

ONCOLOGICAL IMPLICATIONS OF LYMPH NODES RETRIEVAL AND PERINEURAL INVASION IN COLORECTAL CANCER: OUTCOMES FROM A REFERRAL CENTER

OMAR VERGARA-FERNANDEZ^{1*}, ADOLFO NAVARRO-NAVARRO¹, HUGO ANTONIO RANGEL-RÍOS¹, NOEL SALGADO-NESME¹, JOSÉ ARISTEO REYES-MONROY¹ AND DAVID VELÁZQUEZ-FERNÁNDEZ²

¹Department of Colon and Rectal Surgery; ²Department of Endocrine Surgery. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

ABSTRACT

Background: In colorectal cancer (CRC), regional lymphadenectomy provides prognostic information and guides management. The current consensus states that at least 12 lymph nodes (LN) should be evaluated. The aims of this study were to identify whether the number of LN is a predictor for survival and recurrence, and to reveal the role of LN ratio (LNR) and perineural invasion (PNI) in predicting prognosis after curative resection of CRC. **Methods:** We included all patients who underwent surgery for CRC between 2000 and 2016 in an academic medical center in Mexico. The LNR cutoff value was 0.25. We analyzed two groups according to the number of LN retrieved: Group 1 (≥ 12 LN) and Group 2 (< 12 LN). **Results:** We included 305 patients, 13.8% in Stage I, 45.6% in Stage II, and 40.6% in Stage III. The male:female ratio was 1.1. The mean age was 62.6 ± 14 years (range, 19-92). In 233 patients (76.4%), ≥ 12 LN were obtained. Recurrence rates in Groups 1 and 2 were 20.2% versus 26.4%, respectively ($p = 0.16$). PNI was present in 34 patients (13.2%). An LN harvest < 10 increased local and distant recurrences ($p = 0.03$). Stage III patients with an LNR ≥ 0.25 had higher overall recurrence rates ($p = 0.012$) and mortality ($p = 0.029$). In a multivariate Cox regression analysis, PNI-negative tumors were an independent prognostic factor for disease-free survival ($p = 0.011$, hazard ratio = 2.78, 95% confidence interval = 1.26-6.16). **Conclusions:** An LN retrieval < 10 increased local and distant recurrence rates. LNR was an independent prognostic factor for survival in Stage III tumors. PNI was the only significant independent prognostic factor affecting disease-free survival in our patients. (REV INVEST CLIN. 2018;70:291-300)

Key words: Colorectal cancer. Lymph nodes. Perineural invasion.

Corresponding author:

*Omar Vergara-Fernandez,
Department of Colon and Rectal Surgery
Instituto Nacional de Ciencias Médicas
y Nutrición Salvador Zubirán
Vasco de Quiroga, 15
Col. Belisario Domínguez, Sección XVI, Del. Tlalpan
C.P. 14080, Ciudad de México, México
E-mail: omarvergara74@hotmail.com

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INTRODUCTION

Colorectal cancer (CRC) is a common disease that has high morbidity and mortality rates. It is estimated that about 140,250 new cases of CRC are diagnosed annually in the United States and approximately 50,630 people die every year due to this condition¹. CRC mortality has been progressively reduced since 1990 at a rate of about 3% per year². In Mexico, CRC is the third most frequent type of cancer and is the sixth leading cause of cancer death³. Surgical resection is the only curative treatment modality for localized colon cancer. Regional lymphadenectomy, besides, being a quality indicator in CRC surgery, provides prognostic information, and guides post-operative management, such as the administration of chemotherapy. There is a direct correlation between the number of lymph nodes (LN) examined per patient after surgical resection and survival⁴. However, the concept of such sequential progression or metastatic cascade, in which the primary tumor seeds LN metastases that, in turn, seed distant metastases, provides a simplistic theory. Some studies have shown that the removal of LN does not always improve patient survival^{5,6}. Naxerova et al. analyzed variants in hypermutable DNA regions, finding that in 65% of the cases, lymphatic and distant metastases arose from independent subclones in the primary tumor, whereas in 35% of cases they shared a common subclonal origin⁵.

The current consensus in the world literature is that at least 12 LN must be examined for adequate staging. However, recommendations range from 6 to 18 LN⁷⁻¹¹. The American Society of Clinical Oncology recommends the use of adjuvant chemotherapy for patients suffering from node-negative colon cancer if there are < 12 LN in the surgical specimen¹². In a meta-analysis of 17 studies, the number of LN examined per patient correlated significantly with overall survival and 5-year recurrence rates in patients with Stage II and III colon cancer^{4,13-17}. The more obvious explanation is that the greater the removal of LN, the greater the accuracy of the staging classification. However, the strong association between total LN count and survival is not fully explained by an improved staging classification¹⁸⁻²⁰. In this way, the LN number has been proposed as a quality indicator for CRC surgery²¹. The differences between patients with CRC in terms of the number of LN

collected are influenced by multiple factors such as size, location, degree of differentiation, tumor biology, obesity, surgical approach, surgeon's experience, histopathological analysis, and neoadjuvant treatment²²⁻²⁷.

Due to the aforementioned controversies, new parameters have been described to improve the prediction of oncological outcomes. One of these parameters is the LN ratio (LNR), which is calculated by dividing the number of positive LN by the total number of LN examined. There is no consensus about the LNR cutoff value, but most coincide in a value of 0.25²⁸⁻³⁰.

The objectives of our study were to analyze the impact of the number of LN on recurrence and survival in patients who underwent a curative CRC resection and to examine factors that influence LN retrieval. In addition, to examine the role of LNR and perineural invasion (PNI) in predicting prognosis after curative resection of CRC.

MATERIALS AND METHODS

We included all patients who had curative resection for CRC (Stages I, II, and III) at a referral center in Mexico City between January 2000 and December 2016. The diagnosis of CRC was made by histopathological examination. We excluded patients with loss to follow-up ($n = 4$), incomplete pathology report ($n = 5$), operative mortality ($n = 16$), Stage IV cancers ($n = 89$), and those requiring only a derivative stoma due to obstruction ($n = 5$). We obtained data from a prospective database and verified the data with hospital charts. Two groups according to the number of LN retrieved were initially analyzed: Group 1 (≥ 12 LN) and Group 2 (< 12 LN). Similarly, we analyzed several factors that influence the number of LN retrieved: gender, age, localization, body mass index (BMI), laparoscopic surgery, neoadjuvant therapy, and the tumor's histology. Different cutoff values for the total number of LN (6, 9, 12, 15, and 18) were used to analyze if there were differences in recurrence or mortality. LNR was calculated in patients with Stage III tumors, and we took a cutoff value of 0.25 according to the revised bibliography³¹. We also analyzed surgeries performed for each year and classified them into

two groups: those performed before 2009 and those after this year, because since that date, the synoptic pathology report was introduced in our hospital. Board-certified pathologists performed histopathological assessments of hematoxylin and eosin stained slides. PNI was defined as identification of tumor cells spreading to the space surrounding a nerve. The study was approved by the institutional ethics review board (SCI-2206-17/17-1).

Descriptive analysis of the variables registered was conducted using measures of central tendency and spread according to whether they were continuous or categorical variables. Chi-square or Fisher's exact test was used for the statistical contrast of the categorical variables according to whether they were variables with normal distribution or not. Odds ratio with 95% confidence interval was calculated to corroborate the statistical power in the univariate analysis. The influence of variable factors on disease-free survival was estimated using the Kaplan–Meier method. ANOVA was used to determine whether the means of the categorical variables between the groups were the same. We also utilized a Cox proportional hazard model to analyze factors associated with disease-free survival for multivariate analyses. The association between LNR and recurrence was assessed by the receiver operating characteristic curve. The corresponding area under the curve was also calculated. A difference with $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS version 20.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

Between 2000 and 2016, 424 patients underwent CRC surgery in a referral center in Mexico City. A total of 305 patients were included in the study, 42 (13.8%) patients in Stage I, 139 (45.6%) in Stage II, and 124 (40.6%) patients in Stage III. The male:female ratio was 1.1. The mean age was 62.6 ± 14.4 years (range, 19–92). The mean of BMI was 25.5 ± 4.7 (range, 14–44). Tumor localization sites were 106 (34.7%) in the cecum and ascending colon, 16 (5.2%) in the transverse colon, 18 (5.9%) in the descending colon, 71 (23.2%) in the sigmoid colon, and 90 (29.5%) in the rectum. Four (1.3%) patients with synchronous tumor were detected. Surgeries

were performed laparoscopically in 163 patients (53.4%), with a conversion rate of 11.1%.

The surgical procedures were 111 right colectomies, 2 transversectomies, 24 left colectomies, 43 sigmoid resections, 67 low anterior resections, 19 abdominoperineal resections, 15 total colectomies, 7 pelvic exenteration, and 6 proctocolectomies.

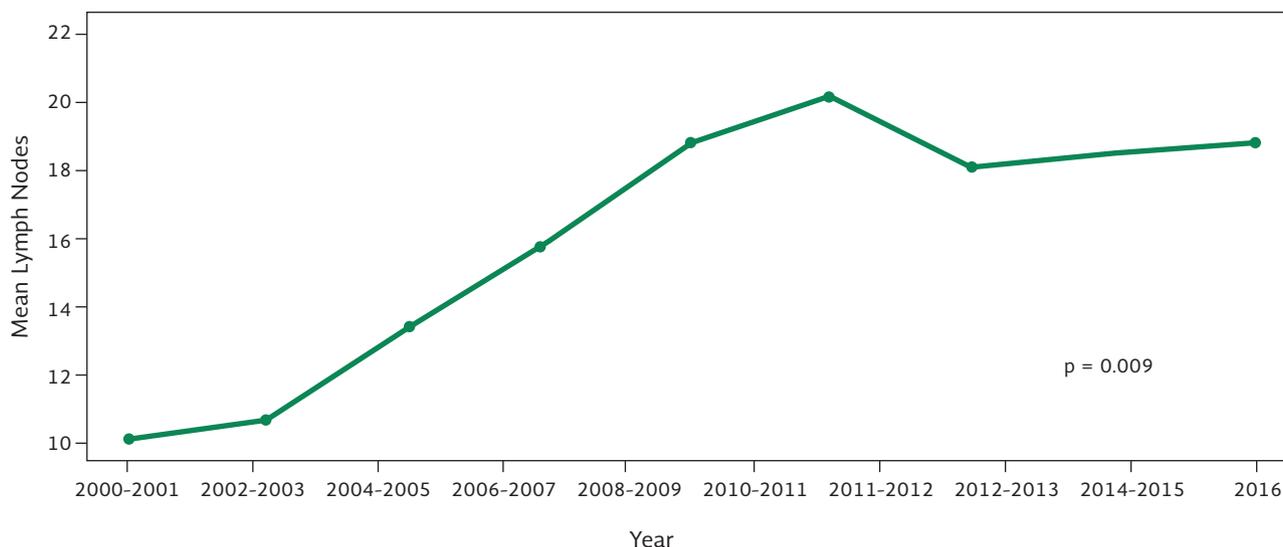
The mean LN harvest was 17.25 with a range from 0 to 63. In 233 (76.4%) patients, 12 or more LN were obtained in the surgical specimen. The average number of LN in Group 1 (≥ 12 LN) and Group 2 (< 12 LN) was 20.89 ± 8.98 and 5.44 ± 4.33 , respectively (Table 1).

We identified that, from 2000 to 2016, the LN harvest increased over time. We also analyzed surgeries in two groups: those performed before 2009 and those after this year. In the first group (2000–2008), 110 surgeries were performed, of which 68 (61.8%) had ≥ 12 LN; of 195 surgeries in the second group (2009–2016), 165 (84.6%) had ≥ 12 LN (odds ratio [OR] 3.397; 95% confidence interval [CI]: 1.966–5.871; $p \leq 0.0001$). The differences of LN retrieval over time are shown in figure 1.

The mean follow-up time was 47.8 months (range from 15 days to 200 months). Overall, the recurrence rate was 21.6% (66 patients), with an average recurrence time of 24.6 months (range from 2 to 132). The recurrence rates in Group 1 (≥ 12 LN) and Group 2 (< 12 LN) were 20.2% and 26.4% ($p = 0.16$), respectively. Overall, 5-year survival was 83.6%. The 5-year survival rates in Group 1 and Group 2 were 90.1% and 87.3% ($p = 0.74$), respectively (Fig. 2). When analyzing overall survival by stages, no significant differences were found between LN harvest ≥ 12 and < 12 : in Stage I cancers, 93.8 versus 90% ($p = 0.46$); in Stage II, 91.7 versus 76.7% ($p = 0.10$); and in Stage III, 83.9 versus 87.1% ($p = 0.36$). The recurrence and mortality rates were assessed according to clinical stages, and we found that Stage III cancers had higher recurrence rates compared with Stages I and II (OR 2.05, 95% CI: 1.18–3.57; $p = 0.007$) (Table 2).

According to the number of LN, we found higher local and distant recurrence rates in patients with < 6 and 9 LN compared to those with ≥ 12 LN, 36.4% and

Figure 1. Differences of the mean lymph node number over time (ANOVA).



34.1% versus 20.2% ($p = 0.03$), respectively. Overall, recurrence rates according to the number of LN were as follows: 36.4% (< 6 LN) versus 19.9% (≥ 6 LN); 34.1% (< 9 LN) versus 19.5% (≥ 9 LN); 26.4% (< 12 LN) versus 20.2% (≥ 12 LN); 25.4% (< 15 LN) versus 19% (≥ 15 LN); and 22.9% (< 18 LN) versus 20% (≥ 18 LN) ($p = 0.0001$). A number of LN retrieved > 12 did not show additional benefits on recurrence or survival (Table 2).

The LNR was calculated in Stage III tumors. In 26 patients (9.9%), the LNR was higher than 0.25. Overall, survival rates in patients with an LNR < 0.25 versus those with an LNR ≥ 0.25 were 88.1% versus 73.1% ($p = 0.009$), respectively. Patients with an LNR ≥ 0.25 had higher recurrence (OR 3.57, 95% CI: 1.56-8.16; $p = 0.012$) and mortality rates (OR 2.94, 95% CI: 1.14-7.57; $p = 0.029$) (Table 2). The overall disease-free survival was 42 months in patients with an LNR < 0.25, and it was 18 months in patients with an LNR ≥ 0.25 ($p < 0.001$) (Figs. 3 and 4).

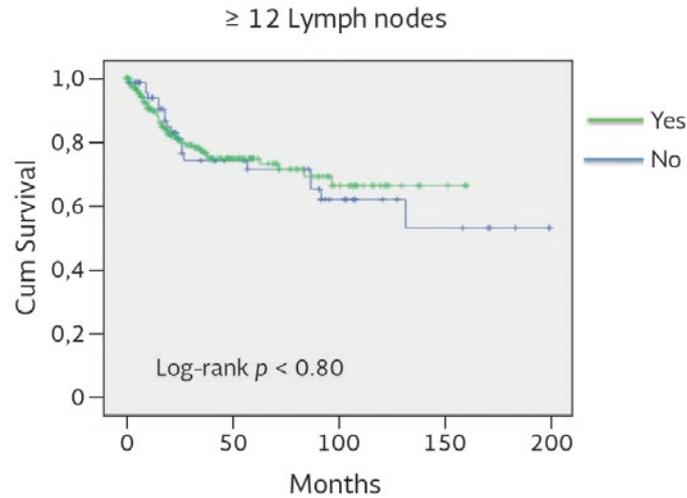
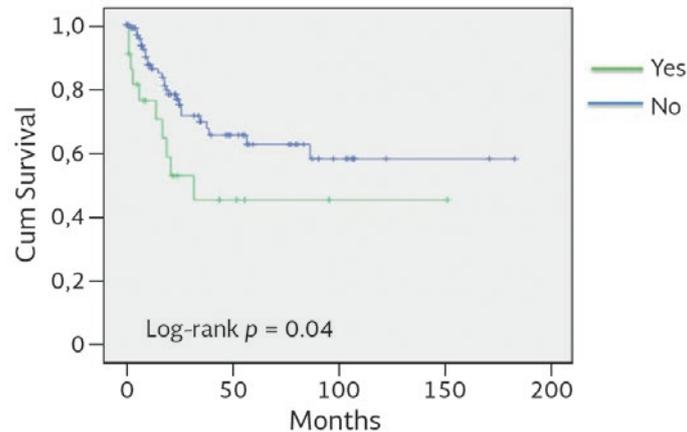
Lymphovascular invasion (LVI) and PNI were present in 61 (23.7%) and 34 (13.2%) cases, respectively. We did not find statistically significant differences by comparing LVI with recurrence (OR 1.02, 95% CI: 0.51-2.03; $p = 0.54$) and mortality (OR 2.05, 95% CI: 0.96-4.35; $p = 0.05$). However, we found higher recurrence (OR 2.79, 95% CI: 1.33-5.86; $p = 0.007$) and mortality (OR 2.87, 95% CI: 1.22-6.73; $p = 0.018$)

when PNI was present (Table 2). The overall disease-free survival was 21.4 months for patients with PNI-positive tumors, and it was 44 months for patients with PNI-negative tumors ($p = 0.001$) (Fig. 5). In a multivariate Cox regression analysis, PNI-negative tumors were an independent prognostic factor for disease-free survival ($p = 0.011$, hazard ratio [HR] = 2.78, 95% CI = 1.26-6.16).

The factors associated with an increased number of LN retrieved were tumors located in the colon, laparoscopic surgeries, and surgeries performed after the introduction of the synoptic pathology report (Table 3).

DISCUSSION

There is currently sufficient evidence to demonstrate that LN involvement is a prognostic factor and quality indicator for CRC surgery⁴. However, the exact number of LN that should be examined has not yet been well determined. In addition, in the literature, there is much controversy on determining a minimum number in which there would be no substaging risk. Hernanz et al. showed that if 6 LN were examined the probability to find at least, a positive LN was 95% and that this probability increased to 99% if 10 LN were examined. Therefore, the authors concluded that 6 LN provided an accurate assessment of the

Figure 2. Analysis of disease-free survival with ≥ 12 lymph node in the surgical specimen.Figure 3. Analysis of disease-free survival according to a lymph node ratio ≥ 0.25 (Stage III).

presence of nodal metastasis³². In our series, LN harvest of < 6 or 9 had a significant impact on recurrence and mortality rates. Goldstein et al. and Maurel et al. showed that the probability of correctly classifying a colorectal tumor as node-positive increased as the number of examined LN. They also reported that this increase had a plateau. In their two series of patients, this plateau was reached when 17 LN in one series and 16 in the other had been examined^{33,34}. We show in our study that an LN count of 12, 15, or 18 had no additional benefit on predicting recurrence or mortality and that a plateau is observed from 12 LN. This

plateau is not observed when the nodal harvest is < 6 or 9 LN. Cianchi et al. found that the 5-year survival rate of Stage II patients with 8 or fewer LN examined was similar to that of Stage III patients. Their results suggested that examining a minimum of 9 LN per surgical specimen may be sufficient for reliable staging of LN-negative tumors¹¹. Swanson et al. classified patients with T3N0 colon cancer into three groups according to the number of LN examined and found that a minimum of 13 LN should be examined to label the cancer as node negative³⁵. Baxter et al. found that in the United States, only

Table 1. Demographic characteristics.

Variable	n (%)
Gender	
Female	152 (49.8)
Male	153 (50.2)
Age	
≥ 65	145 (47.5)
< 65	160 (52.5)
BMI	
≥ 25	159 (52.5)
< 25	144 (47.5)
Not specified	2
Tumor localization	
Left colon and sigmoid	89 (29.2)
Right colon	106 (34.7)
Transverse colon	16 (5.2)
Rectum	90 (29.5)
Synchronous	4 (1.3)
Staging	
I	42 (13.8)
II	139 (45.6)
III	124 (40.6)
Lymph node retrieval	
≥ 12	233 (76.4)
< 12	72 (23.6)
Type of surgery	
Open	132 (43.3)
Laparoscopic	173 (56.7)
LNR (Stage III)	
≥ 0.25	26 (20.9)
< 0.25	98 (79.1)
Perineural invasion	
Positive	34 (13.2)
Negative	223 (86.8)
Not specified	48 (15.7)
LVI	
Positive	61 (23.7)
Negative	196 (76.3)
Not specified	48 (15.7)
Tumor histology	
Adenocarcinoma	271 (88.8)
Mucinous	14 (4.6)
Signet ring	5 (1.6)
Not specified	15 (4.9)

BMI: body mass index, LNR: lymph node ratio, LVI: lymphovascular invasion.

37% of patients received adequate LN evaluation (i.e., at least 12 LN examined), and the median number of LN for all patients was 9³⁶. In our series, more than 75% of patients had 12 or more LN examined in the surgical specimen. We consider that the quality of our surgeries was high in relation to the number of retrieved LN and that the low proportion of patients with < 12 LN was the reason why we did not obtain statistical significance in the multivariate analysis.

More recently, Mason et al. established that only 46% of high-performance hospitals in the United States adhere to an LN collection ≥ 12³⁷. On the other hand, when taking different cutoff values from the LN, we found that a harvest < 6 or 9 had a significant impact on overall recurrence rates. In a study, Zhang et al. showed that LN count did not significantly affect survival, whereas LNR was found to be significant for predicting mortality and recurrence at Stage III²⁹. Similarly, Tsikitis et al analyzed a series of 329 patients in Stage III where they did not find a significant association between ≥ 12 and < 12 nodes on survival; however, they found a positive correlation between the number of positive nodes and survival²².

Variations in the ability of the pathologists to search for LN and the different statistical methods used in the published series are probably the main factors that explain the considerable variation. The number of nodes harvested depends on several factors such as sex, location of the tumor, depth of lesion, extent of lymphadenectomy, and the ability of the surgeon and pathologist to identify and collect LN. Different studies have reported that LN metastases in CRC are often found in small LN (< 5 mm in diameter)^{30,38,39}. In our study, we found that tumors located in the colon, the laparoscopic approach, and surgeries performed after the implementation of a multidisciplinary team management were determinants to obtain a greater number of LN.

Some authors have found that the use of a synoptic pathology report improved the mean number of LN harvested, and more frequently, the minimum number of 12 LN was achieved⁴⁰. At our institution, the proportion of specimens with more than 12 LN increased after the adoption of a synoptic pathology reporting for CRC in 2009.

Figure 4. Receiver operating characteristic curve to assess the association between lymph node ratio and overall recurrences (Stage III). The area under the curve was 0.619, $p = 0.036$ (95% confidence interval, 0.50-0.73).

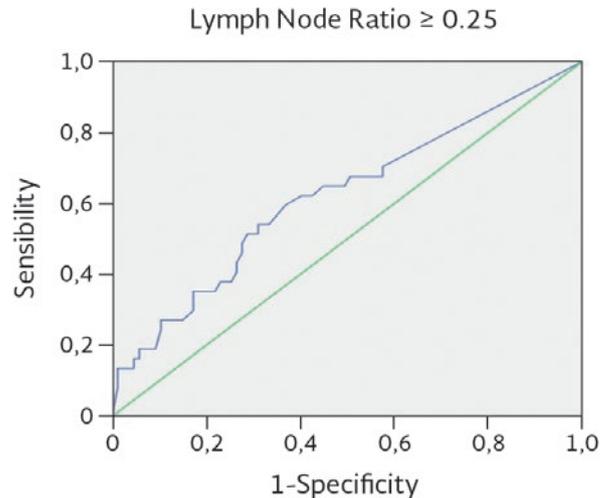
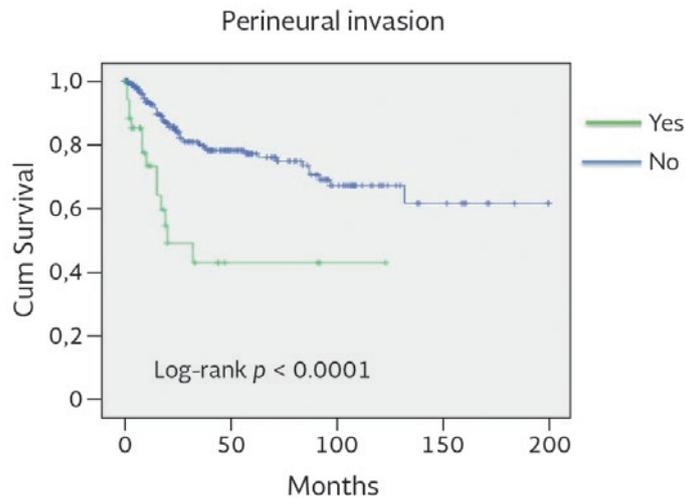


Figure 5. Analysis of disease-free survival according to perineural invasion in colorectal cancer.



On the other hand, there is enough evidence that the laparoscopic approach has the same oncological outcomes compared to the open approach⁴¹⁻⁴⁴. Most of the literature refers to the existence of a larger LN harvest in the open approach⁴⁵. As such, we believe that these results are because, since 2009, only board-certified colorectal surgeons perform all laparoscopic CRC surgeries at our hospital. We obtained a trend toward statistical significance of greater LN

retrieval in rectal cancer patients who did not receive neoadjuvant therapy. Abdel-Misih et al. demonstrated in their study that patients receiving neoadjuvant chemoradiation had a lower number of LN collected with a mean of 15 compared to 17 and 18 for non-neoadjuvant and neoadjuvant chemotherapy, respectively ($p \leq 0.0001$)⁴⁶. We believe that we did not obtain statistical significance due to our small sample size.

Table 2. Factors associated with recurrence and survival.

Variables (n = 305)	Recurrences (n = 66)	p value	OR (95% CI)	5-year survival (n = 38)	p value	OR (95% CI)
Gender						
Male (153)	40 (26.1)	0.037	1.7 (0.98-2.98)	24 (15.7)	0.061	1.83 (0.90-3.69)
Female (152)	26 (17.1)			14 (9.2)		
Age						
≥ 80 (37)	7 (18.9)	0.42	1.21 (0.50-2.89)	8 (21.6)	0.069	2.18 (0.91-5.22)
< 80 (268)	59 (22)			30 (11.2)		
Number of LN						
≥ 6 LN (272)	54 (19.9)	0.03	2.3 (1.06-4.97)	31 (11.4)	0.096	2.09 (0.83-5.22)
< 6 LN (33)	12 (36.4)			7 (21.2)		
≥ 9 LN (261)	51 (19.5)	0.028	2.13 (1.06-4.26)	31 (11.9)	0.29	1.40 (0.57-3.42)
< 9 LN (44)	15 (34.1)			7 (15.9)		
≥ 12 LN (233)	47 (20.2)	0.16	1.41 (.76-2.62)	26 (11.2)	0.15	1.59 (0.75-3.34)
< 12 LN (72)	19 (26.4)			12 (16.7)		
≥ 15 LN (179)	34 (19)	0.11	1.45 (.83-2.51)	20 (11.2)	0.26	
< 15 LN (126)	32 (25.4)			18 (14.3)		1.32 (0.67-2.62)
≥ 18 LN (130)	26 (20)	0.32	1.15 (0.68-2.06)	17 (13.1)	0.45	
< 18 LN (175)	40 (22.9)			21 (12)		1.10 (0.55-2.18)
Stage I (42)	0 (0)	-	-	3 (7.1)	0.19	1.99 (0.58-6.80)
Stage II (139)	30 (21.6)	0.54	0.99 (0.57-1.71)	16 (11.5)	0.38	1.17 (0.59-2.33)
Stage III (124)	36 (29)	0.007	2.05 (1.18-3.57)	19 (15.3)	0.14	1.54 (0.78-3.05)
LVI (61)	13 (21.3)	0.54	1.02 (0.51-2.03)	12 (19.7)	0.05	2.05 (0.96-4.35)
Perineural invasion (34)	14 (41)	0.007	2.79 (1.33-5.86)	9 (26)	0.018	2.87 (1.22-6.73)
LNR ≥ 0.25 (26)	12 (46.1)	0.012	3.57 (1.56-8.16)	7 (26.9)	0.029	2.94 (1.14-7.57)
Colon cancer (214)	44 (20.6)	0.28	1.23 (0.68-2.20)	23 (10.7)	0.11	1.63 (0.81-3.30)
Rectal cancer (91)	22 (24.2)	0.28	1.23 (0.68-2.20)	15 (16.5)	0.11	1.63 (0.81-3.30)

BMI: body mass index, LNR: lymph node ratio, LVI: lymphovascular invasion, LN: lymph node, CI: confidence interval, OR: odds ratio.

LVI and PNI have proven to be independent prognostic factors of recurrence and mortality in CRC. LVI refers to the involvement of small lymphatic or blood (typically venous) vessels by the tumor, and PNI refers to the growth of tumor in, around, and through nerves and nerve sheaths. It is believed that both variables denote an aggressive phenotype, increased

node involvement, poor tumor differentiation, greater depth of tumor invasion, and, therefore, higher rates of recurrence and mortality. Al-Sukhni et al. identified that specific PNI was independently associated with reduced survival (HR 3.55, 95% CI: 1.78-7.09)⁴⁷. Similar to our results, other authors have found that PNI is an independent prognostic factor

Table 3. Variables associated with higher lymph node retrieval.

Variables	≥ 12 LN n = 233 (%)	p value
Gender		
Female (153)	110 (72.4)	0.065
Male (152)	123 (80.4)	
Age		
≥ 65 (145)	105 (72.4)	0.077
< 65 (160)	128 (80)	
BMI		
≥ 25 (159)	124 (78)	0.269
< 25 (144)	107 (74.3)	
Localization of the tumor		
Colon (214)	179 (86.6)	<0.0001
Rectum (91)	54 (59.3)	
Surgical approach		
Laparoscopic (163)	135 (88.8)	0.001
Open (132)	88 (66.7)	
Year of surgery		
2000-2008 (110)	68 (61.8)	<0.0001
2009-2016 (195)	165 (84.6)	
Neoadjuvant treatment in rectal cancer (91)		
Yes (52)	27 (51.9)	0.07
No (39)	27 (69.2)	

affecting disease-free and overall survival in patients with colon cancer^{48,49}.

The LNR has been proposed as an easy way to improve the predictive value of metastatic involvement of LNs, which for some authors would be higher than the number of positive LNs^{50,51}. In different series, LNR has shown to be a relevant prognostic factor in patients with collected positive LN and poorly staged patients initially classified as Stages I and II, especially if the LN count is higher than or equal to 12. The strong interaction between the number of LN

examined, the number of metastatic LN and the LNR does not allow a categorical conclusion of which is the most prominent prognostic factor. In our series, an LNR higher than 0.25 was an independent predictor of recurrence and survival in patients with Stage III tumors.

In conclusion, an LN harvest lower than 10 increased local and distant recurrence rates. The LNR is an independent prognostic factor for recurrence and overall survival in Stage III tumors. In our study, we demonstrated that a greater LN retrieval was associated with tumors located in the colon, a laparoscopic approach, and the absence of neoadjuvant treatment. PNI was the only significant independent prognostic factor affecting disease-free survival.

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