Prognostic Impact of Lymph Node Ratio in Patients Undergoing Preoperative Chemoradiotherapy Followed by Curative Resection for Locally Advanced Rectal Cancer

WONGUEN JUNG¹, KYUBO KIM¹, JIYOUNG KIM¹ and SU JUNG SHIM²

¹Department of Radiation Oncology, Ewha Womans University College of Medicine, Seoul, Republic of Korea; ²Department of Radiation Oncology, Eulji Hospital, Eulji University School of Medicine, Seoul, Republic of Korea

Abstract. Background/Aim: To analyze the prognostic significance of nodal status in patients undergoing preoperative chemoradiotherapy (CRT) followed by curative resection for locally advanced rectal cancer. Patients and Methods: Between 2000 and 2015, 80 consecutive patients with rectal cancer underwent preoperative CRT followed by curative resection. The lymph node ratio (LNR) was defined as the number of positive lymph nodes (LNs) divided by the examined LNs, and log odds of positive lymph nodes (LODDS) was the log of the ratio between positive and negative LNs. The prognostic value of these indicators was evaluated in terms of overall (OS) and disease-free (DFS) survival. Results: The median follow-up period for patients overall was 59 months (range=11-190 months). The median number of examined LNs and number of positive LNs were 10 (range=1-29) and 2 (range=1-27), respectively, and the median LNR and LODDS values were 0.0 (range=0.0-0.96) and −1.0 (range=−1.7-1.3), respectively. The 5-year OS and DFS were 83% and 64%, respectively. In multivariate analysis, LNR was an independent prognostic factor in terms of OS (p=0.041) but not for DFS (p=0.075). LODDS was not significantly associated with OS or DFS. In patients with clinical stage III rectal cancer, LNR was significantly associated with OS and DFS when the number of evaluated LNs was greater than 12 (p=0.038 for OS, p=0.006 for DFS). Conclusion: Our study suggests that LNR is a more effective prognostic factor than LODDS in terms of predicting survival. LNR was a significant predictor for survival for patients with clinical stage III rectal cancer with >12 harvested LNs.

Colorectal cancer is the third most common type of cancer among men and women in the United States and Korea (1, 2). Preoperative concurrent chemoradiotherapy (CRT) has been the standard treatment for rectal cancer since the publication of a landmark randomized trial which demonstrated reduced treatment-related toxicity and improved local control in association with this intervention (3).

Previous studies have shown that nodal status is the strongest predictor of recurrence and survival among patients with rectal cancer (4-7). The lymph node ratio (LNR) is a well-known prognostic factor for breast and stomach cancer (8, 9) as well as colorectal cancer (10). However, the LNR has limitations when it comes to revealing heterogeneous survival outcomes. Log odds of positive lymph nodes (LODDS) is a novel prognostic indicator that has been reported to reduce the risk of staging migration in gastric, breast, and colon cancer (11-13). To date, only a few studies have reported LODDS as a predictor of survival among patients with colorectal cancer (14-16). A recent study on the prognostic value of LNR and LODDS for rectal cancer treated with preoperative radiotherapy demonstrated that LODDS was more discriminatory than LNR for cancer-specific survival (17). This study aimed to assess the prognostic value of LNR and LODDS in terms of predicting survival and recurrence among patients with rectal cancer treated with preoperative CRT.

Patients and Methods

Patients. From April 2000 to May 2015, 80 patients with consecutive rectal cancer who underwent preoperative CRT followed by curative resection were included in the present study. Tumors were staged using the eighth edition of the American Joint Committee on Cancer...
AJCC) guidelines (6). Inclusion criteria were as follows: patients with histologically confirmed rectal adenocarcinoma, with clinical stage II or III rectal cancer, and who underwent surgery after preoperative CRT. Patients were excluded if they had received prior treatment for rectal cancer, had a history of other malignancies, had evidence of distant metastasis, or had received preoperative radiotherapy alone. The present study received Institutional Review Board approval (approval number: 2016-03-058).

Clinicopathological characteristics. Pathological factors considered in the analysis included tumor differentiation, lymphatic invasion, vascular invasion, perineural invasion, resection margin status, and the number of lymph nodes (LNs) with and without metastasis. The LNR was defined as the ratio of the number of positive LNs to the total number of LNs examined. The LODDS was defined as the logarithm of the ratio between positive and negative LNs. The optimal cut-off values for LNR, LODDS, pre-treatment carcinoembryonic antigen (CEA), and postoperative CEA were determined using Maxstat, a maximal chi-square method in R 3.5.1 (R Development Core Team, Vienna, Austria, http://www.R-project.org). Patients were divided into two groups based on the number of dissected LNs (>12 vs. ≤12), which is recommended for nodal sampling accuracy in the AJCC guidelines (6). Downstaging of rectal cancer was defined as a reduction of the final pathological T- or N-stage by comparing with the preoperative clinical T- or N-stage. Pathological complete remission was defined as the absence of tumor cells in the primary lesion and LNs (ypT0N0).

Treatment. A radiation dose of 45.0-50.4 Gy was delivered to the whole pelvis, followed by a boost dose of 0 to 5.4 Gy to the primary tumor. Neoadjuvant chemotherapy consisted of 5-fluorouracil (5-FU, 400 mg/m²) and leucovorin (20 mg/m²) for 5 days in the first and fifth weeks of radiotherapy (n=73, 91.2%) or capecitabine (1,650 mg/m²) daily (n=7, 8.8%). Curative surgery was performed 6-8 weeks after the completion of CRT. Adjuvant chemotherapy was administered for 70 (87.5%) patients. The regimens for adjuvant chemotherapy were 5-FU and LV in 53 (66.2%); doxifluridine or tegafur-uracil in 11 (13.8%); capcitabine in three (3.8%); 5-FU, LV and oxaliplatin (FOLFOX) in two (2.5%); and 5-FU, LV, and irinotecan (FOLFIRI) in one (1.2%).

Follow-up. Locoregional recurrence was defined as recurrent disease detected within the pelvis. Recurrent disease outside the pelvis was considered distant failure. Overall survival (OS) was defined as the interval from the date of diagnosis of rectal cancer until death from any cause or the date of last follow-up. Disease-free survival (DFS) was defined as the interval from the date of diagnosis to the last follow-up, disease recurrence, or death. Patients without recurrence or death were censored at the date of last follow-up.

Table I. Patient and tumor characteristics.

| Variable                        | Value                      |
|---------------------------------|----------------------------|
| Age, years, median (range)      | 57 (26-82%)                |
| Gender, n (%)                   | Male 73.8%                 |
| Distance from anal verge, n (%) | ≤5 cm 56.3%                |
| Histological differentiation, n (%) | WD 35.3% |                      |
| Clinical stage, n (%)           | II 17.2%                   |
| Resection margin, n (%)         | Negative 77.6%             |
| Vascular invasion, n (%)        | Negative 58.2%             |
| Lymphatic invasion, n (%)       | Negative 55.8%             |
| Perineural invasion, n (%)      | Negative 53.6%             |
| ypT stage, n (%)                | T0 8 (10.0%)               |
| ypN stage, n (%)                | N0 53 (66.3%)              |
| Pathological complete remission, n (%) | No 73 (91.3%) |                          |
| Downstaging, n (%)              | No 43 (53.8%)              |

WD: Well-differentiated; MD: moderately differentiated; PD: poorly differentiated.

Statistical analysis. Statistical analysis was performed using SPSS software version 18.0.0 (SPSS Inc., Chicago, IL, USA). OS and DFS rates were calculated using the Kaplan-Meier method. A log-rank test was performed to compare the survival curves.

Figure 1. Kaplan-Meier curves for overall (OS) and disease-free (DFS) survival for patients overall.
proportional hazard regression modeling was used for univariate and multivariate analyses. Variables with a value of \(p<0.2\) in the univariate analysis were included in the multivariate analysis. We performed two different analyses for LODDS and LNR to reduce interference and avoid collinearity during analysis within the same multivariate model. All statistical tests used in this study were two-sided, and values of \(p<0.05\) were considered statistically significant.

### Results

**Characteristics.** Patient and tumor characteristics are summarized in Table I. The median age at diagnosis was 57

**Table II. Univariate analyses for 5-year overall (OS) and disease-free (DFS) survival according to clinicopathological factors.**

| Variable                        | No. | OS (%) | p-Value | DFS (%) | p-Value |
|---------------------------------|-----|--------|---------|---------|---------|
| Age                             |     |        |         |         |         |
| \(\leq 57\) Years               | 44  | 83.8   | 0.390   | 62.8    | 0.719   |
| \(>57\) Years                   | 36  | 82.6   |         | 66.7    |         |
| Distance from anal verge        |     |        |         |         |         |
| \(\leq 5\) cm                   | 45  | 87.6   | 0.412   | 71.4    | 0.108   |
| \(>5\) cm                      | 35  | 77.4   |         | 55.1    |         |
| Histological differentiation    |     |        |         |         |         |
| WD                              | 17  | 77.1   | 0.782   | 59.5    | 0.996   |
| MD, PD                          | 51  | 84.5   |         | 65.1    |         |
| Clinical stage                  |     |        |         |         |         |
| II                              | 17  | 77.0   | 0.763   | 75.3    | 0.220   |
| III                             | 63  | 85.1   |         | 60.8    |         |
| Pre-treatment                   |     |        |         |         |         |
| CEA \(\leq 15.1\) ng/ml         | 69  | 89.3   | <0.001  | 69.6    | 0.004   |
| CEA \(>15.1\) ng/ml             | 9   | 45.7   |         | 20.8    |         |
| Postoperative                   |     |        |         |         |         |
| CEA \(\leq 3\) ng/ml            | 68  | 90.6   | <0.001  | 68.9    | 0.032   |
| CEA \(>3\) ng/ml                | 11  | 51.1   |         | 43.6    |         |
| Surgery type                    |     |        |         |         |         |
| LAR                             | 64  | 86.0   | 0.045   | 69.7    | 0.048   |
| APR                             | 16  | 71.1   |         | 38.7    |         |
| Resection margin                |     |        |         |         |         |
| Negative                        | 77  | 84.1   | 0.105   | 65.6    | 0.055   |
| Positive                        | 3   | 66.7   |         | 33.3    |         |
| Vascular invasion               |     |        |         |         |         |
| Negative                        | 58  | 85.2   | 0.667   | 63.5    | 0.742   |
| Positive                        | 10  | 65.6   |         | 56.0    |         |
| Lymphatic invasion              |     |        |         |         |         |
| Negative                        | 55  | 90.8   | 0.020   | 68.9    | 0.011   |
| Positive                        | 13  | 49.9   |         | 36.9    |         |
| Perineural invasion             |     |        |         |         |         |
| Negative                        | 53  | 89.1   | 0.003   | 72.0    | 0.002   |
| Positive                        | 15  | 49.0   |         | 14.7    |         |
| ypT stage                       |     |        |         |         |         |
| ypT0-2                          | 35  | 92.4   | 0.036   | 79.8    | 0.015   |
| ypT3-4                          | 45  | 76.3   |         | 52.6    |         |
| ypN stage                       |     |        |         |         |         |
| ypN0                            | 53  | 87.2   | 0.148   | 73.8    | 0.017   |
| ypN1-2                          | 27  | 75.5   |         | 46.0    |         |
| No. of dissected LNs            |     |        |         |         |         |
| \(\leq 12\)                     | 52  | 85.3   | 0.255   | 67.8    | 0.830   |
| \(>12\)                         | 28  | 78.8   |         | 64.7    |         |
| LNR \(\leq 0.1\)                | 59  | 88.7   | 0.038   | 71.9    | 0.006   |
| LNR \(>0.1\)                    | 21  | 68.9   |         | 43.3    |         |
| LODDS \(\leq 1.28\)             | 23  | 93.3   | 0.196   | 82.2    | 0.135   |
| LODDS \(>1.28\)                 | 57  | 80.0   |         | 58.5    |         |

WD: Well-differentiated; MD: moderately differentiated; PD: poorly differentiated; CEA: carcinoembryonic antigen; LAR: low anterior resection; APR: abdominoperineal resection; LNs: lymph nodes; LNR: lymph node ratio; LODDS: log odds of positive lymph nodes.
The median examined LN and positive LN counts were 10 (range=1-29) and 2 (range=1-27), respectively. The median LNR and LODDS values were 0.0 (range=0.0-0.96) and −1.0 (range=−1.7-1.3), respectively. The median pre-treatment and postoperative CEA levels were 4.1 (range=0.6-364.6) ng/ml and 1.5 (range=1-13) ng/ml, respectively. Clinical stage II and III disease were noted in 21.2% and 78.8% of patients, respectively. Sixty-four patients (80%) underwent low anterior resection, and 16 (20%) underwent abdominoperineal resection. Complete remission was observed in seven patients (8.7%).

Survival outcomes. The median follow-up duration was 59 (range=11-190) months for patients overall. Eight patients (10%) developed locoregional recurrence, 24% developed distant recurrence, and 23% had died by the end of the study. Median OS and DFS were not reached. The 5-year OS and DFS rates were 83% and 64%, respectively. Survival curves for OS and DFS are shown in Figure 1.

Prognostic factor analysis. In the univariate analysis, seven variables were statistically significantly associated with OS and DFS: Pre-treatment CEA, postoperative CEA, surgery type, lymphatic invasion, perineural invasion, ypT stage, and LNR (Table II). ypN stage was significantly associated with DFS but not OS. The 5-year survival rate according to the number of dissected LNs was 85.3% in the group with ≤12 dissected LNs compared with 78.8% in the group with >12 (p=0.255). The 5-year OS and DFS rates were 88.7% and 71.9% for patients with LNR ≤0.1, and 68.9% and 43.3% for patients with LNR >0.1, respectively, and were significantly different (OS: p=0.038) and (DFS: p=0.006) (Figure 2). In multivariate analyses (Table III), LNR [hazard ratio (HR)=3.361, 95% confidence interval (CI)=1.050-10.757, p=0.041], postoperative CEA (HR=7.004, 95% CI=1.207-40.647, p=0.030), resection margin status (HR=19.335, 95% CI=1.182-316.321, p=0.038), and lymphatic invasion (HR=3.508, 95% CI=1.103-11.157, p=0.033) were independent predictors of OS but LODDS was not (HR=2.406, 95% CI=0.915-6.326, p=0.073 for LNR; HR=2.621, 95% CI=0.766-8.968, p=0.125 for LODDS).

Subgroup analysis. Subgroup analyses were performed to determine whether survival differences according to LNR were associated with the number of dissected LNs among patients with clinical stage III disease (Figure 3). LNR>0.1 was a significant predictor of worse OS and DFS among 25 patients with >12 dissected LNs (5-year OS: 90.9% vs. 56.0%, p=0.020; 5-year DFS: 76.0% vs. 40.0%, p=0.034; Figure 3A). Among 38 patients with ≤12 dissected LNs,
LNR>0.1 was not significantly associated with OS and DFS (5-year OS: 96.4% vs. 75.0%, p=0.498; 5-year DFS: 69.7% vs. 37.0%, p=0.214; Figure 3B).

Discussion

In this study, we confirmed that LNR>0.1 was significantly associated with poor 5-year survival outcomes among patients who underwent preoperative CRT followed by curative surgery for locally advanced rectal cancer.

Various methods can be used to assess nodal status in rectal cancer, including the AJCC pN staging, LNR, and LODDS. Currently, the most widely used LN staging system is the AJCC eighth edition N-stage, based on the absolute number of metastatic LNs (6). However, with the numeric-based N-staging system for rectal cancer, it is difficult to represent the extent of LN dissection despite radical LN dissection being performed, and the impact associated with the total number of harvested LNs is ignored. Our results showed that the ypN category had no impact on OS. This
result may have been affected by the differences in the number of harvested LNs at the same ypN stage. Johnson et al. reported that the number of negative LNs is an important prognostic indicator for patients with stage IIIB and IIIC colon cancer, and having 13 or more negative LNs was found to be independently associated with improved disease-specific survival (18). Several studies have reported an association between the number of LNs evaluated and survival among patients with colorectal cancer (7, 19, 20). Swanson et al. examined 35,787 patients with T3N0 colon cancer and demonstrated that three categories of LN harvest (1-7, 8-12, and >12) were associated with different 5-year survival rates (50%, 56%, and 63%, respectively) (7).

LNR and LODDS were developed to consider the prognostic effect of LN status by analyzing both the total number of LNs harvested and the total number affected. Previous studies have reported LNR to be of higher prognostic value than N-stage for rectal cancer (10, 21). Additionally, Huang et al. reported that LODDS was a better prognostic factor than LNR for patients with stage III rectal cancer (17). On the other hand, the present study demonstrated that LNR>0.1 was significantly associated with poor survival outcomes, whereas LODDS had no association with survival. The lack of statistical significance associated with LODDS was probably related to the different neoadjuvant treatments. Previous reports do not mention whether or not chemotherapy was concurrently administered with radiotherapy, but in the present study all patients were treated with neoadjuvant CRT. For patients with locally advanced rectal cancer, preoperative CRT can induce nodal downstaging by tumor regression (3) and affect yp-LNR and yp-LODDS values. LNR reflects the proportion of evaluated LNs found to be positive, while LODDS is determined by dividing harvested LNs into positive and negative LNs. Thus, when there are no involved LNs, LNR is zero regardless of the total number of harvested LN but LODDS is heterogeneous, making it difficult to determine the optimal cut-off value.

We found that LNR>0.1 was a statistically significant predictor of shorter survival in the subgroup with >12 dissected LNs among patients with clinical stage III disease. Although there is debate regarding the number of LNs needed for accurate staging, the assessment of more than 12 LNs following colorectal surgery is recommended in clinical guidelines (6, 22). Lee et al. reported that low LN harvests (<12) were predictive of poor OS and DFS in stage III colon cancer (23). If the number of metastatic LNs is the same, the higher the number of harvested LNs, the smaller the LNR value. Further investigation is required to confirm whether the same cut-off LNR value can be applied to each subgroup according to the number of dissected LNs.

The present study had a number of limitations. Firstly, the method of determining the cut-off LNR value was different from those of other studies. There are various methods used for determining the cut-off LNR value for rectal cancer investigations, including the mean value (24), median value (25), or quartiles reclassified on the basis of Kaplan-Meier plots (21). Therefore, caution should be taken when interpreting the comparisons of survival outcomes according to LNR in the present study with those of previous studies. Secondly, because there were 53 patients (66.3%) with ypN0 disease, there was a limitation in reflecting nodal status by analyzing LNR. However, there are few published rectal cancer studies that have reported yp-LNR and yp-LODDS data, therefore this study may be useful as a reference. A further prospective study is required to evaluate the prognostic value of LNR and determine its optimal cut-off point among patients who have received preoperative CRT for rectal cancer.

In conclusion, we demonstrated that LNR was a more valuable predictor of survival outcomes than LODDS. Among patients with clinical stage III disease with >12 harvested LNs, LNR was a significant predictor for survival.

References
1 Siegel RL, Miller KD, Fedewa SA, Ahnen DJ, Meester RGS, Barzi A and Jemal A: Colorectal cancer statistics, 2017. CA Cancer J Clin 67(3): 177-193, 2017. PMID: 28248415. DOI: 10.3322/caac.21395
2 Jung K-W, Won Y-J, Kong H-J and Lee ES: Cancer statistics in Korea: Incidence, mortality, survival, and prevalence in 2016. Cancer Res Treat 51(2): 417-430, 2019. PMID: 30913865. DOI: 10.4143/crt.2019.138
3 Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, Martus P, Tscherne A, Hager E, Hess CF, Karstens JH, Liersch T, Schmidberger H and Raab R: Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 341(17): 1731-1740, 2004. PMID: 15496622. DOI: 10.1056/NEJMoa040694
4 Veen T, Nedrebo BS, Stormark K, Soreide JA, Korner H and Soreide K: Qualitative and quantitative issues of lymph nodes as prognostic factor in colon cancer. Dig Surg 30(1): 1-11, 2013. PMID: 23595092. DOI: 10.1159/000349923
5 Greene FL, Stewart AK and Norton HI: A new TNM staging strategy for node-positive (stage III) colon cancer: An analysis of 50,042 patients. Ann Surg 236(4): 416-421, 2002. PMID: 12368669. DOI: 10.1097/00000658-200210000-00003
6 Amin MB and Edge SB: AJCC Cancer Staging Manual. Eighth Edition. Springer: New York, pp. 251-274, 2017.
7 Swanson RS, Compton CC, Stewart AK and Bland KI: The prognosis of T3N0 colon cancer is dependent on the number of lymph nodes examined. Ann Surg Oncol 10(1): 65-71, 2003. PMID: 12513963. DOI: 10.1245/aso.2003.03.058
8 Nelen SD, van Steenbergen LN, Dassen AE, van der Wurff AA, Lemmens VE and Bosscha K: The lymph node ratio as a prognostic factor for gastric cancer. Acta Oncol 52(8): 1751-1759, 2013. PMID: 23317142. DOI: 10.3109/0284186x.2012.754991
9 Xiao XS, Tang HL, Xie XH, Li LS, Kong YN, Wu MQ, Yang L, Gao J, Wei WD and Xie X: Metastatic axillary lymph node
ratio (LNR) is prognostically superior to pN staging in patients with breast cancer—results for 804 Chinese patients from a single institution. Asian Pac J Cancer Prev 14(9): 5219-5223, 2013. PMID: 24175804. DOI: 10.7314/apjcp.2013.14.9.5219

10 Rosenberg R, Friederichs J, Schuster T, Gertler R, Maak M, Becker K, Grebner A, Ulm K, Hofler H, Nekarda H and Siewert JR: 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 248(6): 968-978, 2008. PMID: 19092341. DOI: 10.1097/SLA.0b013e318190eddc

11 Sun Z, Xu Y, Li de M, Wang ZN, Zhu GL, Huang BJ, Li K and Xu HM: Log odds of positive lymph nodes: A novel prognostic indicator superior to the number-based and the ratio-based n category for gastric cancer patients with R0 resection. Cancer 116(11): 2571-2580, 2010. PMID: 20336791. DOI: 10.1002/cncr.24989

12 Vinh-Hung V, Verschraegen C, Promish DI, Cserni G, Van de Steene J, Tai P, Vlastos G, Voordeckers M, Storme G and Royce M: Ratios of involved nodes in early breast cancer. Breast Cancer Res 6(6): R680-688, 2004. PMID: 15535850. DOI: 10.1186/bcr934

13 Wang J, Hassett JM, Dayton MT and Kulaylat MN: The prognostic superiority of log odds of positive lymph nodes in stage III colon cancer. J Gastrointest Surg 12(10): 1790-1796, 2008. PMID: 18709510. DOI: 10.1007/s11605-008-0651-3

14 Arslan NC, Sokmen S, Canda AE, Terzi C and Sarioglu S: The prognostic impact of a log odds of positive lymph nodes in colorectal cancer. Colorectal Dis 16(11): O386-392, 2014. PMID: 24980876. DOI: 10.1111/codi.12702

15 Persiani R, Cananzi FC, Biondi A, Paliani G, Tufo A, Ferrara F, Vigorita V and D’Ugo D: Log odds of positive lymph node ratios in colon cancer: A meaningful ratio-based lymph node classification system. World J Surg 36(3): 667-674, 2012. PMID: 22270984. DOI: 10.1007/s00268-011-1415-x

16 Scarinci A, Di Cesare T, Cavaniglia D, Neri T, Colletti M, Cosenza G and Liverani A: The impact of log odds of positive lymph nodes (LODDS ) in colon and rectal cancer patient stratification: A single-center analysis of 323 patients. Updates Surg 70(1): 23-31, 2018. PMID: 29500795. DOI: 10.1007/s13304-018-0519-3

17 Huang B, Ni M, Chen C, Cai G and Cai S: LODDS is superior to lymph node ratio for the prognosis of node-positive rectal cancer patients treated with preoperative radiotherapy. Tumori 93(1): 87-92, 2017. PMID: 27716883. DOI: 10.5301/tj.5000560

18 Johnson PM, Porter GA, Ricciardi R and Baxter NN: Increasing negative lymph node count is independently associated with improved long-term survival in stage IIIB and IIIC colon cancer. J Clin Oncol 24(22): 3570-3575, 2006. PMID: 16877723. DOI: 10.1200/jco.2006.06.8866

19 Tepper JE, O’Connell MJ, Niedzwiecki D, Hollis D, Compton C, Benson AB, 3rd, Cummings B, Gunderson L, Macdonald JS and Mayer RJ: Impact of number of nodes retrieved on outcome in patients with rectal cancer. J Clin Oncol 19(1): 157-163, 2001. PMID: 11134208. DOI: 10.1200/jco.2001.19.1.157

20 Chang GJ, Rodriguez-Bigas MA, Skibber JM and Moyer VA: Lymph node evaluation and survival after curative resection of colon cancer: Systematic review. J Natl Cancer Inst 99(6): 433-441, 2007. PMID: 17374833. DOI: 10.1093/jnci/djk092

21 Peschaud F, Benoist S, Julie C, Beauchet A, Penna C, Rougier P and Nordlinger B: The ratio of metastatic to examined lymph nodes is a powerful independent prognostic factor in rectal cancer. Ann Surg 248(6): 1067-1073, 2008. PMID: 19092352. DOI: 10.1097/SLA.0b013e31818842ec

22 Nelson H, Petrelli N, Carlin A, Couture J, Fleshman J, Guillem J, Miedema B, Ota D and Sargent D: Guidelines 2000 for colon and rectal cancer surgery. J Natl Cancer Inst 93(8): 583-596, 2001. PMID: 11309435. DOI: 10.1093/jnci/93.8.583

23 Lee CHA, Wilkins S, Oliva K, Staples MP and McMurrick PJ: Role of lymph node yield and lymph node ratio in predicting outcomes in non-metastatic colorectal cancer. BJU Int 101(1): 95-105, 2019. PMID: 30734020. DOI: 10.1111/bju.14596

24 Jiang K, Lei J, Chen W, Gong Y, Luo H, Li Z, Gong R and Zhu J: Association of the preoperative neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios with lymph node metastasis and recurrence in patients with medullary thyroid carcinoma. Medicine 95(40): e5079, 2016. PMID: 27749881. DOI: 10.1097/md.0000000000005079

25 Kang J, Hur H, Min BS, Lee KY and Kim NK: Prognostic impact of the lymph node ratio in rectal cancer patients who underwent preoperative chemoradiation. J Surg Oncol 104(1): 53-58, 2011. PMID: 21416471. DOI: 10.1002/jso.21913

Received February 24, 2020
Revised March 8, 2020
Accepted March 9, 2020