–8.484)	0.153	4.293	(0.582–31.662)
AJCC stage						
3A		1			1	
3B	0.681	1.348	(0.324–5.605)	0.611	0.574	(0.068–4.875)
3C	0.154	2.975	(0.665–13.32)	0.36	0.289	(0.020–4.120)
Differentiation						
Well		1			1	
Moderate	0.816	0.845	(0.204–3.495)	0.271	0.276	(0.028–2.729)
Poor	0.811	1.212	(0.251–5.841)	0.171	0.127	(0.007–2.437)
Serum CEA		1			1	
<10 ng/dl	0.053	2.554	(0.989–6.594)	0.393	1.804	(0.466–6.986)
≥10 ng/dl						
LVI						
Negative		1			1	
Positive	0.170	1.484	(0.845–2.607)	0.439	1.603	(0.485–5.3)

Discussion

En bloc surgical removal of colon and lymph node bearing mesentery is the primary treatment of nonstage 4 colon cancer. For optimal tumor staging, completeness of specimen evaluation and adequate LN examination is crucial in assessment of the actual number of nodal metastases. However, LN retrieval and assessment is potentially influenced by many factors such as the specialty of surgeon, neoadjuvant radiotherapy and/or chemotherapy, and the technique of examination used by the pathologist [15]. Inadequate LN harvesting may represent the poor quality or less extensive surgical resection. This can result in underestimation of the actual number of regional LN metastases and decreases the likelihood of correct staging. The ratio of positive lymph node to total lymph node (pLNR) has been proposed as an alternative LN parameter instead of the total number of metastatic LNs in the conventional TNM staging for predicting long-term survival of patients with colon cancer after curative resection [10-13, 15]. The present study aimed to determine the actual prognostic value of pLNR on stage III colon cancer and only stage III rectal cancer patients who did not receive chemotherapy or radiation before underwent operation were eligible to participate in this study.

This study found pLNR was an independent factor that is significantly associated with the risk of local recurrence and/or distant site metastases irrespective of the number of LN retrievals. This finding supports the study of Klos et al. [14] that proposed LN ratios as a better staging method than absolute positive LN counts. The present study also evaluated the prognostic value of various clinicopathological factors in concordance with pLNR. Although several factors influenced tumor-free survival e.g. serum CEA > 10 ng/ml, AJCC tumor stage 3C, and higher pLNR, pLNR was found to be a solely independent predictor of tumor-free survival while others could not be achieved with multivariate analysis.

A previous study [16] analyzed over 60,000 stage II and stage III colon cancer patients and found a positive association between the increasing number of LN retrieved and survival. In 2000, the College of American Pathologists consensus stated a minimum harvest of 12 LN was an optimal number for adequate staging [3, 4]. As reviewed by Baxter et al. [17], the authors reported that only 37% of all patients received adequate LN evaluation based on data from the Surveillance, Epidemiology, and End Results (SEER) cancer registry. The study found advanced tumor stage, younger, right-sided cancers, and geographical location was significantly associated with adequate lymph node evaluation.

Nevertheless, fewer LN retrieval numbers could be a consequence of poor-quality surgical technique that enhances the risk of local recurrence/distant site metastasis. For technical qualification, all operations were performed or supervised by four board-certified colon and rectal surgeons in the Division of Coloproctology. Sixty-four percent of patients were able to achieve adequate numbers of LN retrieval in our study.

The extent of lymphadenectomy or total number of harvested nodes did not appear to affect the prognostic value of pLNR in our study, similar to the review study [11]. The authors reported 9,610 patients who had fewer than 10 LN examined and the group found a significant difference in survival comparison between LNR2 and LNR4 [11]. Our study found pLNR had a negative impact on survival in the entire cohort and subgroup of patients who had fewer than 12 LN examined.

Limitations of our study are that the pLNR represents the combination of the prognostic significances of the absolute number of metastatic nodes and the total number of retrieved nodes. These two factors depend on not only the quality of surgery, but also the quality of the pathological evaluation. Insufficient sample size for each pLNR range in the subgroup of patients who had fewer than 12 LN examined to consistently demonstrate significantly negative impact on tumor-free survival for all pLNR range. Moreover, cases with rectal cancer comprised only 10% of the entire subjects in our study. As a result, the majority of patients with rectal cancer were excluded since preoperative chemoradiation became the preferred approach in our institution. This may not have allowed a sufficient sample size to yield a sufficient power in extrapolating the results to patients with rectal cancer. Further study with larger samples of rectal cancer is required, even though results of this study revealed that pLNR provided prognostic value irrespective of lymph node retrieval number and would be helpful in optimizing the process of future tumor staging especially cases with inadequate number of lymph nodes retrieval.

The authors declare no conflict of interests in this study.

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