Brief Report

Does the Presence of Matted Nodes in Colon Adenocarcinoma Influence 5-Year Overall Survival?

Karla I Rodriguez-López , Mariana Salazar-Castillo , Leonardo S. Lino-Silva * , Angeles Galán-Ramírez , Luisa F Rivera-Moncada , Emiliano López-Jiménez , Cesar Zepeda-Najar

Posted Date: 11 June 2024

doi: 10.20944/preprints202406.0731.v1

Keywords: matted nodes, lymph node metastasis, colon cancer, rectal cancer, colorectal cancer, overall survival

 doi:10.20944/preprints202406.0731.v1

Article

Does The Presence of Matted Nodes in Colon Adenocarcinoma Influence 5-Year Overall Survival?

Karla I. Rodríguez-López [1,2], Mariana Salazar-Castillo [1], Leonardo S. Lino-Silva [1,*], Ángeles Galán-Ramírez [1], Luisa F. Rivera-Moncada [1,2], Emiliano A. López-Jiménez [2] and César Zepeda-Najar [3]

[1] Surgical Pathology, National Cancer Institute (Mexico), Tlalpan, Mexico City, Mexico; karlaisarolo07012002@gmail.com (K.I.R.-L.); mariana.salazar.cas@gmail.com (M.S.-C.); angelesgalan.rmz@gmail.com (Á.G.-R.); luisafernandarivera08@gmail.com (L.F.R.-M.)
[2] AFINES Program, Medicine Faculty, National Autonomus universiti of Mexico (UNAM), Coyoacán, Mexico City, Mexico; emilianolopezjimenez@gmail.com
[3] Surgical Oncology, Ángeles Tijuana Hospital, Tijuana, Baja California Norte, Mexico
* Correspondence: saul.lino.sil@gmail.com

Abstract: *Background*: Colorectal cancer (CRC) is prevalent globally, constituting 11.9% of cases in Mexico. Lymph node metastases are established prognostic indicators, with extracapsular lymph node extension (ENE) playing a crucial role in modifying prognosis. While ENE is associated with adverse factors, certain aspects, like lymph node conglomerates, are underexplored. Matted nodes, clusters of lymph nodes infiltrated by cancer cells, are recognized as an independent prognostic factor in other cancers. This study investigates the prognostic implications of lymph node conglomerates, particularly matted nodes, in colon cancer. *Methods*: A retrospective analysis of 502 colon cancer cases (2005–2018) identified 255 with lymph node metastasis. Cases were categorized into two groups: 1) lymph node metastasis alone (n=208), and 2) lymph node metastasis with matted nodes (n=47). A comparative survival analysis was performed. *Results*: Of the 255 patients, 38% had lymph node metastasis. Patients with matted nodes (18.4%) showed an association with higher pN stage and lymphovascular invasion. The 5-year survival rate for patients with matted nodes was 47.7%, compared to 60% without; however, this association demonstrated only a statistical tendency. Multivariate analysis identified clinical stage and adjuvant chemotherapy use as independent factors contributing to survival. *Conclusion*: This study underscores matted nodes as potential prognostic indicators in colon cancer, emphasizing their association with higher pN stage and reduced survival. Further research is essential for validating these findings and integrating matted nodes into the broader context of colorectal cancer management.

Keywords: matted nodes; lymph node metastasis; colon cancer; rectal cancer; colorectal cancer; overall survival

1. Introduction

Colorectal cancer (CRC) ranks among the most prevalent malignancies worldwide. In Mexico, recent data from Globocan reveals that CRC accounts for 11.9% of cases, affecting 6.1% of men and women, respectively. [1] The presence of lymph node metastases in CRC is a well-established prognostic indicator. Beyond the mere existence of lymph node metastases, specific characteristics within these metastases can further influence prognosis. Notably, extracapsular lymph node extension (ENE), as previously elucidated [2], plays a pivotal role in modifying prognosis. Various studies underscore the significance of ENE in metastatic lymph nodes across different malignancies. Drawing from the limited evidence available, it is evident that extracapsular LNI is a prevalent occurrence in patients with gastrointestinal malignancies. Furthermore, ENE has been linked with younger age, advanced tumor stage, lymphovascular invasion (LVI), and perineural invasion (PNI) [3].

However, certain aspects of lymph node metastases in colon cancer, such as lymph node conglomerates, remain unexplored. Node conglomerates denote the presence of clusters of lymph nodes infiltrated by cancer cells, causing them to merge with surrounding tissue. The presence of metastatic lymph nodes and their quantity are pivotal indicators for staging and prognosis,

 doi:10.20944/preprints202406.0731.v1

furnishing vital insights into the cancer's aggressiveness and potential treatment strategies. Nevertheless, it remains uncertain whether the presence of clusters exerts a detrimental impact on patients who already harbor lymph node metastases. In other types of cancer, nodal conglomerates have been identified as an independent prognostic factor associated with adverse outcomes. For instance, a systematic review indicates that patients with matted nodes face up to a 1.6-fold higher risk of mortality compared to those without [4].

Given the dearth of literature on the prognostic implications of lymph node conglomerates in colon cancer, our objective was to ascertain whether their presence independently correlates with reduced survival in patients diagnosed with this form of cancer.

2. Materials and Methods

Population. The study identified all consecutive cases of colon cancer treated at our institution spanning from 2005 to 2018, culminating in a cohort of 502 patients. A stringent selection process was applied, focusing on cases presenting with lymph node metastasis. Cases with evidence of metastatic disease at initial presentation were excluded, resulting in a refined subset of 255 cases. These cases were further categorized based on their lymph node metastasis status into two groups: 1) those with lymph node metastasis alone (n=208), and 2) those with lymph node metastasis accompanied by matted nodes (n=47). Matted nodes were meticulously defined in alignment with the National Cancer Institute's criteria, characterized as a cluster of fused lymph nodes validated through histopathological examination. This confirmation was established by the presence of two or more contiguous nodes sharing and adhered by neoplastic cells in their parenchyma and capsules (see Figure 1).

Clinical Features. Relevant clinical and pathological data, alongside established prognostic factors, were systematically collected from the clinical and pathologic records of our institution. The comprehensive dataset included information on sex, age, tumor location, histological type, pathologic T stage, pathologic N stage, surgical margins, distant metastases (identified during follow-up), clinical stage, utilization of adjuvant treatment, follow-up duration in months, and patient outcomes (alive or deceased). Following data collection, a meticulous histopathological review was conducted to authenticate the pathological variables and categorize the cases accordingly.

Statistical Analysis. Upon data compilation, a thorough descriptive analysis of the population was executed, summarizing numerical variables with median and interquartile range and categorical variables with percentages. Subsequently, a bivariate analysis was undertaken, comparing clinicopathological characteristics among the three groups. Numerical variables were scrutinized using the Student's T test, while categorical variables underwent analysis via chi-square testing. A 5-year survival analysis, employing the Kaplan-Meier method, was conducted, comparing clinical and pathological characteristics recognized in the literature as being associated with prognosis, including the study groups. Generated survival curves were subjected to comparison using the log-rank test. Further analyses, stratified by clinical stage, and a multivariate analysis using Cox regression were performed. A significance level of $p < .05$ was employed for all analyses. The statistical software SPSS 29.0 (IBM, Armonk, New York, USA, 2022) facilitated these comprehensive analyses.

3. Results

From a dataset encompassing 502 consecutive patients who underwent colectomy at our institution between 2010 and 2015, 255 cases (38%) with lymph node metastasis were discerned. These patients had a mean age of 57.57 years, spanning from 21 to 88 years, with 54.1% being women and 45.9% men. Predominantly, a significant proportion of patients were in clinical stage III (64.7%), while the remainder were in stage IV. Notably, 166 patients (65%) were still alive at an average follow-up duration of 43 months.

Concerning clinicopathologic features, the distribution of cases based on tumor location revealed a dominance in the right colon (66.3%), followed by the sigmoid (18%), descending colon (11.8%), and transverse colon (3.9%). The median tumor size was 60 mm, with 90% of cases being of the conventional type. Pathologically, 128 cases (50.2%) were classified as stage T3, 89 (34.9%) as stage pT4a, 28 (11%) as stage pT4b, and 10 (3.9%) as stage pT2. The most prevalent histologic grade was

 doi:10.20944/preprints202406.0731.v1

G2 in 123 cases (48.2%), followed by G3 in 111 cases (43.5%), and G1 in 21 cases (8.2%). Lymphovascular invasion was observed in 62.4% of cases, while 39.6% exhibited perineural invasion. The median number of lymph nodes resected was 23 (ranging from 12 to 85), and the median number of lymph nodes with metastasis was 4 (ranging from 1 to 51).

Of the 255 patients, 47 (18.4%) presented with matted nodes. A summary of the clinical and pathological characteristics of these patients, categorized by the presence of matted nodes, is presented in Table 1. The table indicates an association between matted nodes and a higher pN stage, along with an association with lymphovascular invasion.

Table 1. Clinicopathological characteristics of 255 cases of colon cancer according to the presence of matted nodes.

Variable	**No-matted nodes n=208**	**matted nodes n=47**	***p*-value***
Sex, n %)			
Female	138 (52.7)	61 (50)	.626
Male	124 (47.3)	61 (50)	
Age (years)–Median (IQR)	58 (48–68)	58 (48–69)	.695
Location - N (%)			
Right	132 (63.5)	37 (78.7)	.080
Left	76 (36.5)	10 (21.3)	
Tumoral diameter (mm), Median (IQR)	57 (40–80)	60 (50–80)	.186
Resected lymph nodes, Median (IQR)	24 (18–32)	23 (18–32)	.959
Metastatic lymph nodes, Median (IQR)	3 (1–6)	6 (4–8)	**<.001**
Histologic grade, n (%)			
1	19 (9.1)	2 (4.3)	.493
2	98 (47.1)	25 (53.2)	
3	91 (43.8)	20 (42.5)	
Lymph node status, n (%)			
pN1	118 (56.7)	4 (8.5)	**<.001**
pN2	90 (43.3)	43 (91.5)	
Clinical stage, n (%)			
Stage III	137 (65.9)	28 (59.6)	.415
Stage IV	71 (34.1)	19 (40.4)	
Lymphovascular invasion. n (%)			
No	85 (40.9)	11 (23.4)	**.026**
Yes	123 (59.1)	36 (76.6)	
Venous invasion, n (%)			
No	132 (63.5)	33 (70.2)	.382
Yes	76 (36.5)	14 (29.8)	
Perineural invasion, n (%)			
No	126 (60.6)	28 (59.6)	
Yes	82 (39.4)	19 (40.4)	.899
Surgical margins, n (%)			
Negative	198 (95.2)	46 (97.9)	
Positive	10 (4.8)	1 (2.1)	.414
Outcome, n (%)			
Alive	140 (67.3)	25 (53.2)	.097
Dead	68 (32.7)	22 (46.8)	
Adjuvance, N (%)			
No	34 (16.3)	7 (14.9)	.807
Yes	174 (83.7)	40 (85.1)	
Subtype			
Not otherwise specified	94 (45.2)	24 (51.1)	.823
Mucinous	37 (17.8)	6 (12.8)	
Other	77 (5.8)	17 (36.2)	

*Chi square test for categorical variables. T-Student test for numerical variables.; IQR=interquartile range.

 doi:10.20944/preprints202406.0731.v1

Table 2 details the factors linked to survival among patients with lymph node metastasis. Factors such as pN stage, clinical stage, lymphovascular invasion, perineural invasion, and the utilization of adjuvant chemotherapy were considered.

Table 2. Clinicopathological characteristics associated with survival of 255 cases of colon cancer with lymph node metastasis.

Variable	5- year overall survival (%)	*p*-value*
Sex		
Female	53.8	.066
Male	61.7	
Location		
Right	57.9	.556
Left	57.7	
Histologic grade		
1	78.6	.162
2	55.9	
3	54.9	
Lymph node status		
pN1	69.9	<.001
pN2	45.7	
Clinical stage		
Stage III	71.0	<.001
Stage IV	28.1	
Lymphovascular invasion.		
No	69.4	.004
Yes	50.4	
Venous invasion		
No	63.6	.034
Yes	45.7	
Perineural invasion		
No	65.8	.005
Yes	44.9	
Surgical margins		
Negative	58.8	.242
Positive	34.3	
Adjuvance		
No	37.9	<.001
Yes	61.5	
Matted nodes		
No.	60	.096
Yes	47.7	

*Log-rank test.

 doi:10.20944/preprints202406.0731.v1

Matted nodes exhibited a statistical tendency in their association with survival. Multivariate analysis discerned that independent factors contributing to survival were clinical stage and the use of adjuvant chemotherapy (Table 3).

Table 3. Multivariate analysis of factors associated with survival in 255 cases of colon cancer with lymph node metastasis.

Variable	Chi square value	Hazard ratio (95% confidence intervale)	*p*-value*
Clinical stage (III vs IV)	24.509	3.104 (1.982-4.859)	<.001
Adjuvance (No vs Yes)	23.422	.272 (.161-.461)	<.001
Lymph node status (pN1 vs pN2)	3.582	1.602 (.983-2.610)	.058
Lymphovascular invasion (No vs Yes)	3.157	1.669 (.949-2.936)	.076
Matted nodes (No vs Yes)	.805	1.278 (.748-2.186)	.369
Perineural invasion (No vs Yes)	.387	1.162 (.724-1.864)	.534
Venous invasion (No vs Yes)	.050	.945 (.575-1.553)	.823

4. Discussion

In our series of 255 cases of colon cancer with lymph node metastasis, we found that matted nodes presented in 18.4%, their presence was associated with lymph vessel invasion and with a higher pN stage. Five-year survival of patients with matted nodes was 47.7%, compared with 60% in patient without mated nodes, however, this has only statistical tendency and the multivariable analysis demonstrated that they are not associated with the survival.

Colorectal cancer (CRC) stands as a significant global health concern, with recent data from Globocan indicating its prevalence, constituting 11.9% of cases in Mexico and impacting both men and women at rates of 6.1% [1]. Within CRC, the presence of lymph node metastases serves as a well-established prognostic indicator, offering crucial insights into disease progression. However, recent attention has shifted towards a specific aspect of lymph node involvement – matted lymph nodes – and their potential impact on patient outcomes. Extracapsular lymph node extension (ENE), plays a central role in modifying CRC prognosis [5]. This extracapsular involvement has been associated with younger age, advanced tumor stage, lymphovascular invasion (LVI), and perineural invasion (PNI). Notably, matted lymph nodes, defined as clusters of fused nodes adhered by neoplastic cells, represent a distinctive form of ENE. While ENE has been explored across various malignancies, limited evidence is available regarding the prognostic implications of matted lymph nodes in colon cancer [6].

Our study contributes to the evolving understanding of lymph node involvement by investigating matted lymph nodes specifically. In other cancer types, matted nodes have been identified as an independent prognostic factor associated with adverse outcomes. For instance, a systematic review, patients with matted nodes face up to a 1.6-fold higher risk of mortality compared to those without [4]. Addressing a gap in the existing literature, this study sought to elucidate whether the presence of matted lymph nodes independently correlates with reduced survival in patients diagnosed with colon cancer. By focusing on this distinctive form of lymph node involvement, the study aims to provide valuable insights into its prognostic implications and potential influence on treatment strategies. Our findings reveal that patients with matted lymph nodes are associated with a higher pN stage and lymphovascular invasion. Furthermore, the analysis of factors linked to survival among patients with lymph node metastasis identified matted nodes as showing a statistical tendency in association with reduced survival. Multivariate analysis emphasized that clinical stage and the utilization of adjuvant chemotherapy were independent factors contributing to survival.

5. Conclusions

In conclusion, this study sheds light on the underexplored territory of matted lymph nodes in colon cancer, indicating their potential as significant prognostic indicators. The association of matted nodes with higher pN stage and reduced survival underscores the importance of considering this

 doi:10.20944/preprints202406.0731.v1

specific lymph node characteristic in treatment planning and prognostic assessments for colon cancer patients. Further research and validation studies are warranted to solidify these findings and integrate matted lymph nodes into the broader context of CRC management.

Author Contributions: "Conceptualization, all authors.; methodology, LSLS; software, LSLS.; validation, all authors; formal analysis, LSLS, investigation, all authors; resources, all authors.; data curation, all authors ; writing—original draft preparation, all authors; writing—review and editing, all authors; visualization, all authors; supervision, all authors; project administration, LSLS.; funding acquisition, LSLS All authors have read and agreed to the published version of the manuscript."

Funding: his research received no external funding.

Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics and research institutional board of the National Cancer Institute (INCAN No. 2023/085). Informed consent was waived by Ethics and research institutional board because the retrospective nature of the study and there is no information (personal or clinical) of the patients.

Informed Consent Statement: Informed consent was waived by Ethics and research institutional board because the retrospective nature of the study and there is no information (personal or clinical) of the patients.

Data Availability Statement: Data of the study is available freely at a reasonable request via email.

Acknowledgments: none.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today, accessed [20 November 2023].
2. Yamano T, Semba S, Noda M, Yoshimura M, Kobayashi M, Hamanaka M, Beppu N, Yano A, Tsukamoto K, Matsubara N, Tomita N. Prognostic significance of classified extramural tumor deposits and extracapsular lymph node invasion in T3-4 colorectal cancer: a retrospective single-center study. BMC Cancer. 2015;15:859.
3. Wind J, Lagarde SM, Ten Kate FJ, Ubbink DT, Bemelman WA, van Lanschot JJ. A systematic review on the significance of extracapsular lymph node involvement in gastrointestinal malignancies. Eur J Surg Oncol. 2007;33(4):401-8.
4. Veronese N, Nottegar A, Pea A, Solmi M, Stubbs B, Capelli P, Sergi G, Manzato E, Fassan M, Wood LD, Scarpa A, Luchini C. Prognostic impact and implications of extracapsular lymph node involvement in colorectal cancer: a systematic review with meta-analysis. Ann Oncol. 2016;27(1):42-8.
5. Li T, Yang Y, Wu W, Fu Z, Cheng F, Qiu J, Li Q, Zhang K, Luo Z, Qiu Z, Huang C. Prognostic implications of ENE and LODDS in relation to lymph node-positive colorectal cancer location. Transl Oncol. 2021;14(11):101190.
6. Puppa G, Maisonneuve P, Sonzogni A, Masullo M, Capelli P, Chilosi M, Menestrina F, Viale G, Pelosi G. Pathological assessment of pericolonic tumor deposits in advanced colonic carcinoma: relevance to prognosis and tumor staging. Mod Pathol. 2007;20(8):843-55.