

Relationship between Lymph Node Ratio and Survival Rate in Preoperative Chemoradiation Rectal Cancer Patients

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Background: Number of positive lymph nodes is one of the most-important prognostic factors in rectal cancer. Rectal cancer patients who undergo colorectal surgery following neoadjuvant chemoradiation therapy are sometimes unable to retrieve an adequate amount of lymph nodes.

Objective: We proposed to confirm the new way to predict outcome of rectal cancer patients based on positive lymph node ratio.

Materials and Methods: This is a retrospective, single-centered study, collecting data of patients from January 2011 to December 2017. Data from 149 patients with rectal cancer who underwent colorectal surgery following neoadjuvant chemoradiation were analyzed. Cox regression and Kaplan-Meier survival analysis were used to determine the prognostic values of lymph node ratio, total lymph nodes harvested, and TNM staging.

Results: A higher positive lymph node ratio significantly related to poorer survival rate of patients with rectal cancer who received neoadjuvant chemoradiation. There was no statistically significant difference between total lymph nodes harvested and survival rate. There was no statistical difference in survival rate among pathological stages II, IIIA, IIIB, and IIIC. Five-year survival rates after neoadjuvant chemoradiation therapy were 86.18%, 75%, 86.50%, and 83.33% in rectal cancer patients stage II, IIIA, IIIB, and IIIC, respectively.

Conclusion: The lymph node ratio can be used as predictor for survival in post-surgery rectal cancer patients who received neoadjuvant chemoradiation therapy. Future research is needed to find the optimum cut-off value.

Keywords: Rectal cancer; Lymph node ratio; Survival rate

J Med Assoc Thai 2021;104(Suppl5): S16-20

Website: <http://www.jmatonline.com>

Colorectal cancer (CRC) is the 3rd most common cancer in the world. It is the most common malignancy of the gastrointestinal (GI) tract⁽¹⁾. TNM staging is recommended as a guideline in management and to determine the prognosis of CRC⁽²⁾. In stage II and III CRC, neoadjuvant chemoradiation therapy has played an important role in the reduction of the disease recurrence and increasing overall survival of the patients^(3,4).

Positive lymph nodes after surgical treatment is directly related to increases in the staging and prognosis of

the disease. Oncologic resection of rectal cancer involves removing the tumor with clear margins and harvesting an adequate amount of lymph nodes. The American Joint Committee on Cancer (AJCC, 8th edition) recommends at least 12 lymph nodes as an adequate number harvested⁽⁵⁾.

After neoadjuvant therapy, inadequate lymph nodes harvested may result from difficult tumor location, fibrosis from preoperative radiotherapy, and down staging of the disease⁽⁶⁻⁸⁾. Therefore, to overcome the limitations, we proposed to use "lymph node ratio (LNR)" as a prognostic factor for patients with rectal cancer after neoadjuvant therapy.

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How to cite this article:

Punmeechao P, Supsamutchai C, Janbavonkij T, Wilasrusmee C, Thampongsa T, Jirasiritham J, Palitnonkiat V, Choikura P. Relationship between Lymph Node Ratio and Survival Rate in Preoperative Chemoradiation Rectal Cancer Patients. *J Med Assoc Thai* 2021;104 (Suppl5): S16-20
doi.org/10.35755/jmedassocthai.2021.S05.00063

Materials and Methods

A cohort of patients who were diagnosed with rectal cancer and received neoadjuvant chemoradiation therapy were collected from electronic medical records of the Faculty of Medicine Ramathibodi Hospital, Mahidol University from January 2011 to December 2017. A total of 732 colorectal cancer patients who received neoadjuvant chemoradiation therapy were gathered by ICD10 code. Colorectal cancer patients who did not complete their course of neoadjuvant chemoradiation therapy, did not receive surgical treatment, lost follow-up, or whose recorded data was incomplete were excluded. This study was registered on clinicaltrials.gov (NCT04096118). A total of 149 patients were included in

the present study (Figure 1). The demographic data included age, sex, surgeons, staging of disease, carcinoembryonic antigen (CEA) level, diagnostic variables, histology, treatment course, and outcomes (recurrence of tumor and survival), total lymph nodes (LN) harvested, and positive lymph nodes were collected and analyzed.

Cox regression and Kaplan-Meier survival analysis were used to determine the relationship between LN ratio, total lymph node harvested and survival of patients. All statistical analyses were performed using Stata version 14. The p-values <0.05 were considered as significant level.

The present study was approved by ethics committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University (No. MURA2017/426).

Results

A total of 149 rectal cancer patients who were treated with neoadjuvant chemoradiation therapy and followed by curative surgery were included in the analysis. Characteristic data of this cohort is shown in Table 1. The mean age was 59.43 years old (SD=10.70). Sixty-five percent of patients were male. From 149 cases. Most of pre-operative staging of patients were stage III disease, 119 cases (79.87%) whereas 54 cases (36.24%) which had pathological complete response (pCR) and histological subtypes were moderately different, 119 cases (79.87%). The median follow-up time was 36 months.

The median number of total of LN harvested was 13 (p25, p75=9, 17). The median number of positive LN was 0 (p25, p75=0, 1). The median of total LN harvested by each surgeon were 13 (SD=7.94). There was no statistical difference between the surgeons (p=0.272).

As shown in Table 2, the positive of lymph nodes from the specimen significantly associated with the survival rate of patients with Hazard ratio (95% CI) 1.309 (1.111, 1.541; p=0.001). Corresponding with the LN ratio that was also significantly associated with survival rate. Higher lymph node ratio in every 0.1 fold reflected poorer survival rate with Hazard ratio (95% CI) of 1.299 (1.063, 1.587; p-value 0.011). For 3 groups of lymph node ratio; LNR=0, LNR

<0.2 and LNR ≥0.2, patient with LNR ≥0.2 had significantly lower survival rate than patients with LNR=0 as Figure 2 (p=0.038). On the other hand the number of total harvested lymph node less than 12 has the higher survival rate than ≥12 lymph nodes groups but no statistical significance as

Table 1. Characteristic data

Characteristic data	Number (149)
Age, mean (SD)	59.43 (10.70)
Sex, n (%)	
Male	98 (65.77)
Female	51 (34.23)
Total LN harvested, median (p25, p75)	13 (9, 17)
Total LN <12	61 (40.94%)
Total LN ≥12	88 (59.06%)
Positive LN, median (p25, p75)	0 (0, 1)
Pathological LN results	
pN 0	104 (69.80)
pN 1	35 (23.49)
pN 2	10 (6.71)
CEA, median (p25, p75)	3.9 (2.4, 8.6)
Pre-operative staging after neoadjuvant therapy, n (%)	
Stage II	30 (20.13)
Stage IIIA	3 (2.01)
Stage IIIB	99 (66.4)
Stage IIIC	17 (11.41)
Pathological staging, n (%)	
Stage 0	54 (36.24)
Stage II	55 (36.91)
Stage IIIA	6 (4.03)
Stage IIIB	28 (18.79)
Stage IIIC	6 (4.03)
Pathological results, n (%)	
Adenocarcinoma	
Well differentiation	16 (10.74)
Moderately differentiation	119 (79.87)
Poorly differentiation	5 (3.36)
Mucinous carcinoma	9 (6.04)
Proximal margin	
Negative	149
Distal margin, n (%)	
Negative	149
Circumferential margin, n (%)	
Negative	146 (97.99)
Positive	3 (2.01)

LN = lymph nodes; CEA = carcinoembryonic antigen

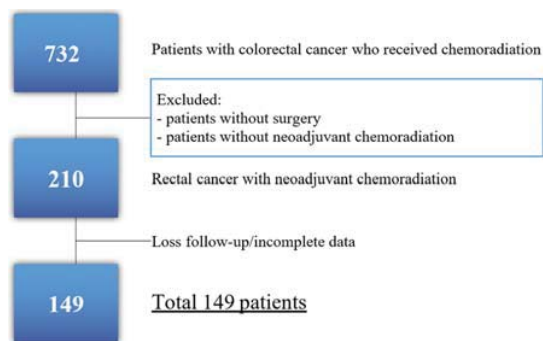


Figure 1. Flow chart of patient inclusion.

Table 2. Association between LN ratio including other risk factors and survival rate

Characteristics	Survive n=133	Dead n=16	Univariate	
			HR (95% CI)	p-value
LN all, median (p25, p75)	13 (9, 17)	13 (10, 18)	1.000 (0.941, 1.070)	0.903
LN harvest				
<12	55 (41.35)	6 (37.50)	1.239 (0.45, 3.41)	0.41
≥12	78 (58.65)	10 (62.50)		
LN positive, median (p25, p75)	0 (0, 1)	1 (0, 4.5)	1.309 (1.111, 1.541)	0.001
LN ratio, median (p25, p75)	0 (0, 0.043)	0.069 (0, 0.231)	1.299* (1.063, 1.587)	0.011
LN ratio				
0	97 (72.93)	7 (43.75)	-	-
0 to 0.2	23 (17.29)	4 (25)	2.36 (0.69 to 8.08)	0.170
>0.2	13 (9.77)	5 (31.25)	3.95 (1.25 to 12.47)	0.038
Age, mean (SD)	59.06 (10.74)	62.56 (10.14)	1.037 (0.986, 1.090)	0.155
Sex				
Male	88 (66.17)	10 (62.5)	1.162 (0.422 to 3.198)	0.77
Female	45 (33.83)	6 (37.5)		
CEA, median (p25, p75)	3.60 (2.2, 7.5)	9.05 (4.25, 15.7)	0.999 (0.978, 1.021)	0.968
Histology, n (%)				
Adenocarcinoma				
Well differentiation	13 (9.77)	3 (18.75)	-	
Moderately differentiation	107 (80.45)	12 (75)	0.599 (0.168, 2.125)	0.428
Poorly differentiation	4 (3.01)	1 (6.25)	1.304 (0.135, 12.56)	0.818
Mucinous carcinoma	9 (6.77)	0	-	-

Hazard ratio in every 0.1 fold of the LN ratio difference

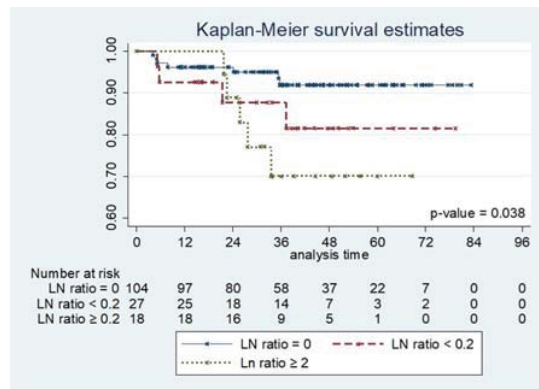


Figure 2. Kaplan-Meier survival graph divided by lymph node ratio.

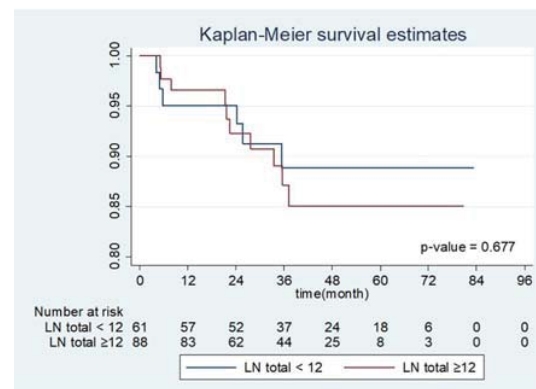


Figure 3. Kaplan-Meier survival graph divided by total lymph node yield at cut-off value of 12.

Figure 3. For age, sex, CEA, and histology were not significantly associated with survival rate.

There was no statistical difference in survival rate among all stages. The overall 5-year survival rate was 84.99%.

Five-year survival after neoadjuvant chemoradiation therapy in rectal cancer patients was 86.18%, 75%, 86.50%, and 83.33% in rectal cancer patients stage II, IIIA, IIIB, and IIIC, respectively.

Discussion

Based on the American Joint Committee on Cancer (AJCC) and TNM staging, the number of positive lymph nodes is one of the major prognostic factors in patients with rectal cancer. The higher number of positive lymph nodes reflected poorer prognosis. The gold-standard number of harvested lymph nodes within current guidelines is more than 12. Number of total lymph nodes which were fewer than 12 was found to have a higher risk of missing positive lymph nodes in the specimen, which resulted in under-staging the disease. Norwood, et al⁽⁹⁾ supported the concept of 12 nodes being required for accurate staging and showed that the survival in patients with Dukes' A and B cancers was significantly reduced if fewer than 12 LNs were sampled. However, Cianchi, et al⁽¹⁰⁾ reported that harvesting and examining a minimum of 9 LNs per surgical specimen may be sufficient for reliable staging of lymph node-negative tumor.

In our study, the median number of total LN harvested from surgical patients who received neoadjuvant chemoradiation therapy was 13 (p25, p75=9, 17). Eighty-eight out of 149 patients (59.06%) had total LN harvested of 12 or higher. However, the analysis showed no significant difference in survival rate between lower lymph node harvested (<12) and lymph node harvested ≥12 (p=0.575). Norwood, et al⁽⁹⁾ reported that preoperative chemoradiotherapy, operation type, specimen length and patient age independently influenced lymph node retrieval. In our cohort, radiation therapy may induce fibrosis and resulted in a decrease of total lymph nodes harvested. That reflects and underestimation of pN staging and nodal number may not be clinically relevant in this group of patients.

Abdel-Misih, et al⁽⁵⁾ found that neoadjuvant chemoradiation therapy had the statistically lowest median lymph node yield compared with no-neoadjuvant and neoadjuvant chemotherapy. They concluded that LN yield and status were not good predictors of overall survival. Elder, et al⁽⁶⁾ supported that patients with rectal cancer treated with preoperative radiotherapy had a lower number of LN harvested compared with non-radiation.

The findings from our study supported that lymph node ratio (LNR) could be used as a predictor of survival outcome in this patient group. Higher lymph node ratio in every 0.1 fold reflected poorer survival rate with Hazard ratio (95% CI) of 1.299 (1.063, 1.587; p-value=0.011). When we divided by the range of LNR, patients who had LNR ≥0.2 had statistically significant poorer survival rate than LNR=0 (p=0.038) but in range of 0 to 0.2, there was no significance. Many studies showed that LNR was significantly associated with survival rate and had superior prognostic stratification in Stage III colorectal cancer. However the cut-off values were still different among studies⁽¹¹⁻¹³⁾.

Ceelen, et al⁽¹¹⁾ systematically reviewed the

prognostic significance of the LNR in CRC. 16 studies which included 33,984 patients with Stage III colon or rectal cancer showed that the LNR allowed superior prognostic stratification in Stage III colorectal cancer than the number of positive nodes (N stage). The pooled hazard ratios for overall and disease-free survival were 2.36 (95% confidence interval (CI), 2.14 to 2.61) and 3.71 (95% CI, 2.56 to 5.38), respectively. Vaccaro, et al⁽¹³⁾ and Wang, et al⁽¹²⁾ reported higher disease-free survival rates, cancer-specific, and overall survival rates in lower LNR groups.

In our studies, we calculated a cut-off point at 0.2 which had the highest difference in hazard ratio. Our study had several limitations, such as this was a retrospective study which performed in single-centered hospital, the sample size was small, and the follow-up time was short. In the future, a prospective study with large sample size are need to confirm the impact of LNR and its cutoff point.

Conclusion

In summary, the LNR can be used as good predictor for survival in post-surgery CRC patients who received neoadjuvant chemoradiation therapy. Future researches are needed to find the optimum cut-off value.

What is already known on this topic?

The number of positive lymph nodes is one of the major prognostic factors in patients with rectal cancer. Base on the American Joint Committee on Cancer (AJCC) and TNM staging, the gold-standard number of harvested lymph nodes is more than 12. However patients who receive neoadjuvant chemoradiation trend to receive the lymph nodes form surgery fewer than non neoadjuvant chemoradiation groups and might be less than 12 that's underestimation of pN staging.

What this study adds?

The findings from our study supported that lymph node ratio (LNR) could be used as a predictor of survival outcome in this patient group. Higher lymph node ratio in every 0.1 fold reflected poorer survival rate with Hazard ratio (95% CI) of 1.299 (1.063, 1.587; p-value=0.011).

Potential conflicts of interest

The authors declare no conflict of interest.

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