

# The Prognostic Significance of the Metastatic Lymph Node Ratio versus the Number of Affected Lymph Nodes in Patients with Colorectal Cancer Stage III Undergoing Potentially Curative Surgery

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## Abstract

**Background:** Many investigators have questioned the prognostic power of the TNM system in the prognosis of colorectal cancer because of the possibility of stage migration, and have proposed alternative prognostic methods; one of those is the lymph node ratio.

**Aim of Work:** The objective of this study is to compare the prognostic significance of the LNR with the absolute number of affected lymph nodes for resected colorectal adenocarcinoma stage III regarding overall and disease specific survival.

**Patients and Methods:** 55 patients with colorectal cancer stage III who underwent curative surgery were enrolled in a retrospective cohort study reviewing their medical charts from Medical Oncology Department between January 2005 and December 2006, and their five years follow-up period regarding local recurrence, metastasis and survival.

**Results:** The mean follow-up time was  $55.1 \pm 18$  months (range 6-72, median 60 months). During this time period, 12 (21.8%) patients died of disease, 20 (36.4%) patients developed local recurrence or metastasis. Overall Survival (OS) was 90.9%, 85.5%, 78.2% at 1.5, 3, 5 years respectively. Disease Specific Survival (DSS) was 90.9%, 74.5%, 63.6% at 1.5, 3, 5 years respectively.

Five year overall survival rates was significantly worse in colorectal cancers with LNR  $>40\%$  ( $p$ -value  $<0.01$ , hazard ratio 0.022, 95% CI 0.003-0.17) and also worse 5 year disease specific survival ( $p$ -value  $<0.01$ , hazard ratio 0.182, 95% CI 0.075-0.44). Total LN  $\leq 11$  and positive number of LNs  $>4$  showed significant worsening in the 5 year DSS only ( $p$ -value  $<0.05$ , hazard ratio 2.8, 95% CI 1.025-7.7) vs. ( $p$ -value  $<0.05$ , hazard ratio 0.32, 95% CI 0.13-0.8) respectively.

**Conclusion:** LNR was a robust prognostic indicator for node-positive colon cancers undergoing curative surgery. Because this ratio-based staging was demonstrated to reduce stage migration and to aid in identifying high-risk patients,

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application of the pLNR improved patient stratification in colorectal cancer and may be considered in future staging systems, it could be proposed as a standard tool for colon cancer staging.

**Key Words:** Lymph node ratio – Colorectal cancer.

## Introduction

**COLORECTAL** Cancer (CRC) is the fourth most common cancer and the second-leading cause of cancer deaths overall in men and women in the US [1].

Studies in individuals with colorectal cancer have shown that both disease-free survival and overall survival are correlated with the number of lymph nodes resected [2]. However, the number of lymph nodes identified in the surgical specimen is directly related to the experience of the surgeon performing the resection of the neoplasm, the histopathological technique used to recover them and the experience of the pathologist in identifying them [3].

Few studies have evaluated the LNR in relation to the survival of patients with colorectal cancer [4]. The validity of using the LNR as a variable relating to survival in colorectal cancer patients is still controversial. Some studies have not shown any relationship between the LNR and survival among colorectal cancer patients [5] while others have considered the LNR to be more important than the simple presence of lymph node involvement [6]. Thus, the importance of the LNR as an independent prognostic factor for staging in colorectal cancer still requires better assessment.

## Patients and Methods

It's a retrospective cohort study, the data were collected from medical charts of 55 patients who underwent curative surgery for colorectal carcinoma stage III at a single institution (the Department of Surgery at Kasr Al-Ainy University Hospital) between January 2005 and December 2006, reviewing their five years follow-up period regarding local recurrence, metastasis and survival.

The prognostic effect of positive Lymph-Node Ratio (pLNR) on patients with stage III Colorectal Cancer (CRC) was evaluated in comparison to the positive number of lymph nodes.

### *Inclusion criteria:*

All patients with a diagnosis of colorectal adenocarcinoma who are classified as stage III according to 7<sup>th</sup> edition of AJCC cancer staging manual [7], and had undergone complete resection of the primary tumour (R0) and lymphadenectomy extended beyond involved nodes at post-operative pathologic examination with negative apical lymph node(s) were considered eligible for the study. Also we included all eligible cases regardless of the number of lymph nodes harvested in this group.

### *Exclusion criteria:*

Patients with positive macroscopic or microscopic residual tumor (R1, R2) were excluded from this study, patients who met the Amsterdam criteria for hereditary nonpolyposis colorectal cancer syndrome or patients who have carcinomas associated to inflammatory bowel disease, Sarcomas, lymphomas, and carcinoid tumors were considered ineligible.

## Results

The total number of harvested nodes was (652) LNs mean was  $11.85 \pm 7$  (range 3-30, median 10 nodes). In 32 patients (58.2%) resected LNs was less than 12 and in 23 patients (41.8%) resected LNs was 12 or more.

When stratifying for the parameter N of the TNM staging system, the lymph node ratio ranged from 6.25%-50% (mean  $27.6 \pm 12.5$ , median 25) in 32 patients with pN1, and from 16%-100% (mean  $40.3 \pm 28.2$ , median 26) in 17 patients with pN2a, and from 38.4%-100% (mean  $68.3 \pm 23.2$ , median 71.6) in 6 patients with pN2b.

The mean follow-up time was  $55.1 \pm 18$  months (range 6-72, median 60 months). During this time period, 12 (21.8%) patients died of disease, 20 (36.4%) patients developed local recurrence or metastasis. Overall Survival (OS) was 90.9%, 85.5%, 78.2% at 1.5, 3, 5 years respectively. Disease Specific Survival (DSS) was 90.9%, 74.5%, 63.6% at 1.5, 3, 5 years respectively.

Five year Overall survival rates was significantly worse in colorectal cancers with LNR >40% ( $p$ -value <0.01, hazard ratio 0.022, 95% CI 0.003-0.17) and also worse 5 year disease specific survival ( $p$ -value <0.01, hazard ratio 0.182, 95% CI 0.075-0.44). Total LN  $\leq 11$  and positive number of LNs >4 showed significant worsening in the 5 year DSS only ( $p$ -value <0.05, hazard ratio 2.8, 95% CI 1.025-7.7) vs. ( $p$ -value <0.05, hazard ratio 0.32, 95% CI 0.13-0.8) respectively. Table (1).

According to this LNR cutoff value (40%), the hazard ratio for disease-specific survival was 0.18 (95% CI 0.075-0.44), corresponding to a 47% increase in the 5-year survival rate in patients showing a low LNR and a 82% reduction in the estimated relative risk of cancer-related death in this group.

LNR stratification disclosed survival rate discrepancies both in pN and TNM staging system clearly related to the stage migration phenomenon. In our series, probability of stage migration in the pN staging system might be inferred from the finding that 5-year OS of 40% for pN1 group with high LNR was less favorable than that of 90.9% for pN2a group with low LNR, also 5-year OS of 33.3% for pN2a group with high LNR was less favorable than that of 100% for pN2b group with low LNR.

When stratifying patients according to TNM stage, patients in the less favorable stage (IIIB) and a low LNR ( $\leq 40\%$ ) were shown to live much longer than patients in a more favorable stage (IIIA) and a high LNR (>40%) (96% vs. 0%, respectively), also patients in the less favorable stage (IIIC) and a low LNR ( $\leq 40\%$ ) were shown to live much longer than patients in a more favorable stage (IIIB) and a high LNR (>40%) (100% vs. 42.8%, respectively).

However stage III by itself shows a significant difference in 5 year OS and DSS among groups IIIA, IIIB, IIIC. Thus showing that LNR may identify more homogeneous groups (IIIA, B, C) controlled by the T stage, thereby reducing the phenomenon of stage migration.

It was much more evident stratifying patients according to TNM staging system and LNR. Patients categorized in the same stage (i.e., stages IIIA, IIIB, and IIIC) were shown to significantly differ in long-term survival rates when grouped according to LNR stratification.

The number of positive LNs was significantly increased by the increasing number of harvested nodes ( $r=0.548, p<0.05$ ) patients with <12 resected nodes showed a lower number of metastatic nodes compared with patients with 12 or more LNs but

it didn't reach a significance ( $p=0.06, 95\% \text{ CI } 0.79-3.9$ ).

LNR increased by 3.88% as the number of metastatic nodes increased by 1 ( $r=0.524, <0.05$ ), and decreased by 0.99% as the number of total LNs increased by 1 ( $r=-0.303, p<0.05$ ).

Lymph node ratio has a bigger inverse correlation with overall survival and disease specific survival if compared with positive number of lymph nodes ( $r=-0.64, -0.55$ ) vs. ( $r=-0.37, -0.23$ ) respectively.

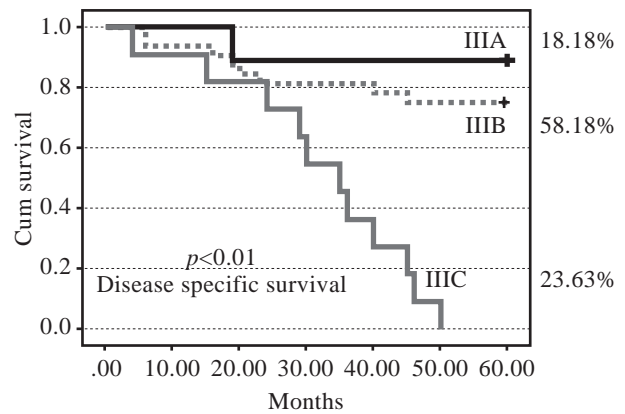
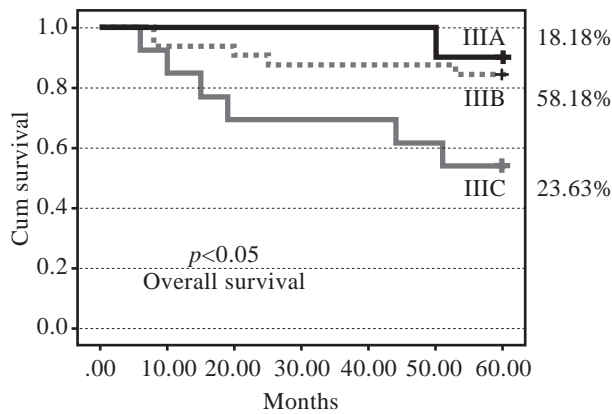


Fig. (1): 5-year survival rates in 55 patients stage III colorectal cancer underwent curative surgery according to TNM stages (IIIA, IIIB, IIIC).

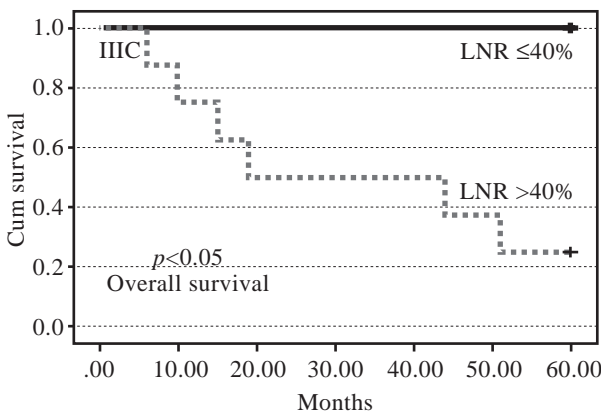
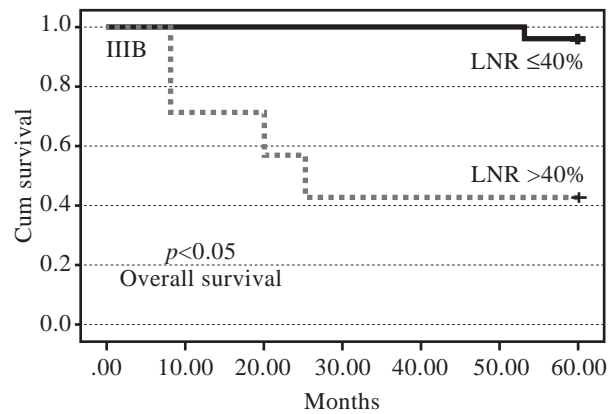
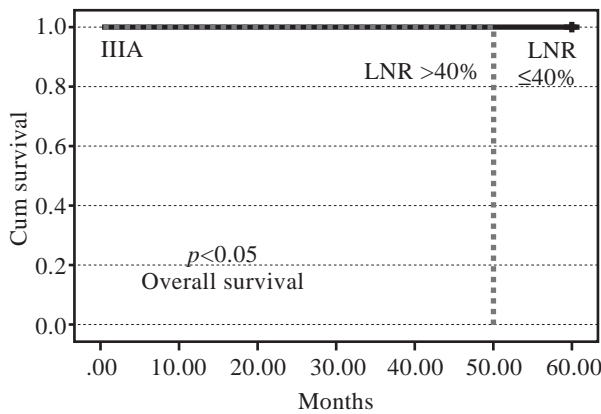


Fig. (2): 5-year overall survival rates in 55 patients stage III colorectal cancer underwent curative surgery according to TNM stage (IIIA, IIIB, IIIC) with LNR stratification: Lymph node ratio (cutoff >40%).

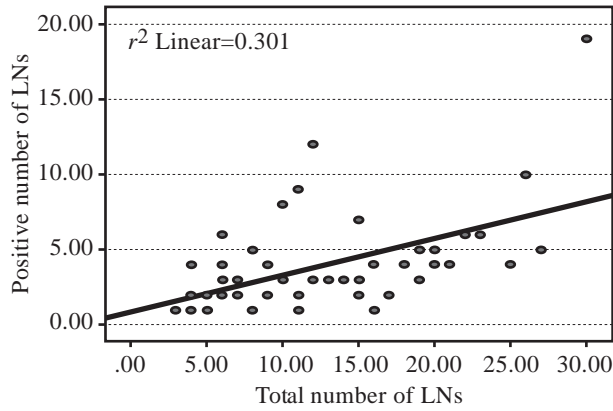


Fig. (3): Linear correlation between the total number of LNs and positive number of LNs ( $r=0.548$ ) ( $p<0.05$ ).

Table (1): 5-year survival rates in 55 patients stage III colorectal cancer underwent curative surgery according to cutoff values selected by ROC analysis: Lymph node ratio (>40%), positive number of LNs (>4), LNR (>40%).

	Overall survival				Disease specific survival			
	p-value	HR	95% CI HR		p-value	HR	95% CI HR	
			Lower	Upper			Lower	Upper
Total LN ≤11	0.195	2.37	0.64	8.77	<0.05	2.8	1.025	7.7
+LN >4	0.07	0.34	0.11	1.1	<0.05	0.32	0.13	0.8
LNR >40%	<0.01	0.022	0.003	0.17	<0.01	0.182	0.075	0.44

Table (2): Survival analysis in 55 patients with stage III colorectal cancer underwent curative surgery according to lymph node stage and the highest accuracy LNR value (40%).

N stage	Survival	LNR		Hazard ratio	95% CI HR		p-value
		≤40%	>40%		Lower	Upper	
N1 (32)	OS	0/27-100%	3/5-40%	0.00	0.00	8.71	0.74
	DSS	7/27-74%	1/5-80%	0.89	0.11	7.25	0.91
N2a (17)	OS	1/11-90.9%	4/6-33.3%	0.081	0.009	0.74	<0.05
	DSS	2/11-81.8%	5/6-16.6%	0.086	0.016	0.47	<0.01
N2b (6)	OS	0/1-100%	4/5-20%	0.032	0.00	731	0.5
	DSS	1/1-0%	4/5-20%	0.024	0.00	220.2	0.422

### Discussion

Current recommendations to examine at least 12-15 LNs are based on an amalgamation of data, the AJCC 7<sup>th</sup> edition recommends examination of 12 LNs [7] with the article by Scott and Grace [8] often cited as the source of the recommendation of 12 LNs after fat clearance of the mesorectum. Increased retrieval and evaluation of LNs does not improve detection of stage III CRC or identify more patients with positive nodes, according to research published in Archives of Surgery [9] however, our results oppose this, showing that the more LNs harvested from the mesentery, the more positive LNs yielded ( $r=0.548$ , slope=0.243,  $p<0.05$ ) consistent with results of other researches [4,10].

The large majority of collected and reviewed studies represents a population of node positive (stage III) or mixed (stage II and III) colon cancer patients. In all but one trial [11] the prognostic value of the LNR (other than pathological nodal involvement) was assessed in the presence of possible confounding covariates by Cox multivariate regression. This information is of a paramount importance because it would confirm that LNR is now considered to be an independent prognostic variable that has greater meaning than, and is superior to, the TNM-AJCC classification with regard to disease substaging in stage III disease.

Also selected four positive nodes, perfectly corresponding to the current pN staging system

[7], the best LNR value was 40% to be the most accurate in predicting DSS and OS, higher than other experiences from single institutions [11,12] (20%) or larger series [13] (30%), thus allowing to be confident with this method.

In our study, LNR was a robust prognostic factor for long-term outcome; surviving patients showed significantly lower LNRs than deceased patients, and compared with the number of metastatic and harvested nodes, LNR showed the widest area under the ROC curve confirming its statistical power. As already stated by Wang [14], although questioned by others [12,13], LNR prognostic significance held steady regardless of the number of harvested nodes, suggesting that LNR stratification could obviate a wrong downstaging due to failure to examine an adequate number of nodes.

On multivariate analysis, LNR was shown to be an independent prognostic factor for both disease-specific and disease-free survival rates (both  $p < 0.01$ ). According to this LNR cutoff value (40%), the hazard ratio for disease-specific survival was 0.18 (95% CI 0.075-0.44), corresponding to a 47% increase in the 5-year survival rate in patients showing a low LNR and a 82% reduction in the estimated relative risk of cancer-related death in this group.

Our results are consistent with an analysis by Moug et al., [15], who compared the number of positive LNs and the pLNR in both univariate and multivariate analysis predicting survival rates. pLNR maintained its significance as a prognostic factor in both DSS and OS, whereas the number of positive LNs was not found to be significant in OS ( $p = 0.07$ ).

#### Conclusion:

The ratio-based staging (pLNR) of CRC is a more accurate and clinically useful prognostic method than the number of positive LNs resected or the total number of LNs retrieved for predicting the course of patients with stage III CRC.

LNR was a robust prognostic indicator for node-positive colon cancers undergoing curative surgery. Because this ratio-based staging was demonstrated to reduce stage migration and to aid in identifying high-risk patients, application of the pLNR improved patient stratification in colorectal cancer and could be considered in future staging systems, it may be proposed as a standard tool for colon cancer staging.

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## دراسة الأهمية التنبؤية لنسبة الغدد الليمفاوية الإيجابية بالمقارنة مع العدد الإيجابي للغدد الليمفاوية لسرطان القولون والمستقيم المرحلة الثالثة والتي يتم معالجتها جراحيا

تم مراجعة السجلات الطبية لخمسة وخمسون مريضا بسرطان القولون والمستقيم المرحلة الثالث الذين يخضعون لإستئصال الورم السرطاني جذريا في دراسة إستيعادية بمراجعة المخططات الطبية الخاصة بهم من قسم علم الأورام الطبية بمستشفى القصر العيني بين يناير سنة ألفان وخمسة إلى ديسمبر ألفان وستة ومتابعة سجلاتهم لمدة خمس سنين من تاريخ إجرائهم للجراحة من حيث إرتجاع الورم بالجسم أو وفاتهم بسبب إنتشار الورم مع إنشاء علاقة تنبؤية مع العدد الإيجابي للغدد الليمفاوية ونسبة الغدد الليمفاوية الإيجابية لتحديد أيهما أكثر أهمية وقدرة على التنبؤ بالحالة المستقبلية الصحية لهؤلاء المرضى.

وقد أثبتت النتائج على قدرة نسبة العقد الليمفاوية الإيجابية على التغلب على العدد الإيجابي للعقد الليمفاوية بمنظور التنبؤ بإرتجاع الورم الخبيث بالجسم وأيضا على البقاء على قيد الحياة، وتقلص نظرية هجرة التدرج السرطاني بالقولون إذا ما قورنت بالعدد الإيجابي لغدد الليمفاوية المستأصلة، مما ينبغي إقتراح تطبيق هذه النسبة كأداة في أنظمة التدرج السرطاني للقولون والمستقيم بالمستقبل.