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Lymph node evaluation and survival after resection of colorectal cancer

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Abstract
Recent studies have demonstrated that lymph nodes ratio (LNR) might provide a significant prognostic role for colorectal cancer. We retrospectively analyzed the data of the patients with colorectal cancer and assessed a possible correlation between lymph node parameters and survival. We conducted a retrospective chart review of patients who underwent a radical colon surgery involving removal of mesocolic lymph nodes due to colorectal cancer. Prognostic significance of the removed lymph node number (LNs), metastatic LNs, lymph node ratio (LNR) and other factors were compared. This retrospective study included 190 patients (117 males and 73 females). The estimated survival period was found to be 87.70 months [confidence interval (CI) of 95% (80.64-94.76)]. LNR, LNs and N stage were found to have significant correlation with survival. Among these factors, LNR had the biggest correlation (r = 0 .138, P =0.028). Multivariate regression analysis of survival with lymph node parameters showed that LNR and N stage were significantly correlated with survival. However, LNR was found to be the most significant prognostic factor [P >0.0001, 95% CI; 3.12 (1.55-5.75)]. LNR is a better prognostic factor in patients with colorectal cancer compared to lymph node stage and number.

Keywords: Colorectal cancer, prognostic factors, lymph node metastasis, lymph node ratio, survival analysis

Introduction

Lymph node involvement appears as an important prognostic factor in non-metastatic colorectal cancer cases. Lymph node metastasis is a parameter that increases survival and local recurrence [1,2]. An accurate report about the status of lymph nodes, including harvested lymph node number (LNs) and metastatic node number, plays a vital role in making a decision about applying adjuvant chemotherapy or radiotherapy, as well as providing information on prognosis. However, there is controversy about how many lymph nodes need to be assessed in order to make an accurate colorectal cancer staging. The recommended lymph node number ranges from 6 to 18 in the literature, while the American Joint Committee on Cancer (AJCC) suggested that 12 or more lymph nodes should be assessed, and recent studies have recommended examining at least 9 to 12 lymph nodes in order to provide an accurate staging [3-6]. Furthermore, some researchers have reported that extended lymphadenectomy yields therapeutic benefit, while others have stated that the procedure merely offers a better accuracy in terms of colorectal cancer staging [7].

However, inadequate evaluation of lymph nodes remains problematic, consequently leading to inaccurate staging in the majority of colorectal cancer patients whose lymph nodes are examined in a limited number [8]. Recent studies have demonstrated that lymph nodes ratio (LNR), defined as the ratio of positive lymph nodes to the total number of lymph nodes examined, might provide a significant prognostic role for colorectal cancer [9-15].

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Objective

We retrospectively analyzed the data of the patients who underwent a radical colon surgery involving removal of mesocolic lymph nodes to assess a possible correlation between lymph node parameters, including the number of removed lymph nodes, LNR, lymph node stage (N), and survival.

Material and Methods

In this retrospective observational study, we conducted a retrospective chart review of patients aged 18 years or older who underwent surgery due to colorectal cancer at the Department of General Surgery, Turkey, between September 2005 and July 2015. The study was conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects.

All patients included in the study were provided with surgical operation by two surgeons. Surgical specimens of all subjects were assessed by 2 pathologists. The specimens were assessed by being fixed with 10% formalin

and embedded in paraffin. Patients were staged according to 7th edition of the AJCC TNM staging [3].

The patients were regularly and frequently followed up during the postoperative period. They were checked once in three months during first 2 years, and once in six months up to 5 years, and once a year after 5 years following surgical operation. During the follow-up, their full blood count, biochemical analyses, carcinoembryonic antigen levels, liver ultrasound and chest radiography were taken. Following surgical operation, colonoscopy was conducted once a year and once every two years afterwards.

The patients who had distant metastasis, recurrent colorectal cancer and multiple primary cancers or those who received neoadjuvant chemotherapy and those who died in the first 3 months postoperatively, or the patients lost to follow up were excluded from the study.

Surgical operations, pathological data including TNM stage, the number of removed lymph nodes, positive lymph node(s), and findings, surgeries and outcomes including death during follow-up, and hematological, biochemical and radiographic analyses of the patients were recorded in a computer database. As regard to the total number of retrieved lymph nodes, the patients were divided into three groups: those who had their <12 or 12-18 or >18 nodes retrieved. LNR was defined as the ratio of positive nodes to the total number of lymph nodes removed, and the LNR was divided into four groups according to quartile: LNR1 (<0.11), LNR2 (0.111-0.200), LNR3 (0.200-0.429) and LNR4 (≥0.429).

Statistical analysis

Power analysis was not conducted. Statistical analysis was performed using a computer software package (SPSS for Windows, version 13.0; SPSS Inc., Chicago, IL, USA). Statistical analysis data [mean ± standard deviation, (minimum-maximum) or confidence interval of 95%] were presented as %. The significance limit in all statistical analyses was adopted as a P <0.05 value. Frequency tests, Spearman's Rho nonparametric correlation tests and Kaplan-Meier survival tests were conducted. Multivariate and univariate regression tests were implemented.

Results

This retrospective study included 265 patients who had colorectal cancer surgery. However, 75 patients were excluded due to several reasons (25 patients had distant metastasis, and 10 patients had recurrent colorectal cancer, and 5 patients had multiple primary cancers, and 20 patients received neoadjuvant chemotherapy, and 10 died in the first 3 months postoperatively, and 5 were lost to follow up) Consequently, the analysis included the remaining 190 patients who met the study criteria.

Of 190 patients, 117 were males and 73 were females. The average age of the patients was 66.9±13.9. Tumor localizations were mostly in the rectum (60 patients, 31.6%) and sigmoid colon (58 patients, 30.5%). The average lymph node number was 16.24± 11.29 (1 -105). The average follow-up period of the patients was 40.21±26.68 months. 106 patients postoperatively received 5 – fluorouracil -based chemotherapy. The estimated survival period was found to be 87.70 months [confidence interval of 95% (CI) (80.64-94.76)] (**Figure 1**).

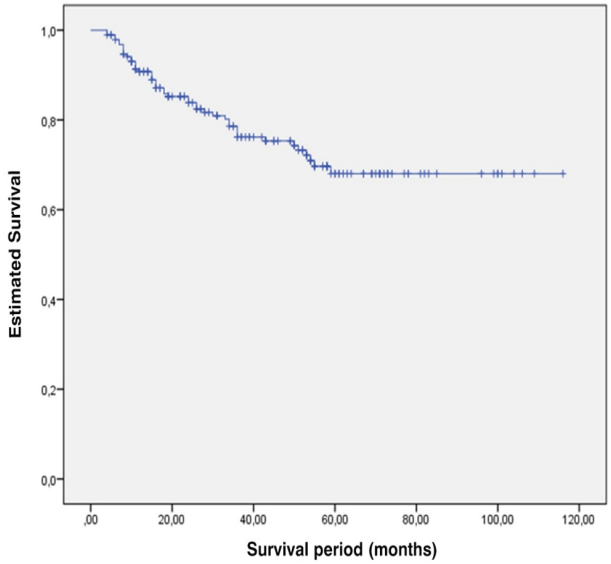

Figure 1. Kaplan-Meier overall survival curves for 190 patients resected for colorectal cancer.

Table 1 summarizes the characteristics of the patients and their cancer details. According to T stage, the rate of patients with T4 was found to be the largest patient group with 46.8% (89 patients). According to N stage, the rate of patients with N0 was found to be the largest patient group with 58.9% (112 patients). The patient group with the largest lymph node removal number had 12-18 lymph nodes removed, with a rate of 44.7% (85 patients). The patient group with the largest LNR had >0.111 with a rate of 64.2% (122 patients). The number of patients surviving follow-up was 145 (76.3%) (Table 1).

Primarily, LNR, LNs and N stage, as factors whose impact on survival was being investigated, were found to have significant correlation with survival (Table 2). Among these factors, LNR had the biggest correlation (r = 0 .138, P =0.028) (Figure 2, 3 and 4, respectively).

Table 1. ThePatient -Tumor Characteristics and overall survives

Factors	n	%	OS	P-value
Age, y				0.750
≤55	43	22.6	81.4	
>55	147	77.4	74.8	
Sex				0.996
Male	117	61.6	75.9	
Female	73	38.4	77.0	
Tumor Stage				0.038
T1-2	38	2.6	92.1	
T3	63	33.2	81.0	
T4	89	46.8	66.3	
N stage				0.010
N0	112	58.9	83.0	
N1	45	23.7	71.1	
N2	33	17.4	60.6	
Tumor size, cm				
≤5	147	77.3		
>5	43	22.7		
Lymphatic- vascular invasion				0.056
Negative	80	42.1	83.5	
Pozitif	110	57.9	71.5	
Perineural invasion				0.214
Negative	129	67.9	79.8	
Positive	61	32.1	68.9	
Total LN examined				0.518
<12	58	30.5		
12-18	85	44.7		
>18	47	24.7		
LNR				0.001
LNR1	122	64.2	83.6	
LNR2	22	11.6	77.3	
LNR3	11	5.8	63.6	
LNR4	35	18.4	54.3	

*LNR = lymph node ratio; N, lymph node.

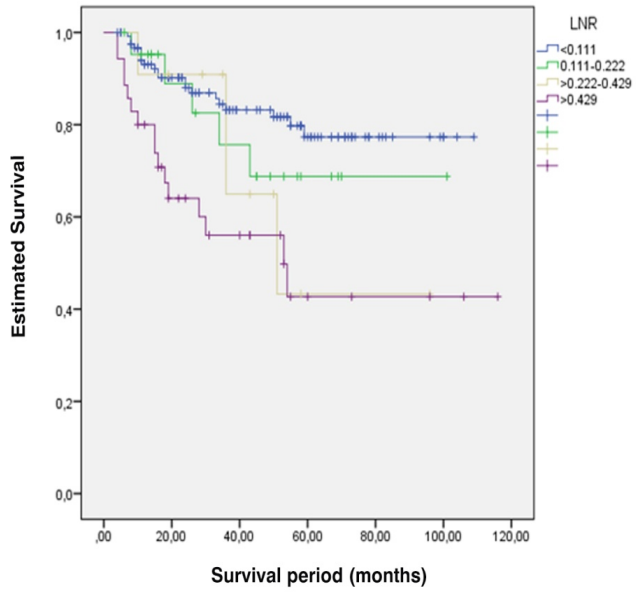

Figure 2. Kaplan–Meier overall survival curves for patients with lymph nodes ratio (LNR).

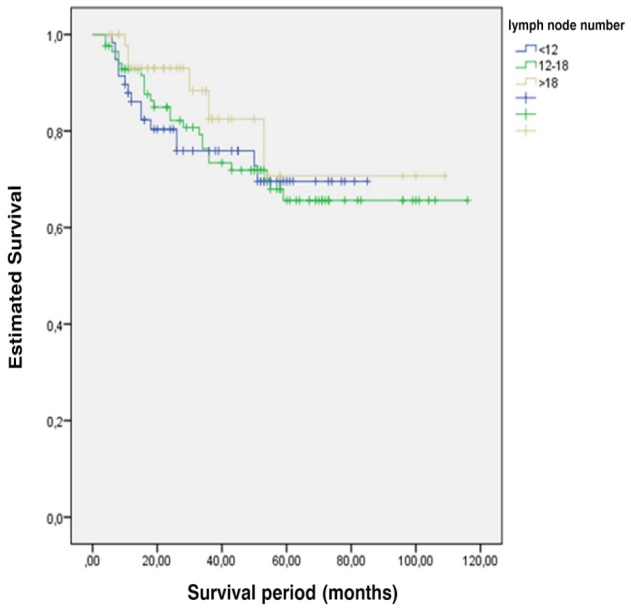

Figure 3. Kaplan–Meier overall survival curves for patients with lymph node number(LNs).

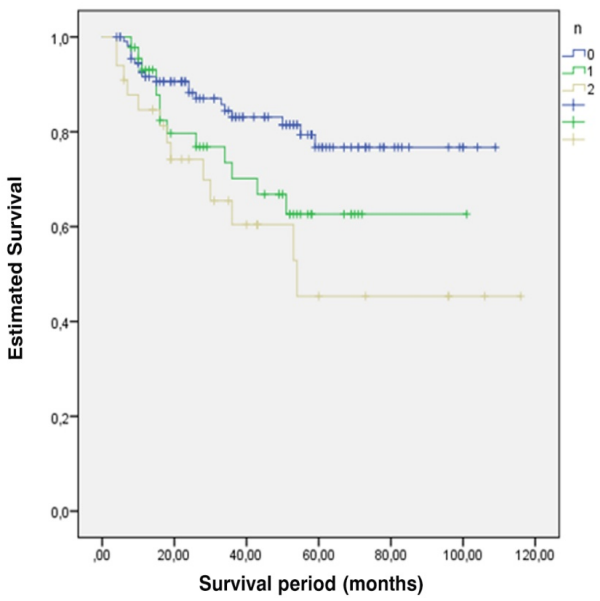

Figure 4. Kaplan–Meier overall survival curves for patients with N stage.

Table 2. Factors Affecting Survival.

+	r-value	P-value
LNR	0.138	0.028
N stage	0.121	0.041
LNs	0.124	0.044

*LNR = lymph node ratio; N, lymph node; LNs, LN number.

There was a significant association between removed lymph node number and lymph node stage (N) (r = 0.822, P <0.0001) (Table 4). Yet, no significant association was found between removed LNs and LNR and survival (r = 0.025, P =0.85 and r=0.134, P =0.065, respectively) (Table 3).

Table 3. Correlation between removed lymph node number, and LNR, N and survival

LNs	r-value	P-value
LNR	0.025	0.852
N stage	0.822	<0.0001
Survival	0.134	0.065

*LNs, LN number; LNR = lymph node ratio; N, lymph node.

Table 4. Univariate regression analysis of survival and some parameters

		P-value
Age (≤55/>55)	43/147	0.376
Sex (M/F)	117/73	0.920
LNR		<0.0001
N stage		0.002
LNs		0.003

*LNR = lymph node ratio; N, lymph node; LNs, LN number.

Univariate regression analysis of survival with some parameters was conducted, and LNR, N stage and LNs were significantly associated with survival. The biggest significance was in LNR (P <0.0001). However, no significant association was found in terms of age and sex (Table 4).

Multivariate regression analysis of survival with lymph node parameters was conducted, and LNR and N stage were found to be significantly correlated with survival. LNR was found to be the most significant prognostic factor [P >0.0001, 95% CI; 3.12 (1.55 - 5.75)]. However, LN did not appear as a prognostic factor (Table 5).

Table 5. Multivariate regression analysis of survival and some parameters

	(95% CI)	P-value
LNR	3.12 (1.55-5.75)	<0.0001
N stage	2.27 (1.25-4.78)	0.016
LNs	1.32 (0.75-2.78)	0.064

CI = confidence interval; *LNR = lymph node ratio; N, lymph node; LNs, LN number.

There was a significant correlation with N stage in patients whose removed lymph nodes numbered less than 12. It did not have a significant correlation with LNR (r=0.850, P < 0.0001 and r = 0.025, P =0.852, respectively) (Table 6).

Table 6. The correlation between LNR and N stage in patients whose removed lymphnode number is less than 12

	r-value	P-value
LNR	0.025	0.852
N stage	0.850	<0.0001

*LNR = lymph node ratio; N, lymph node.

Patients with N1 and N2 had significant correlation primarily in terms of LNR and LN (Table 1). It was found that there was a strong correlation between N1 and N2 stage, and LNR (r = 0.610, P <0.0001) (Table 7).

Table 7. Correlation between LNR, and LNs and stage in patients with N1 and N2

	r-value	P-value
LNR	0.610	<0.0001
LNs	0.281	0.013

*LNR = lymph node ratio; N, lymph node; LNs, LN number.

Discussion

A number of factors are taken into consideration while evaluating prognosis in patients with colorectal cancer. Lymph node positivity is one of such significant parameters [16,17]. There are ongoing studies and conflicts in the literature regarding presence of lymph node metastasis, number of metastatic lymph node, number of lymph node removed during resection, radical lymph node dissection and LNR. 7th edition of the AJCC staging system for colorectal cancer suggests that the number of positive nodes provides basis for N staging, and TNM classification of malignant tumors has adopted the method of stage classification by the number of lymph node metastases (LNM) [3,18]. Moreover, postoperative

adjuvant chemotherapy is suggested as a treatment for colorectal cancer with positive nodes [19].

Removal and pathologic examination of minimum 12 nodes for resectable primary colorectal cancer is advised by the National Comprehensive Cancer Network (NCCN) [20]. Biologically, the number 12 does not have any special significance, but it is possibly drawn from a statistical probability distribution. In such a distribution, after more than 12 nodes are assessed, there will be quite small chance of missing any positive mesenteric nodes [21]. There is actually no agreement upon the optimal number of lymph nodes to be removed [22,23].Thus, there are large variations in the number of LNs reported with colectomy. This could be a result of different patients, pathologists, surgeons and several other factors involved [7]. A recent study found that rather than the operating surgeon, the pathologist was the dependent factor in lymph node harvest in multivariate analysis [24].

Surgical resection quality appears as a significant factor. This stems from the fact that a surgeon is required to provide sufficient amount of specimen consisting of the segment of intestine with tumor ingredients and its related mesentery up to the level of the origin of the draining vessels. Surgical quality could be indicated by factors such as surgeon or hospital volume since these two have been shown to associate with outcomes such as local failure rates after surgical treatment of colorectal cancer, long-term survival and other malignancies [25-27].

It has been shown that the increase in both absolute lymph node harvest and prognosis for the patients are induced by radical or complete mesocolic excision [28,29]. The reports from Europe, Japan and USA have suggested more radical surgery for treatment of colon cancer [30-31]. In addition, the presence of association between increased survival and evaluation of an adequate number of lymph nodes has been found by a number of observational studies [17,32,33]. Yet, some recent studies yielded results that contradict such findings [34-37]. As a result of their evaluation of 329 patients with Stage III colorectal cancer, Tsikitis et al. argued that the number of total lymph node removed does not have any prognostic effect on cancer-specific and disease-free survival [34].

In a study conducted in the USA between 1981 and 2001 investigating 116995 patients, it was found that accepting sufficient number of lymph node to be 12, proper lymph node sampling was only achieved in 37% of the patients, and the number of average lymph node removed was 9 [8]. Several studies have reported that few patients in the United States, Canada, France, the Netherlands, or Sweden are undergoing an adequate lymph node evaluation [38-41].

In the present study, while average number of removed lymph node was 16.24, lymph node dissection involving more than recommended 12 lymph nodes was conducted in 69.4% of the patients, and we found that a statistically significant increase was marked in overall survival as the number of removed lymph node increased. Nevertheless, our study included a small population and covered patients with colon cancer as well as those with rectal cancer.

Increased number of removed lymph nodes will possibly increase the number of positive nodes, and this will consequently lead to a higher N stage. This stage shift was first defined by Feinstein et al. in 1985 [42], and was termed as Will Rogers phenomenon. Likewise, while the number of removed lymph node increased in our study, a shift took place in N stage classification.

LNR is the ratio of metastatic lymph nodes to the total number of lymph nodes examined [43,44]. It was first investigated in gastric cancer, and was indicated as a significant prognostic factor in some subgroups of patients with stomach cancer containing lymph node involvement. The association between LNR and survival was first researched by Berger et al [45] and they stated that LNR was found to be a significant prognostic factor affecting survival, disease-free survival and cancer-specific survival in the group where 10 and more lymph nodes were removed among 3411 patients. In the study conducted by Rosenberg et al [43] and published in 2008, 3026 patients who went through surgery between 1982 and 2006 were examined, and LNR, lymph node stage, removed lymph node number, T value, M value, resectability and tumor grade were found to be independent prognostic factors associated with survival, and LNR was indicated to be a better prognostic marker compared to lymph node stage. Wang et al [9] reported that LNR's prognostic significance is independent of the number of total lymph nodes removed. The present study found that LNR is an effective factor on prognosis regardless of the cases where lymph node dissection is sufficient or insufficient, and our findings were consistent with the other studies [46-49]. However, Noura et.al [44] have recently reported an interesting and somewhat more cautious editorial and stated that even though the LNR seemed to be a more reliable prognostic factor, in reality its validity could not be completely agreed upon.

The fact that increased number of removed lymph nodes also increases the chances of pathologic stage change of such nodes is something known in general. Several studies argued that LNR is not affected by the number of the lymph nodes removed. The present study found a correlation between the number of positive lymph nodes and the number of removed lymph nodes, but still there was no correlation between LNR and the total number of removed lymph nodes. Moreover, LNR in the patient group with less than 12 removed lymph nodes (58 patients 30.5%) (inadequate lymph nodes group) was not affected by the number of lymph node removed. LNR was the

parameter having the highest correlation with survival compared to N stage and LNs. We found through multivariate analysis that LNR had the highest correlation with survival.

Our study has several limitations. Firstly, it has limitations of having a retrospective nature. Secondly, the study has relatively small sample size from a single center. Thirdly, our sample was heterogeneous, including colon and rectal cancer. Fourthly, it would be inadequate to evaluate prognosis in patients with colorectal cancer only through lymph node even though lymph node is a quite important prognostic factor. These shortcomings reduce the power of the results from our study and limit their generalizability.

In the retrospective and single-center study, LNR is a better prognostic factor in patients with colorectal cancer compared to lymph node stage and number. Therefore, we believe that LNR might provide better insight in evaluation of lymph node compared to N stage. After reaching a consensus on LNR cut-off value, which largely varies in the literature, future prospective studies might yield more valuable prognostic information using LNR.

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