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Importance of Metastatic Lymph Node Ratio in Non-Metastatic, Lymph Node-Invaded Colon Cancer: A Clinical Trial

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Background: The aim of this study was to evaluate the prognostic importance of the metastatic lymph node ratio for stage III colon cancer patients and to find a cut-off value at which the overall survival and disease-free survival change.





Material/Methods: Patients with pathological stage III colon cancer were retrospectively evaluated for: age; preoperative values of Crp, Cea, Ca 19-9, and Afp; pathologic situation of vascular, perineural, lymphatic, and serosal involvement; and metastatic lymph node ratio values were calculated.

Results: The study included 58 stage III colon cancer patients: 20 (34.5%) females and 38 (65.5%) males were involved in the study. Multivariate analysis was applied to the following variables to evaluate significance for overall survival and disease-free survival: age, Crp, Cea, perineural invasion, and metastatic lymph node ratio. The metastatic lymph node ratio (<0.25 or ≥ 0.25) is the only independent variable significant for overall and disease-free survival.

Conclusions: Metastatic lymph node ratio is an ideal prognostic marker for stage III colon cancer patients, and 0.25 is the cut-off value for prognosis.

MeSH Keywords: **Colonic Neoplasms • Lymph Nodes • Prognosis**

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Background

Each year, more than 1 million people are diagnosed with colorectal cancer. As a result, 715 000 deaths were reported in 2010 around the world. In 1990, only 490 000 deaths were reported. Colorectal cancer is the second most common cancer in females and the third most common cancer in males [1,2]. Due to the epidemiologic effects of colorectal cancer, many observers attempt to study prognostic factors for cancer-related mortality and survival.

According to the American Joint Committee on Cancer, tumor-node metastasis (TNM) systems and non-metastatic, lymph node-invaded colon cancers are at the 3rd stage. As a result, lymph node invasion is the dominant prognostic factor for non-metastatic colon cancer and is the basic indicator for adjuvant treatment after curative resection. Some patients will have recurrence after curative resection, which may be due to residual nodal disease after insufficient lymphadenectomy. According to quality standards of the National Comprehensive Cancer Network (NCCN) and the American College of Physicians, a minimum number of 12 lymph nodes are advised for resection and pathological examination. Pathological examination of a minimum of 12 lymph nodes may help to correctly differentiate stage 3 patients from stage 1–2 patients. The metastatic lymph node ratio (MLNR) is the number of metastatic lymph nodes divided by the number of totally resected lymph nodes. The MLNR ranges between 0 and 1. Recent studies have shown the importance of the MLNR in estimating prognosis of colon cancer, showing that the MLNR is more valuable than the N value of the TNM stage [3].

The purpose of this study was to evaluate the prognostic importance of the MLNR in stage 3 colon cancer patients and to determine the cut-off value at which overall survival (OS) and disease-free survival (DFS) change.

Material and Methods

Fifty-eight third-stage colon cancer patients were included in this retrospective study. These patients were diagnosed and operated on at Vakif Gureba Training and Research Hospital (Istanbul, Turkey) between 2006 and 2011 and at Erzincan University Hospital (Erzincan, Turkey) between 2009 and 2014. A 4-year follow-up was included in the study. Follow-up protocols adhered to NCCN guidelines [4]. The files of the patients were scanned and age, pre-operative values of Crp, Cea, Ca19-9, Afp, pathologic vascular, perineural, lymphatic, serosal involvement, and MLNR values were imported into Microsoft Excel (2007). The correlation among these values and the effectiveness of these parameters with regards to OS and DFS were studied. A cut-off value of 0.25 was determined for the MLNR and the effect

Table 1. Survivals of each group.

Three-year survivals	Overall survival rate	Disease-free survival rate
MLNR <0.25 group	.883	.880
MLNR ≥0.25 group	.563	.540

of the MLNR on OS and DFS was studied. R0 resections were done on all patients. Exclusion criteria included patients who had to be operated on only urgently and patients with fewer than 12 resected lymph nodes. The power analysis of the study is 0.82 for MLNR value. This study was conducted according to the Declaration of Helsinki. Local ethics committee approval was obtained. Informed consent was obtained from all patients.

Statistical analysis

Descriptive statistics such as frequency, arithmetic mean, standard deviation, and percentage were used to analyze the data. Non-parametric Mann-Whitney U and chi-squared tests were used for comparison. Spearman's rho correlation coefficient was used for correlation analysis. The Kaplan-Meier method was used for survival analysis. Multivariate analysis according to Cox regression was conducted for the parameters that were meaningful for univariate analysis. A 95% confidence interval, combined with a p-value less than 0.05, was considered statistically significant. We used SPSS v 17.0 (IBM Corporation, Armonk, NY, USA) for statistical analysis.

Results

Fifty-eight patients were involved in this study: 20 females (34.5%) and 38 males (65.5%). The mean age was 59.2±13.8 years and the median of age value was 60. By the end of 4-year follow-up, 5 patients had died. All of the deceased patients had MLNRs ≥0.25. The 3-year survival rate for all patients was 74.3% and the DFS rate for all patients was 72.0%. The survival rates of each group are listed in Table 1.

Descriptive values for age, Crp, Ca19-9, Cea, Afp, MLNR, overall follow-up time, and disease-free follow-up time are listed in Table 2 and the pathologic involvement of vascular, perineural, lymphatic, and serosal invasions are listed in Table 3.

We list the correlations between age, Crp, Ca19-9, Cea, Afp, and MLNR in Table 4. As age increases, Cea, Afp, and MLNR values decrease. As the MLNR increases, Crp, Ca19-9, Cea, and Afp values increase.

As shown in Table 5, all variables except Afp were significant when compared with the MLNR groups.

Table 2. Descriptive values for age, Crp, Ca19-9, Cea, Afp, MLNR, overall follow-up time, and disease-free follow-up time.

	Min.	Max.	Mean	Std. Dev.
Age (years)	29	84	59.2	13.83
Crp (mg/dl)	.201	20.000	4.533	5.844
Ca19-9 (U/ml)	.600	695.000	33.449	93.268
Cea (ng/ml)	.605	244.000	15.956	44.867
Afp (ng/ml)	.610	4.210	1.762	0.957
MLNR	.034	0.929	0.286	0.247
Overall follow-up time (months)	8	48	35.69	12.735
Disease-free follow-up time (months)	6	48	35.29	13.456

Table 3. Descriptive values for pathologic involvement of vascular, perineural, lymphatic, and serosal invasion.

Invasion status	Frequency (n)	Percent (%)
Vascular	-	39
	+	19
Perineural	-	40
	+	18
Lymphatic	-	35
	+	23
Serosal	-	33
	+	25

As shown in Table 6, all pathological involvements were statistically significant compared with the MLNR groups.

The mean OS time of each MLNR groups for the 4-year follow-up is listed in Table 7. The log rank test yielded $p=0.011$ ($p<0.05$). The mean OS time of the group with MLNR <0.25 group was longer than the mean OS time of the group with MLNR ≥ 0.25 . The mean

DFS times of each of the MLNR groups for the 4-year follow-up are listed in Table 7. The log rank test result was $p=0.008$ ($p<0.05$). The mean DFS time of the group with MLNR <0.25 group was longer than the mean DFS time of the group with MLNR ≥ 0.25 .

The OS curves of the MLNR groups for the 3-year follow-up are shown in Figure 1 and the DFS curves of the MLNR groups for the 3-year follow-up are shown in Figure 2.

The variables that were statistically significant for OS and DFS in the univariate analysis, including age ($<$ or ≥ 60 years) ($p=0.003-0.043$), Crp ($<$ or ≥ 0.9 mg/dl) ($p=0.035-0.04$), Cea ($<$ or ≥ 5 ng/ml) ($p=0.032-0.048$), perineural invasion (negative or positive) ($p=0.042-0.04$), and the MLNR ($<$ or ≥ 0.25) ($p=0.001-0.002$); these parameters were used for multivariate analysis. Cox regression was also applied. As a result, only the MLNR ($<$ or ≥ 0.25) was statistically significant for OS and DFS (Table 8).

Discussion

For non-metastatic colon cancers, lymph node invasion is the most important prognostic factor. A correct evaluation is

Table 4. Correlation analysis of age, Crp, Ca 19-9, Cea, Afp, and MLNR.

Spearman's Rho	Age	Crp	Ca19-9	Cea	Afp	MLNR
Age	1.000					
Crp	-.206	1.000				
Ca19-9	.061	.459**	1.000			
Cea	-.387*	.124	.375**	1.000		
Afp	-.317*	.513**	.296*	.043	1.000	
MLNR	-.293*	.642**	.264*	.496**	.330*	1.000

* Correlation is significant at the 0.05 level (2-tailed); ** Correlation is significant at the 0.01 level (2-tailed).

Table 5. Comparison of MLNR groups with age, Crp, Ca 19-9, Cea, and Afp.

	MLNR groups	Frequency (n)	Mean	Std. dev.	U	p
Age (year)	<0.25	32	61.219	12.707	352.5	0.019*
	≥0.25	26	56.846	15.017		
Crp (mg/dl)	<0.25	32	3.143	3.472	369.0	0.032*
	≥0.25	26	5.662	7.081		
Ca19-9 (U/ml)	<0.25	32	28.980	33.055	264.5	0.018*
	≥0.25	26	38.950	135.725		
Cea (ng/ml)	<0.25	32	5.100	13.137	115.0	0.000***
	≥0.25	26	24.777	58.163		
Afp (ng/ml)	<0.25	32	1.667	1.138	414.0	0.975
	≥0.25	26	1.839	0.683		

Table 6. Pathological involvement status compared with MLNR groups.

Invasion status	<0.25	≥0.25	p
Vascular	-	30	0.04
	+	2	
	Total	32	
Perineural	-	28	0.03
	+	4	
	Total	32	
Lymphatic	-	32	0.000
	+	0	
	Total	32	
Serosal	-	29	0.009
	+	3	
	Total	32	

important for adjuvant treatment. To state that a patient is node negative, a large enough number of lymph nodes must be resected. Consensus guidelines set this threshold at 12 or above [4–7]. If enough lymph nodes cannot be resected, stage migration (the Will Rogers phenomenon) may be observed. Will Rogers stage migration states that for an increasing number of diagnoses, more disease-free people will be re-evaluated as patients. When these disease-free people (real patients) move from the disease-free people group to the patient group, the mean survival rates of people in the true disease-free group change. Similarly, the people who move will be healthier than patients in the previously-ill group. Therefore, the survival rates of patients in the group increase. In each group, there is a statistically significant increase in survival rate. Regardless of treatment changes, the early detection of cancer causes more time to pass in the patient group [8,9]. Because the MLNR does not cause Will Rogers phenomenon as N value of the TNM stage, it is a better prognostic marker for gastric cancers [10,11] and solid tumors [12,13].

Table 7. Mean overall survival time of each MLNR groups for four-year follow-up time.

Survivals	MLNR	Mean (months)			
		Estimate	Std. error	95% Confidence Interval	
				Lower bound	Upper bound
Overall survival time	<0.25	42.313	1.208	39.945	44.680
	≥0.25	31.367	2.802	25.874	36.859
	Overall	37.727	1.549	34.691	40.763
Disease-free survival time	<0.25	42.344	1.210	39.971	44.716
	≥0.25	30.838	2.883	25.187	36.488
	Overall	37.636	1.575	34.549	40.723

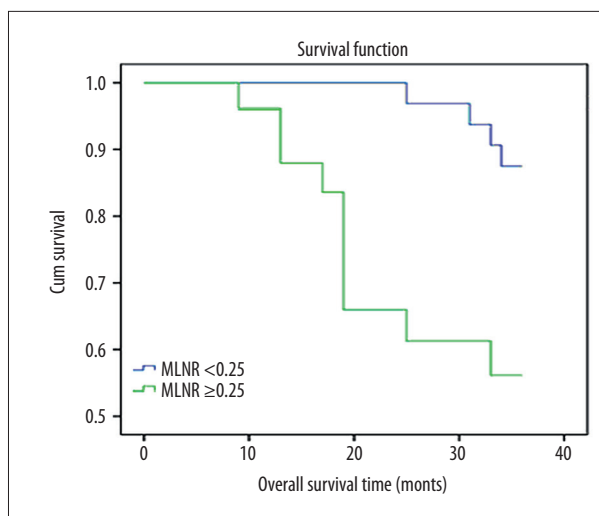


Figure 1. Overall survival curve according to MLNR < and ≥0.25.

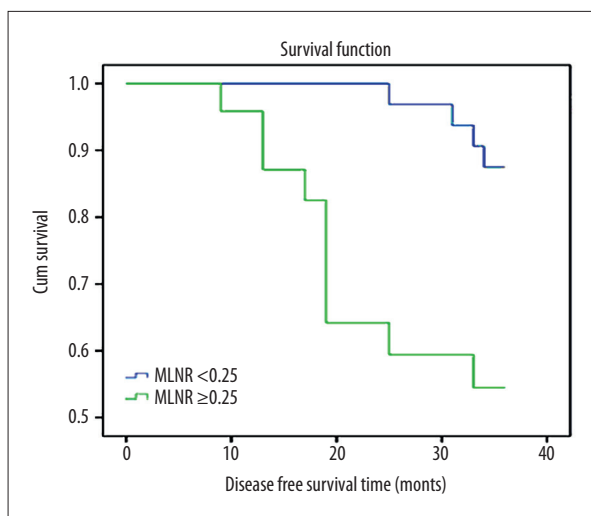


Figure 2. Disease free survival curve according to MLNR < and ≥0.25.

Table 8. Multivariate analysis of MLNR for survivals.

Survivals	p	Exp (B)	95.0% CI for Exp (B)	
			Lower	Upper
Overall survival	.042	1.712	.982	2.984
Disease-free survival	.039	1.736	.997	3.024

Table 9. Miscellaneous studies about MLNR at stage 3 colon cancer.

Author	Year	Nature	Number of patients	Cutoff value
Ramos	2010	Retrospective	29	0.25
Schumacher	1998–2004	Retrospective	57	0.18
Chin	1995–2003	Retrospective	490	0.4–0.7
Vaccaro	1980–2005	Retrospective	362	0.25
Park	1996–2006	Retrospective	318	0.059–0.23
Present	2006–2011/2009–2014	Retrospective	58	0.25

In the present study, as age decreases, Crp, Ca19-9, Cea, Afp, and MLNR values increase. These findings show the strength of the MLNR in the present study. Similar results (except Afp) were found when the MLNR was divided into 2 groups. The involvement status between the 2 groups (MLNR <0.25 and MLNR ≥0.25) was statistically significant in the present study. Since vascular, perineural, lymphatic, and serosal invasions reveal tumor aggressiveness and these properties are correlated with the MLNR ≥0.25 group in the present study, a poor prognosis for the MLNR ≥0.25 group is expected. Park et al. [14] constructed 3 groups based on the MLNR for individuals with stage 3 colon cancers who had 12 or more resected lymph nodes (Table 9). These authors found that the DFSs of

patients between the 3 groups were statistically significant. The DFS of the MLNR >0.23 group was 55%, comparable to the results of DFS for our MLNR ≥0.25 group (54%). The OS and DFS of our results were similar, which may be due to the delayed diagnosis of recurrent tumors and the aggressiveness of recurrent tumors.

Ramos-Esquivel et al. studied 3-year OSs and DFSs of 29 stage 3 colon cancer patients and determined a cut-off value of the MLNR of 0.25. In their retrospective study, the MLNR was the independent variable [15]. Schumacher et al. determined a cut-off value of the MLNR of 0.18 for the DFS of 57 stage 3 colon cancer patients who had more than 12 lymph nodes resected

[16]. Chin et al. found that the MLNR was the only independent variable for the 5-year DFS of 490 patients with stage 3 colon cancers. These authors also found that the N value of the TNM was a dependent variable [17]. Similar to the present study, Vaccaro et al. showed that the MLNR was an independent survey parameter and determined a cut-off value for the MLNR of 0.25 [18] (Table 9).

The certainty regarding metastatic lymph nodes increases as the number of resected lymph nodes increases. At the same time, prognoses can be improved by increasing the number of totally resected lymph nodes (i.e., achieving MLNR <0.25). In the TNM classification, stage 3 colon cancers are broken into 3 substages: 3a, 3b, and 3c. This convention combines the T and N stages of the tumor. This decreases the prognostic importance of lymph node involvement. Furthermore, 1 metastatic lymph node may cause a change in stage or stage migration if an insufficient lymph node resection is performed. However, this effect will not be so pronounced in the case of the MLNR. The number of metastatic lymph nodes remains constant in the case of sufficient lymph node resection. However, the MLNR may change according to the operation and is dependent on the surgeon. Therefore, the prognosis of the patient may be improved in higher-quality surgeries.

It is likely that the exact number of metastatic lymph nodes is affected by the pathological evaluation (micrometastasis or metastatic cells cannot be evaluated as metastasis by pathology). Therefore, increasing the number of resected lymph nodes will increase patient safety. In this case, the MLNR will be above 0.25 if the lymph node resection was insufficient. On the other hand, the MLNR will be under 0.25 if a sufficient resection was done. The 0.25 threshold may have only mathematical importance, because the number of metastatic lymph nodes that are not evaluated as being metastatic by pathology

will be reduced by increasing the number of resected lymph nodes. Therefore, the survival rate will increase because the patient will no longer have metastatic lymph nodes. In this viewpoint, the number of totally resected lymph nodes will be more important than the MLNR. An increased number of immune cells in colon cancer patients decreases lymph node metastasis and causes the MLNR to decrease. Furthermore, an increased number of immune cells reveals a strong host immunity or a less aggressive tumor biology, both of which lead to better survival. MLNR \geq 0.25 stage 3 colon cancer patients may be evaluated as stage 4 and aggressive adjuvant treatment such as oxaliplatin may be added to fluorouracil-based chemotherapies, which are used worldwide for the treatment for stage 3 colon cancers.

Conclusions

The disadvantage of the present study is the shortness of the follow-up time; however, recurrences were observed mostly within the first 2 years. There were fewer patients in the present study than in some other relevant studies, but patients who had fewer than 12 lymph nodes resected were excluded from the present study. This criterion increased the power of the study but decreased the total number of patients. Epidemiologic and experimental prospective studies are needed [19,20].

As a result, the MLNR is an ideal prognostic marker for stage 3 colon cancer patients. A cut-off value of 0.25 for the MLNR represents the point at which the prognosis deteriorates.

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