Archives of Clinical & Experimental Surgery

Prognostic Value of the Lymph Node Ratio in Rectal Cancer

Mehmet Ince [1], Yavuz Ozdemir [2], Ahmet Ziya Balta [2], Kazim Duman [3], Ergun Yucel [2], Ilker Sucullu [2], Mehmet Levhi Akin [2]

Abstract

Objective: The pathologic staging of rectal cancer is an important prognostic factor. A sufficient number of harvested lymph nodes is necessary for accurate staging. In patients with an insufficient number of dissected lymph nodes, the lymph node ratio (LNR) can be used as a prognostic factor. The aim of this study was to determine the effect of the LNR on the prognosis of patients with rectal cancer.

Materials and Methods: A total of 130 patients who had rectal adenocarcinoma and who underwent surgery between 1996 and 2011 were included in this study. Age, gender, serum carcinoembryonic antigen, type of surgery, and pathological features were retrieved retrospectively. Cut-off values for LNR were 1/12, 1/4, and 1/2; patients were stratified into four groups according to this ratio. The relationship between disease-free survival (DFS) and overall survival (OS) and LNR was investigated. Cumulative survival curves were calculated by the Kaplan Meier method, and survival differences between groups were calculated by the log-rank test.

Results: The mean number of lymph nodes examined was 11.5±8. In 75 of all patients (57.7%), fewer than 12 lymph nodes were harvested. Seventy-six patients (58.5%) were evaluated as N0, 35 (26.9%) were N1, and 19 (14.6%) were N2. The number of patients in these LNR groups was 87 (66.9%), 13 (10%), 17 (13.1%), and 13 (10%), respectively. The 5-year survival rate was found to be 72.3% in the LNR1 group, 55.6% in the LNR2 group, 44.4% in the LNR3 group, and 22.2% in the LNR4 group. The difference in OS and DFS rates was significant ($p<0.001$ for both).

Conclusion: The LNR for rectal cancer has a prognostic effect on both DFS and OS. Thus, it may be beneficial for adjuvant therapy decisions, especially in patients with an insufficient number of dissected lymph nodes.

Key words: *Lymph node ratio, rectal cancer*

[1] Department of Emergency Medicine Gulhane Military Medical Academy Ankara, Turkey

[2] Department of General Surgery Gulhane Military Medical Academy Haydarpasa Training Hospital Istanbul, Turkey

[3] Department of Internal Medicine Gumussuyu Military Hospital Istanbul, Turkey

Received: December 05, 2013
Accepted: January 02, 2014
Arch Clin Exp Surg 2014;3:207-212
DOI: 10.5455/aces.20140102022542

Corresponding author:
Mehmet Ince, MD
Department of Emergency Medicine
Gulhane Military Medical Academy
General Tevfik Saglam Cd.
06018 Etlik, Ankara, Turkey
drmince@yahoo.com

Introduction

In Turkey, colorectal cancer is the third leading cancer in women, and the fourth leading cancer in men according to Turkish National Surveys [1]. Pathological staging is the most important prognostic factor for rectal cancer. The presence of lymph node (LN) metastasis related to the retrieved number of LNs varies with age, tumor grade, surgical extent, and tumor site. Nodal status according to TNM staging system proposed by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) [2] is one of the most important prognostic factors in patients who undergo surgery for rectal cancer [3-6]. The prognostic value of the lymph node ratio (LNR), which is the ratio of metastatic to total harvested LNs, was recently evaluated for several cancers including colon cancer [7]. and it was reported that using the LNR may be benefi-

cial for deciding adjuvant chemotherapy, especially in patients with an insufficient total number of harvested LNs [8,9]. However, the evaluation of LNs is more difficult and less consistent after rectal cancer resection, because of the effect of neoadjuvant chemoradiotherapy on the size and number of LN availability [10-13]. Additionally, retrieved numbers of LNs are frequently under 12, which is the recommended number for adequate staging in patients with rectal cancer, regardless of the quality of surgery and pathologic analysis. There is still controversy about adjuvant therapy in patients with an insufficient total number of harvested LNs. Therefore; the goal of this study was to evaluate the prognostic value of LNR in rectal cancer.

Patients and Methods

Between January 1996 and December 2011, data of patients with rectal cancer were collected retrospectively from the colorectal cancer database of the Department of General Surgery, Haydarpasa Military Hospital (Istanbul, Turkey). A total of 496 patients (334 colon and 162 rectal) were recorded in this database at the end of 2011. Patients who underwent palliative resection (26 patients), who had a diagnosis other than adenocarcinoma (2 patients), and who had insufficient pathologic information (4 patients) were excluded from the study, and the remaining 130 rectal cancer patients were analyzed.

All patients were treated according to standard treatment guidelines [14]. Patients were evaluated by digital rectal examination, complete blood cell count, liver function analysis, and serum carcinoembryonic antigen (CEA). Preoperative diagnosis and staging involved a full colonoscopy and biopsy, thoraco-abdominal computed tomography (CT), pelvic magnetic resonance imaging (MRI), or endorectal ultrasonography (ERUS). While total mesorectal (TME) excision was performed for mid and low rectal cancers, high rectal cancers were treated with a partial mesorectal excision. Patients with T3 or T4 and/or node-positive rectal cancer, were referred for neoadjuvant chemoradiation therapy (CRT), and surgery was planned 8 to 10 weeks after the end of CRT. The data recorded included patient characteristics, and tumor characteristics such as location, stage, numbers of retrieved and metastatic LNs, tumor differentiation, and time of follow-up. Patients were staged according to the TNM staging system of AJCC, version 7 [15]. Patients were divided into four groups with respect to LNR, which is defined as the number of metastatic LNs divided by that of retrieved LNs. Cut-off values for predicting the ratio between metastatic LNs and total harvested LNs were chosen as 1/12, 1/4, and 1/2 (Group LNR1 was the ratio under 1/12, LNR2 was between 1/12 and 1/4, LNR3 was between 1/4 and 1/2, and LNR4 was >1/2). For accurate staging, at least 12 LNs needed to be retrieved. Therefore, we accepted 1/12 as the first cut-off value. Other cut-off values were determined as the ¼ and 1/2. Patients were evaluated weekly by physical examination and the appropriate blood tests during treatment sessions. Patients presented for follow-up after 2 weeks, then after 1, 2, 3, and 6 months, and finally, twice per year until 2 years post-surgery. After 2 years, patients were followed up annually. Overall survival (OS) was our primary endpoint, and local and distant tumor control was accepted as the secondary endpoint. The 5-year survival rate was defined as the proportion of patients who were alive at the end of their fifth-year follow-up.

Statistical Analysis

Data obtained from the study were evaluated using the Statistical Package for Social Sciences (SPSS Inc. Chicago, IL) for Windows, version 16.0. The correlation between the total number of metastatic LNs and LNR was calculated by Pearson correlation coefficient. Distribution of patient demographics and tables of probability were determined using ANOVA for continuous variables and the chi-square test for categorical variables. Survival curves were generated by the Kaplan Meier method, and the log-rank test was used to calculate p values for different variables. Cox regression analysis was used to determine the factors that may affect survival. P values less than 0.05 were considered statistically significant.

Results

The mean patient age was 64.7±13.1 years. The study cohort was comprised of 73 males and 57 females. Clinical and pathologic characteristics of the patients are summarized in Table1. Of the 130 patients, 72 (58.5%) were N0, 41 (26.9%) were N1, and 17 (14.6%) were N2. The mean number of LNs examined was 11.5±8. In 75 (57.7%) of all patients, the

Table 1. Clinical and pathologic features of the patients.

Characteristic	No. of patients	%	Characteristic	No. of patients	%
Age, year			**Pathologic T stage**		
Mean	64,7 ± 13,1		T1	6	4.6
≤ 40	8	6.2	T2	25	19.2
41-60	34	26.2	T3	91	70
≥60	88	67.7	T4	8	6.2
Gender			**Pathologic N stage**		
Male	73	43.8	N0	76	58.5
Female	57	56.2	N1	35	26.9
Type of surgery			N2	19	14.6
LAR	94	72.3	**Pathologic M stage**		
APR	34	26.2	M0	113	86.9
Total Proctocolectomy	2	1.5	M1	17	13.1
Preoperative CEA level			**LN examined**		
Median	3.4 (0.3-684)		Mean	11.5 ± 8	
≤5 ng/ml	56	62.2	<12	75	57.7
>5 ng/m	34	37.8	≥12	55	42.3
Type of operation			**Differentiation**		
Emergency	2	1.5	Well	26	20
Elective	128	98.5	Moderate	99	76.2
Stage of Tumor			Poorly	5	3.8
I	24	18.5	**Metastatic LNR**		
II	48	36.9	1	87	66.9
III	41	31.5	2	13	10
IV	17	13.1	3	17	13.1
			4	13	10

LAR: Low Anterior Resection, **APR:** Abdominoperineal Resection, **CEA:** Carcinoembryonic Antigen, **LNR:** Lymph Node Ratio

Table 2. Distribution of the patients according to TNM Stage and Lymph Node Ratio.

	LNR 1	LNR 2	LNR 3	LNR 4	p
pT stage					
1	6	0	0	0	<0.001
2	24	1	0	0	
3	55	12	14	10	
4	2	0	3	3	
pN stage					
0	76	0	0	0	<0.001
1	11	12	10	2	
2	0	1	7	11	
pM stage					
0	82	11	12	8	0.001
1	5	2	5	5	
Tumor stage					
I	24	0	0	0	<0.001
II	48	0	0	0	
III	10	11	12	8	
IV	5	2	5	5	

total number of harvested LNs was fewer than 12. The median pre-operative CEA level was 3.4 (0.3-684) ng/ml. The number of patients in groups stratified according to LNR was 87 (66.92%), 13 (10%), 17 (13.07%), and 13 (10%). There was no significant difference in age (p=0.684) and gender (p=0.275) between LNR groups. Distribution of patients according to T, N, and M stages are shown in Table 2. Four patients with negative nodal status (all were treated with neoadjuvant chemoradiotherapy) had liver metastasis at the time of surgery; metastasectomy (three patients) or segmentectomy (one patient) was performed simultaneously.

The median follow-up time was 77 months. The follow up time for 38 patients was shorter by 5 years. The 5-year survival rate was calculated in patients out of above and was 63% (58 patients were alive of 92 patients). Local recurrence was observed in 19 patients

Table 3. Follow-up results according to LNR.

LNR (n)	LNR 1 (87)	LNR 2 (13)	LNR 3 (17)	LNR 4 (13)	p
Age (year)					
Mean± S.D	65.3±13.4	65.6±14.2	62±11.6	63.7±13.4	0.799
Local Recurrence					
Yes	11	5	3	0	0.041
No	76	8	14	13	
Distant Metastasis					
Yes	13	5	11	7	<0.001
No	74	8	6	6	
Follow-up					
Live	59	6	6	4	0.014
Ex	28	7	11	9	
Overall survival time (month)					
Mean ± S.D	51.3±5,7	42.2±7	33.5±8,4	32.9±10,8	0.001
Disease-free survival time (month)					
Mean± S.D	45.6±5,7	30.2±8	25.9±8,2	25.3±11,9	<0.001
5-Year survival Rate (%)	72.3 (47/65)	55.6 (5/9)	44.4 (4/9)	22.2 (2/9)	

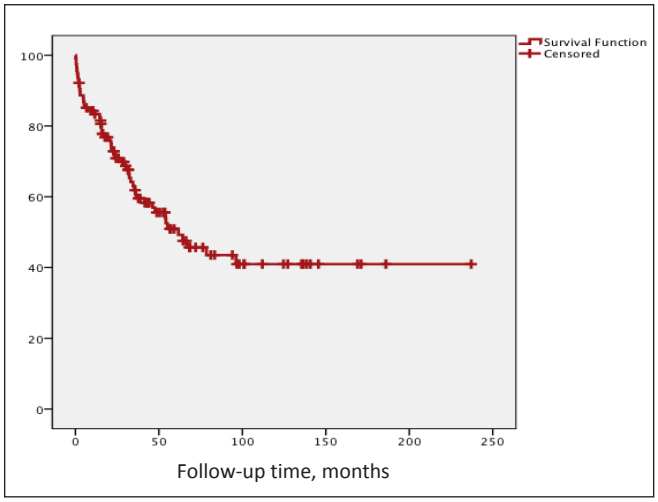

Figure 1. Survival rate according to follow-up time.

(16.1 %), and distant metastasis was observed in 36 patients (31.9%) during the study period. The 5-year survival rate of LNR groups were 72.3%, 55.6%, 44.4%, and 22.2%, respectively. There was a statistically significant difference between LNR groups for disease-free survival (DFS; p<0.001), distant metastasis (p<0.001) and OS (p<0.001), (Table 3), (Figure 1). However, there were no statistically significant differences between LNR groups for tumor differentiation grade (p=0.43), pre-operative CEA levels (p=0.3), or type of surgery (p=0.87).

Discussion

Our study shows that the LNR for rectal cancer has a prognostic effect on both DFS and OS, and can be beneficial while deciding on adjuvant therapy, especially in patients with insufficient LN dissection. LN involvement and total number of LNs examined are important determinants of prognosis in patients with colon cancer. It is recommended that a minimum of 12 LNs be examined in patients with colorectal cancer [16-18]. Nevertheless, this recommendation may not be applicable to rectal cancers, as the number of malignant LNs in rectal cancer depends upon the number of retrieved LNs, which varies with treatment, patient, and tumor characteristics.

Techniques for mesorectal excision and pathologic examination have been well documented by authors [19,20]; however considerable variability remains in the total number of LNs examined in patients with rectal cancer. In this study, patients with low and mid rectal cancer underwent a standardized total mesorectal excision, and those with high rectal cancer were treated with a partial mesorectal excision. Seventy-five (57.7%) patients had fewer than 12 LNs examined, despite an appropriate surgical technique. Pre-operative

treatment may decrease the number of LNs available for pathologic examination. Therefore, the total number of LNs examined is not a sufficiently reliable marker of prognosis in patients with rectal cancer.

In our study, the local recurrence rate of 13.8% at a median follow-up time of 77 months was higher than the 7.4% recurrence rate reported in a study performed in France [21]. There may be several reasons for this. The follow-up time in their study was 38±20 months, and only the recurrence rate in the third year of follow-up was reported. In this study, we reported the recurrence rate at the end of the 5-year follow-up period, and it has been shown that local recurrence rates increase with time [3]. In addition, 23% of patients in the French trial had stage I tumors, compared to only 18.5% patients in this study.

The presence of metastatic LN is known to be associated with poor prognosis for OS and DFS in patients with rectal cancer [22]. Some studies only considered the presence or absence of metastatic LN, and did not assess the prognostic value of the LNR. However, the LNR has also been evaluated in other gastrointestinal malignancies [23,24]. LNR has been shown at many cancer sites, including the esophagus [25] and stomach [26]. Rosenberg et al. [27] analyzed 3,026 patients with colorectal cancer at a single surgical center over a 25-year period, and found that the 5-year OS was 60.6%, 34.4%, 17.6%, and 5.3% of patients with increasing LNR ($p<0.001$). Thus, the LNR had a better prognostic value than the pN category ($p<0.05$). Kim et al. [28] investigated the impact of LNR in 232 rectal cancer patients to determine its usefulness for assessing prognosis in rectal cancer, as in colon cancer. They found that the 5-year survival rate significantly decreased as the LNR increased ($p<0.001$), similar to our results. Peschaud et al. [21] investigated the utility of the LNR in 307 rectal cancer patients by dividing them into four groups; LNR=0, LNR=0.01 to 0.07, LNR>0.07 to 0.2, and LNR>0.2. In the multivariate analysis, LNR was the most significant prognostic factor for both DFS ($p=0.006$) and OS ($p=0.0003$), whereas the presence and absence of metastatic LNs was not a significant factor. We found the same result when there were fewer than 12 LNs.

The limitations of this study are that it is a retrospective analysis with a small patient sample size. In addition, in 75 (57.7%) of all patients, fewer than 12 lymph nodes were harvested. However, this may be related to the pre-operative neoadjuvant therapy before surgery, and 34 patients (26.2%) underwent abdominoperineal resection.

Conclusion

This study confirmed that LNR has a prognostic impact on the recurrence and OS in patients with rectal cancer. The LNR may be useful as a new staging classification in large prospective studies. Additionally, the LNR could be beneficial for deciding adjuvant chemotherapy in patients with rectal cancer.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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