

## Lymphnodal Ratio in Prognostication of Stage III Colon Cancer

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### Abstract

*Introduction:* Colon cancer is one of the most common malignancies accounting to the 4th most frequent cancer in men and 3rd in women. Though the most commonly used system for cancer staging is TNM classification, it has some prognostic limitations in stage III disease. Node related factors that are of prognostic interest include lymph node size, distribution as well as the lymph node ratio (LNR) which is the quota between positive and total assessed lymph nodes.

*Aim and objectives:* The aim of this study was to evaluate and to describe the lymph node ratio as a prognostic parameter for patients with stage III colon cancer by assessing disease free survival period.

*Methods:* The study is retrospective and included all the patients diagnosed with stage III colon cancer during 2010 to 2014. LNR was calculated and quartile groups were created. LNR and associated parameters were analyzed with reference to disease-free survival (DFS) by follow up of these patients.

*Results:* The Karl Pearson's correlation analyses was used to determine the correlation coefficient, the Kaplan Meier method was used to analyze survival and the Cox proportional hazard regression model was used for multivariate analysis. The results showed that the lymph node ratio was a prognostic factor in stage III colorectal cancer and had a better prognostic value than did N stage of TNM classification.

*Conclusion:* The lymph node ratio, that is the quota between the number of metastatic lymphnodes and total assessed lymph nodes proved to be a significant prognostic factor in stage III colon cancer as is determined by disease free survival time during follow up of the patients.

**Keywords:** Colon Cancer; Disease Free Survival; Lymph Node Ratio; Prognostic Parameter.

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**Introduction**

Colon cancer is one of the most common malignancies accounting to the 4<sup>th</sup> most frequent cancer in men and 3<sup>rd</sup> in women [1]. Once, colon carcinomas are diagnosed, they have to be staged by using a cancer staging system which has the ability to guide appropriate clinical decisions regarding postoperative management and can provide an accurate prognosis and follow-up.

Currently, the most widely used staging system is the tumor, nodes, metastasis (TNM) classification system. This staging system classifies patients into prognostic groups according to the depth of the primary tumor (T), presence of regional LN metastases (N) and evidence of distant metastatic spread (M). Regional LN status (N) is determined on the basis of the number of positive LNs retrieved and is classified as follows: No regional LN metastasis as N0, metastasis in 1-3 regional LNs as N1 and metastasis in 4 or more regional LNs as N2.

TNM Staging is systematic and functional but within stage III colon cancers there are prognostic limitations such as stage III is often treated as an entity and the differences in prognosis within the group are not clear. This affects the treatment as well as follow-up.

The other staging systems include AJCC staging system, in which the N stage of the colorectal cancer is based on the number of positive nodal involvement and as the number of removed lymph nodes increases, the number of positive lymph nodes tend to increase which corresponds to a higher N stage. However, the number of removed lymph nodes depends on the patient, surgeon, pathologist and others factors [2].

Therefore, the TNM Staging and AJCC staging system regarding Stage III colorectal cancer have some limitations. Some researchers, however, believe that the TNM staging system may not result in optimal staging and have proposed alternative LN parameters such as lymph nodal ratio (LNR), which is defined as the ratio between the positive lymph nodes to the total number of removed lymph nodes. If LNR can be considered a prognostic factor, it may also have the advantage of being

less dependent on the number of removed lymph nodes than N staging.

Hence, this study was done to determine the relationship between LNR and survival and to assess whether LNR could provide reliable and clinically relevant prognostic information.

*Aim and Objectives*

The aim of this study was to evaluate and describe the lymph node ratio (LNR) as a prognostic parameter for patients with Stage III colon cancer by assessing disease free survival period.

**Materials and Methods**

*Materials:* The present study was done in our department from January 2010 to December 2014. A total of 52 cases of Stage III Colonic Adenocarcinoma that were diagnosed on histopathological examination by using conventional Hematoxylin & Eosin stained sections and who underwent radical colectomy surgery followed by adjuvant chemotherapy were included in the study.

The basic clinical parameters such as sex, age, diagnosis, type of surgery as well as pathology data such as T stage, tumor differentiation grade and lymph nodes were taken into consideration.

*Methods:* N stage was divided into N1 and N2 according to the number of regional positive lymph nodes: N1 = 1 to 3 positive lymph nodes and N2 = more than 3 positive lymph nodes. There were 32 cases of N1 stage disease and 20 cases of N2. Focus was kept on number of nodes with metastatic growth (Figure 1) correlated to the number of assessed lymphnodes.

*Lymph node ratio (LNR):* Lymph node ratio was calculated as the quota between metastatic positive nodes and total assessed lymph nodes.

*Lymph node ratio groups (LNRG):* LNR groups were created on the basis of ratio quartiles as:

Group 1 (LNR 1) with quartile < 0.21

Group 2 (LNR 2) with quartile between 0.21- 0.35

Group 3 (LNR 3) with quartile between 0.35-0.75 and

Group 4 (LNR 4) with quartile >0.75

There were 15 cases under LNR 1, 11 cases in LNR 2, 14 cases in LNR 3, and 12 cases in LNR 4.

*Follow up:* Post operatively patients were followed up for every three months during the first two years after the surgery, once in every six months for the next three years and there after once in a year. Chemotherapy based on the 5 fluorouracil (5FU) regimen, including 5FU plus calcium folinate (CF) or oxaliplatin plus 5FU and CF was given.

*Survival:* A 3-year disease-free survival data is used as a prognostic instrument since this parameter is an accepted way to reflect on the future long-term prognosis [3].

*Inclusion criteria:* Radical colectomy specimens that were reported as Stage III colonic Adenocarcinomas on histopathological examination.

*Exclusion criteria:* Cases with familial adenomatous polyposis, multiple primary colorectal cancers, synchronous malignancies, or N1c stage disease (No regional lymph nodes are positive, but there are tumor deposits in the subserosa, mesentery or non peritonealized pericolic, or perirectal/mesorectal tissues), neo adjuvant radio chemotherapy cases and cases that had lost follow up.

#### Statistical methods

Med Calc version 18.6 software is used for statistical analysis. Karl Pearson's correlation analyses was used to determine the correlation coefficient. The chi square test and ANOVA were applied to compare the clinical and pathologic factors. Survival was analyzed using the Kaplan Meier method. Log rank test was used to compare survival differences between LNR groups.

**Table 1:** Patients demographics and pathology data in LNR groups

	LNRG 1	LNRG 2	LNRG 3	LNRG 4	p value (chi- square)
<b>Age</b>					0.622
≤60	9	9	9	9	
>60	6	2	5	3	
<b>Sex</b>					0.297
F	4	5	4	7	
M	11	6	10	5	
Tumor size	4.6 ± 1.6	4.36 ± 1.68	5.14 ± 2.90	3.66 ± 1.6	0.343 (ANOVA)
<b>Tumor differentiation</b>					0.446 (chi square)
Well	10	6	5	5	
Moderate	4	3	4	2	
Poor	1	2	4	5	
<b>Total no. of assessed lymphnodes</b>	10 ± 12.45	9.45 ± 6.53	9.57 ± 6.45	4.66 ± 3.22	0.288 (ANOVA)
Median	7	8	8.5	4.5	
Range	5 to 55	3 to 22	3 to 27	1 to 10	

Multivariate analysis was performed using Cox proportional hazard regression and was considered significant if p value was < 0.05.

## Results

### Lnr and Clinicopathologic Parameters

The number of cases included in the study was 52 cases, of which 20 were females and 32 were males. The mean age was 51 years. A total of 452 lymph nodes were removed from all the 52 patients and the average number of removed lymph nodes per patient was 8.7. The total number of positive lymph nodes detected was 167 with the average number of positive lymph nodes per patient being 3.21 and the average LNR was 0.47. In the present study, LNR showed positive correlation with the number of metastatic lymphnodes ( $r=0.38$ ,  $p=0.005$ ) and with N stage ( $r=0.33$ ,  $p=0.01$ ), whereas a negative correlation was found between the LNR and total number of assessed lymph nodes ( $r = -0.34$ ,  $p = 0.012$ ).

### Univariate Analysis

Univariate analysis showed that among the various clinicopathological parameters that were considered in the study, the number of metastatic lymphnodes and N stage were associated with disease free survival of patients with stage III colorectal cancer, whereas age, sex, tumor size, tumor differentiation, and the number of assessed lymph nodes were not. These results are shown in Table 1

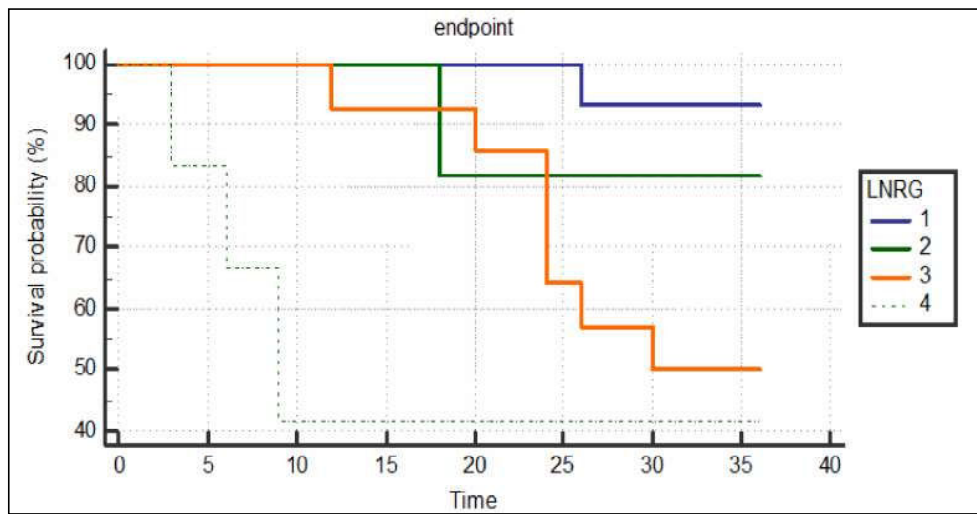
<b>Metastatic lymphnodes</b>	1.26 ± 0.69	2.72 ± 1.73	4.7 ± 3.09	4.25 ± 2.73	0.001 (ANOVA)
Median	1	2	4	4	
Range	1 to 3	1 to 6	2 to 13	1 to 8	
<b>N Stage</b>					0.002 (chi square)
N1	15	7	5	5	
N2	0	4	9	7	

*Kaplan- Meier survival analysis between LNR, N stage and diseased free survival period*

The 3 year disease free survival rates among various LNR groups was as follows: 93% for LNR 1, 81% for LNR 2, 50% for LNR 3, and 41% for LNR 4. The difference among their survival rates was significant (p= 0.002) and is shown in Figure 1

*Multivariate analysis*

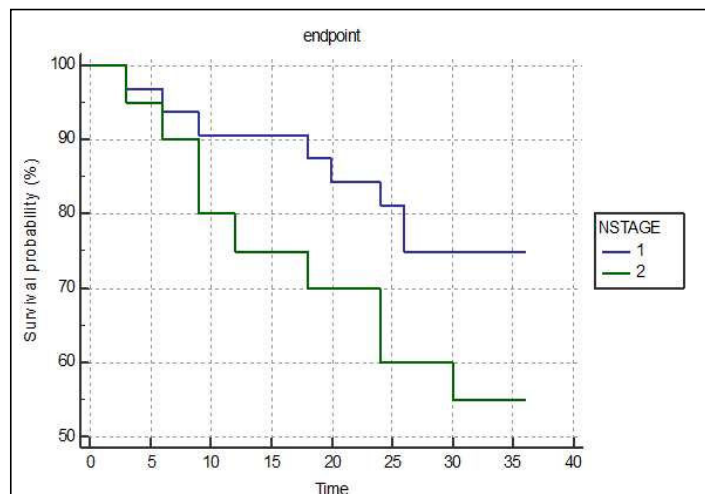
Multivariate analysis showed that LNR and tumor differentiation were independent prognostic factors for disease free survival of patients in stage III colorectal cancer (< 0.05), whereas N stage failed to achieve significance (p = 0.7687). According to multivariate analysis, LNR remained a highly



**Fig.1:** Disease free survival in LNR groups

In N stage, the 3 year disease free survival rates for patients with N1 and N2 diseases was 75% and 55%, respectively. But the difference among their survival rates was not significant (p= 0.12) and is shown in Figure 2.

significant factor along with grade of tumor differentiation in disease free survival and is shown in Table 2.



**Fig. 2:** Disease free survival in N stage

**Table 2:** Multi variant analysis for prognosis in stage III Colon carcinomas

Covariate	b	SE	Wald	p	Exp (b)	95% CI of Exp (b)
T Stage	-0.8618	0.5900	2.1338	0.1441	0.4224	0.1329 to 1.3425
N Stage	-0.1595	0.5422	0.08651	0.7687	0.8526	0.2946 to 2.4677
LNR	1.1304	0.3543	10.1779	0.0014	3.0970	1.5464 to 6.2024
Tumor Differentiation	1.1144	0.3357	11.0165	0.0009	3.0477	1.5783 to 5.8853

### Discussion

In the present study, we found that LNR which is the quota between the number of lymph node metastasis and total assessed lymph nodes positively correlated with the number of positive lymph nodes and N stage. Also there was a negative correlation between LNR and the number of removed lymph nodes, indicating that as the number of removed lymph nodes increases, LNR decreases.

The average number of lymphnodes removed in the present study was 8.69, ranging from 1-55. Though, The National Comprehensive Cancer Network (NCCN) recommends the removal and pathologic examination of at least 12 nodes for resectable primary colorectal cancers, the number 12 does not hold any particular biological significance and can be a statistical probability distribution indicating that if more than 12 nodes have been assessed, the likelihood of missing any positive metastatic nodes becomes very small [4]

According to the study done by Huh JW et al., [5] LNR was an independent prognostic factor for both overall survival and disease free survival and suggested LNR could be a good staging complement for patients with stage III colorectal cancer when less than 12 lymph nodes are removed.

Among the various clinicopathologic parameters that were considered in the study, the number

of metastatic lymphnodes and N stage were associated with LNR grouping in patients with stage III colorectal cancer, whereas other factors such as age, sex, tumor size, tumor differentiation, and the number of assessed lymph nodes were not.

Our study showed that LNR was one of the prognostic factors in stage III colon cancer, both by Kaplan Meier survival analysis and by Multivariate analysis and found to be having better prognostic value than N stage.

The results are similar to the studies done by Hong et al. [6], Vaccaro et al. [7] and Jing Qing Ren et al. [8] who reported that the prognostic value of LNR was better than that of N stage in stage III colorectal cancer.

Several studies have investigated the prognostic value of LNR in CRC and are showed in Table 3.

Berger et al. [9] were the first to investigate the relationship between LNR and survival in patients with colon cancer. In their study, multivariate analysis showed that LNR was found to be a significant factor for overall survival (OS), disease free survival (DFS) and cancer-specific survival (CSS).

Other studies include De Ridder et al [10], Rosenberg et al. [2], Wang et al. [11,12] and Chin et al. [13]. All these studies proved that LNR was an independent predictor of survival in stage III colorectal cancers.

**Table 3:** Lymph node ratio in colorectal cancer comparison with other studies

Author, year	Study size	Selection of cases	Cut off LNR	Overall survival	Multivariate analysis
Berger et al. [9] 2005	3411	Stage II and III	< 0.05	79	NS
			0.05-0.19	73	<0.0001
			0.2-0.39	63	<0.0001
			0.4-1.0	52	
De Ridder et al. [10], 2006	26181	Node-positive colon cancer	<0.4	56	<0.0001
			>0.4	25	
Rosenberg et al. [2], 2008	3026	Colorectal cancer	0	87	<0.001
			0.01-0.17	60	
			0.18-0.41	34	
			0.42-0.60	17	
			0.70	05	
Wang et al. [11,12], 2008, 2009	24 477	Stage III colon cancer	<1/14	64.8	<0.0001
			1/14-0.25	56.2	
			0.25-0.50	45.1	
			0.50-<1.0	29.6	

Chin et al. [13], 2009	490	Stage III colon cancer	<0.4 0.4-<0.7 >0.7	66 35	0.001 <0.001
Vaccaro et al. [7], 2009	362	Stage III colon cancer	<0.25 ≥0.25	64.9 38.3	0.005
Jin Q ing Ren et al. [8], 2012	145	Stage III colon cancer	>0.111 0.111 to ≤0.200 ≥0.200 to 0.429 >0.429	54.8 36.8 19.2 0	<0.001
Present study, 2018	52	Stage III colon cancer	< 0.21 0.21- 0.35 >0.35-0.75 >0.75	93 81 50 41	0.0014

## Conclusion

Based on the results obtained from Kaplan Meier survival analysis, Multivariate analysis and comparing with other similar studies, we concluded that LNR was a prognostic factor in stage III colon cancer and found that its prognostic value was better than N stage.

However, large scale, prospective studies with specific valid cutoff point for LNR are required to achieve prognostic stratification and to further confirm the value of lymph node ratio as prognostic factor in Stage III colon cancers.

*Prior publication:* nil

*Support :* nil

*Conflicts of interest:* nil

*Permissions:* nil

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