Lymph node ratio predicts tumor recurrence in stage III colon cancer

O índice de linfonodos comprometidos como um preditor para a ocorrência de recidivas tumorais no câncer de cólon estádio III

Tiago L. Dedavid e Silva[1]; Daniel C. Damin[2]

ABSTRACT

Objective: To evaluate the lymph node ratio as a predictor for tumor recurrence in stage III colon cancer patients. **Methods:** Patients with stage III colon cancer who underwent curative resection between January 2005 and December 2010 were retrospectively reviewed. The main outcomes were tumor recurrence and death. The impact of lymph node ratio and other clinicopathological factors on disease-free survival were evaluated by uni- and multivariate analysis. Receiver operator characteristic (ROC) analysis was conducted in order to identify the best cutoff value for lymph node ratio to predict tumor recurrence. Disease-free survival was estimated by the Kaplan-Meier method. **Results:** Seventy patients were included in the study (50% male). The mean age was 64 years. Univariate analysis identified four factors for tumor recurrence: carcinoembryonic antigen, N stage, number of positive lymph nodes and lymph node ratio. Lymph node ratio was the one with the greatest magnitude of association. Receiver operator characteristic analyzes identified 0.15 as the best cutoff value. Patients with a lymph node ratio < 0.15 had a disease-free survival of 90% in 3 years (versus 64%, p = 0.011). **Conclusion:** Lymph node ratio is a strong predictor for tumor recurrence in stage III colon cancer.

Key words: Lymph nodes. Colonic neoplasms. Lymphatic metastasis. Neoplasm staging. Survival.

INTRODUCTION

Colorectal cancer (CRC) is the third most frequent tumor diagnosed in Brazil, with an incidence estimated in 28,000 new cases in 2010 [1]. Worldwide, it has been assessed that over 1.2 million new cancer cases were diagnosed and 608,700 deaths have occurred in 2008 [2]. *En bloc* resection of the primary tumor with removal of regional lymph nodes is the cornerstone therapy for patients with curable disease[3,4].

Prognosis in CRC is clearly related to the degree of tumor infiltration through the bowel wall and the presence or absence of lymph node involvement. These two factors are the basis of the staging system elaborated for this disease [5]. Almost 80 years after Dukes published his pioneer classification [6], all the attempts to improve his proposal were mostly based on refinements of these two data, creating subgroups. Among the current staging systems, the AJCC (American Joint Committee on Cancer) and UICC (International Union Against Cancer) TNM Classification of Malignant Tumors is the most widely accepted [7].

In TNM classification, CRC patients with lymph node metastases are classified as stage III. This is a heterogeneous group [8]. It is well known that not only the mere presence of lymph node metastases determines prognosis, but also the number of positive ones [9], a fact corroborated by recent studies[10,11]. More recently, the total number of resected lymph nodes has also been shown to be an independent prognostic factor [12]. Trying to associate these two observations, in order to obtain a single better prognostic factor, the lymph node ratio (LNR), i.e., the ratio of positive nodes divided by the total number of examined nodes, has been proposed by different authors [13].

Several studies have evaluated the LNR in CRC, but few attempted to identify the ideal cutoff to establish prognosis and these were based only on the concepts of disease-specific survival and overall survival. None specifically evaluated the LNR in tumor recurrence, which is vital, considering that treatments for patients with stage III disease have curative intent. The aim of this study is to provide an evaluation of the LNR in disease-free survival in patients with colon cancer.

MATERIALS AND METHODS

Patients

The study included all the patients who underwent resection of a primary colorectal cancer with curative intent attended by the staff of the Division of Coloproctology at the Porto Alegre Clinics Hospital (HCPA) from January 2005 to December 2010, and who were on stage III disease according to the 7th edition of the AJCC/UICC TNM Classification of Malignant Tumors. The inferior border of the tumor must have been above the peritoneal reflection. Patients were excluded if they presented: (1) an R1 or R2 resection (microscopic evidence of invasive tumor in the resection margin or within 1 mm from it, or gross residual tumor that was not resected); (2) synchronic colorectal tumors in different segments, demanding total or subtotal colectomy; (3) familial adenomatous polyposis; (4) inflammatory bowel disease; and (5) other primary malignant tumors.

Surgeries were carried out predominantly through open access under oncologic principles. All patients received routine adjuvant chemotherapy consulting. Different chemotherapy regimens were possible.

Follow-up

All patients were followed up every 3 months for the first 2 years, every 6 months for the following 3 years and then once a year. Additional visits occurred when necessary. Blood tests with carcinoembryonic antigen measurement, chest X ray and ultrasonography of the liver were carried out. Surveillance colonoscopy and abdominal computed tomography were performed one year after surgery in most cases. Additional imaging studies were performed when recurrences were suspected.

Pathology

Surgical specimens were fixed in 10% buffered neutral formalin. The traditional inspection and palpation method was applied for lymph node harvesting. In cases in which fewer than 12 lymph nodes were detected, additional fat clearance was performed with Carnoy's solution in order to help identifying missing lymph nodes. Tissues were paraffin-embedded and histological evaluation was performed using hematoxylin-eosin staining. Metastatic deposits were defined as lymph nodes if these structures resembled nodes but contained no visible lymphatic tissue.

Data extraction

The following demographic and clinicopathological parameters were retrieved from patients' charts: age, gender, cancer site (right and left colon, by using middle transverse colon as partition), baseline carcinoembryonic antigen (CEA) serum level, body mass index (BMI), type of surgery (right or left colectomy, sigmoidectomy, anterior resection), tumor-node-metastasis (TNM) stage, degree of histological differentiation (well, moderate or poor), lymphatic or venous invasion, number of resected nodes, number of metastatic nodes, lymph node ratio, adjuvant chemotherapy, regimen and number of cycles and follow-up time.

Primary endpoints were tumor recurrence and death. Tumor recurrence was defined as unequivocal evidence of disease from imaging methods or biopsy. For purpose of disease-free survival calculation, the date from the exam that proved recurrence was used. Operative death was defined as any death, regardless of cause, occurring (1) within 30 days after surgery in or out of hospital or (2) after 30 days during the same hospitalization subsequent to the operation.

Statistics

The chi-square test was used to compare groups with respect to categorical variables. Continuous variables were compared with the Student's t test or the Mann-Whitney U test. Cox proportional hazards regression model was used to identify the variables that could independently influence outcomes. Only covariates with trend-significance (o < 0.20) in univariate analysis were entered in multivariate analysis. Survival curves were estimated by the Kaplan-Meier method and compared using the logrank test. ROC analysis was performed to find the best lymph node ratio value predicting outcome. IBM SPSS (Statistical Package for the Social Sciences) version 18.0 (IBM Corp. Armonk, NY, USA) was used for the whole statistical analysis. A p value less than 0.05 was considered statistically significant.

RESULTS

Patient population

During the six years of the study period, 236 patients were submitted to surgical resection of intraperitoneal colorectal tumors with curative intent. Of these, 70 had stage III cancer and were in accordance with the inclusion and exclusion criteria. The mean follow-up time was 31.89 months (median 33, range 1 72). Operative mortality was 2.9%. Tumor recurrence was identified in 13 patients. Only 1 patient showed tumor recurrence after 36 months of follow-up, and in 85% of the cases, recurrence was within the first 2 years after surgery. Seven deaths were registered in the study, including the operative ones.

According to the 7th edition of the AJCC/UICC TNM Classification of Malignant Tumors, five patients were on stage IIIA, 57 on IIIB, and eight on IIIC. In 90% of the cases, at least a 12 lymph node harvest has been achieved (median 18.5, range 5 51).

Tumor recurrence analysis

Univariate analysis identified 4 factors predictive of tumor recurrence: CEA, N stage, positive

lymph node number and lymph node ratio. The lymph node ratio was the one with the greatest magnitude of association. These data, as well as the demographic and clinicopathological characteristics of the patients are displayed in Table 1.

Two multivariate analysis models were developed. The first one considered all the covariates with p < 0.20 in univariate analysis. None of these was found to be an independent prognostic factor, but the tendency for a strong magnitude of association for lymph node ratio remained (Table 2). Considering the strong interdependency between N stage, positive lymph node number and lymph node ratio, a second model analyzed only CEA and lymph node ratio. The latter was the only independent factor for tumor recurrence (p = 0.029, hazard ratio 74.887, 95% confidence interval 1.550 3617.011).

ROC analysis identified a lymph node ratio value of 0.1491 (mnemonic 0.15) as the highest accuracy value to predict tumor recurrence.

Group analysis

Based on ROC analysis, patients were grouped according to lymph node ratio. There were 38 patients with lymph node ratio < 0.15 and 32 with lymph node ratio e" 0.15. The characteristics of both groups are summarized in Table 3.

Patients with lymph node ratio < 0.15 had a higher disease-free survival, estimated on 90% (versus 64%) at 36 month (Figure 1). This benefit was observed even when only patients in stage IIIB were considered (Figure 2). A lymph node

ratio < 0.15 was also associated with an impact on overall survival (Figure 3).

Table 1- Demographic and clinicopathological characteristics and univariate analysis related to tumor recurrence.

	All patients (N = 70)*		Univariate analysis		
	N	(%)	R R	IC 95%	P
Age†	64	(38.9 - 82.6)	0.998	(0.948 - 1.051)	0.942
Gender. Male/Female	35/35	(50 / 50)	0.978	(0.328 - 2.914)	0.968
BMI‡	23.7	(6.1)	0.980	(0.789 - 1.093)	0.717
CEA§	3.10	(1.86 - 8.43)	1.026	(1.003 - 1.049)	0.024
Tumor location					
Right colon	25	(36)			
Left colon	45	(64)	1.236	(0.414 - 3.690)	0.704
T Stage					
T1/T2	8	(11)			
T3/T4	62	(89)	0.730	(0.161 - 3.304)	0.683
N Stage					
N1	49	(70)			
N2	21	(30)	3.981	(1.323 - 11.981)	0.014
Histological grade					
Well/Moderately differentiated	61	(87)			
Poorly differentiated	9	(13)	1.242	(0.275 - 5.618)	0.778
Positive lymph nodes ll	2	(1 - 4)	1.172	(1.033 - 1.330)	0.014
Total lymph nodes ll	18.5	(14 - 26)	0.999	(0.942 - 1.059)	0.966
LNR¶	0.156		89.644	(2.425 - 3313.874)	0.015
Adjuvant therapy	59	(86)	0.569	(0.125 - 2.580)	0.465

* Data are number of patients (percentage), unless otherwise indicated. HR = hazard ratio. CI = confidence interval. † Age, mean (range), years. ‡ BMI = body mass index, mean (standard deviation), kg/m². § CEA = carcinoembryonic antigen, median (interquartile range), ng/mL. ll Number of lymph nodes, median (interquartile range). ¶ LNR = lymph node ratio, mean.

Table 2 - Multivariate analysis related to tumor recurrence*.

Covariate	H R	CI 95%		P
CEA	1.019	(0.994 - 1.045)		0.135
N Stage	2.157	(0.358 - 12.995)		0.401
Positive lymph node	0.965	(0.721 - 1.291)		0.808
	20.828	(0.018 - 23575.358)		0.397

* Only covariates with trend-significance (p < 0.20) in univariate analysis were entered in multivariate analysis. HR = hazard ratio. CI = confidence interval. CEA = carcinoembryonic antigen. LNR = lymph node ratio.

DISCUSSION

The objectives of the TNM Classification of Malignant Tumors have been stated as: to aid the clinician in the planning of treatment; to give some indication of prognosis; to assist in evaluation of the results of treatment; to facilitate the exchange of information between treatment centers; to contribute to the continuing investigation of human cancer [7]. Since its 6th edition, the AJCC and the UICC have been working in the direction of rendering the stage III colorectal cancer group of patients less heterogeneous. The subdivision of patients in stages IIIA, IIIB and IIIC is an example of this development. Nevertheless, most patients were placed in subgroup IIIB, providing no solution for this important question.[8,14,15] The 7th edition added complexity to the system, with the creation of N1 and N2 subdivisions A and B, and redefined stage III subgroups, accounting for an even greater heterogeneity in subgroup IIIB [16, 17].

The LNR has been proposed as a better prognostic factor than the number of metastatic lymph nodes[13]. Our study clearly demonstrates the magnitude of association of this factor with tumor recurrence. However, to incorporate this information in a staging system, it must be simplified

as a cutoff, not as a continuous variable. Different approaches have been used for this aim, mainly based on quartile division. It is our opinion that the better way do determinate a cutoff is trough the ROC analysis.

Two previous studies assessed this method on colon cancer based on different outcomes. Galizia *et al.* studied the impact of LNR on disease-specific survival, finding a cutoff of 0.18 [18]. Greenberg *et al.* applied ROC analysis to overall survival, identifying 0.13 as the best cutoff [19]. Our study is the first to use this method in disease-free survival, resulting in a value of 0.15. The similar cutoffs to LNR found in three independent studies, each one based on different outcomes, reinforce the importance of considering incorporating this tool in future editions of the TNM classification.

Although frequently discussed together, some studies indicate differences in lymph node spread patterns between colon and rectum cancers. Wang *et al.* assessed patients with colorectal carcinoma and showed that rectum surgical specimens tend to present lower lymph node retrieval, but a higher number of metastatic ones, which results in a higher lymph node ratio, even after T stage consideration [20]. Therefore, the cutoff values found in colon cancer may not be the same for rectal cancer. In fact, studies

Table 3 -   Group comparing according to LNR*.

	LNR < 0.15		LNR > 0.15		P¶
	N	(%)	N	(%)	
Patients	38	(52)	32	(48)	
Age†	65.1	(10.33)	62.8	(10.63)	0.376**
Gender. Male/Female	16/22	(42 / 58)	19/13	(59 / 41)	0.150
BMI‡	22.6	(3.9)	25.9	(6.6)	0.025**
CEA§	3.20	(2.25 -10.50)	2.60	(1.69 - 8.20)	0.313††
Tumor location					
Right colon	13	(34)	12	(38)	
Left colon	25	(66)	20	(62)	0.775
T Stage					
T1/T2	2	(5)	6	(19)	
T3/T4	36	(95)	26	(81)	0.130
N Stage					
N1	36	(95)	13	(41)	
N2	2	(5)	19	(59)	0.000
Histological grade					
Well/Moderately differentiated	34	(89)	27	(84)	
Poorly differentiated	4	(11)	5	(16)	0.722
Positive lymph nodes ‖	1	(1 - 2)	4	(3 - 6)	0.007††
Total lymph nodes ‖	21	(16 -27.25)	15	(13 -23.75)	0.000††
> 12 lymph nodes	36	(95)	27	(84)	0.234
Adjuvant therapy	33	(89)	26	(81)	0.469

* Data are number of patients (percentage), unless otherwise indicated. LNR = lymph node ratio. † Age, mean (standard deviation), years. ‡ BMI = body mass index, mean (standard deviation), kg/m². § CEA = carcinoembryonic antigen, median (interquartile range), ng/mL. ‖ Number of lymph nodes, median (interquartile range).
¶ Chi-square test, unless otherwise indicated. ** Student t test. †† Two tailed Mann-Whitney U test.
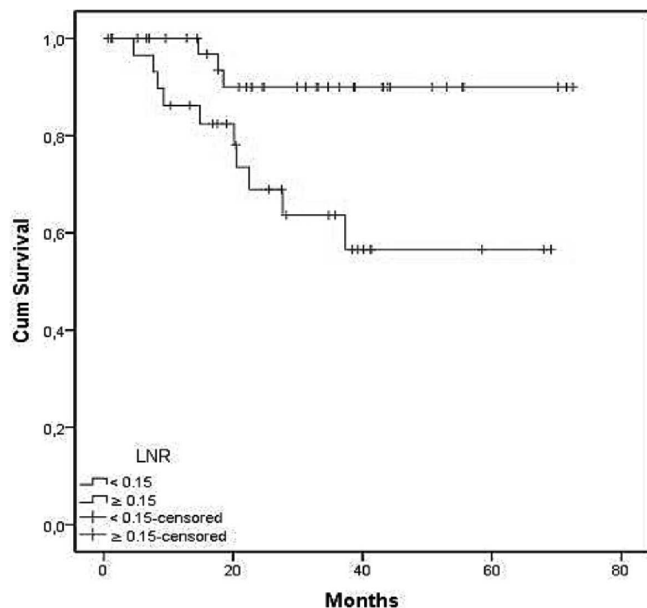
Figure 1 -   *Kaplan-Meier disease-free survival curves for patients with LNR < 0.15 (superior line) and > 0.15 (inferior line). Logrank test p = 0.011.*
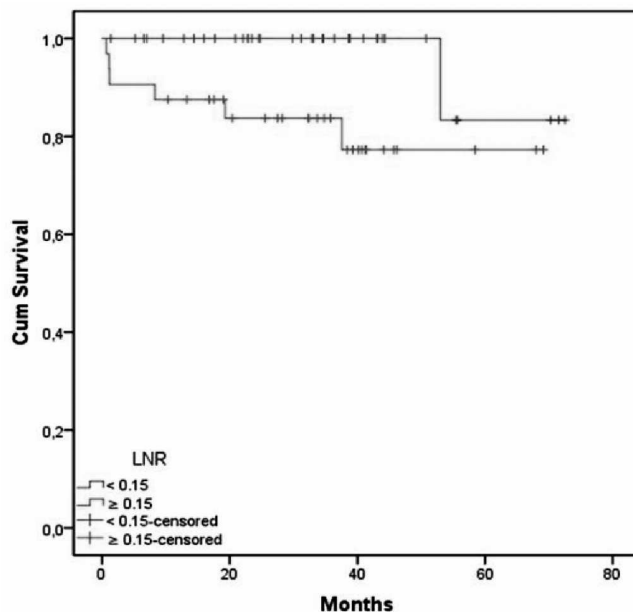

Figure 3 -   *Kaplan-Meier overall survival curves for patients with LNR < 0.15 (superior line) and > 0.15 (inferior line). Logrank test p = 0.024.*
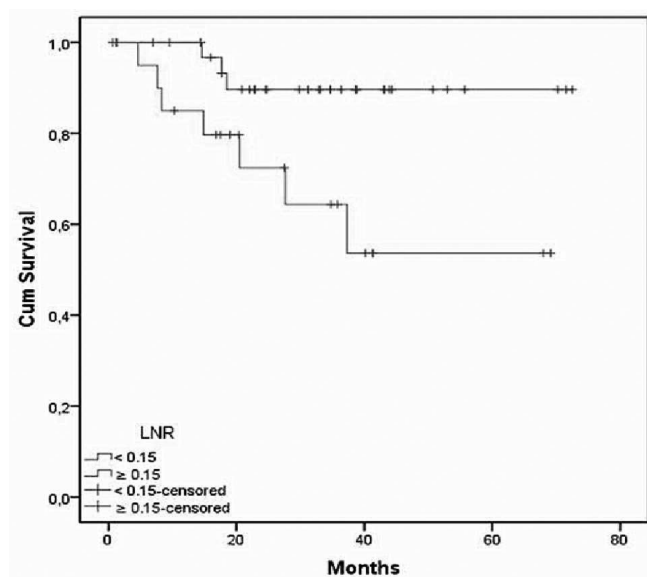

Figure 2 -   *Kaplan-Meier disease-free survival curves for stage IIIB patients with LNR < 0.15 (superior line) and > 0.15 (inferior line). Logrank test p = 0.016.*

on rectal cancer addressing this issue found diverse results, ranging from 0.21 to 0.60 [21, 22]. This variability can be largely explained by the use of preoperative radiotherapy. It seems clear that the interpretation of the nodal status of patients previously submitted to radiotherapy must be done in separate, and it is possible that in the future colon and rectum staging systems become independent, as recently occurred to appendix cancer.

This study included only patients with intraperitoneal colorectal tumors. Although some patients with rectosigmoid junction tumors have been included, with tumors whose inferior borders could be located in the upper rectum, this procedure is in accordance with inclusion criteria of major clinical trials on colon cancer adjuvant therapy [23, 24], thus reflecting common clinical practice.

Stratification of the patients according to their lymph node ratio showed that patients with an LNR greater than or equal to 0.15 had both a higher number of positive nodes and a lower number of lymph nodes retrieved. This trend was found by other authors [25, 26]. This observation agrees with studies that analyzed the impact of lymph node harvest on colon cancer prognosis, which suggests that factors other than staging accuracy may account for the improvement in survival associated with the increased number of lymph nodes evaluated [12,27].

The explanation of the aforementioned trends could be in the immune system. It is very plausible that the number of nodes present in a given patient reflects, at least in part, the underlying interaction between tumor and host [28]. Galon *et al.* [29] have found that type, density, and location of immune cells within the colorectal cancer formed patterns of immune response that could predict the survival of some patients more accurately than standard histopathologic staging methods. George *et al.* [30], in a study on the relationship between node number and survival in colon cancer patients, observed that patients with prominent lymphocytic infiltration in the primary tumor had a survival advantage; these patients also tended to present higher lymph node counts. Thus, the apparent success of the LNR as a better prognostic factor than the simple number of metastatic lymph nodes may reside in the fact that it adds a new dimension to staging, providing information not only

on tumor aggressiveness, but also on patient immune response.

The minimum number of lymph nodes resected for the LNR to be considered a reliable prognostic factor is still under debate. The American College of Surgeons, the American Society of Clinical Oncology and the National Quality Forum endorsed that at least 12 lymph nodes should be removed and pathologically examined in resectable primary colon cancer as the quality measure of hospital performance [31-33]. This recommendation is also present in TNM classification[7]. Four studies evaluated the influence of lymph node harvest on LNR in colon cancer, with mixed results. The largest of these studies, published by Wang *et al.*, demonstrated that the LNR remained an independent prognostic factor even in patients with less than 10 lymph nodes examined [34], a fact also confirmed by Vaccaro *et al.*[35] Controversially, Berger *et al.* found that the LNR lost its discriminatory capacity in patients with less than 10 lymph nodes harvested, but these authors included patients with stage II colon cancer in their statistical analysis [36]. In the study by Park *et al.*, the LNR had no prognostic significance in patients with less than 12 resected lymph nodes, but interpretation of this observation is hampered by the choice of the LNR cutoffs being based on previous data from gastric cancer [37].

In our study, only 10% of patients had less than 12 resected lymph nodes. The limited size of our sample prevents an analysis of this subgroup of patients. In fact, the major limitations of our study reside in our sample size and its retrospective nature. The small number of deaths observed during follow-up also prevented us to perform a detailed analysis on the influence of the LNR in disease-specific survival or overall survival.

CONCLUSION

Lymph node ratio is a strong predictor for tumor recurrence on colon cancer. Future editions of TNM Classification of Malignant Tumors should consider the inclusion of this factor in the stratification of patients with stage III disease.

R E S U M O

Objetivo: avaliar o índice de linfonodos comprometidos na ocorrência de recidivas tumorais em pacientes com câncer de cólon estádio III. *Métodos:* foram avaliados de maneira retrospectiva todos os pacientes com câncer de cólon estádio III submetidos à ressecção curativa do tumor primário entre janeiro de 2005 e dezembro de 2010. Os desfechos de interesse foram a ocorrência de recidivas tumorais e morte. O impacto do índice de linfonodos comprometidos e das demais variáveis clínico-patológicas na sobrevida livre de doença foi avaliado através de análise uni e multivariável. De modo a identificar-se o ponto de corte de maior acurácia para utilização do índice de linfonodos comprometidos como um preditor de recidivas tumorais realizou-se a análise da curva característica de operação do receptor. A sobrevida livre de doença foi avaliada através de curvas de Kaplan-Meier. *Resultados:* setenta pacientes foram incluídos no estudo (50% masculinos). A média de idade foi 64 anos. A análise univariável identificou quatro fatores determinantes para a ocorrência de recidivas tumorais: antígeno carcinoembrionário, estadiamento N, número de linfonodos positivos e índice de linfonodos comprometidos. O índice de linfonodos comprometidos foi o que demonstrou a maior magnitude de associação. A análise da curva característica de operação do receptor identificou 0,15 como o ponto de corte ideal. Pacientes com um índice de linfonodos comprometidos <0,15 apresentavam uma sobrevida livre de doença de 90% em três anos (versus 64%, P=0,011). *Conclusão:* o índice de linfonodos comprometidos é um forte preditor para recidivas tumorais no câncer de cólon estádio III.

Descritores: Linfonodos. Neoplasias do colo. Metástase linfática. Estadiamento de neoplasias. Sobrevivência.

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Address for correspondence:

Dr. Daniel C. Damin
E-mail: damin@terra.com.br