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

Ji-Yoon Kim*, Su-Mi Chung*, Byung-Ock Choi*, In-Kyu Lee†, Chang-Hyeok An†, Jong-Man Won†, and Mi-Ryeong Ryu*

Departments of *Radiation Oncology and †General Surgery, The Catholic University of Korea College of Medicine, Seoul, Korea

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.

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

INTRODUCTION

Colorectal cancer is the third most frequently diagnosed cancer in Korea and it has been continuously increasing over the past two decades with similar trends in the West. 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. 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. 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. 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.
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-

| 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) | 71.0 |
| Female        | 45              | 36.3 | <12            | 34             | 27.4 |
| Distance from anal verge | |    | ≥12            | 88             | 71.0 |
| Median        | 5               | 30.6 | Lymphovascular invasion |                |    |
| ≥8            | 38              | 30.6 | Yes            | 55             | 44.4 |
| ≥5, <8        | 29              | 23.4 | No             | 69             | 55.6 |
| ≥0, <5        | 49              | 39.5 | Missing        | 2              | 1.6 |
| 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  | Close          | 15             | 12.1 |
| Differentiation |             |    | Negative       | 101            | 81.5 |
| Well          | 12              | 9.7  | CEA, ng/mL     |                |    |
| Moderate      | 107             | 86.3 | >5             | 26             | 21.0 |
| Poorly        | 5               | 4.0  | ≤5             | 71             | 57.3 |
| Pathologic T stage |          |    | Missing        | 27             | 21.7 |
| T1            | 1               | 0.8  |                 |                |    |
| 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 Institutional 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).](image1)

![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).](image2)
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       | 87.4±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       | ≤12                       | 34              | 67.2±8.1       | 79.3±6.9       |
| Female                    | 45              | 68.6±0.1       | 62.9±7.4       | ≥12                       | 88              | 68.6±4.9       | 61.4±5.3       |
|                           |                 | p=0.7727       | p=0.3111       |                           | p=0.7611        | p=0.5117       |                |
| Distance from anal verge  |                 |                |                | LNR                       |                 |                |                |
| ≥8                        | 38              | 62.5±8.0       | 66.7±7.9       |                           | 38              | 62.5±8.0       | 66.7±7.9       |
| ≥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       |
|                           | p=0.0325        | p=0.0001       |                |                           |                 |                |                |
| Type of surgery           |                 |                |                | Lymphovascular invasion   |                 |                |                |
| LAR                       | 72              | 71.8±5.4       | 67.5±5.8       |                           | 55              | 45.7±6.9       | 44.7±7.0       |
| APR                       | 47              | 65.8±6.9       | 68.1±6.8       | Yes                       | 69              | 85.4±4.3       | 83.2±4.6       |
| Others                    | 5               | 40.0±22.0      | 40.0±22.0      | No                        | 5               | 40.0±22.0      | 40.0±22.0      |
|                           |                 | 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       |                           | 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       |                           |                 |                |                |
| Pathologic T stage        |                 |                |                | Circumferential margin status |             |                |                |
| T1-2                      | 10              | 90.0±9.5       | 90.0±9.5       | Positive                  | 8               | 62.5±17.1      | 50.0±17.7      |
| T3-4                      | 114             | 66.1±4.5       | 64.4±4.6       | Close                     | 15              | 80.0±10.3      | 79.0±10.8      |
|                           |                 | p=0.1509       | p=0.1094       | Negative                  | 101             | 66.8±4.7       | 66.1±4.8       |
|                           |                 | p=0.7516       | p=0.8360       |                           |                 |                |                |
| Tumor size, cm            |                 |                |                |                           |                 |                |                |
| ≤5                        | 63              | 67.1±6.1       | 67.7±6.2       |                           | 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.
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 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       | 2.934 (1.391-6.190)         | 0.005                   | 2.686 (1.265-5.703)      | 0.010                   |
| Yes      | 3.053 (1.544-6.037)         | 0.001                   | 2.833 (1.425-5.636)      | 0.003                   |
| PNI      |                             |                         |                         |                         |
| Negative | 1.556 (0.783-3.091)         | 0.207                   | 1.610 (0.828-3.129)      | 0.160                   |
| Positive | 1.459 (0.752-2.830)         | 0.264                   | 1.523 (0.808-2.874)      | 0.194                   |
| Pathologic N |                      |                         |                         |                         |
| N0       | 1                           | 1                       | 1                        | 1                       |
| N1       | 2.234 (0.800-6.244)         | 0.125                   | 1.808 (0.608-5.376)      | 0.287                   |
| N2       | 4.895 (1.853-12.930)        | 0.001                   | 2.059 (0.574-7.378)      | 0.268                   |
| LNR      |                             |                         |                         |                         |
| 0        | 1                           | 1                       | 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.

### 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
considered between 10 and 14.

sected and histopathologically assessed for accurate staging is
Dutch TME trial.

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median LN yield varies from 3.5 to 17 between different pathol-
wide variation in the surgical extent and LN examination. The
pends on the number of retrieved LNs, which varies with treat-

LNs) and pN2b (metastasis in 7 or more regional LNs).

has been subdivided into pN2a (metastasis in 4 to 6 regional
LNs), and pN2 (metastasis in 4 or more regional LNs)

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).13

However, the number of malignant LNs in rectal cancer de-
pends on the number of retrieved LNs, which varies with treat-
ment, 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 pathol-
gy 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 re-
sected and histopathologically assessed for accurate staging is
considered between 10 and 14.13 However, there is a tendency
for higher number of retrieved nodes to be associated with in-
creased 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 har-
vested. 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 dissec-
tion, 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,5 stomach,7 and
corpus uteri.6 In breast cancer, Vinh-Hung et al.5 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.5 Similarly, several studies investigated the LNR in
colorectal cancer. Rosenberg et al.14 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 collect-
cive 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 sig-
nificant 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.19 investigated the utility of LNR in 307 rectal cancer pa-
tients 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

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,
evidence of distant metastases. Recently, the AJCC TNM
stage was updated and the T and N stages were further speci-
fied 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).13

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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

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

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

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