Lymph node ratio as a prognostic factor in stage III colon cancer

Emad Sadaka, Alaa Maria and Mohamed El-Shebiney.

Clinical Oncology department, Faculty of Medicine, Tanta University, Egypt
alaamaria1@hotmail.com

Abstract: Background: Staging system of cancer colon is dependant on the number of positive lymph nodes (LNs) and hence the number of retrieved LNs. In current study we investigated the lymph node ratio (LNR) as a prognostic factor in stage III colon cancer. **Material and Methods**: Ninety-three patients with stage III colon cancer between Jan. 2001 & Dec. 2007 were enrolled in this study. The total number of retrieved LNs was defined as <12 and ≥12 nodes. Lymph node ratio (LNR) was defined as the ratio of positive nodes to the total number of LNs removed, and the LNR was divided into four groups according to quartile: LNR1 (<0.16), LNR2 (≥0.16 - <0.31), LNR3 (≥0.31 - <0.61), and LNR4 (≥0.61). The disease free survival (DFS) rate was analyzed using the Kaplan-Meier method. Multivariate analysis was performed using Cox proportional hazard regression model. **Results:** The LNR was significantly correlated with T stage (p=0.011), N stage (p<0.001) and grade of differentiation (p=0.018). The 5-year DFS rates for the LNR groups were 95.45% for LNR1, 72.73% for LNR2, 17.36% for LNR3, and 0% for LNR4, (p<0.0001). In multivariate analysis, T stage (p=0.032), LNR (p=0.006) and preoperative CEA level (p=0.026) were independent prognostic factors. Nodal stage was not an independent prognostic factor (p=0.66). **Conclusion:** The current study found that LNR was an independent prognostic factor in stage III colon cancer patients.

Keywords: Colon cancer, lymph node ratio, stage III colon cancer.

1. Introduction

Colon cancer is the most common gastrointestinal malignancy and the second-leading cause of cancer death in the United States. [1] Surgery remains the definitive treatment for patients with this disease. In non-metastatic colorectal cancer, lymph node (LN) status is the strongest pathologic predictor of patient outcome. [2]

Because of the high risk for recurrence of colon cancer, adjuvant chemotherapy is recommended for patients with LN metastases (stage III) and for selected patients without LN metastases (stage II) but with adverse prognostic features, such as poorly differentiated tumors or lymphovascular or perineural invasion by tumor

Lee et al [13] & Vaccaro et al [14] evaluated the prognostic significant of the LN ratio in patients with stage III colon cancer and they concluded that LN ratio was an independent prognostic factor for stage III colon cancer regardless the number of LN.

2. Materials and Methods

This retrospective study was conducted at Clinical Oncology Department, Tanta University Hospital, between January 2001 and December 2007. Ninety-three patients with stage III colon cancer underwent radical surgery and confirmed pathologically to have adenocarcinoma of the colon.

Patients data were recorded including; age, sex, performance status (PS), physical examination, pathology, carcinoembryonic antigen (CEA), blood

cells. [3, 4] Staging accuracy, disease specific and overall survivals are improved with increasing nodal examination and analysis. [5-7]

There has been an effort to determine the minimum number of nodes that need to be evaluated. Estimates have varied from 6 to 40 LNs. However, numerous studies have suggested that examination of 12 regional LNs is a reasonable minimum for adequate nodal evaluation for colon cancer. [8-12]

The number of LNs reported with colectomy varies widely and may be a result of variation in surgical technique, pathologist-related variables, or the actual number of regional LNs. There is evidence that the ratio of metastatic to examined LNs (LNR) is an important prognostic factor. [2, 8] chemistry (liver and renal functions tests), complete blood profile, imaging studies (X-ray, abdominopelvic ultrasound, CT, MRI), and colonoscopy. All patients had 0-2 ECOG PS [15] and received 5-fluorouracil (5-FU) based regimen (5-FU + Leucovorin) as adjuvant chemotherapy.

Patients were staged according to AJCC TNM staging 2010 [16] where N stage was divided into N1 and N2 according to the number of regional positive LNs, N1 = 1-3 positive nodes and N2 ≥4 positive nodes. As regard to the total number of retrieved LNs, patients was defined as <12 and ≥12 retrieved nods. Lymph node ratio (LNR) was defined as the ratio of positive nodes to the total number of LNs removed, and the LNR was divided into four groups according to quartile: LNR1

(<0.16), LNR2 (≥0.16 - <0.31), LNR3 (≥0.31 - <0.61), and LNR4 (≥0.61).

Statistical methods

The chi-square test was applied to compare the clinical and pathological factors of LNR groups. The disease free survival (DFS) rate was analyzed using the Kaplan-Meier method.[17] Multivariate analysis was performed using Cox proportional hazard regression model.[18] Statistical analysis was performed using Statistical Package for Social Sciences software (SPSS, V.12). Significance was prespecified as $p<0.05$.

3. Results

This study evaluated a total of 93 patients with stage III colon cancer. Patients' age ranged from 41 to 71 years (median 55 years) with 31 months median follow-up period (range 8 to 91 months). Median number of retrieved LNs was 10 (range 4 to 18) of which median 3 (range 1 to 11) LNs proved to be metastatic.

Table 1 shows the correlation between the LNR and clinicopathologic characteristics; the LNR was significantly correlated with T stage ($p=0.011$), N stage ($p<0.001$), LN retrieved ($p=0.005$), mean number of both retrieved and positive LNs ($p<0.001$ for both), grade of differentiation ($p=0.018$), pathology ($p=0.006$) and preoperative serum CEA level ($p=0.001$).

Overall 5-year DFS rate in this analysis was 45.65%. The 5-year DFS rates for the LNR groups were; 95.45% for LNR1, 72.73% for LNR2, 17.36% for LNR3, and 0% for LNR4, and the difference was statistically significant ($p<0.0001$) as shown in table 2. In univariate analysis, there were significant 5-year DFS rate with T stage ($p<0.0001$), N stage ($p<0.0001$), number of LNs retrieved ($p=0.007$), grade of differentiation ($p=0.004$), pathological type ($p=0.019$), intestinal obstruction ($p=0.010$) and serum CEA level ($p=<0.0001$). Table (2), Fig. (1-3)

Table (1): Correlation between LNR and clinicopathological characteristics

Factors	Total pt (%)	LNR1 (%)	LNR2 (%)	LNR3 (%)	LNR4 (%)	*p*-value
Age #						
≤55	47 (50.5)	11 (47.8)	15 (68.2)	10 (41.7)	11 (45.8)	0.29
>55	46 (49.5)	12 (52.2)	7 (31.8)	14 (58.3)	13 (54.2)	
Gender						
Male	51 (54.8)	12 (52.2)	12 (54.5)	14 (58.3)	13 (54.2)	0.98
Female	42 (45.2)	11 (47.8)	10 (45.5)	10 (41.7)	11 (45.8)	
T Stage						
T2	37 (39.8)	15 (65.2)	10 (45.5)	7 (29.2)	5 (20.8)	0.011*
T3	56 (60.2)	8 (34.8)	12 (54.5)	17 (70.8)	19 (79.2)	
N Stage						
N1	55 (59.1)	23 (100)	22 (100)	9 (37.5)	1 (4.2)	<0.001*
N2	38 (40.9)	0 (0)	0 (0)	15 (62.5)	23 (95.8)	
LN retrieved						
<12	63 (67.7)	10 (43.5)	16 (72.7)	15 (62.5)	22 (91.7)	0.005 *
≥12	30 (32.3)	13 (56.5)	6 (27.3)	9 (37.5)	2 (8.3)	
Mean number of LN retrieved ≈		12.26 ± 3.25	10.55 ± 2.15	10 ± 3.88	8.54 ± 3.15	<0.001*
Mean number of positive LN ≠		1.39 ± 0.5	2.27 ± 0.46	4.58 ± 2.12	6.46 ± 2.21	<0.001*
Grade						
1-2	48 (51.6)	18 (78.3)	11 (50)	11 (45.8)	8 (33.3)	0.018*
3-4	45 (48.4)	5 (21.7)	11 (50)	13 (45.2)	16 (66.7)	
Pathology						
Mucinous	39 (41.9)	6 (26.1)	6 (27.3)	10 (41.7)	17 (70.8)	0.006*
Non-mucinous	54 (58.1)	17 (73.9)	16 (72.7)	14 (58.3)	7 (29.2)	
Intestinal obstruction						
Yes	34 (36.6)	5 (21.7)	7 (31.8)	11 (45.8)	11 (45.8)	0.244
No	59 (63.4)	18 (78.3)	15 (68.2)	13 (54.2)	13 (54.2)	
CEA						
Normal	37 (39.8)	17 (73.9)	9 (40.9)	5 (20.8)	6 (25)	0.001*
Elevated	56 (60.2)	6 (26.1)	13 (59.1)	19 (79.2)	18 (75)	
PS						
0	35 (37.6)	12 (52.2)	5 (22.7)	10 (41.6)	8 (33.3)	0.165
1	37 (39.8)	7 (30.4)	14 (63.6)	7 (29.2)	9 (37.5)	
2	21 (22.6)	4 (17.4)	3 (13.7)	7 (29.2)	7 (29.2)	

#Median 55 years, mean 55.27±8.54, range 41-71   ≈Median 10, range 4-18   ≠Median 3, range 1-11
*Significant p<0.05; CEA: Carcinoemberyonic antigen; PS: performance status

Table (2): Univariate Analysis of Factors Affecting 5-year DFS rate

Factors		5-year DFS (%)	p-value
Age	≤55	47.85	0.708
	>55	43.33	
Gender	Male	50.64	0.393
	Female	39.75	
Stage (T)	T2	78.38	<0.0001*
	T3	24.70	
Nodal stage (N)	N1	71.25	<0.0001*
	N2	8.77	
LN ratio	LNR1	95.45	<0.0001*
	LNR2	72.73	
	LNR3	17.36	
	LNR4	0	
LN retrieved	<12	35.06	0.007*
	≥12	68.36	
Grade	1-2	58.38	0.004*
	3-4	32.35	
Pathology	Mucinous	31.37	0.019*
	Non-mucinous	55.73	
Intestinal obstruction	Yes	21.16	0.010*
	No	58.51	
CEA	Normal	74.27	<0.0001*
	Elevated	26.92	

Table (3): Multivariate Analysis of Factors Affecting 5-year DFS rate

Factors	HR (95%CI)	p-value
Stage (T)	2.72 (1.09 - 6.79)	0.032*
Nodal stage (N)	1.28 (0.42 - 3.86)	0.660
LN ratio	2.52 (1.31 - 4.84)	0.006*
LN retrieved	1.10 (0.46 - 2.62)	0.827
Grade	1.78 (0.92 - 3.44)	0.087
Pathology	1.09 (0.57 - 2.10)	0.795
Intestinal obstruction	1.17 (0.62 - 2.20)	0.638
CEA	2.52 (1.12 - 5.67)	0.026*

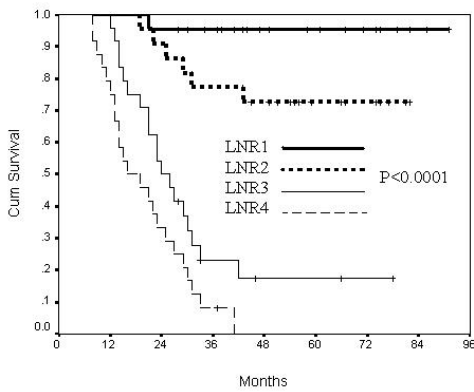*p significant <0.05; HR (95% CI): Hazard ratio (95% confidence interval)

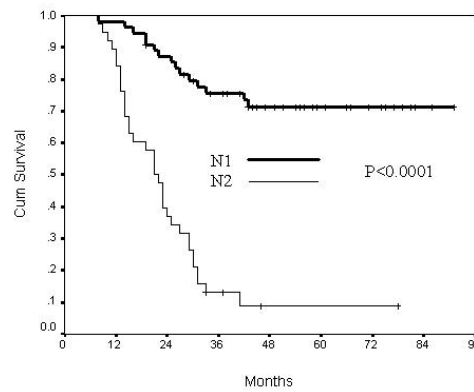Fig (1): 5-year DFS rate according to LNR
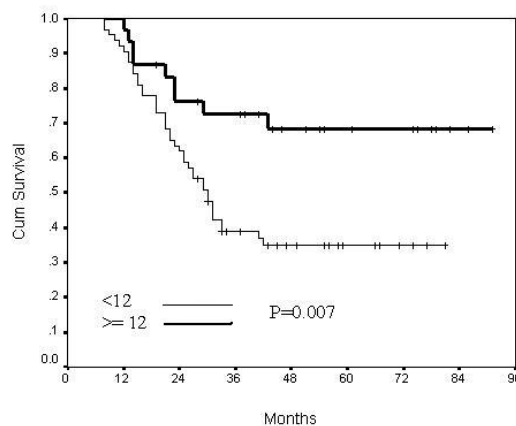

Fig (2): 5-year DFS rate according to N stage

Fig (3): 5-year DFS rate according to number of LNs retrieved

A multivariate analysis using the Cox proportional hazard regression model was performed. As shown in Table (3), there were significant 5-year DFS rate with T stage (*p*=0.032), LNR (*p*=0.006) and preoperative CEA level (*p*=0.026). However, N stage was not found to be an independent prognostic factor (*p*=0.660).

4. Discussion

Determination of regional LN status has long been considered to be one of the most important factors in predicting the likelihood of long-term survival in colon carcinoma. The National Comprehensive Cancer Network (NCCN) recommends removal and pathological examination of at least 12 nodes for primary colorectal cancer as they found that once more than 12 nodes have been assessed, the possibility of missing any positive mesenteric nodes becomes very small.[19, 20]

Rather than number of LNs alone as a prognostic factor, some have proposed LNR also as an important measure. A significance of the LNR relevant to oncologic prognosis in colon cancer has been presented.[2, 13, 21]

In this study we evaluated the significance of LNR among 93 patients with stage III colon cancer. LNR was positively correlated with the T stage, number of LNs retrieved, the number of positive LNs and N stage. Also there were a positive correlation with tumor grade, pathology and preoperative serum CEA level.

In current study, univariate analysis revealed that T stage ($p<0.0001$), N stage ($p<0.0001$), LNR ($p<0.0001$), number of LNs retrieved ($p=0.007$), grade of differentiation ($p=0.004$), pathological type ($p=0.019$), intestinal obstruction ($p=0.010$) and preoperative serum CEA level ($p=<0.0001$) were significantly affecting the 5-year DFS rate of stage III colon cancer. Multivariate analysis showed that T stage ($p=0.032$), LNR ($p=0.006$) and preoperative CEA level ($p=0.026$) were independent prognostic factors for DFS, whereas N stage was not ($p=0.66$).

Ren et al.[22] evaluated a total of 145 patients with colorectal cancer (CRC), LNR was not correlated with the number of lymph nodes retrieved ($p=0.065$), but LNR was positively correlated with the number of positive lymph nodes ($p<0.001$) and N stage ($p<0.001$). The univariate analysis showed that T stage, N stage, tumor configuration, intestinal obstruction, serum CEA, and LNR significantly affect the DFS of stage III colorectal cancer. Multivariate analysis showed that serum CEA concentration, T stage, and LNR were independent prognostic factors for DFS ($p<0.05$), whereas N stage failed to achieve significance ($p=0.664$).

Berger et al.[2] investigated the relationship between LNR and survival in patients with colon cancer. In a multivariate analysis, LNR was found to be a significant factor for OS and DFS in patients in whom 10-15 LNs and more than 15 LNs were removed, but not for patients in whom less than 10 LNs were removed. Wang et al.[23] evaluated the 5-year DFS rate of the stage IIIC colon cancer patients according to LNR and they concluded that LNR was an independent predictor of survival ($p<0.0001$). Chin et al.[24] determined the relationship between LNR and survival in 624 stage III colon cancer patients and revealed that LNR is a more precise predictor of 5-year DFS than the number of positive LNs [LNR1 vs. LNR2: $p=0.001$; LNR1 vs. LNR3: $p<0.001$].

Rosenberg et al.[25] reported the prognostic impact of LNRs in CRC patients. In multivariate analysis, both LNR and N stage were found to be independent prognostic factors. LNR had a better prognostic value than the N stage ($p<0.05$). The analysis of a subgroup of patients classified into colon and rectal cancer patients confirmed the identified LNRs as an independent prognostic factor ($p<0.001$).

Vaccaro et al.[14] reported the prognostic value of LNR in 362 patients with stage III colon cancer. Univariate analysis showed that both LNR and N stage were associated with significantly different for DFS ($p<0.001$). In a multivariate analysis, LNR was found to be an independent prognostic factor for DFS ($p=0.001$) and OS ($p=0.005$). However, N stage was not an independent prognostic factor for DFS ($p=0.41$), and OS ($p=0.58$). In addition, the number of harvested LNs was not a prognostic factor for DFS ($p=0.39$ and 0.72, respectively), and OS ($p=0.23$ and 0.66, respectively) by univariate and multivariate analyses.

Huh et al.[26] evaluated 514 cases of colorectal cancer. Patients categorized into four groups on the basis of quartiles. The 5-year OS rates were 79%, 72%, 62%, and 55%, respectively ($p<0.001$) and the 5-year DFS rates were 73%, 67%, 54%, and 42%, respectively ($p<0.001$). LNR was an independent prognostic factor for both OS and DFS in multivariate analysis, and the study suggested that it could be a good stage complement for patients with stage III colorectal cancer patients when <12 LNs are harvested.

In conclusion, LNR was found to be an independent prognostic factor in stage III colon cancer patients. The current study suggests that the LNR is a better prognostic factor than the N stage disease. Although the value of the LNR is widely accepted, the cutoff value is not yet established. The methods used to choose the cutoff value are different according to the used parameters such as quartiles and median values. Further larger studies are necessary to determine a specific valid cutoff point for LNR to achieve prognostic stratification.

5. Abbreviations:

LNs, lymph nodes; LNR, lymph node ratio; FU, fluorouracil; PS, performance status; CEA, carcinoembryonic antigen; CT, computerized tomography; MRI, magnetic resonance imaging; ECOG, Eastern Cooperative Oncology Group; AJCC, American Joint Committee on Cancer; CRC, colorectal cancer; DFS, disease free survival; OS, overall survival.

6. Corresponding author:
Alaa Mohamed Maria
Clinical Oncology Department, Faculty of Medicine, Tanta University, Al Gaish St., Tanta 11312, Gharbia, Egypt.
alaamaria1@hotmail.com

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