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RESEARCH ARTICLE

Impact of Lymph Node Ratio as a Prognostic Factor for Survival in Colorectal Cancer Patients

Murat Bulut Özkan[1], Ahmet Erdoğan[2], Cem Emir Güldoğan[3], Erdinç Çetinkaya[4], Ahmet Keşşaf Aşlar[5]

[1]Hitit University Faculty of Medicine, Department of General Surgery, Çorum, Turkey
[2]Elbistan State Hospital, Clinic of General Surgery, Kahramanmaraş, Turkey
[3]Liv Hospital, Clinic of General Surgery, Ankara, Turkey
[4]Ankara City Hospital, Clinic of General Surgery, Ankara, Turkey
[5]Ankara Yıldırım Beyazıt University Faculty of Medicine, Department of General Surgery, Ankara, Turkey

ABSTRACT

Aim: The aim of this study was to investigate the impact of the ratio of metastatic lymph nodes to total harvested lymph nodes on survival rates.
Method: Data from patients with colorectal cancer undergoing surgery in Ankara Numune Training and Research Hospital, Clinic of General Surgery between June 2010 and June 2015 was retrospectively analyzed. We gathered data about patients' age, gender, operational status (elective or emergency), operation format (with laparotomy or laparoscopic), performed procedures, localization of the tumor, TNM stage, Dukes' stage, adjuvant/neoadjuvant chemoradiotherapy history, harvested lymph nodes, lymph node ratio (LNR) and overall survival. We conducted univariant and multivariant analyses to determine the relation between LNR and survival.
Results: Forty-five patients were excluded, resulting in a study cohort of 391 patients with a mean age of 62.7±13.7 years, of whom 234 (59.8%) were male. Based on the results of univariant analysis, the cut-off values for LNR 0.2 and 0.5 showed a significant association with survival (LNR: 0.2 $p<0.05$ and LNR: 0.5 $p<0.05$). These LNR values maintained a significant relationship with survival after multivariant analysis (LNR: 0.2 $p<0.05$ and LNR: 0.5 $p<0.05$).
Conclusion: In this retrospective study LNR was a significant prognostic factor for survival in patints undergoing surgery for colorectal cancer. To determine the prognosis of the patients with suboptimal lymph node yield and decide the adjuvant therapy choices, LNR can be used as a helpful indicator with the total number of harvested lymph nodes and the number of positive lymph nodes.
Keywords: Colon cancer, rectal cancer, lymph node ratio

Introduction

Colorectal cancer is one of the most common cancers, both globally and in Turkey, and is also one of the leading causes of cancer-related deaths. The prevalence is 24 per 100,000 in men and 15 per 100,000 women in Turkey.[1]

The stage of the disease varies according to the degree of invasion of the tumor (T), the number of metastatic lymph nodes (N), and the presence of distant metastases (M). At least 12 (10-14) lymph node sampling is required for an accurate N-staging.[2] Although a sample of 12 lymph nodes seems sufficient for accurate staging, studies have shown that removing more lymph nodes affects survival and causes a stage shift in some patients.[3,4] In the last few years, there have been studies suggesting that not only the number of lymph nodes removed but also the ratio of the number of metastatic lymph nodes to the total number of lymph nodes removed, called the lymph node ratio (LNR) should be used as a prognostic factor.[5]

TNM stage is the most important prognostic factor. While a 5-year survival of over 90% is expected in stage 1 patients, this rate is around 10% in stage 4 patients.[6] Tumor depth, the number of metastatic lymph nodes, and presence of metastases adversely affect survival separately. Despite the recommendation of sampling at least 12 lymph nodes for accurate TNM staging, after neoadjuvant protocols there has been a tendency for a decrease in the number of lymph nodes removed. In these patients, there have been reports

Address for Correspondence: Murat Bulut Özkan MD, Hitit University Faculty of Medicine, Department of General Surgery, Çorum, Turkey
E-mail: bulutozkan@gmail.com **ORCID ID:** orcid.org/0000-0003-4683-3772
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that the positive LNR is reliable to both decide on the proper adjuvant therapy and make a more accurate decision about the prognosis have started to appear recently.[7,8]

Materials and Methods

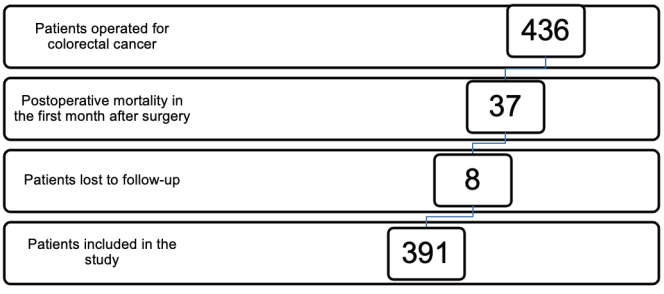
This study retrospectively analyzed the records of patients who were operated for colorectal cancer in Ankara Numune Training and Research Hospital between June 2010 and June 2015. Demographic data, date of surgery, tumor location, which operation was performed, whether the operation was emergency or elective, whether the procedure was conservative or laparoscopic, and whether the patient received adjuvant or neoadjuvant chemo/radiotherapy were examined. Disease parameters collected included the stage of the tumor, the total number of removed lymph nodes, the number of positive lymph nodes, the ratio of the number of positive lymph nodes to the total number of lymph nodes (lymph node positivity rate), the grade of the tumor, the stage according to the Dukes' (modified Astler Coller) classification, and the presence of metastases examined. Data such as survival, disease-free survival, presence of recurrence, time of recurrence, and date of death were analyzed in the postoperative follow-up.

Data from a total of 436 patients who were operated on for colorectal cancer between these dates were available. However, 45 patients were excluded from the study because: eight were lost to follow-up; 28 died in the early postoperative period (14 emergency surgery, 14 elective surgery); and nine died in the first month (three emergency, six elective surgery) (Flow Chart 1).

Approval for this study was obtained from the Ankara Numune Training and Research Hospital Clinical Research Ethics Committee (approval number: 734/2016). All patients informed consent was obtained.

Statistical Analysis

Statistical analysis was performed using the SPSS, version 23 (IBM Inc., Armonk, NY, USA). Chi-square test and univariate analysis test were used for descriptive statistical analyzes between groups. The Kaplan-Meier method was used for the analysis of survival times. The multivariate analysis test was used to analyze the factors affecting survival. A p-value of <0.05 was accepted for statistical significance.



Flow Chart 1. Flow chart of patient selection

Results

Of the study cohort of 391 patients, 157 (40.2%) were female, and 234 (59.8%) were male. The ages of the patients ranged from 32 to 95. Therefore, the mean ± standard deviation age was 62.7±13.7 years, ranging from 32 to 95 years.

Of the operations performed, 89 (22.8%) were performed as an emergency, and the remaining 302 (77.2%) were performed electively. The procedures of 63 (16.1%) patients, mostly after 2013, were completed laparoscopically, and the operations of 15 patients (3.8%) were started laparoscopically and switched to laparotomy for various reasons. The remaining 313 cases (80.1%) were performed by laparotomy. All emergency cases were performed by laparotomy.

Tumor location was as follows: rectum n=148 (38%); sigmoid colon n=96 (24.7%) and the cecum n=48 (13.3%). Tumors were staged according to the cancer staging atlas published by the American Joint Committee on Cancer in 2012. Tumor staging was: n=4 (1.0%) carcinoma *in situ* (Tis); T1-stage n=17 (4.3%); T2-stage n=25 (6.4%); T3-stage n=137 (35.0%); and T4-stage accounted for more than half of cases, n=204 (52.2%). Thus very few cases were diagnosed at an early stage. Therefore, 4 (1.0%) patient were diagnosed as stage 0, 37 (9.6%) patient as stage 1, 179 (46.5%) patient as stage 2 and 117 (30.4%) patient as stage 3, and 48 patients (12.5%) had metastatic disease at the time of diagnosis.

In terms of overall survival 297 (75.9%) of 391 patients survived, and 94 (24.1%) died. When the univariate analyzes of parametric data on survival was examined, there was no statistical relationship between gender and survival. Subtotal colectomy tended to be associated with the highest mortality rate, but there is no statistical correlation between the operations performed and survival. When the survival of the patients was assessed in terms of surgery technique, the survival of cases performed laparoscopically was higher, probably as a result of selection of patients suitable for laparoscopy and it was notable that none of the emergency cases was operated with laparoscopy. The survival of emergency cases was found to be lower than that of elective cases.

The survival rates of our population according to TNM stage, N-stage, and pathological grade of the tumor decrease as the stage and grade increase, which is consistent with the general population. While there are very low mortality rates in stage 0 and stage 1 patients according to TNM stage, we see mortality rates up to 41% in stage 4 patients.

When patients were stratified into groups according to the N-stage of the TNM classification, there were 235 patients in the N0 stage group, 107 patients in the N1-stage, and 42 patients in the N2-stage. In the survival analysis according to N-stage, the N-stage was found to be associated with survival. As seen in Table 1, when the LNR was set at 0.2, the survival rate of 58 patients above this rate was 46.6%, while the survival rate of 333 patients below this rate was 81.1.2%. When the LNR was set at 0.5, the survival rate was 42.9% in 28 patients above this value and 78.5% in 363 patients below this value. These results suggest a statistically significant relationship between LNR and survival.

The age, total lymph node counts, positive lymph node counts, LNR and follow-up times of living and deceased patients were compared by univariate analysis (Table 2).

Table 1. Survival rates by lymph node characteristics

	Total	Alive	Dead	p
LNR: 0.2				
LNR <0.2	333	270 (81.1)	63 (18.9)	<0.001*
LNR >0.2	58	27 (46.6)	31 (53.4)	
LNR: 0.5				
LNR <0.5	363	285 (78.5)	78 (21.5)	<0.001*
LNR >0.5	28	12 (42.9)	16 (57.1)	
N-stage				
N0	235	192 (81.7)	43 (18.3)	
N1	107	73 (68.2)	34 (31.8)	0.012*
N2	42	29 (69.0)	13 (31.0)	

Data are shown as n (%). LNR: Lymph node ratio, *: Statistically significant

The analysis of deaths showed that 69.1% of the deaths occurred within the first 24 months. In summary, age, the low total number of lymph nodes, a high number of positive lymph nodes, a high rate of positive lymph nodes, and a short follow-up period are statistically associated with poor survival outcomes.

Subsequently, multivariate analysis was performed to assess factors associated with survival. According to the results obtained when the parameters of gender, surgery status (emergency/elective), TNM stage, pathological grade, adjuvant/neoadjuvant chemo/radiotherapy history, N-stage, and LNR as 0.2 and 0.5 were included in the model, the TNM stage, pathological grade, adjuvant chemotherapy, N-stage, and LNR >0.2 had an effect on survival (Table 3). This model suggested that a positive LNR of 0.5 had no effect on survival because, by definition those with a LNR >0.2 also included those with a LNR >0.5. For this reason, those with a LNR >0.5 statistically reduce the effect. Therefore, we created a new model to investigate the effect of using a 0.5 LNR threshold value on survival which only included the parameter of LNR >0.5 in the model (Table 4). In this new model TNM stage, pathological grade, history of adjuvant chemotherapy, neoadjuvant radiotherapy, and LNR >0.5 were associaited with survival this time.

The relationship between N-stage, positive LNR and survival was examined by performing a projection analysis with Kaplan Meier. This showed that the average life expectancy in N0 was approximately 51 months, the average life expectancy in a patient in N2 stage was approximately 40 months. As seen in Figure 1, there was a significant difference between survivals according to lymph node stage.

In the projection analysis using a threshold value of 0.2 for the positive LNR, the average life expectancy in patients

Table 2. Univariate analysis results for non-parametric data

		Age (years)	Total LN	Positive LN	LNR	Follow-up period
	Mean	61.38	16.38	1.13	0.0672	27.3367
	Median	61.00	15.00	0.00	0.0000	25.0000
Alive	Standard deviation	13,597	11.981	2.463	0.15616	18.54180
	Minimum	32	0	0	0.00	2.00
	Maximum	89	65	17	1.00	66.00
	Mean	66.84	12.29	1.99	0.1914	19.2234
	Median	68.50	9.00	1.00	0.0400	15.5000
Dead	Standard deviation	13,093	9.487	4.007	0.28855	14.21430
	Minimum	25	0	0	0.00	2.00
	Maximum	95	41	28	1.00	56.00
p		0.001*	0.001*	0.003*	0.001*	0.001*

LN: Lymph node, LNR: Lymph node ratio, *: Statistically significant

Table 3. Multivariate analysis results - 1

Effect	Model fitting criteria	Likelihood ratio tests		
	-2 Log likelihood of reduced model	Chi-square	df	p
Intercept	182,716[a]	0.001	0	-
Gender	182,784	0.068	1	0.794
Emergency/elective	182,761	0.046	1	0.831
TNM stage	193,804	11,088	4	0.026*
Grade	196,600	13,884	3	0.003*
Adjuvant chemotherapy	190,019	7,303	1	0.007*
Neoadjuvant chemotherapy	184,006	1,290	1	0.256
Adjuvant radiotherapy	184,215	1,499	1	0.221
Neoadjuvant radiotherapy	186,327	3,611	1	0.057
LNR >0.2	191,355	8,639	1	0.003*
LNR >0.5	183,777	1,061	1	0.303
N-stage	190,951	8,235	2	0.016*

*: Statistically significant, LNR: Lymph node ratio

Table 4. Multivariate analysis results - 2

Effect	Model fitting criteria	Likelihood ratio tests		
	-2 Log likelihood of reduced model	Chi-square	df	p
Intercept	188,583[a]	0.001	0	-
Gender	188,635	0.052	1	0.819
Emergency/elective	188,754	0.172	1	0.679
TNM stage	199,355	10,773	4	0.029*
Grade	204,167	15,585	3	0.001*
Adjuvant chemotherapy	194,220	5,637	1	0.018*
Neoadjuvant chemotherapy	190,807	2,225	1	0.136
Adjuvant radiotherapy	189,901	1,318	1	0.251
Neoadjuvant radiotherapy	193,389	4,806	1	0.028*
LNR >0.5	197,385	8,802	1	0,003*
N-stage	190,675	2,092	2	0,351

*: Statistically significant, LNR: Lymph node ratio,

with a LNR<0.2 was approximately 51 months, and the life expectancy in patients with a LNR >0.2 was approximately 34 months (Figure 2) Similarly,when the LNR threshold was set at 0.5, the average life expectancy in patients with

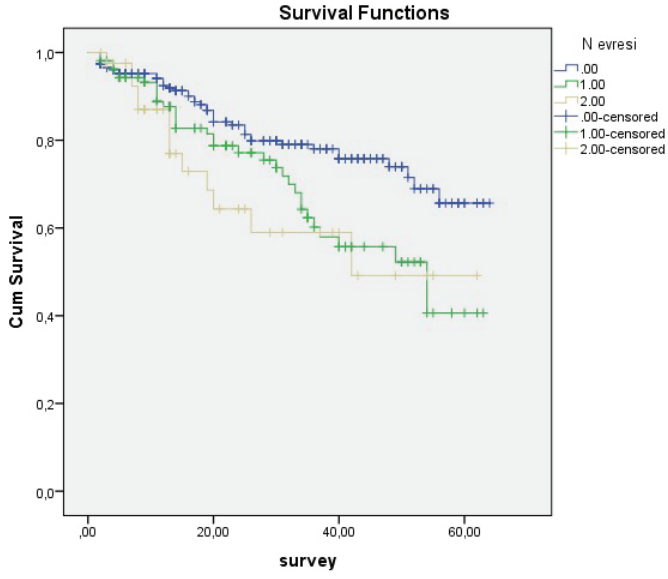


Figure 1. Projection analysis between lymph node stage (N) and survival

LNR<0.5 was approximately 49 months, while the average life expectancy in those with LNR >0.5 was approximately 33 months (Figure 3).

The estimated life expectancy of patients with insufficient lymph node number, when the LNR threshold was 0.5, was approximately 42 months for those with a LNR <0.5 and approximately 33 months for those with a LNR >0.5 (Figure 4).

The patient population was limited to only lymph node-positive patients and this resulted in a sub-group of 117 patients. Univariate analysis of this sub-group showed

that patient gender, the operation performed, emergency/elective status, and the type of operation had no effect on survival but the pathological grade of the tumor and LNR were found to have an impact on survival. When the LNR threshold value was set at 0.2, the survival rates were 79.0% in patients with LNR <0.2, while it was 58.3% in patients with LNT >0.2 (p<0.05). Similarly using a LNR threshold of 0.5, the survival rate was 74.8% in patients with LNR <0.5 and 57.1% in patients with LNR >0.5 (p>0.05).

In this sub-group using projection analysis and a LNR threshold of 0.2, the estimated life expectancy was approximately 40 months for LNR >0.2 and significantly longer at 49 months for LNR <0.2 (Figure 5). Repeating this analysis with an LNR threshold of 0.5 showed the estimated life expectancies to be 35 and 47 months for patients with LNR >0.5 and <0.5, respectively (Figure 6) which was significantly different.

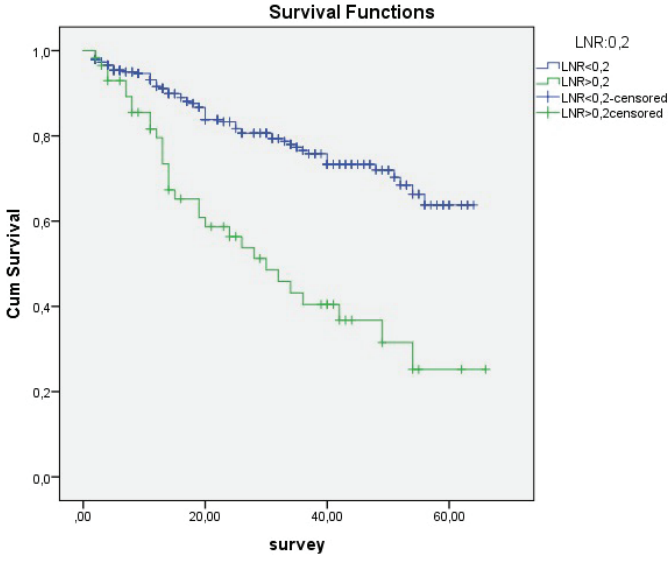


Figure 2. Projection analysis between lymph node ratio (LNR) and survival (LNR is accepted as 0.2)

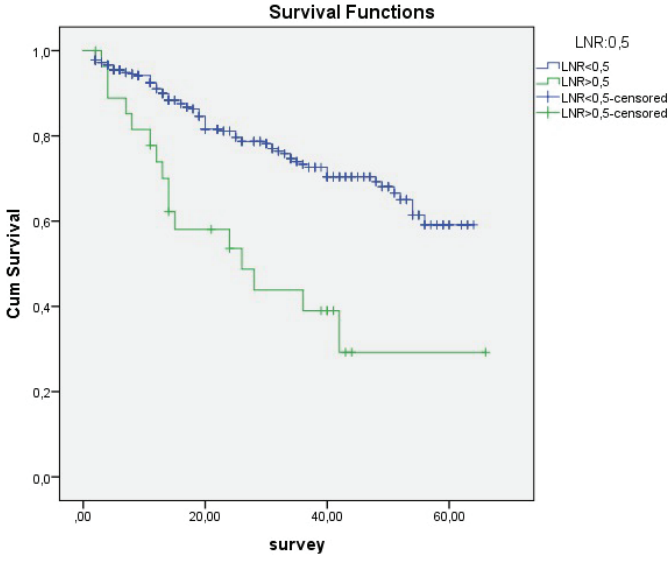


Figure 3. Projection analysis between lymph node ratio (LNR) and survival (LNR is accepted as 0.5)

Discussion

Colorectal cancer is one of the most common cancers in the world and one of the most common causes of death. Most (90%) cases occur in people aged 50 and over.[9] However, in recent years, there has been an increase in the incidence of colorectal cancer among the young population in Western

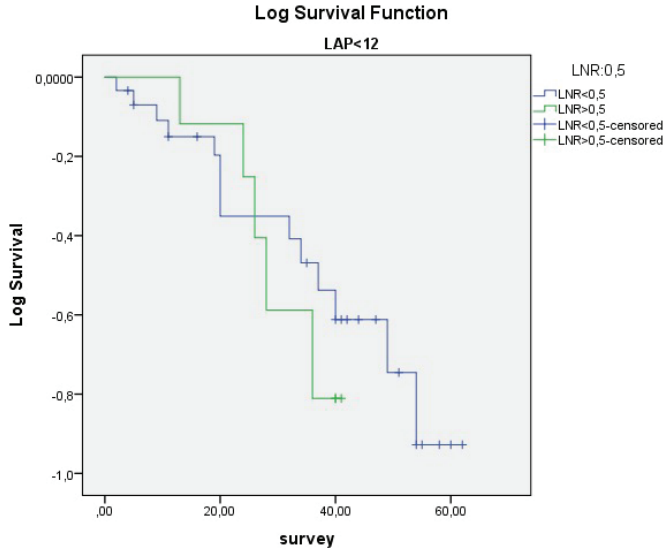


Figure 4. Projection analysis between lymph node ratio (LNR) and survival in patients with less than 12 lymph nodes removed (when LNR is accepted as 0.5)

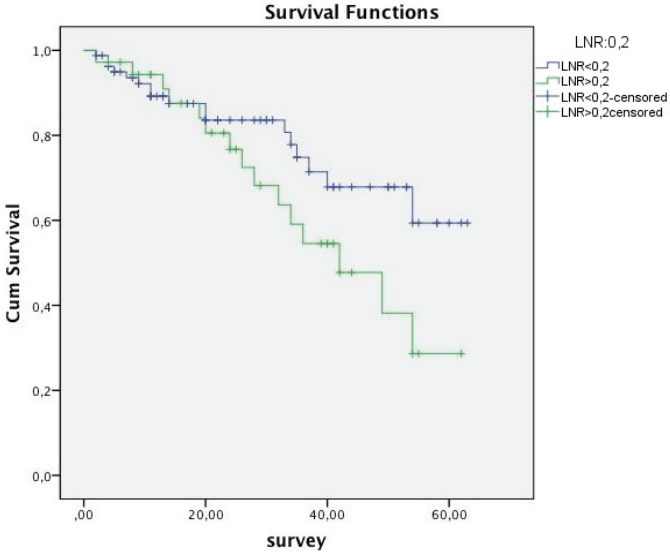


Figure 5. Projection analysis between lymph node ratio (LNR) and survival in lymph node-positive patients (LNR accepted as 0.2)

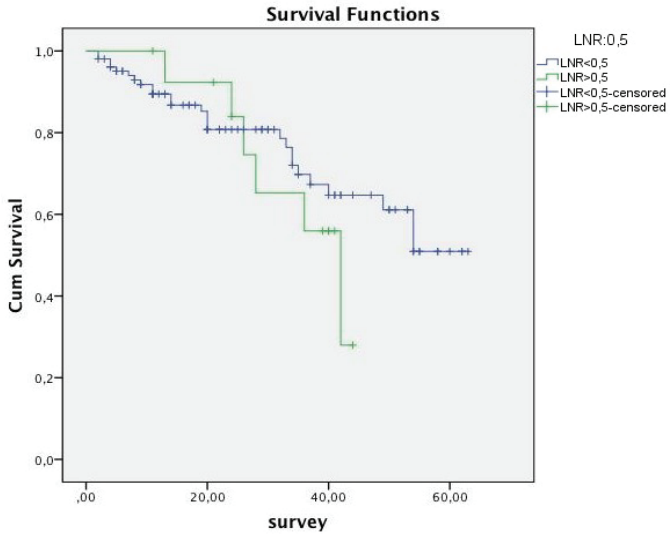


Figure 6. Projection analysis between lymph node ratio (LNR) and survival in lymph node-positive patients (LNR accepted as 0.5)

countries.[10] A decrease in colorectal cancer mortality has been reported as a result of colorectal cancer screening programs.[11] Therefore, prognostic factors are once more gaining importance, as the incidence in younger patients and survival times increase and as mortality decreases. With the widespread use of neoadjuvant chemoradiotherapy, the total number of lymph nodes removed had tended to decrease, and the LNR has gained importance in terms of both staging and prognosis.

In a study conducted by Bando et al.[12], in 650 patients who underwent curative gastrectomy and D2 lymph node dissection, a significant relationship between the rate found when the number of metastatic lymph nodes was divided by the total number of lymph nodes and 5-year survival was reported. Similarly, in a study conducted by van der Wal et al.[13] on LNR in axillary lymph nodes and survival in patients with breast cancer, it was concluded that LNR was a good predictor of survival. Berger et al.[14] also reported that LNR was a prognostic factor for both overall survival and disease-free survival in patients with pancreatic adenocarcinoma who underwent pancreaticoduodenectomy.

Rullier et al.[15] conducted a study on 495 patients, of whom 332 received preoperative chemoradiotherapy, and who were operated on for rectal cancer. When the groups that did and did not receive chemoradiotherapy were compared, it was found that there was a significant difference in the total number of lymph nodes removed and the number of positive lymph nodes.[15] In other similar studies and meta-analyses, it has been reported that preoperative chemoradiotherapy can reduce the total number of lymph nodes removed by up to 50% and that approximately 30% of patients may have insufficient lymph node numbers for staging.[16,17,18]

In our study population male patients were more common than females. While the global female/male ratio in the world is 1:1.2, this ratio was 1:1.5 in our population. This was closer to the rate in developing countries.[19] The mean and median ages were 62.6 and 63 years, respectively, which is consistent with the literature. In terms of tumor location, our study population was consistent with the literature in that rectum was the most common location followed by sigmoid colon and then cecum. TNM stage is the most important prognostic factor in colorectal cancers. In our study, most of the patients were diagnosed at stage 2 and later, and very few at stage 0 and stage 1. The survival rates, in accordance with the literature, decreased as the stage increased. While survival was 100% at stage 0, it was 58.3% in patients with TNM stage 4 disease.

Lymph node involvement is a decisive consideration for both prognosis and adjuvant therapy. The relationship between LNR and survival in colorectal cancers was first suggested by Berger et al.[6] Wang et al.[20], in an analysis of 24,477 patients, suggested that LNR was a more accurate prognostic factor than the N-stage in stage 3 patients. When our patients were classified according to the N-stage there was an assocaition between N-stage and survival. When the LNR threshold value was 0.2, the survival rate was found to be 81.1% in patients below this value and 46.6% in patients above this value. Similarly, when the LNR threshold value was 0.5, these rates changed to 78.5% and 42.9%, respectively. The multivariate analysis showed that both LNR threshold values were factors affecting survival. It was concluded that in patients with insufficient lymph nodes removed for staging, survival was shorter in patients with LNR >0.5 than in patients with LNR <0.5.

Klos et al.[21] performed a study in patients who had undergone rectal cancer surgery after neoadjuvant chemoradiotherapy and found that the probability of having less than 12 lymph nodes removed in patients was increased and that LNR was a better staging method than the number of positive lymph nodes in these patients. Similarly, in a study conducted by Sjo et al.[22], it was shown that LNR was a stronger prognostic factor than the total number of lymph nodes in stage 3 patients. A study conducted in Ireland suggested that LNR remained unchanged despite a decrease in the total lymph node number in patients receiving neoadjuvant therapy, and it was a more reliable prognostic tool for patients in this group.[23] There are also studies comparing positive lymph node rates with TNM staging. In these studies, LNR is complementary to the TNM stage, especially in stage 3 patients, since it gives more accurate results in estimating survival than the N-stage.[24,25]

The factors affecting the number of lymph nodes removed are not limited to neoadjuvant therapy. These may be related

to the patient (age, body mass index, time of diagnosis), tumor (location, T-stage, size), surgeon, and pathologist examining the specimen[26,27,28]. As there are so many factors affecting the number of sampled lymph nodes, it seems plausible that not only the number of lymph nodes but also the LNR should be a determining factor in the prognosis of colorectal cancer.

In our study, only patients who were operated on within the last five years were retrospectively investigated. Therefore, the relatively short follow-up period, the retrospective nature of the study, and the small number of patients are limiting factors of the study.

Conclusion

Colorectal cancer remains a serious health problem, despite the prevalence of screening programs and emerging treatment options. The increase in its incidence in younger patients and the prolongation of life expectancy once again emphasize the value of useful prognostic factors for the treatment of future patients.

In this study, which examined LNR as a prognostic factor, it was shown to be an important factor affecting survival. It can be used as a useful marker in addition to the number of lymph nodes removed or the number of positive lymph nodes in determining the prognosis and adjuvant treatment options in patients with insufficient lymph nodes removed for staging.

Ethics

Ethics Committee Approval: Approval for this study was obtained from the Ankara Numune Training and Research Hospital Clinical Research Ethics Committee (approval number: 734/2016).

Informed Consent: All patients informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.B.Ö., A.E., C.E.G., E.Ç., A.K.A., Concept: A.K.A., M.B.Ö., Design: A.K.A., E.Ç., C.E.G., M.B.Ö., Data Collection or Processing: A.E., M.B.Ö., Analysis or Interpretation: A.K.A., E.Ç., M.B.Ö., Literature Search: M.B.Ö., A.E., C.E.G., E.Ç., A.K.A., Writing: A.K.A., M.B.Ö.

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