THE ROLE AND PROGNOSTIC IMPACT OF *LYMPH NODE RATIO* ON STAGE III COLORECTAL CANCER

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Abstract

Aim. *The aim of this study was to evaluate the prognostic significance of the lymph node ratio (LNR) in patients with stage III colorectal cancer.*

Materials and Methods. *We included 35 stage III colorectal cancer patients who underwent a curative resection at the County Clinic Hospital, Cluj-Napoca, 5th Surgical Clinic between January 2006-July2008. Patients were categorized into LNR groups 1 to 5 according to cut-off points: <0.1; 0.21; 0.36; 0.6; >0.61. The Kaplan-Meier and the Cox proportional hazard models were used to evaluate the prognostic effect according to the LNR.*

Results. *From one hundred forty-eight patients who underwent colorectal cancer resection, 33.1 % were stage III and 35 patients met the study inclusion criteria. The five-year survival rate in N1 group was 64.62% compared to the N2 group, where it was 8.57% (p<0.001) The lymph node ratio (LNR) groups consisted of 5 cases (14.2%) in LNR1 group (<0.1), five-year survival rate 100%, 6 cases (17.14%) in LNR2 group (0.11-0.21), five-year survival rate 83.33%, 8 cases (22.8%) in LNR3 group (0.22-0.36), five-year survival rate 37.5%, 12 cases (34.28%) in LNR4 group (0.37-0.60), survival rate 0%, and LNR5 group (>0.6). The relationship between the five-year survival rates in the five LNR groups results in a statistically significant proportionality (p<0.001).*

Conclusion. *Lymph node ratio can be considered a more accurate and potent modality for prognosis in stage III colorectal cancer and may improve stratification in this heterogenous group of patients.*

Keywords: colorectal cancer, lymph node, prognostic factor, staging.

Introduction

Colorectal cancer is one of the most common causes of morbidity and mortality from malignant tumors of the gastrointestinal tract. The prevalence of colorectal cancer is increasing in the population of Romania, this condition ranking second in the incidence of malignant tumors worldwide [1].

The most widely used staging of colorectal cancer is that of the American Joint Committee of Cancer (AJCC), known as the TNM staging system [2]. Within this cancer staging, stage N describes the number of lymph nodes invaded by the tumor. Thus, the larger the number of excised lymph nodes, the higher the number of lymph nodes invaded by the tumor, which will result in a more advanced N stage. The number of excised lymph depends on various factors, being influenced by the surgeon, the pathologist and by factors related to the patient (immune status, age, tumor location, T stage).

There are studies showing that the total number of invaded lymph nodes does not allow accurate staging of colorectal cancer [3], requiring the identification of other pathological markers which would enable accurate staging

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for further treatment. Lymph node ratio (LNR) is defined as the ratio of the number of metastatic lymph nodes over the total number of resected lymph nodes. Multiple studies confirm the influence of LNR on survival in breast cancer [4], bladder cancer [5], pancreatic cancer [6], gastric cancer [7] and lung cancer [8]. The study aims to highlight the role and impact of LNR on survival of patients with stage III colorectal cancer, who underwent radical surgery in our clinic.

Material and methods

To achieve this objective, the evaluation was performed on patients with stage III colorectal cancer who underwent radical surgery at the County Clinic Hospital, Cluj-Napoca, 5th Surgical Clinic, between January 2006 and July 2008. Patients with histopathological type of cancer other than adenocarcinoma and those with incomplete data or lost from the study were excluded. The data analyzed were represented by: age, gender, tumor location, stage (IIIA, IIIB, IIIC), T stage, N stage, number of excised lymph nodes, number of invaded lymph nodes, lymph node ratio (LNR). LNR was calculated by dividing the number of metastatic lymph nodes to the total number of excised lymph nodes. Based on this criterion, patients were divided into 5 groups, the cut-off points where set at <0.10, 0.11-0.21, 0.22-0.36, 0.37-0.6, and >0.61 respectively. Patients were evaluated during a postoperative follow-up period of 5 years, at every 6 months in the first two years and at 1 year over the next three years. Statistical analysis was used in order to calculate cancer-specific survival after 5 years (60 months) and the correlations between the different parameters considered in the study.

Qualitative data were presented as counts and percentages. The association between qualitative variables was assessed using the Chi square test or the Fisher exact test. The normal distribution of data was checked with strip-chart, quantile-quantile plot, Shapiro-Wilk test. Quantitative data was presented as median and interquartile range (for non-normally distributed data). To check for differences between two independent groups of quantitative data, the Mann Whitney U test (for non-normally distributed data) was used. Comparisons between three or more groups regarding quantitative variables were performed with the Kruskal Wallis test for non normally distributed data. Then, post-hoc pair-wise tests were performed with the Tukey Kramer test. To evaluate the association between quantitative data we used the Spearman correlation coefficient (for data without normal distribution), the test of statistical significance and a scatter plot chart type. Survival data was described by presenting the number of deaths, censored data, the percentage of survival at different points in time and quantiles of survival with associated 95% confidence intervals, respectively graphically by Kaplan-Meier survival curves. Comparisons between groups for survival data were performed using the log-rank test. We calculated the hazard ratio for different explanatory variables to assess their association with survival using Cox regression, the hazard and the 95% confidence interval associated with it. Proportional hazard assumption was checked graphically and by using a statistical test. For all the statistical tests the significance level alpha was set at 0.05 and the two-tailed p value was computed. The statistical analysis was performed in R environment for statistical computing and graphics, version 1.15.1 [9].

This study was approved by the medical ethical commission of the County Clinic Hospital, Cluj-Napoca.

Results

One hundred forty-eight patients with colorectal cancer underwent surgery at the County Clinic Hospital, Cluj-Napoca, 5th Surgical Clinic, between January 2006 and July 2008. Of these, 49 were stage III, of which 35 met the inclusion criteria in the study. Of these, 14 (40%) were women and 21 (60%) men. 31.4% (11 cases) were aged under 60 and 68.6% (24 cases) were aged over 60. The survival of patients aged over 60 was significantly higher than of those under 60 when testing the difference in survival based on age (by means of both logrank test, $p<0.021$ and Cox regression, $p<0.026$). Clinical and pathological characteristics of patients and the 5-year survival are shown in Table I.

Table I. Clinico-pathological characteristics of stage III colorectal cancer patients and 5-year survival.

Characteristic	No. of cases	5-year survival (%)	P-value
Age			
<60	11 (31.4)	18.18	0.021
>60	24 (68.6)	54.71	
Sex			
male	21 (60)	45.38	NS
female	14 (40)	40.18	
T stage			
T2	9 (25.7)	66.67	NS
T3	23 (65.7)	33.82	
T4	3 (8.6)	33.33	
N stage			
N1	21 (60)	64.62	<0.001
N2	14 (40)	8.57	
TNM stage			
IIIA	8 (22.8)	75	<0.001
IIIB	13 (37.2)	55	
IIIC	14 (40)	10.71	

NS, not significant

In terms of topography, 9 cases were located in the right colon, 11 in the left colon and 15 in the rectum. The number of lymph nodes excised during surgery for cancer of the right colon was significantly higher ($p<0.001$), but when considering the number of 12 nodes excised as a resectability criteria, the number of excised lymph nodes was not statistically significant based on tumor location.

The five-year survival rate, according to the number of excised lymph nodes, is 34.62% in the group with <12 nodes compared to 45.45% in the group with >12 nodes,

not statistically significant.

The number of malignant lymph nodes is statistically correlated with the five-year survival (p<0.001). Thus, each unit increase determines a 1.54-fold hazard increase (95% CI (1.28-1.85). Survival improves as the number of invaded lymph nodes decreases.

The comparison of the relationship between the number of excised lymph nodes and the number of invaded lymph nodes reveals a positive trend (linear relationship), but not confirmed statistically (Spearman correlation coefficient: 0.10431 (p=0.01431).

The five-year survival by stage was higher in stage IIIA cancer (75%) than in stage IIIB cancer (55%) (not statistically significant) and superior to stage IIIC cancer (10.71%), this time statistically significant (p<0.006).

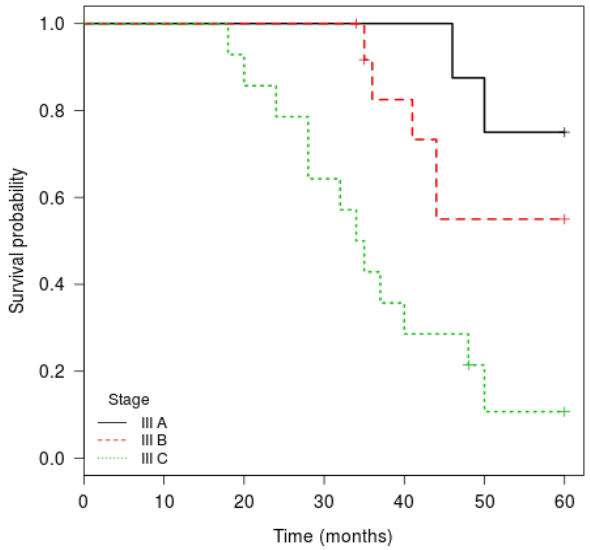

Figure 1. Kaplan-Meier survival curve by stage IIIA, IIIB, IIIC colorectal cancer.

The increase in T stage determines a decrease in survival. Survival in T2 group compared to T3 and T4 groups reveals a higher value, but not statistically significant.

The analysis of N stage shows that 21 patients (60%) were N1 stage and the remaining 14 (40%) were N2 stage. The five-year survival rate in N1 group was 64.62% compared to the N2 group, where it was 8.57%. The difference was statistically significant for both logrank test (p<0.001) and Cox regression (p<0.001), as shown in Figure 2.

The lymph node ratio (LNR) groups consisted of 5 cases (14.2%) in LNR1 group (<0.1), five-year survival rate 100%, 6 cases (17.14%) in LNR2 group (0.11-0.21), five-year survival rate 83.33%, 8 cases (22.8%) in LNR3 group (0.22-0.36), five-year survival rate 37.5%, 12 cases (34.28%) in LNR4 group (0.37-0.60), survival rate 0%, and LNR5 group (>0.6), survival rate 0% (Figure 3).

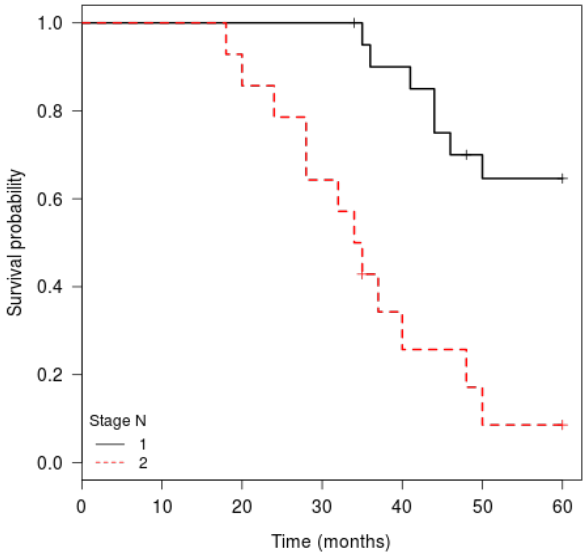

Figure 2. Kaplan-Meier survival curve by stage N1, N2 colorectal cancer.

Table II. 5-years survival in LNR groups.

Lymph node ratio	Number of cases	Five-year survival (%)
LNR1	5	100%
LNR2	6	83.33%
LNR3	8	37.5%
LNR4	12	0%
LNR5	4	0%

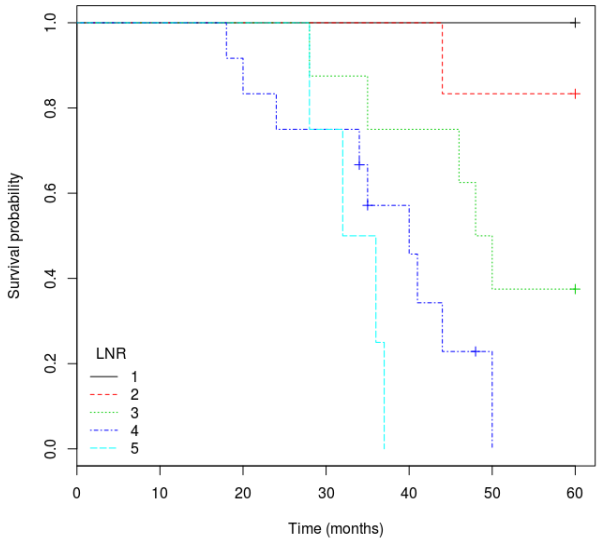

Figure 3. Kaplan-Meier survival curve by LNR groups.

The relationship between the five-year survival rates in the five LNR groups results in a statistically significant proportionality (p<0.001) (logrank), as shown in Figure 3.

Table III. 5-year survival in stage N and LNR groups.

LNR	LNR 1	LNR 2	LNR 3	LNR 4	LNR 5	P-value
Stage N (1)	5 (100%)	6 (100%)	5 (62.5%)	4 (33.33%)	1 (25%)	0.00742
Stage N (2)	0 (0%)	0 (0%)	3 (37.5%)	8 (66.67%)	3 (75%)	0.00567

The association between the five LNR groups and N stage attained a p=0.007 value (statistically significant) during Fisher's exact test, showing that LNR is associated with N stage (Figure 4). In patients staged N1 or N2 and divided in subgroups using LNR, five-years survival rates was different between N1 and also N2 stage.

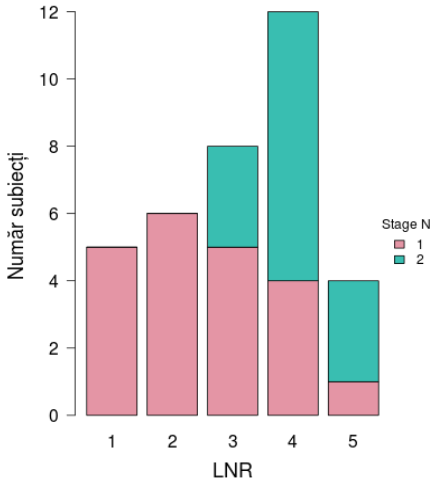

Figure 4. Distribution of stage N colorectal cancer by LNR groups.

Discussion

More studies support the importance of the LNR in predicting survival after colorectal cancer resection [10]. Berger et al. [11], in their study, based on a large number of patients undergoing complete resection and adjuvant chemotherapy for colon cancer, analysed the LNR using groups based on quantiles. Overall survival (OS), disease-free survival (DFS) and cause-specific survival (CSS) were used as end points. Survival decreased significantly as LNR increased, for all three end points. In their study, Vaccaro et al. [12], used the same three end points in patients undergoing curative resection for stage III colon cancer and the results were similar and on multivariate analysis, the number of positive lymph nodes was not found to be a significant predictor of survival. Chin et al. [13] have also found the LNR to be a significant predictor of survival in stage III colon cancer, but they included only those patients in which 12 or more lymph nodes had been identified by the pathologist. The total number of positive nodes was not a significant predictor of survival. Such results have been reported by Derwinger et al. [14], in stage III colon cancer followed for a period of three years.

In rectal cancer the LNR also been shown to be an independent prognostic factor, in studies like Perschuad et al. [15] who analysed a number of three hundred seven patient undergoing curative rectal and mesorectal excision.

Rosenberg et al. [16] analyzed both colonic and rectal cancers, with the aim of identifying more precise cut-off values for the LNR to increase prognostic value. The cut-off points for LNR providing the highest level of discrimination to determine survival were 0.17, 0.41, and 0.69. Galizia et al. [17] used receiver operating characteristic (ROC) statistical analysis to reach a LNR cut-off value of 0.18, set again the LNR as an independent prognostic indicator for patient with stage III colorectal cancer following radical resection. Several studies have used various cut-off points for the LNR, most of them determined the cut-off points by using the LNR to draw the Kaplan-Meier survival curve [18].

In our study we established the cut-off points of the LNR at <0.1; 0.21; 0.36; 0.6; >0.61, applied in previous studies [10] and divided the patients in five groups (1 to 5) based on cut-off interval and shown a statistically significant proportionality in the relationship between the five-year survival rates and the five LNR groups.

According to the results of this study, when the patients in N1 and N2 stage were divided by LNR, respectively, the five-year survival rates were different by LNR in patients in the N1 and N2 stage. This data shows that the patients divided by N staging based on the absolute number of metastatic lymph nodes are not distributed consistently and the use of LNR, along with the current TNM staging, can give a better prognosis. In studies that analyzed patients with stage N divided by LNR, Yo Han Park et al. [1], shows the five-year survival rates of the patients in N2 stage were not different by LNR and that because of cut-off points values chosen. This demonstrates once again that the cut-off value is not universal and methods used to choose the cut-off vary in each study [19,20], although the value of the LNR is widely accepted, appropriate stratification for LNR remains unclear [21]. Thus, if the LNR is to be used as a prognostic factor, a standardization of cut-off points for the LNR is necessary for stratification of stages with better correlation with the prognosis [22].

Conclusions

The LNR provides superior prognostic stratification as compared to the number of positive nodes. The use of LNR, along with the current TNM staging, can better predict the prognosis for N1 and N2 stage colorectal cancer and may be an independent prognostic factor in stage III

colorectal cancer. Future large scale prospective studies are needed to define cut-off points for LNR to play a role as an independent prognostic factor in stage III colorectal cancer and to allow optimal separation by subgroups of patients and to verify if the LNR could be used to direct adjuvant therapy.

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