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Prognostic Significance of the Lymph Node Ratio Regarding Recurrence and Survival in Rectal Cancer Patients Treated with Postoperative Chemoradiotherapy

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Background/Aims: To evaluate the prognostic impact of the lymph node ratio (LNR: the ratio of positive lymph nodes to the total number of lymph nodes examined) on disease recurrence and survival among rectal cancer patients who received curative surgery and postoperative chemoradiotherapy (CRT). **Methods:** Between 1995 and 2008, 124 patients with pathologic T3-4 or node-positive rectal cancer underwent curative surgery and postoperative CRT. Postoperative radiotherapy was delivered at a median dose of 50.4 Gy (range, 45 to 59.4 Gy) for 6 weeks. Chemotherapy consisted of a bolus injection of 5-fluorouracil and leucovorin in the first and last week of radiotherapy (91.9%) or daily capecitabine during radiotherapy (8.1%). Further adjuvant chemotherapy was administered after chemoradiation. **Results:** The median follow-up was 5.1 years. In the multivariate analysis, pathologic N (pN) stage and lymphovascular invasion were significantly associated with disease-free survival and disease-specific survival ($p<0.05$). However, when the LNR with a cutoff value of 0.2 was included as a covariate in the model, the LNR was highly significant ($p<0.001$), and the pN stage lost its significance ($p>0.05$). **Conclusions:** The LNR predicts recurrence and survival more accurately than pN stage. The pN stage and the LNR should be considered together when estimating the risk of disease recurrence among rectal cancer patients. **(Gut Liver 2012;6:203-209)**

Key Words: Rectal neoplasms; Lymph nodes; Combined modality therapy

INTRODUCTION

Colorectal cancer is the third most frequently diagnosed cancer in Korea[1] and it has been continuously increasing over the past two decades with similar trends in the West.[2] In locally advanced rectal cancer, curative surgery with neoadjuvant or adjuvant chemoradiotherapy (CRT) became standard treatment in most clinical institutes. Recent advances that improved the outcome of rectal cancer include radical surgical technique incorporating total mesorectal excision (TME), CRT and biologic therapy.[3] It has not been clearly demonstrated if intensification of CRT by adding other chemotherapeutic agents to 5-fluorouracil (5-FU) and leucovorin (LV) regimens or by dose escalation of pelvic radiotherapy to more than 45-50 Gy will improve treatment outcome or survival with the price of increased treatment related toxicities.[4,5] Therefore, it is important to determine the clinical and pathological factors to predict poor prognosis of rectal cancer and define patient subgroups who will benefit from intensified therapy.

Lymph node (LN) involvement and the number of involved regional nodes are among the most important prognostic factors in rectal cancer. LN ratio (LNR), which is defined as the number of positive LNs divided by the total number of LNs examined, was introduced as a significant predictor for survival in other malignancies.[6-9] However, the evidence is still limited in rectal cancer. In the postoperative adjuvant setting, pathologic stage is not affected, thus staging is accurate, particularly nodal status. In this study, the prognostic impact of LNR-based classification was evaluated together with other clinical prognostic factors, to determine if it could improve prognostic information when compared with the number of positive LNs for rectal cancer patients who received curative resection and postoperative CRT.

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MATERIALS AND METHODS

1. Patients and pretreatment evaluation

Between 1995 and 2008, a total of 152 rectal cancer patients underwent curative surgery and postoperative radiotherapy. Among them, 28 patients were excluded from this study (19 had local excision, 6 were lost to follow-up, 3 received radiotherapy alone). The remaining 124 patients were included in the analysis. All patients had primary rectal cancer of adenocarcinoma. To establish the diagnosis and determine staging, patients underwent pre-operative investigations, including digital rectal examination, complete blood cell count, liver function analysis, serum carcinoembryonic antigen, colonoscopy with biopsy, computed tomography (CT) of the abdomen and pelvis and bone scan. Chest CT, magnetic resonance imaging of the pelvis or liver, and F-18 deoxyfluoroglucose positron emission tomography were performed when required.

2. Treatment

All patients underwent surgery with curative intent by five colorectal surgeons. TME was performed in all patients. Surgery included low anterior resection or abdominoperineal resection (APR) without lateral pelvic node dissection. The pathologic stage was determined according to the sixth edition of the American Joint Committee on Cancer (AJCC) staging manual.[10]

Adjuvant CRT was scheduled for 4-8 weeks after surgery (me-

Table 1. Clinical and Pathologic Features of the Patients

Characteristic	No. of patients	%	Characteristic	No. of patients	%
Age, yr			Pathologic N stage		
Median	62 (range, 21-80)		N0	51	41.1
<60	58	46.8	N1	35	28.2
≥60	66	53.2	N2	38	30.6
Gender			LN examined		
Male	79	63.7	Median	18 (range, 6-81)	
Female	45	36.3	<12	34	27.4
Distance from anal verge			≥12	88	71.0
Median	5		Missing	2	1.6
≥8	38	30.6	Lymphovascular invasion		
≥5, <8	29	23.4	Yes	55	44.4
≥0, <5	49	39.5	No	69	55.6
Missing	8	6.5	Perineural invasion		
Type of surgery			Yes	35	28.2
LAR	72	58.1	No	89	71.8
APR	47	37.9	Margin status		
Others	5	4.0	Positive	8	6.5
Differentiation			Close	15	12.1
Well	12	9.7	Negative	101	81.5
Moderate	107	86.3	CEA, ng/mL		
Poorly	5	4.0	>5	26	21.0
Pathologic T stage			≥0, ≤5	71	57.3
T1	1	0.8	Missing	27	21.7
T2	9	7.3			
T3	103	83.1			
T4	11	8.9			
Tumor size, cm					
Median	5 (range, 1.5-15)				
≤5	63	50.8			
>5	51	41.1			
Missing	10	8.1			

LAR, low anterior resection; APR, abdominoperineal resection; LN, lymph node; CEA, carcinoembryonic antigen.

dian 77 days; range, 30 to 134 days). Postoperative radiotherapy was delivered to the whole pelvis at a median dose of 50.4 Gy (range, 45 to 59.4 Gy) for 6 weeks. Chemotherapy included bolus injection of 5-FU and LV for the first and last week of radiotherapy (n=114, 91.9%) or capecitabine administered daily during radiotherapy (n=10, 8.1%). Further adjuvant chemotherapy (5-FU and LV) was administered after CRT. A total of 6 cycles of chemotherapy was administered to 121 patients (97.6%). Written informed consent was obtained from all patients before treatment. Catholic Medical Center Central Instituional Review Board approved the conduct of this retrospective study.

3. Follow-up and response evaluation

Clinicians evaluated the patients weekly during treatment by physical examination and the appropriate blood tests. The patients presented for follow-up after 2 weeks and then 1, 2, 3, and 6 months after CRT, and then twice per year until 2 years post-surgery. After 2 years, patients were followed up annually until 5 years post-surgery.

Treatment outcomes were evaluated as follows. Local failure was defined as any recurrence in the pelvic radiation field, and distant metastasis as outside the radiation field. Disease-free survival (DFS) was calculated from the end of treatment to the time of local or distant failure. The survival end event was defined as death from rectal cancer. Disease-specific survival (DSS) was censored at the time of death from rectal cancer or at the end of follow-up.

4. Statistical analysis

The probability of survival was calculated using the Kaplan-Meier method. To evaluate parameters predictive of survival, univariate analysis was performed by comparing survival rates using the log-rank test. After ascertaining that the LNR was significantly associated with DFS and DSS, various LNR cutoffs were evaluated, ranging from 0.05 to 0.95 at intervals of 0.05. We selected cutoff points by the minimum p-value approach, at which the most significant difference in DFS and DSS was observed.

Variables which attained univariate statistical significance were further assessed in multivariate analyses using Cox's proportional hazard model to analyze correlations between various parameters and survival probability. The prognostic significance of the LNR was evaluated by multivariate analysis with and without LNR as covariate. Statistical tests were 2-sided and performed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA). A p-value of less than 0.05 was considered statistically significant.

RESULTS

The study cohort was comprised of 79 males and 45 females. The median age was 62 years (range, 21 to 80 years). The median number of LNs removed was 18 (range, 6 to 81). Patient characteristics are summarized in Table 1. By the minimum p-value approach, 0.2 was deemed the cutoff value of LNR at which the most significant difference in DFS and DSS was observed. Patients were classified into three groups: patients who were LN negative, those with LNR more than 0 and less than 0.2, and those with LNR of 0.2 or greater.

1. Pattern of failure and survival

Median follow-up duration was 5.1 years (range, 0.4 to 16.0 years). Overall, local recurrence developed in 17 patients (13.7%). Distant metastases occurred in 35 patients (27.4%). The site of distant failure was as follows: liver, 13 patients; lung, 11 patients; para-aortic LN, 7 patients; peritoneal carcinomatosis, 4 patients. At the time of analysis, 46 patients had died and 78 patients were alive. Among 46 deaths, 36 patients died of rectal cancer and 10 died of other causes, including cardiac conditions and lung cancer. The corresponding Kaplan-Meier estimates (±standard error) for 5-year DFS and DSS rate was 68.0±4.3%

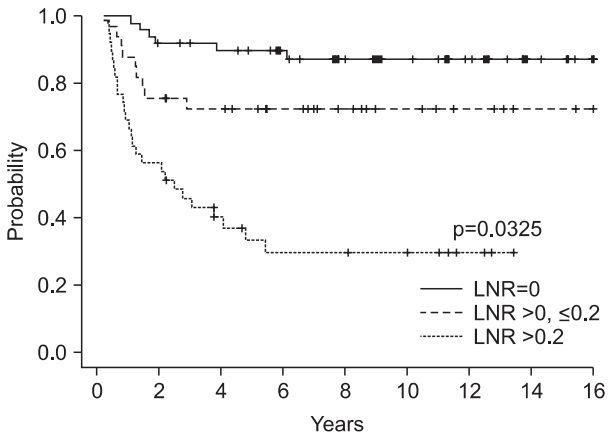

Fig. 1. The disease-free survival (DFS) curve according to the groups by lymph node ratio (LNR). The 5-year DFS rates were 89.9±4.3%, 72.5±7.8%, and 33.4±8.0% with increasing LNRs (p=0.0325).

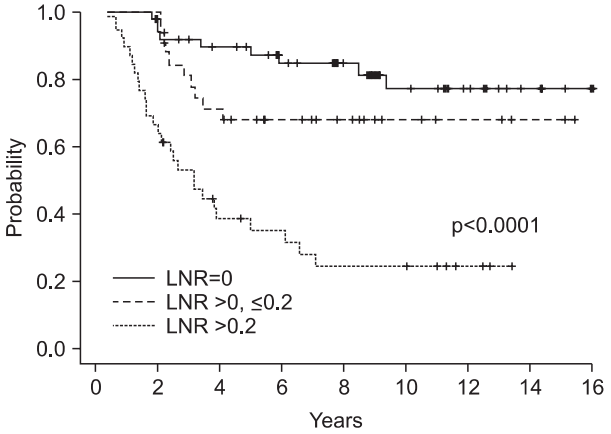

Fig. 2. The disease-specific survival (DSS) curve according to the groups by lymph node ratio (LNR). The 5-year DSS rates were 87.4±4.8%, 68.1±8.3%, and 35.3±8.1% with increasing LNRs (p<0.001).

and 66.4±4.4%, respectively. Five-year overall survival (OS) rate was 66.5±4.4%.

2. Analysis of prognostic factors for survival

Pathologic N (pN) stage, lymphovascular invasion, perineural invasion, and LNR-based classification achieved statistical significance in univariate analysis for DFS and DSS. The DFS and DSS curves according LNR groups are shown in Figs 1 and 2, respectively. The 5-year DFS rate was 89.9±4.3%, 72.5±7.8%, and 33.4±8.0% with increasing LNRs (p=0.0325). The 5-year DSS rate was 87.4±4.8%, 68.1±8.3%, and 35.3±8.1% with increasing LNRs (p<0.001) (Table 2).

Cox regression analysis was performed to evaluate whether the LNR was associated with DFS and DSS. The results of multivariate analyses are presented in Table 3. pN stage and lymphovascular invasion were significant prognostic factors when the LNR was not included in the analysis. However, when the LNR-based classification was included in the model as a covariate, LNR was highly significant (LNR=0, hazard ratio [HR], 1; LNR <0.2, HR, 1.818, confidence interval [CI], 0.619 to 5.339, p=0.277; LNR ≥0.2, HR, 5.438, CI, 2.083 to 14.429, p=0.001 for DFS and LNR=0, HR, 1; LNR <0.2, HR, 1.295, CI, 0.504 to 3.325, p=0.591; LNR ≥0.2, HR, 4.115, CI, 1.807 to 9.373, p=0.001 for DSS, respectively). Thus, pN stage lost its significance (p>0.05)

Table 2. The 5-Year Kaplan-Meier Values for DFS and DSS according to Prognostic Factor

Characteristic	No. of patients	5-yr DFS, %±SE	5-yr DSS, %±SE	Characteristic	No. of patients	5-yr DFS, %±SE	5-yr DSS, %±SE
Age				Pathologic N stage			
<60	58	68.5±0.1	71.8±6.0	N0	51	90.1±4.2	87.7±4.7
±60	66	67.7±0.1	61.5±6.2	N1	35	67.6±8.1	69.2±8.1
		p=0.8832	p=0.4367	N2	38	38.5±8.1	34.8±8.0
Gender						p<0.0001	p<0.0001
Male	79	67.8±0.1	68.5±5.4	LN examined			
Female	45	68.6±0.1	62.9±7.4	<12	34	67.2±8.1	79.3±6.9
		p=0.7727	p=0.3113	≥12	88	68.6±4.9	61.4±5.3
Distance from anal verge						p=0.7611	p=0.5117
≥8	38	62.5±8.0	66.7±7.9	LNR			
≥5, <8	29	68.6±8.7	59.7±9.6	0	50	89.9±4.3	87.4±4.8
≥0, <5	49	67.2±6.7	67.2±6.7	>0, <0.2	33	72.5±7.8	68.1±8.3
		p=0.6961	p=0.7062	≥0.2	39	33.4±8.0	35.3±8.1
Type of surgery						p=0.0325	p<0.0001
LAR	72	71.8±5.4	67.5±5.8	Lymphovascular invasion			
APR	47	65.8±6.9	68.1±6.8	Yes	55	45.7±6.9	44.7±7.0
Others	5	40.0±22.0	40.0±22.0	No	69	85.4±4.3	83.2±4.6
		p=0.2333	p=0.4442			p<0.0001	p<0.0001
Differentiation				Perineural invasion			
Well	12	91.7±8.0	90.0±9.5	Yes	35	48.0±8.6	47.1±8.6
Moderate	107	66.6±4.6	64.7±4.8	No	89	75.8±4.6	73.9±4.8
Poorly	5	40.0±22.0	20.0±17.9			p=0.0002	p=0.0004
		p=0.1979	p=0.0945	Circumferential margin status			
Pathologic T stage				Positive	8	62.5±17.1	50.0±17.7
T1-2	10	90.0±9.5	90.0±9.5	Close	15	80.0±10.3	79.0±10.8
T3-4	114	66.1±4.5	64.4±4.6	Negative	101	66.8±4.7	66.1±4.8
		p=0.1509	p=0.1094			p=0.7516	p=0.8360
Tumor size, cm							
≤5	63	67.1±6.1	67.7±6.2				
>5	51	66.5±6.6	64.3±6.8				
		p=0.7538	p=0.6507				

DFS, disease-free survival; SE, standard error; DSS, disease-specific survival; LAR, low anterior resection; APR, abdominoperineal resection; LN, lymph node; LNR, lymph node ratio.

Table 3. Multivariate Analysis of the Prognostic Factors for DFS and DSS

Variable	Without LNR as a covariate				With LNR as a covariate			
	DFS		DSS		DFS		DSS	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
LVI								
No	1		1		1		1	
Yes	2.934 (1.391-6.190)	0.005	3.053 (1.544-6.037)	0.001	2.686 (1.265-5.703)	0.010	2.833 (1.425-5.636)	0.003
PNI								
Negative	1		1		1		1	
Positive	1.556 (0.783-3.091)	0.207	1.459 (0.752-2.830)	0.264	1.610 (0.828-3.129)	0.160	1.523 (0.808-2.874)	0.194
Pathologic N								
N0	1		1		1		1	
N1	2.234 (0.800-6.244)	0.125	1.434 (0.577-3.563)	0.438	1.808 (0.608-5.376)	0.287	1.234 (0.469-3.247)	0.670
N2	4.895 (1.853-12.930)	0.001	3.938 (1.728-8.975)	0.001	2.059 (0.574-7.378)	0.268	1.938 (0.632-5.936)	0.247
LNR								
0					1		1	
>0, <0.2					1.818 (0.619-5.339)	0.277	1.295 (0.504-3.325)	0.591
≥0.2					5.483 (2.083-14.429)	0.001	4.115 (1.807-9.373)	0.001

LNR, lymph node ratio; DFS, disease-free survival; DSS, disease-specific survival; HR, hazard ratio; CI, confidence interval; LVI, lymphovascular invasion; PNI, perineural invasion.

on multivariate analysis. This means that LNR is a more significant prognostic factor than the absolute number of nodes in the present analysis.

We performed the survival analysis based on the LNR in patients with stage III. The LNR had a prognostic impact on DFS and DSS in patients with stage III (p=0.0012 and p=0.0005, respectively). The survival outcome was analyzed by the LNR in each pN stage. The LNR had a prognostic significance on the DFS in patients with pN1. However, for the patients with pN2, the LNR was not associated with the survival. It might be attributed to that the group with pN2 and the LNR <0.2 consisted of only 5 patients. The results of above analyses were presented in Table 4.

Table 4. DFS and DSS Rates Indicated by the LNR in Patients with Stage III Cancer

Stage III	No. of patients		Kaplan-Meier estimates, %±SE	
			5-yr DFS	5-yr DSS
All patients		LNR		
	33	>0, <0.2	72.5±7.8	68.1±8.3
	39	≥0.2	33.5±8.0	35.3±8.1
		p-value	0.0012	0.0005
pN1		LNR		
	28	>0, <0.2	74.6±8.3	69.5±9.0
	6	≥0.2	33.3±19.3	62.5±21.4
		p-value	0.0128	0.0883
pN2		LNR		
	5	>0, <0.2	60.0±22.0	60.0±22.0
	33	≥0.2	34.9±8.6	30.5±8.5
		p-value	0.3564	0.1827

SE, standard error; DFS, disease-free survival; DSS, disease-specific survival; LNR, lymph node ratio; pN, pathologic N stage.

3. Adverse events related to treatment

Acute treatment-related toxicities are summarized in Table 5. Diarrhea and radiation dermatitis were most frequently observed. No treatment related death was observed. Late toxicity developed in 14 patients (11.3%). Among them, 10 patients experienced adhesive ileus. Four patients required surgical treatment for adhesiolysis and 6 patients recovered after conservative care. Chronic rectal spotting was observed in 1 patient and it was diagnosed as radiation proctitis by colonoscopy. Skin necrosis developed along the perineal scar in 1 patient who needed flap surgery. Enterovaginal fistula was observed in 1 patient who developed vaginal invaded rectal mass and had partial vaginectomy with the initial surgery. She recovered after

Table 5. Treatment-Related Acute Toxicity according to the Radiation Therapy Oncology Group Acute Radiation Morbidity Scoring Scheme

	Grade			
	1	2	3	4
Hematologic	0	2	0	0
Hemoglobin				
Leukocytes	2	18	2	0
Platelets	0	0	0	1
Nausea/Vomiting	12	2	0	0
Gastrointestinal	21	17	3	1
Skin	11	31	6	0
Urinary	0	1	0	0
Liver	0	1	0	0

surgical repair of the fistula.

DISCUSSION

The most widely used staging system for colorectal cancer is the AJCC tumor, nodes, metastasis (TNM) classification system, which classifies patients into prognostic groups according to the depth of the primary tumor, presence of regional LN metastases, and evidence of distant metastases. Recently, the AJCC TNM stage was updated and the T and N stages were further specified to improve prognostic capacity. More emphasis has been made to the number of retrieved malignant LNs. Accordingly, pN1 (metastasis in 1 to 3 regional LNs) has been subdivided into pN1a (metastasis in 1 regional LN) and pN1b (metastasis in 2 to 3 regional LNs), and pN2 (metastasis in 4 or more regional LNs) has been subdivided into pN2a (metastasis in 4 to 6 regional LNs) and pN2b (metastasis in 7 or more regional LNs).[11]

However, the number of malignant LNs in rectal cancer depends on the number of retrieved LNs, which varies with treatment, patient, and tumor characteristics. There is, in practice, wide variation in the surgical extent and LN examination. The median LN yield varies from 3.5 to 17 between different pathology laboratories and individual pathologists according to the Dutch TME trial.[12] Neoadjuvant therapy before surgery, APR operation, tumor location in the lower rectum, small tumor size, old age, and obesity have been reported to be associated with lower LN yield.[12,13]

In rectal cancer, the minimum number of nodes to be resected and histopathologically assessed for accurate staging is considered between 10 and 14.[11] However, there is a tendency for higher number of retrieved nodes to be associated with increased incidence of nodal positivity. As was demonstrated in the study of node examination techniques, the fat-clearance technique enables upstaging of more than 50% of stage II cases to stage III, by allowing the identification and examination of previously undetected LNs.[14] Therefore, there is a potential for stage migration when an inadequate number of LNs is harvested. Patients with inadequate LN dissection could receive less efficient adjuvant treatment and it may result in inferior treatment outcome. The analysis of Mekenkamp *et al*.[12] supports this hypothesis that node negative patients in whom seven or less LNs were examined had lower recurrence free interval than patients in whom at least 8 LNs were examined (17% vs 10.7%; p=0.016).

The LNR, which takes into account the extent of LN dissection, has been investigated in other malignancies previously. From the Surveillance, Epidemiology, and End Results (SEER) population data, the importance of LNR has been shown at many cancer sites, including the esophagus,[7] stomach,[15] and corpus uteri.[8] In breast cancer, Vinh-Hung *et al*.[6] suggested that the LNR should be considered an alternative to pN staging because of stronger statistical power to predict breast cancer-specific survival from patient analysis of the Geneva Cancer Registry.[6] Similarly, several studies investigated the LNR in colorectal cancer. Rosenberg *et al*.[16] analyzed 3,026 patients with colorectal cancer at a single surgical center over a 25-year period. The optimal cut-off values for prognostic differentiation of LNRs were statistically calculated as 0.17, 0.41, and 0.69. The 5-year OS was 60.6%, 34.4%, 17.6%, and 5.3% with increasing LNRs (p<0.001). The LNR had better prognostic value than pN category (p<0.05).[16] These cut-off values (0.17, 0.41, and 0.69) were further investigated in a large population based collective of patients with colorectal cancer (n=27,803). The LNR was shown to be a strong independent prognostic factor again.[17] Kim *et al*.[18] investigated the impact of LNR in 232 rectal cancer patients who received postoperative CRT to determine if this ratio is useful for the assessment of prognosis in rectal cancer as in colon cancer. Patients were grouped as LNR ≤0.1, LNR ≤0.2, LNR ≤0.4 and LNR >0.4. The 5-year survival rate significantly decreased as the LNR increased (p<0.001). The LNR was a significant prognostic factor for OS on Cox regression analysis.[18]

Performing preoperative CRT before curative resection has the oncologic advantage of reduced local recurrence although it did not improve OS.[19] However, the total number of retrieved LNs may decrease or the proportion of patients with fewer than 12 LNs examined may increase after preoperative CRT. Peschaud *et al*.[20] investigated the utility of LNR in 307 rectal cancer patients who received neoadjuvant therapy by dividing them into 4 groups; LNR=0, LNR=0.01 to 0.07, LNR >0.07 to 0.2, and LNR >0.2. In the multivariate analysis, LNR was the most significant prognostic factor for both DFS (p=0.006) and OS (p=0.0003), whereas presence and absence of metastatic LNs was not. LNR remained a significant prognostic factor in patients whom fewer than 12 LNs were examined (p=0.0058).[20]

The LNR was investigated even in node negative colorectal cancer by Oh *et al*.[21] Immunohistochemical staining with anti-cytokeratin antibody panel can detect LN micrometastasis in node negative cases. This method detected micrometastasis in

26.6% of node negative patients by hematoxylin-eosin staining. The micrometastasis LNR (mmLNR) was calculated by dividing the number of LNs in which LN micrometastasis was detected by the total number of resected LNs. mmLNR greater than 0.25 was significantly associated with low 3-year DFS (p=0.03).[21]

The present study has the shortcomings of a retrospective analysis with small patient sample size. However, the number of retrieved LNs (median 18) was sufficient to evaluate the prognostic value of LNRs in rectal cancer patients, although 47 patients (37.9%) underwent APR which could have reduced LN yield. Moreover, this study can be differentiated from other studies that the significance of the LNR was analyzed with the DSS which could predict the association of the variable and the survival outcome more exactly from the viewpoint of rectal cancer. The impact of LNRs on recurrence and survival of rectal cancer has been confirmed again in this study. To assess the prognosis and to make informed decisions about further treatment, accurate staging information is very important for both patients and clinicians. Although there is no clear consensus on the optimal cutoff points for LNRs required for staging classification, the potential advantages of LNRs in the staging system as an additive or alternative to the absolute number of positive LNs need to be investigated in large prospective studies.

CONFLICTS OF INTEREST

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

REFERENCES

1. Jung KW, Park S, Kong HJ, et al. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2008. Cancer Res Treat 2011;43:1-11.
2. Kwon JH, Choi MG, Lee SW, et al. Trends of gastrointestinal diseases at a single institution in Korea over the past two decades. Gut Liver 2009;3:252-258.
3. Enker WE, Thaler HT, Cranor ML, Polyak T. Total mesorectal excision in the operative treatment of carcinoma of the rectum. J Am Coll Surg 1995;181:335-346.
4. Sebag-Montefiore D, Glynne-Jones R, Falk S, Meadows HM, Maughan T. A phase I/II study of oxaliplatin when added to 5-fluorouracil and leucovorin and pelvic radiation in locally advanced rectal cancer: a Colorectal Clinical Oncology Group (CCOG) study. Br J Cancer 2005;93:993-998.
5. Pfeiffer P. High-dose radiotherapy and concurrent UFT plus l-leucovorin in locally advanced rectal cancer: a phase I trial. Acta Oncol 2005;44:224-229.
6. Vinh-Hung V, Verkooijen HM, Fioretta G, et al. Lymph node ratio as an alternative to pN staging in node-positive breast cancer. J Clin Oncol 2009;27:1062-1068.
7. Greenstein AJ, Litle VR, Swanson SJ, Divino CM, Packer S, Wisnivesky JP. Prognostic significance of the number of lymph node metastases in esophageal cancer. J Am Coll Surg 2008;206:239-246.
8. Chan JK, Kapp DS, Cheung MK, et al. The impact of the absolute number and ratio of positive lymph nodes on survival of endometrioid uterine cancer patients. Br J Cancer 2007;97:605-611.
9. De Ridder M, Vinh-Hung V, Van Nieuwenhove Y, Hoorens A, Sermeus A, Storme G. Prognostic value of the lymph node ratio in node positive colon cancer. Gut 2006;55:1681.
10. Greene FL, Page DL, Fleming ID, et al. AJCC Cancer Staging Manual. 6th ed. New York: Springer-Verlag, 2002:113-119.
11. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC Cancer Staging Manual. 7th ed. New York: Springer, 2009:143-159.
12. 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 the pathologist. Am J Surg Pathol 2009;33:1547-1553.
13. Thorn CC, Woodcock NP, Scott N, Verbeke C, Scott SB, Ambrose NS. What factors affect lymph node yield in surgery for rectal cancer? Colorectal Dis 2004;6:356-361.
14. Hermanek P, Giedl J, Dworak O. Two programmes for examination of regional lymph nodes in colorectal carcinoma with regard to the new pN classification. Pathol Res Pract 1989;185:867-873.
15. Inoue K, Nakane Y, Iiyama H, et al. The superiority of ratio-based lymph node staging in gastric carcinoma. Ann Surg Oncol 2002;9:27-34.
16. Rosenberg R, Friederichs J, Schuster T, et al. Prognosis of patients with colorectal cancer is associated with lymph node ratio: a single-center analysis of 3,026 patients over a 25-year time period. Ann Surg 2008;248:968-978.
17. Rosenberg R, Engel J, Bruns C, et al. The prognostic value of lymph node ratio in a population-based collective of colorectal cancer patients. Ann Surg 2010;251:1070-1078.
18. Kim YS, Kim JH, Yoon SM, et al. lymph node ratio as a prognostic factor in patients with stage III rectal cancer treated with total mesorectal excision followed by chemoradiotherapy. Int J Radiat Oncol Biol Phys 2009;74:796-802.
19. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731-1740.
20. Peschaud F, Benoist S, Julié C, et al. The ratio of metastatic to examined lymph nodes is a powerful independent prognostic factor in rectal cancer. Ann Surg 2008;248:1067-1073.
21. Oh TY, Moon SM, Shin US, Lee HR, Park SH. Impact on prognosis of lymph node micrometastasis and isolated tumor cells in stage II colorectal cancer. J Korean Soc Coloproctol 2011;27:71-77.