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Number of lymph nodes dissected in colorectal cancer and probability of positive nodes, angiolymphatic/perineural invasion, and intracellular mucin in a referral service

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ABSTRACT

Among the malignancies, colorectal cancer ranks fourth in incidence in Brazil. The main prognostic measure is related to the amount of affected lymph nodes. Thus, many studies try to correlate the number of extracted lymph nodes, with the probability of obtaining positive nodes.

Study objectives: Determine whether dissection ≥12 lymph nodes increases probability of finding neoplastic involvement in relation to resection of fewer. Assess the presence of angiolymphatic invasion; perineural and intracelluar mucin and correlate it with tumor differentiation and TNM classification. Correlate the average of positive nodes with angiolymphatic and perineural involvement.

Methods: Pathological reports of patients operated for CRC from 1997 to 2013 were analyzed. A probability (p) less than 0.05 was considered to indicate statistical significance.

Results: Median of lymph nodes sent to analysis was 12 nodes. Average number of lymph nodes affected was higher when a number ≥12 lymph nodes were dissected ($p = 0.001$) (Kruskal–Wallis). There was positive association between average of affected lymph nodes and presence of angiolymphatic ($p < 0.0001$) or perineural invasion ($p = 0.024$). Angiolymphatic and intracellular mucin are less present in well-differentiated adenocarcinomas. Perineural and angiolymphatic were more present in T4 stages.

Conclusions: Dissection ≥12 lymph nodes increases chances of finding positive nodes. There is relation between angiolymphatic invasion; perineural and intracellular mucin and type of tumor differentiation, as well as TNM classification. Average number of lymph nodes affected was higher in presence of perineural or angiolymphatic invasion.

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Número de Linfonodos Dissecados no Câncer Colorretal e Probabilidade de Nodos Positivos, Invasão Angiolinfática, Perineural e Mucina Intracelular em Serviço de Referência

Palavras-chave:
Neoplasias colorretais
Linfonodos
Excisão de linfonodo

RESUMO

Dentre as neoplasias malignas, o câncer colorretal ocupa o quarto lugar em incidência no Brasil. Uma das principais medidas de prognóstico está relacionada à quantidade de linfonodos acometidos. Sendo assim, muitos trabalhos estudam meios de correlacionar o número de linfonodos dissecados, com a probabilidade de se obterem linfonodos positivos.

Objetivos do estudo: Determinar se a dissecção ≥ 12 linfonodos aumenta a probabilidade de se encontrar acometimento neoplásico nos mesmos em relação à menor ressecção. Avaliar a presença de invasão angiolinfática; perineural e mucina intracelular e correlacioná-la com diferenciação tumoral e classificação TNM. Correlacionar a média de nodos positivos com acometimento angiolinfático e perineural.

Métodos: Foram analisados laudos anatomopatológicos de pacientes operados por câncer colorretal (CCR) de 1997 a 2013. A probabilidade (p) menor que 0,05 foi considerada para indicar significância estatística.

Resultados: A média de linfonodos comprometidos foi maior quando um número ≥ 12 linfonodos foram dissecados (p = 0,001) (Kruskal-Wallis). Houve associação positiva entre a média de linfonodos afetados e a presença de invasão angiolinfática (p < 0,0001) ou perineural (p = 0,024). A invasão angiolinfática e a mucina intracelular estavam menos presentes em adenocarcinomas bem diferenciados. Invasão perineural e angiolinfática estiveram mais presentes nos estádios T4.

Conclusões: A dissecção ≥ 12 linfonodos aumenta as chances de se encontrar nodo positivo. Existe relação entre invasão angiolinfática; perineural e mucina intracelular e o tipo de diferenciação tumoral, bem como a classificação TNM. A média de linfonodos comprometidos foi maior na presença de invasão perineural ou angiolinfática.

Introduction

Colorectal cancer (CRC) is the fourth most frequent malignancy in Brazil. It is estimated that in 2014, 32,600 new CRC cases were diagnosed in this country. Of these, 15,070 were male and 17,530 were female subjects, corresponding to an estimated risk of 15.44 and 17.24 cases per 100,000 population for men and women, respectively.[1] In the world, CRC is the third most prevalent cancer; and in Western countries, is the second leading cause of cancer-related deaths.[2]

Due to the high prevalence of CRC, a great emphasis is given to the publication of studies to evaluate the characteristics of this disease, as well as the determinant factors of its course. In 1932, Dukes proposed that the depth of tumor invasion in the colonic wall, lymph node involvement, and the presence of metastases would be determining factors for tumor staging and, to date, these are considered the most important findings for disease prognosis.[3]

In recent years, the relationship between the number of resected lymph nodes and those compromised by CRC, *i.e.* the lymph node ratio (LNR), has been subject to evaluation in several studies. Research evaluating LNR in patients with primary tumors of the stomach, bladder, breast, and pancreas revealed the existence of a relationship between the proportion of positive lymph nodes, disease-free survival, and overall survival.[4–8]

The minimum number of lymph nodes that must be dissected has been the subject of some studies, and some of them suggested 12 as the minimum number of lymph nodes to be dissected.[9,10] This is also the number that has been accepted by the American Joint Committee on Cancer and the World Congress of Gastroenterology in order to stratify the patients as free of metastatic disease. In addition to these organizations, in 2007 the Association of Coloproctology of Great Britain and Ireland also started recommending an average of 12 lymph nodes.[11]

Lymph node dissection in CRC cases managed to establish itself as an important method for prognostic evaluation. Thus, it has become critical that more studies be published in order to evaluate this method, so that one can determine more precisely its true potential in relation to what it can represent in terms of knowledge and prognosis with respect to CRC.

The objectives of this study are set forth below.

Primary objective

(1) To determine if the dissection of ≥12 lymph nodes increases the probability of finding neoplastic involvement in these structures, compared with a lesser number of resected lymph nodes.

Secondary objectives

(2) To evaluate the presence of angiolymphatic and perineural invasion and intracellular mucin and to correlate the findings with tumor differentiation and TNM classification;

(3) To correlate the average of positive nodes with angiolymphatic and perineural involvement.

Methods

All pathology reports of surgical specimens of patients undergoing elective or non-elective surgery for CRC from January 1997 to December 2013, operated in the Hospital Nossa Senhora da Conceição, in the city of Tubarao – SC, were analyzed in a case-series, cross-sectional, retrospective study. The data were selected with the use of a collection instrument developed by the authors, which included the following variables: date of the pathology report, patient' s genre, year, patient' s age, tumor location, size of the surgical specimen, TNM classification, Astler–Coller classification, type of surgery performed, number of dissected lymph nodes, number of affected lymph nodes, tumor differentiation, presence of intracellular mucin, angiolymphatic invasion, and perineural invasion.

All pathology reports of surgical specimens diagnosed with colorectal adenocarcinoma, classified as belonging to any TNM classification stage, were included in this study. Patients who met the following criteria were excluded:

1. CRC diagnosis associated with inflammatory bowel disease (Crohn's disease or ulcerative colitis).
2. Neoplasms with a histopathologic diagnosis not compatible with adenocarcinoma.
3. Patients undergoing neoadjuvant therapy.

All patients were operated on by laparotomy or laparoscopy, and the surgical treatment chosen followed the conventional pattern of resection, including lymphadenectomy and, in the case of rectal tumors, mesorectal resection.

The study was approved by the Research Ethics Committee (CEP) of the Universidade do Sul de Santa Catarina (protocol number 13.004.4.01.III). The study followed the regulations of Resolution 466 of 2012. Thanks to the absence of a direct contact with patients in the study, the free and informed consent term (FICT) was not necessary. Consent of the institutions involved for the use of the data was obtained.

Data were cataloged in the form of an electronic spreadsheet (Microsoft Excel) and transferred for statistical analysis to EpiInfo/SPSS version 18 software. Qualitative variables were described by absolute and relative frequencies, and quantitative variables were described as a mean, median and standard deviation. Statistical analyses were performed using the chi-squared test, Student's *t*-test, Kruskal–Wallis test and Fisher test with Monte Carlo correction, as needed. The level of significance was set at 5%.

Results

In total, the study involved 290 patients who underwent surgical treatment for CRC resection between 1997 and 2013. The mean age was 61.9 (SD = 13.4) years and the median age was 63 years. Male subjects were slightly more affected *versus* female subjects. Of all patients, 149 (51.4%) were men. The mean age of the patients at the time of surgery was 62.8 years for men and 61.0 years for women. T3 is the most prevalent tumor staging among patients (229 cases, *i.e.* 73% of the total). Of the 290 patients, 151 (52.10%) had ≥12 lymph nodes dissected. The median of the number of lymph nodes sent for histopathological analysis was 12 (range: 1–53). Fig. 1 illustrates the median for lymph nodes dissected over the studied years.

Of all the patients studied, only 17 had metastasis (M1) by TNM classification at the time of surgery, representing 5.9%. The most common tumor differentiation was a well-differentiated adenocarcinoma for 212 patients (73.1%). Table 1 lists the information related to the following variables: gender, anatomical site, tumor invasion (T), affected regional lymph nodes (N), distant metastasis (M) and tumor differentiation. Table 2 lists the proportion of positive lymph nodes, according to the number of analyzed ganglia.

The study showed that when ≥12 lymph nodes are dissected, the probability of finding a positive node is higher *versus* a smaller number of nodes resected ($p = 0.001$) (Table 3).

The probability of an angiolymphatic invasion was lower in the well-differentiated type than in moderately differentiated and undifferentiated types ($p = 0.0005$). The well-differentiated type was that that presented least intracellular mucin in relation to moderately differentiated and undifferentiated types ($p = 0.001$) (Fisher' s exact test with Monte Carlo correction).

Perineural invasion was significantly more present in cases of moderately differentiated adenocarcinoma *versus* other subtypes ($p < 0.01$) (Fisher test). This same poor prognosis

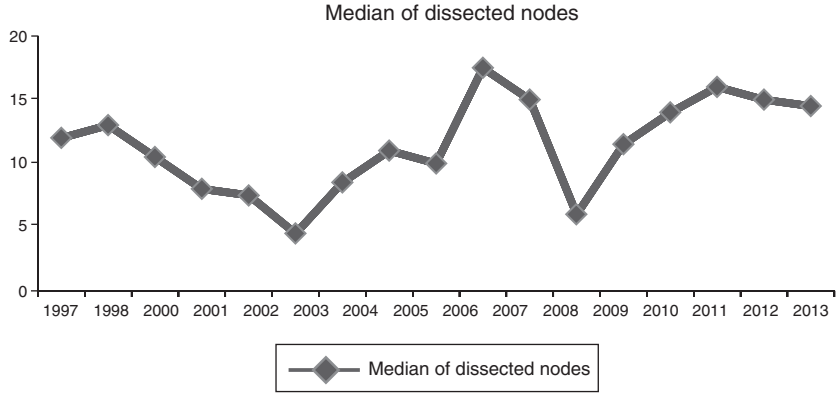

Fig. 1 – Median of dissected nodes over the years.

Table 1 – General characteristics of the study sample.

Variable	Total		<12 resected nodes		≥12 resected nodes		*p*-Value
	n	%	*n*	%	*n*	%	
Gender							
Male	149	51.4	69	46.31	80	53.69	0.570
Female	141	48.6	70	49.65	71	50.35	
Anatomic location							
Colon, unspecified	108	37.2	54	50.00	54	50.00	0.475
Rectosigmoid	82	28.3	39	47.56	43	52.44	
Right colon	33	11.4	11	33.33	22	66.67	
Colon and rectum	21	7.2	12	57.14	9	42.86	
Sigmoid	16	5.5	9	56.25	7	43.75	
Rectum	11	3.8	7	63.64	4	36.36	
Left colon	9	3.1	5	55.56	4	44.44	
Large intestine and anus	5	1.7	1	20.00	4	80.00	
Transverse colon	4	1.4	1	25.00	3	75.00	
Left colon and sigmoid	1	0.3	0	0.00	1	100.00	
Tumor invasion (T)							
T0	0	0					0.020
T1	6	2.1	4	66.67	2	33.33	
T2	26	9	19	73.08	7	26.92	
T3	229	79	106	46.29	123	53.71	
T4	29	10	10	34.48	19	65.52	
Affected regional lymph nodes (N)							
N0	154	53.1	82	53.25	72	46.75	<0.001
N1	67	23.1	41	61.19	26	38.81	
N2	68	23.4	15	22.06	53	77.94	
N3	1	0.3	1	100.00	0	0.00	
Distant metastasis (M)							
MX	273	94.1	135	49.45	138	50.55	0.038
M0	0	0	0		0		
M1	17	5.9	4	23.53	13	76.47	
Tumor differentiation							
Well differentiated	212	73.1	101	47.64	111	52.36	0.184
Moderately differentiated	42	14.5	21	50.00	21	50.00	
Undifferentiated	13	4.5	3	23.08	10	76.92	
Other[a]	23	7.9	14	60.87	9	39.13	

[a] Ranked among well- to moderately undifferentiated ($n = 22$) and adenomucinous ($n = 1$).

Table 2 – Proportion of positive lymph nodes according to the number of ganglia analyzed.

Number of nodes examined	Number of patients	Patients with +nodes	% +nodes	Mean of +nodes	Standard deviation
0–4	36	14	38.9	0.78	1.10
5–9	71	29	40.8	1.21	1.98
10–14	75	33	44	2.20	3.53
15–19	53	29	54.7	4.28	5.11
20–24	30	15	50	2.23	4.16
25–29	15	10	66.7	7.20	8.89
≥30	10	5	50	8.50	11.68

Table 3 – Mean of positive nodes in connection with the dissection of 12 or more lymph nodes.

Lymph nodes	Patients	Compromised lymph nodes	Mean	Variance	Standard deviation
<12	139	179	1.2878[a]	4.8731	2.2075
≥12	151	587	3.8874[a]	35.7139	5.9761

[a] $p = 0.001$ (Kruskal–Wallis).

Table 4 – Comparison between the mean number of compromised lymph nodes and the presence of perineural or angiolymphatic invasion.

	Mean of compromised nodes	Number	Standard deviation
Perineural invasion present	5.28[a]	18	7.25
Perineural invasion absent	2.59[a]	247	4.63
Angiolymphatic invasion present	4.19[b]	112	5.99
Angiolymphatic invasion absent	1.74[b]	153	3.54

[a] $p = 0.024$.
[b] $p < 0.0001$.

factor was also more prevalent in T4 (24%) compared to T3 (5.6%), T2 (0%) and T1 (0%) staging ($p = 0.013$). Perineural invasion was also more present when there was at least one affected regional lymph node (N1) (10.9%) or four or more affected lymph nodes (N2) (10.8%) *versus* lymph nodes with no involvement (N0) (2.9%) ($p = 0.028$).

Angiolymphatic invasion was significantly more present when the tumor was at T4 stage (72%) *versus* a lesser degree of invasion ($p = 0.01$). Regarding the presence or absence of metastasis, the angiolymphatic invasion was more prevalent in cases with distant metastasis (40.2%) (chi-squared test = 0.006246). Positive lymph node involvement also showed a higher prevalence of angiolymphatic invasion than in the absence of affected lymph nodes (N0, 29.4%), (N1, 53.1%), (N2, 58.5%) ($p = 0.0001$).

The presence of intracellular mucin had a significant correlation only on tumor differentiation, being more present in undifferentiated adenocarcinoma (30.8%) ($p = 0.005$).

In the comparison between the mean number of affected lymph nodes with perineural or angiolymphatic invasion, it was observed an increase in the mean of positive nodes when these factors are present (Table 4).

The most commonly performed surgeries in the study and the percentage of compromised ganglia by type of surgery are listed in Table 5.

Discussion

According to the Centers for Disease Control and Prevention (CDC), the majority of patients diagnosed with CRC in the United States belong to the male gender, with a percentage of 51.8% (70,099 patients) in a population of 135,260 patients diagnosed in the year 2011 (the most recent year available).[12] Similar to the US data, this study also found a greater prevalence of men, with 51.4%. By comparison, the Brazilian data cite an estimated 32,600 new cases of CRC diagnosed in 2014.[1]

This study showed that the mean age at the time of tumor resection is approximately 61 years. When one adds to this the fact that, in our sample, most of the patients were seen in advanced stages, both in the TNM classification, with a prevalence of T3 and in the Astler–Coller classification, with B2 class, one can verify that the diagnostic of CRC is not timely obtained. Thus, it should be noted the importance of an adequate CRC screening, especially since this tumor has a slow evolution, allowing considerable time for its detection and treatment.

Other studies have also presented T3 and N0 stages as the most prevalent,[13–15] as is the case in the study by Oliveira et al. of 74 patients with colorectal cancer; in this study, 62.1% of patients had a T3 classification and 59.5% were in N0 stage. For the sake of comparison, Jacomo et al. studied 90 patients with rectal cancer, excluding patients with colonic tumor, with similar findings for T3 (55.5%) and N0 (67.7%) stages.

Based on collected data, one can trace a curve that shows the lymph node dissection over the years – a valuable data to verify the performance of the health service in the area since lymph node collection has been used as a measuring instrument of medical care quality.[16] Thus, it is possible to report that in the last four years the median for extracted lymph nodes remained above the minimum number indicated. This monitoring becomes important when we consider that Lanza et al. concluded that the evaluation of a few regional lymph nodes can result in an understaging of N0 tumors.[17]

The median of resected lymph nodes was 12, which agrees with the number proposed by various agencies and studies.[9,11] However, considering the results in Table 3, it appears that only 52.07% of patients underwent resection of >12 lymph nodes. Thus, the use of the median as the sole form of assessment is not fully indicated, since a large part (47.93%) of

Table 5 – Percentage of number of axillary nodes according to the type of surgery.

Type of resection	Number of patients	Patients with node+	%	Mean of ganglia+	Standard deviation
Rectosigmoidectomy	190	88	46.3	2.77	4.98
Total colectomy	20	6	30	0.85	2.25
Hemicolectomy, unspecified	20	13	65	4.4	7.01
Amputation of rectum	17	8	47.1	2.76	4.01
Colectomy, unspecified	14	7	50	2.36	3.43
Hemicolectomy	10	3	30	0.7	1.16
Left sigmoidectomy	7	4	57.1	1.43	1.62
Right hemicolectomy	6	3	50	3.5	4.72
Transversectomy	3	1	33.3	2.67	4.62
Proctocolectomy	3	2	66.7	2.67	3.79

patients had less than 12 of their lymph nodes resected. Thus, besides the median, we should also assess the percentage of patients undergoing resection of 12 or more lymph nodes.

We could not set the real reason for the numerical decline of lymph node dissections in 2002 and 2008, shown in figure. However, one possible explanation is the fact that the vast majority of surgeries performed in this study consisted of rectosigmoidectomy procedures. One study which examined 388 patients with CRC showed a greater tendency for the resection of fewer lymph nodes in the distal regions of the colon, compared to what occurs more proximal regions.[18]

But it becomes clear the importance of such monitoring for the resection of lymph nodes. Baxter et al., in a population-based study, found that in 2001 the majority of patients with CRC were still receiving an inadequate lymph node evaluation in the United States, where only 37% of the patients were having ≥12 lymph nodes resected.[9]

Still with regard to the number of dissected lymph nodes, this study demonstrated that when one gets ≥12 nodes, it becomes more likely the finding of a node affected by the tumor. However, Yoshimatsu et al. report that ≥9 lymph nodes would be the minimum number to be obtained in the case of colorectal tumors with a B classification in the Duke's system – the stage most commonly found so that one could assess the negativity of lymph node involvement.[10] On the other hand, Kim et al., by dividing the lymph node resection into 0–4, 5–9, and 10–14 groups, found a significantly higher probability of finding positive nodes from a number of 10–14 resected nodes[19] – a very similar result to that obtained in the present study. Thus, a resection of 12 lymph nodes is suggested, taking into account that a three times larger mean number of positive lymph nodes was obtained when ≥12 lymph nodes were resected. This finding underlines the importance of an accurate lymph node resection, by allowing a greater number of detections of nodal involvement, which would agree with previous studies and with what has been proposed by the main guidelines.[9–11]

CRC may exhibit some features that are associated with a poor prognosis, such as perineural invasion, angiolymphatic invasion and the presence of intracellular mucin,[20–22] although some authors also comment on the need for more studies on the prognostic value of such elements.[23] In our sample, it was found that in the well-differentiated subtype there was a decrease in angiolymphatic invasion. This fact reveals an inverse association between these variables, suggesting that a neoplasia with a higher degree of differentiation is less likely to progress with involvement of blood and lymph vessels. Intracellular mucin was also less prevalent in such subtype, which could be envisaged when one takes into account the expectation of a less aggressive behavior with a well-differentiated tumor.

The finding of a correlation of intracellular mucin solely with tumor differentiation may suggest that this characteristic is not related to the level of invasiveness, but only with the differentiation of the neoplastic cells. However, this still remains a poor prognostic indicator, due to the association with poorly differentiated adenocarcinoma.

We also observed that the mean number of compromised lymph nodes was significantly higher in cases with perineural or angiolymphatic invasion; however, during our database survey, no studies evaluating these associations were found.

The site specifically most affected by CRC was the rectosigmoid, despite the large number of patients whose reports did not indicate the tumor site, which affected the analysis of this variable. However, by checking the most common type of surgery, it was observed that rectossigmoidectomy was the most common procedure, indicating that this was indeed the preferred site of the neoplasm. Saad-Hossne et al. also demonstrated that sigmoid and rectum were the most common sites.[24]

Conclusion

This study agrees with other similar studies; we could demonstrate that the dissection of ≥12 lymph nodes increases the chances of finding a positive node compared to the dissection of fewer nodes. It was also observed a relationship between angiolymphatic invasion, perineural invasion and intracellular mucin and the type of tumor differentiation and TNM classification. In addition, another finding was that the mean number of compromised lymph nodes is significantly higher when a perineural or angiolymphatic invasion is present.

Conflicts of interest

The authors declare no conflicts of interest.

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