Original Article

The impact of lymph node ratio on overall survival in patients with colorectal cancer

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ABSTRACT

Background: Lymph node metastasis is a predominant prognostic indicator in colorectal cancer. Number of lymph nodes removed surgically was demonstrated to correlate with staging accuracy and oncological outcomes. However, number of lymph nodes removed depends on uncontrolled variables. Therefore, a more reliable prognostic indicator is needed. Calculation of ratio of positive lymph nodes to total number of removed lymph nodes may be an appealing solution.

Materials and Methods: We retrospectively analyzed data of 156 Stage III colorectal cancer patients whom underwent surgery between 2008 and 2015. Patients' demographic characteristics, tumor grade, location, vascular-perineural invasion status, number of removed lymph nodes, and ratio of positive lymph nodes to number of removed lymph nodes were recorded. Spearman correlation analysis was used to determine the correlation coefficient while Kaplan–Meier method and Cox proportional hazard regression model were performed for the prediction of survival and multivariate analysis, respectively.

Results: Number of removed lymph nodes did not correlate with survival, but it was inversely correlated with number of positive lymph nodes. Multivariate analysis showed that ratio of removed positive lymph nodes to the total number of lymph nodes was a significant prognostic factor for survival for a ratio equal or above 0.31 was a poor prognostic indicator (108 months vs. 34 months, hazard ratio: 4.24 [95% confidence interval: 2.15–8.34]; $P < 0.019$). Tumor characteristics failed to demonstrate any prognostic value.

Conclusions: This study showed that positive lymph node ratio (PLNR) is an important prognostic factor for Stage III colorectal cancer. Although 0.31 can be taken as threshold for "PLNR," prospective trials including larger patient groups are needed to validate its role as a prognostic indicator.

KEY WORDS: Colorectal cancer, lymph node, prognosis, ratio, survival

INTRODUCTION

The most important determinant of prognosis in colorectal cancer patients is lymph node involvement. Lymph node involvement decreases the 5-year survival rates from 80% to 30%–60%.[1,2] In addition, the number of lymph nodes removed with the surgical specimen affects both staging accuracy and oncological outcomes. However, the number of removed lymph nodes is affected by many variables such as patient age, body mass index, tumor location, and the extent of surgical resection.[2-5] In order to prevent downstaging due to inadequate sampling, College of American Pathologists (CAP) and the American Joint Committee on Cancer (AJCC) staging system recommended removal of a minimum of 10–14 lymph nodes per specimen.[6-8] Despite this recommendation, a population-based study showed that only 37% of colon cancer patients had adequate lymph node sampling and assessment.

The nodal staging methodology of the AJCC staging system is based on the number of positive lymph nodes. However, this methodology, which focuses on the numbers only, may pave the way for staging errors and/or under-staging, especially when a suboptimal number of lymph nodes are removed. Since under-staging may lead to under treatment, another parameter which has the potential to decrease the risk of under-staging during lymph node specimen assessment is needed. In this study, we sought to determine if the ratio of positive lymph nodes to total number of lymph nodes removed (i.e., positive lymph node ratio [PLNR]) could take this role and provide reliable and clinically relevant

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prognostic information during the nodal assessment of colorectal cancer.

MATERIALS AND METHODS

Between January 2008 and 2015, 414 patients were diagnosed with colorectal cancer in Ankara Diskapi Research and Training Hospital. Among these patients, 166 were found to have Stage III disease and underwent radical surgery. After the approval of the ethics committee, patients were evaluated. Exclusion criteria were the presence of familial adenomatous polyposis (FAP), multiple primary colorectal cancers, history of neoadjuvant chemotherapy or radiotherapy, early recurrence or death within 3 months' postsurgery. Patients who were lost to follow-up were also excluded. Files of these patients were reviewed retrospectively. Variables such as age, gender, family history, and chief complaint at presentation were all recorded. Histopathological data, including tumor location, grade, vascular-perineural invasion status, number of total lymph nodes extracted, and positive lymph nodes, were obtained from pathological assessment reports, all of which were signed by two experienced colorectal pathologists.

The PLNR was defined as the ratio of positive lymph nodes to the total number of removed lymph nodes. This parameter was calculated for each patient with the guidance of the pathology reports. Survival was calculated for each patient based on the time of diagnosis and the time of death or the last date of follow-up.

SPSS Statistics 20.0 (IBM-SPSS Inc., Chicago, IL, USA) software was used for statistical analysis. Shapiro–Wilk's test was used; histograms and q-p plots were plotted to assess the data normality. Values were expressed as frequencies and percentages or median and 25^{th}–75^{th} percentiles. Spearman's nonparametric test was used for correlation analysis. Survival probabilities were predicted by Kaplan–Meier method and group comparisons were performed by log-rank test. Univariate and multivariate Cox regression analysis was used to determine the most significant risk factors. Significant variables on univariate analysis were taken into multivariate model, and backward stepwise selection was performed using Wald statistic at $P < 0.10$ stringency level. Hazard ratios (HRs) were also given with 95% confidence intervals (CIs). $P < 0.05$ was considered as statistically significant. Receiver operating characteristic (ROC) curve analysis was used for determining the cutoff value for q/p ratio.

After the surgery, patients were followed up every 3 months for 2 years, then every 6 months for 3 years and every year thereafter. The follow-up assessments included detailed history, physical examination, complete blood count, liver function tests, carcinoembryonic antigen (CEA) level, chest X-ray, abdominal ultrasound, and colonoscopy. Thoracoabdominal computed tomography scans and abdominal magnetic resonance imaging were performed as needed.

RESULTS

After application of the exclusion criteria, 156 patients were included in this study. Among 156 Stage III colorectal patients, 80 (51.3%) were male and 76 (48.7%) were female. The mean age of all patients was 59.1 ± 13.7 years. A family history of malignancy (other than FAP) was found in 26 cases (16.7%). The most common main complaints at the time of diagnosis were abdominal pain ($n = 50$), rectal bleeding ($n = 44$), constipation ($n = 23$), and weight loss ($n = 3$). Curative surgery was performed in all patients and of those 8 were emergent cases [Table 1].

Rectum was the most common tumor location ($n = 49$, 31.4%). It was followed by the sigmoid colon ($n = 42$, 26.9%), ascending colon ($n = 28$, 17.9%), caecum ($n = 13$, 8.3%), descending colon ($n = 12$, 7.7%), and transverse colon ($n = 12$, 7.7%). The median follow-up time was 31.6 months. Median overall survival for entire group was 100.73 ± 37.6 months. There was no relation between tumor location and overall survival ($P > 0.05$).

Tumor grades had been reported in 118 of all pathology reports. These tumor grades varied from well-differentiated adenocarcinoma in 26 cases (22%) to moderately differentiated in 78 cases (66.1%) and poorly differentiated in 14 cases (11.9%). There was no correlation between the survival rate and tumor grades ($P > 0.05$). Vascular and perineural invasion were also evaluated in the pathology reports; 55 (56.1%) patients were found to have vascular invasion, whereas perineural invasion was detected in 41 (48.2%) patients. Vascular and perineural invasion did not have a correlation with patient survival.

Table 1: The patients' characteristics

Variables	*n*=156
Gender, *n* (%)	
Female	76 (48.7)
Age (years), mean±SD	59.1±13.7
Main complaint at presentation, *n* (%)	
Rectal bleeding	44 (28.2)
Abdominal pain	50 (32.0)
Constipation	23 (14.7)
Weight loss	3 (1.9)
Tumor location, *n* (%)	
Rectum	49 (31.4)
Sigmoid colon	42 (26.9)
Descending colon	12 (7.7)
Transverse colon	12 (7.7)
Ascending colon	28 (17.9)
Caecum	13 (8.3)
Elective/emergent setting, *n* (%)	148 (94.8)/8 (5.2)
Tumor grade, *n* (%)	
Well-differentiated	26 (22)
Moderate differentiated	78 (66.1)
Poor differentiated	14 (11.9)
Vascular invasion	55 (56.1)
Neural invasion	41 (48.2)
Total number of lymph nodes examinated, mean±SD	14.15±10
Number of positive lymph nodes, mean±SD	4.05±4.71

SD=Standard deviation

Among 156 Stage III colorectal cancer patients, the mean number of total lymph nodes removed was 14.15 ± 10. The mean number of positive lymph nodes was 4.05 ± 4.71. The total number of lymph nodes evaluated did not correlate with patient survival ($P > 0.05$). However, the number of positive lymph nodes was inversely correlated with survival. In the ROC analysis for the number of positive lymph nodes, the cutoff value was found 4. There was statistically significant difference in overall survival between the patients above and below this value (108 vs. 38 months, HR: 2.12 [95% CI: 1.12–4.00], $P = 0.020$).

In the Kaplan–Meier analysis, The patients who have N2 stage have significantly longer overall survival compared to N1 group (108 vs. 43 months, HR: 1.97 [95% CI: 1.04–3.69], $P < 0.036$ for N2 vs. N1 group), this OS difference was also present in PLNR ≥0.31 group compared to <0.31 group (108 vs. 34 months, HR: 8.98 [95% CI 1.43–56.25]; $P < 0.001$) [Figure 1]. This relation was not detected between tumor grade and overall survival ($P > 0.05$). In multivariate analysis, significant correlation with overall survival was detected solely for PLNR value (HR: 4.24 [95% CI: 2.15–8.34]; $P < 0.019$) [Table 2]. The ROC curve analysis showed that PLNR ratio of 0.31 was the cutoff value for predicting survival (area under the curve: 0.704; with a sensitivity 65%, specificity 65%; $P < 0.001$) [Figure 2].

DISCUSSION

Colorectal cancer is one of the most common malignancies; nearly 600,000 cases are diagnosed annually worldwide.[6-8] During the past decades, the 5-year survival rate improved from 33% in 1970s to 55.3% in 1990s and 60% more recently.

The variables associated with survival in the setting of colorectal cancer are continuously being studied.[8-10] These variables include age at the onset of disease, gender, stage at diagnosis, lymph node status, presence of distant metastasis, tumor grade, location, lymphatic and vascular invasion, preoperative CEA level, and liver function tests. Among these parameters, lymph node status is considered to be the most important prognostic factor.

In 1932, Dukes recognized the importance of lymph node status for the first time and formed a staging system for rectal cancer.[10] A few years later, Simpson and Mayo applied this system to colon cancer patients.[11] Today, tumor-node-metastasis (TNM) staging system is widely used. According to the current TNM staging system, N category is determined by the number of positive lymph nodes. The breakpoints for defining patients as N1 (a/b/c) or N2 (a/b) is solely based on the number of positive lymph nodes. Therefore, this system disregards the total number of lymph nodes examined in each specimen. Ignorance of the number of removed lymph nodes and PLNR has the potential to lead to "under staging" given that number of removed lymph nodes depends on many factors which can often cause inadequate lymph node sampling [Table 3]. These factors may be patient, tumor, pathologist or surgeon-related. However, regardless of the cause, it may cause under-staging and under treatment. The CAP and AJCC Stating System recommended having a minimum of 10–14 lymph nodes per specimen.[7,8,12] In alignment with these recommendations, the mean number of lymph nodes examined in our patient series was 14.15 ± 10.

Our study showed that the total number of lymph nodes evaluated did not correlate with patient survival ($P > 0.05$); however, the number of positive lymph nodes was inversely correlated with survival. In the ROC analysis, for the number of positive lymph nodes, the cutoff value was found 4. There was statistically significant difference in overall survival between the patients above and below this value (108 vs. 38 months, HR; 2.12, [95% CI: 1.12–4.00], $P = 0.020$). This finding is also supported by the study of Le Voyer *et al.*[2]

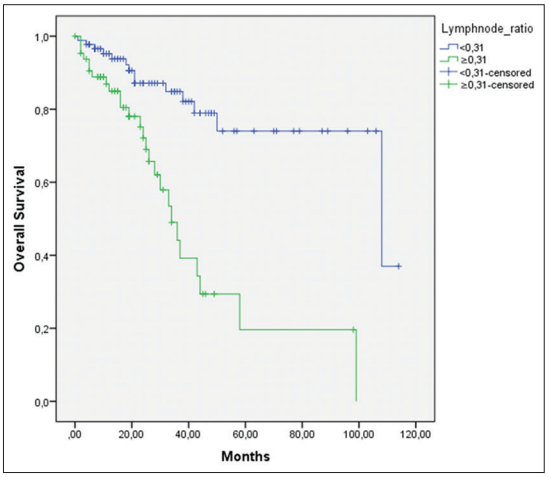

Figure 1: The overall survival according to cutoff value (0.31) positive to negative lymph node ratio

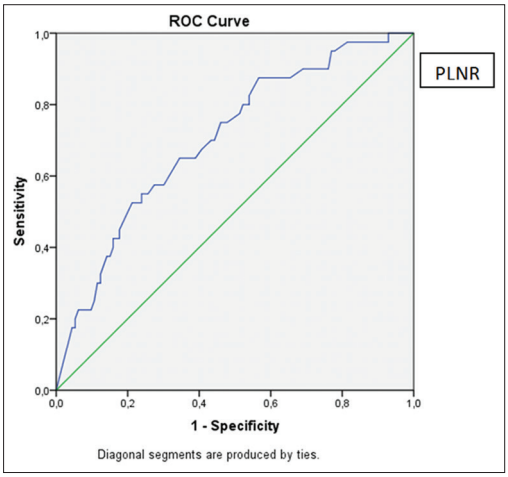

Figure 2: The receiver operating characteristic curve for positive to total lymph node ratio

Table 2: Univariate and multivariate Cox regression analysis for overall survival

Variables	Univariate analysis HR (95% CI)	*P*	Multivariate analysis HR (95% CI)	*P*
Age	1.01 (0.98-1.03)	0.574		
Gender				
Female	1.00		-	-
Male	0.59 (0.31-1.12)	0.106		
Histopathological grade				
1	1.00		-	-
2	2.59 (0.60-11.15)	0.202		
3	4.77 (0.96-23.72)	0.056		
LVI				
No	1.00		-	-
Yes	2.03 (0.98-4.13)	0.057		
PNI				
No	1.00		-	-
Yes	1.95 (0.76-4.96)	0.162		
T stage				
1-2	1.00		-	-
3	0.37 (0.11-1.29)	0.119		
4	1.28 (0.37-4.35)	0.691		
N stage				
1	1.00		-	-
2	1.97 (1.04-3.69)	0.036		
Positive LN				
<4	1.00		-	-
≥4	2.12 (1.12-4.00)	0.020		
PLNR				
<0.31	1.00		1.00	
≥0.31	8.98 (1.43-56.25)	<0.001	4.24 (2.15-8.34)	0.019

HR=Hazard ratio, CI=Confidence interval, LVI=Lymphovascular invasion, PNI=Perineural invasion, PLNR=Positive to total lymph node ratio, LN=Lymph node

Table 3: The factors are causes of inadequate lymph node sampling

Factors	Variables
Extent of surgical resection	Segmental versus extended surgical resection
Patient age	Elderly versus young
BMI	Obesity versus normal weight
Tumor location	Right colon versus left colon or rectum
Pathology technique	Slice thickness, serial sectioning, immunohistochemically staining
Tumor-host response	Presence versus absence of immunologic reaction to tumor
Surgeon dependent factors	Colorectal surgeon versus general surgeon
Resection technique	Laparoscopic versus open surgery

BMI=Body mass index

Since inadequate lymph node sampling may lead to downstaging and significant changes in treatment planning, solutions were sought to improve lymph node sampling and histological assessment. The utilization of PLNR may diminish the possible stage migration. As a potential prognostic indicator, PLNR has been studied in different types of solid tumors including breast, stomach, and esophagus cancers with promising results.

Hatoum *et al*. analyzed the data of nonmetastatic breast cancer patients and concluded that axillary PLNR was a significant predictor of overall survival.[13] In multivariate analysis, PLNR ≥0.25 has been determined as a stronger independent predictor of survival than the number of positive surgically removed lymph nodes. In 536 esophageal cancer patients, Mariette *et al*. found that the presence of more than 4 positive lymph nodes and a PLNR of >0.2 were the only predictors of poor prognosis ($P < 0.001$ for both).[14]

As per our knowledge, four independent study groups reported evidence favoring PLNR as a prognostic indicator in the setting of colorectal cancer.[15-18] However, these series included a relatively small number of patients with positive lymph nodes. Our study is unique to reflect the Turkish population with sufficient power to detect differences and produce a ROC curve.

The ROC curve plot analysis performed in our study showed the cutoff value of 0.31 to be a significant predictor for survival in patients with Stage III Colorectal Cancer. Elias *et al*. followed a similar methodology and divided the patients into two groups as per PLNR in their retrospective analysis.[15] They analyzed the data of 164 Stage III colon cancer patients and compared the survival rates based on PLNR. They concluded that 1, 5, and 10 years' survival rates were 94.1%, 77.3%, and 60.6%, respectively, for patients with PLNR of ≤0.4 while they were 86.2%, 40.6%, and 0%, respectively, for patients with PLNR higher than 0.4 ($P = 0.02$).[19] The same PLNR threshold level

of 0.4 was also tested by De Ridder *et al*. in Stage III colon cancer patients and these authors found that PLNR >0.4 was a strong independent prognostic risk factor ($P < 0.0001$).[16] Different PLNR cutoff levels such as 0.18 and 0.25 were reported in Stage III colon cancer patients for predicting survival by different study groups.[17,18]

In addition to PLNR, patient and tumor characteristics have also been studied as potential prognostic indicators in the setting of colorectal cancer.[19-26] Patients' age of >75 years at the time of diagnosis was associated with poor prognosis while patient age of <69 indicated a better prognosis.[20,21] Factors related to old age such as presence of comorbidities, performance of a "less aggressive" surgery, and discontinuation of adjuvant treatment has been implicated.[20,22] On the other hand, Hemminki *et al*. showed that female gender was a favorable prognostic factor (HR: 0. 55 [95% CI: 0. 46–0. 67]).[26] In our study, we did not find any correlation between survival and patients' gender or age.

Several studies have demonstrated that the presence of perineural invasion is associated with a significantly worse prognosis.[27-29] A retrospective analysis of 269 colorectal cancer patients found a 4-fold greater 5-year survival in patients without perineural invasion compared to patients with perineural invasion.[27] The analysis of patients with Stages II and III colorectal cancer has shown that patients with perineural invasion have a significantly worse 5-year disease-free survival versus the ones without.[28,29] In our study, the presence of perineural invasion and vascular invasion was not significantly correlated with survival. However, it must be considered that we analyzed 3-year survival rates in contrast to these studies which reviewed 5-year survival.

The relation between the number of surgically removed lymph nodes and survival has been studied previously. Le Voyer *et al*. analyzed the association of survival with the number of removed lymph nodes in Stages II and III colon cancer patients who were recruited to the Intergroup Trial INT-0089.[2] They revealed that the number of lymph nodes removed is a significant variable that affects survival in both node negative and node positive patients, regardless of the number of positive nodes. They also postulated that patients with a higher number of lymph nodes identified in their pathologic specimen had probably undergone both a more complete resection of their cancer and a more thorough pathological staging process.

CONCLUSION

Our study demonstrated that PLNR – but not the total number of removed lymph nodes – can provide reliable prognostic information and a ratio above 0.31 was found to be a poor prognostic indicator in the setting of surgically treated Stage III colorectal cancer. Despite the fact that this finding supports the utilization of PLNR as a prognostic marker, it must be considered that our study is a retrospective analysis which bears all potential disadvantages of a retrospective type study. However, we strongly believe that prospective trials involving larger patient groups will validate the role of PLNR as a prognostic indicator during the management of Stage III colorectal cancer patients.

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Conflicts of interest

There are no conflicts of interest.

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