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Prognostic impact of the number of resected lymph node on survival in Colorectal Cancer

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ABSTRACT

Introduction: Colorectal Cancer (CRC) is the third most common cancer and the second leading cause of death in Western countries. In Portugal, in the North, emerges as the second most common cancer. The presence of lymph node metastasis is an important predictor of overall and disease-free survival and several studies recommend the evaluation of at least 12–14 regional lymph nodes, as it contributes to improve cancer staging and patient outcomes.

Aims: Epidemiological characterization of the studied population and identify a possible relationship between the number of lymph nodes evaluated in the surgical specimen and survival.

Methods: We preceded to the study of 1065 CCR patients, submitted to surgical resection between 1 January 2000 and 31 August 2012, in Braga Hospital.

Discussion/Conclusion: The results of the epidemiological characterization of this population are coincident with those described in the literature. It was observed a significant correlation between age, tumor size, serosal invasion, differentiation, tumor penetration, venous and lymphatic invasion, metastasis, TNM stage and the number of lymph nodes evaluated. However, we did not observe a statistically significant correlation between patient survival and number of lymph nodes evaluated ($p > 0.05$). A possible explanation is the practice of oncologists, addressing patients with less than 12 nodes identified in the surgical specimen as "N-positive" and undergoing adjuvant therapy. A better harvest and careful analysis of lymph nodes would lead to more accurate staging, avoiding overtreatment and side effects associated, and allow better economic management of hospital resources, in real N0 patients.

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Impacto prognóstico do número de linfonodos ressectados na sobrevida de pacientes com câncer colorretal

Palavras-chave:
Câncer colorretal
Linfonodos
Estadiamento
Sobrevida

RESUMO

Introdução: O câncer colorretal (CCR) ocupa o terceiro lugar em termos de frequência e, além disso, é a segunda causa principal de morte nos países ocidentais. Em Portugal, no norte, CCR surge como o segundo câncer mais comum. A presença de metástase aos linfonodos é preditor importante de sobrevida em geral e de sobrevida livre da doença; vários estudos recomendam a avaliação de pelo menos 12–14 linfonodos regionais, pois tal procedimento contribui para aprimorar o estadiamento do câncer e os desfechos para os pacientes.
Objetivos: Caracterização epidemiológica da população estudada e identificação de possível relação entre o número de linfonodos avaliados no espécime cirúrgico e sobrevida.
Métodos: Estudo de 1065 pacientes com CCR, submetidos à ressecção cirúrgica entre 1 de janeiro de 2000 e 31 de agosto de 2012 em um hospital em Braga.
Discussão/Conclusão: Os resultados da caracterização epidemiológica dessa população coincidem com os resultados descritos na literatura. Foi observada uma correlação significativa entre idade, tamanho do tumor, invasão da serosa, diferenciação, penetração tumoral, invasão venosa e linfática, metástase, estágio TNM e número de linfonodos avaliados. Mas não observamos uma correlação estatisticamente significativa entre sobrevida do paciente e número de linfonodos avaliados ($p > 0,05$). Uma explicação possível é a prática dos oncologistas, que tratam pacientes com menos de 12 nodos identificados no espécime cirúrgico como "N-positivos", prosseguindo com terapia adjuvante. Uma coleta mais apropriada e uma análise cuidadosa dos linfonodos resultaria em um estadiamento mais preciso, evitando o tratamento excessivo e os efeitos colaterais associados, além de permitir um tratamento com melhor custo-benefício para os recursos hospitalares em pacientes realmente N0.

Introduction

The Colorectal Cancer (CRC) is the third most common cancer and the second leading cause of death in the United States and in Western countries.[1] In the north of Portugal, it arises as the second most common cancer, with an incidence rate of 41.6%, and 34% in the district of Braga.[2] Data from the *World Health Organization* between 1997 and 2007 revealed that the mortality rate declined about 2% per year: 19.7 to 17.4/100 000 for men (world standardized rates), and from 12.5 to 10.5/100 000 for women and this decrease is due to early diagnosis and treatment, with a consequent increase in survival.[3]

The stage of the CRC at diagnosis is the primary determinant of survival and the main predictor of mortality.[4] The survival rates at five years may be higher than 90% if the diagnosis is made at an early stage, however only 37% of the cases are diagnosed at this stage.[5] Lymph node metastases are an important factor for the indication of adjuvant chemotherapy and perform an important predictor of overall and disease-free survival. There is evidence of improved oncological outcomes and cancer staging as greater the number of lymph nodes identified.[6,7] However, the number of lymph nodes that should be evaluated remains controversial.[8] The *International Union against Cancer*, the *American Joint Committee on Cancer*, the *American College of Surgeons* and the *National Quality Forum* consider that is necessary to review at least twelve lymph nodes to exclude the achievement of disease.[9,10] In the 7th edition of the *AJCC Cancer Staging Manual*, it is recommended to evaluate at least twelve to fourteen regional lymph nodes as a prognostic factor of CRC, and evaluation of fewer than twelve lymph nodes have low discriminative power.[11] Statistical analysis showed that probability of finding a single metastasis in lymph nodes increases with the number of nodes and decreases about 46% when only eighteen nodes are found.[12] Thus, it is recommended that small ganglia between 0.1 and 0.2 cm in diameter must be located. Nevertheless, further investigations revealed that over 60% of U.S. institutions fail in achieving the proposed target of a minimum of twelve lymph nodes assessed.[13] Some researchers believe that radical lymphadenectomy has a beneficial therapeutic effect while others believe that this only provides a more accurate staging.[14]

Factors contributing to the number of nodes evaluated

It has been shown that the relation between the number of nodes evaluated and staging is not simple. Three major factors influencing this relation were identified: the hospital (quality of oncological and surgical care and number of cancer cases), the patient characteristics (younger age ≤ 60 years, female sex), and tumor properties (larger size and greater tumor extension (pT), right colon localization, and higher stage). These factors are associated with higher lymph nodes achievement. Thus, a low number of nodes examined can be an indicator of poor surgical and oncological care.[6,15] Among the factors contributing to the number of nodes evaluated

in resected specimens, the methodology used in pathological practice is the most important (namely in collection of lymph nodes and processing for microscopic examination). The non-uniformity of this approach is currently the most problematic factor,[15] making the role of the pathologist essential given that an extensive pathologic diagnosis will allow a correct staging.[16]

Other factors contributing to the variation in the number of nodes contained in the surgical specimen are the surgical technique and the variations in the specimens manipulation: diligence of search for lymph nodes, the use of solutions to increase macroscopic visualization of nodes; threshold for acceptable number of lymph nodes using half *versus* all lymph nodes found for microscopic evaluation; amount of tissue acquired for observation, and the separation of nodes by anatomic site. Thus, it is recommended that all lymph nodes found should be sectioned, and it has been demonstrated that twelve to fifteen negative nodes are predictors of negative regional lymph node invasion. If less than twelve nodes are found, then additional techniques to improve visualization should be considered.[15]

Another factor in rectal cancer that influences the number of nodes evaluated is neoadjuvant therapy,[17,18] including preoperative radiation therapy.[19] According to some authors, this therapy improves resectability, sphincter preservation and local control of the disease, although its survival benefit is controversial since the reduction of recurrence does not necessarily translate into increased survival rate.[17,20–22] In addition, the neoadjuvant therapy is associated with reduction in tumor mass, but also with increased tissue fibrosis, which hampers identification of the lymph nodes.[23] The hypothesis that fewer lymph nodes are detected in the surgical specimen after neoadjuvant therapy has been confirmed by several authors.[24–26] There are currently no recommendations on the actual number of lymph nodes that should be found after neoadjuvant therapy (staging ypN), however in the literature the mean nodes found varies between four and fourteen.[27,28]

Neoadjuvant therapy also appears to have an important effect on mesorectal lymph nodes, contributing to decrease in their size.[29–31] Murphy et al.[32] have identified the size of lymph nodes as an independent prognostic indicator of survival in negative nodes after primary surgery. It is believed that a significant number of mesorectal lymph nodes micrometastases, smaller than 0.5 cm are not detected by manual lymph nodes counting and by typical pathological diagnosis methods.[17] Some authors concluded that the absence of nodes (ypNx) or decreased number of nodes found in patients with stage ypN-negative does not imply a poorer oncologic outcome. The number of nodes seems to have no impact on survival and recurrence in patients' ypN-negative.[33] If fewer than twelve lymph nodes are found and there is no opportunity to find more, adjuvant therapy is recommended in high risk situations. The failure to reach a minimum mark of twelve nodes found is currently used by oncologists in their treatment decisions.[17]

Given the controversial theme and the absence of studies in Portugal, this study was conducted in order to characterize epidemiologically patients operated by CRC in the period January 1, 2000 to August 31, 2012, at Braga Hospital and identifies a possible relation between the number of lymph nodes examined and the survival of patients operated for CRC.

Materials and methods

Data from 1065 patients treated in Braga Hospital, north of Portugal, between January 1, 2000, and August 31, 2012 with CRC diagnosis and submitted to surgical treatment was collected retrospectively.

Data collected from clinical and preoperative diagnostic examinations includes: age, gender and tumor location. Histopathological reports include: tumor size, serosal extension, presence of sincrone tumors, histological type, tumor differentiation, macroscopic tumor appearance, tumor extent (T), number of lymph nodes evaluated and extent of spread to the lymph nodes (N), lymphatic and blood vessel invasion, and TMN staging. The level of positive lymph nodes was not described in all specimens. Two experienced pathologists determined the histological type of CRC and the tumor staging was graded according to TNM classification, 6th edition.

All patients were followed up periodically and their outcomes were investigated and collected until August 2012. Follow-up data recorded included recurrence of the disease and time of death.

Statistical analysis

All data was collected and stored in an Excel PC database and statistically analyzed using the Statistical Package for the Social Sciences, version 22.0 (SPSS Inc., Chicago, Illinois, USA). A simple descriptive analysis of each one of the variables was realized, with determination of the total number of cases and relative frequencies. The median and mean was determined for the number of lymph nodes assessed.

All comparisons were examined for statistical significance using Pearson's chi-square (χ^2) test and Fisher's exact test (when $n < 5$), with the threshold for significance p values < 0.05.

Overall survival (OS) was defined as time from disease diagnosis until death from any cause, and it was assessed using the Kaplan–Meier method.

Ethics committee approval

The study protocol was approved by the Ethics Committee of Braga Hospital.

Results

1384 patients were identified with the diagnosis of CRC, and 1065 of these met the inclusion criteria previously defined.

Epidemiological characterization of the patients is presented in Table 1, as well as the median and the mean lymph nodes retrieved for each variable analyzed. The median (Md) of lymph nodes retrieved, in this population, was eleven and the mean was thirteen nodes. The frequency of CRC was higher in men (59.8%, $n = 637$) than in women (40.2%, $n = 428$), reaching more patients aged less than 71.5 years (53.8%, $n = 573$). The median lymph nodes retrieved was equal in both sexes, eleven lymph nodes.

Table 1 – Epidemiological characterization of patients and its relationship with the mean and median number of lymph nodes evaluated.

Variable	*n*	%	Median number of nodes retrieved	Mean number of nodes retrieved
Overall	1065	100	11	13
Sex				
Female	428	40.2	11	13
Male	637	59.8	11	13
Age (years)				
≤71.5	573	53.8	11	14
>71.5	492	46.2	10	12
Location				
Right colon	243	22.8	13	15
Left colon	486	45.6	10	12
Rectum	336	31.5	10	13
Tumor size (cm)				
≤4.5	597	56.1	9	12
>4.5	419	39.3	13	15
Serous invasion				
Absent	257	24.1	8	12
Present	791	74.3	11	13
Sincrone tumors				
No	1034	97.1	11	13
Yes	30	2.8	11	16
Histological type				
Adenocarcinoma	898	84.3	10	13
Mucinous adenocarcinoma	121	11.4	13	15
Invasive adenocarcinoma	36	3.4	9	10
Signet ring & mucinous cells	10	0.9	12	31
Histological grade				
Differentiated	438	41.1	10	11
Undifferentiated	53	5.0	11	12
Depth of invasion				
Tis	13	1.2	7	19
T1	50	4.7	7	9
T2	148	13.9	9	12
T3	758	71.2	11	13
T4	63	5.9	11	16
Nodes retrieved				
<12	583	54.7	-	-
≥12	457	42.9	-	-
Invaded nodes				
0	606	56.9	-	-
01/mar	289	27.1	-	-
≥4	145	13.6	-	-
pN				
pN0	596	56.0	10	13
pN1	293	27.5	10	11
pN2	149	14.0	13	15
pM				
pM0	820	77.0	11	13
pM1	125	11.7	11	15
Resection margins				
Without involvement	1007	94.6	11	13
Involved	36	3.4	11	15
Venous Invasion				
Without	595	55.9	10	13
With	407	38.2	11	13

Table 1 – (*Continued*)

Variable	*n*	%	Median number of nodes retrieved	Mean number of nodes retrieved
Lymphatic Invasion				
Without	383	36.0	10	13
With	478	44.9	11	13
Stage				
I	168	15.8	8	12
II	392	36.8	10	13
III	369	34.7	11	15
IV	126	11.8	11	15
Relapse				
Absent	790	74.2	11	14
Present	151	14.2	11	11

Differentiated, well and moderately differentiated tumors; Undifferentiated, poorly differentiated and undifferentiated tumors; Tis, intramucous/*in situ carcinoma*; T1, submucous invasion; T2, muscularis propria invasion; T3, subserosous/not peritonized pericolic conjunctive tissue invasion; T4, organs and structures invasion.

More nodes were found in patients aged less than 71.5 years (median 11 nodes). Regarding its location, the tumors were more often in the colon (68.4%, $n = 729$), particularly in the left colon (45.6%, $n = 486$). The median lymph nodes evaluated was greater in the right colon (Md = 13), followed by the left colon and rectum, both with the same median (Md = 10). In 56.1% ($n = 597$) of cases, the tumor showed a dimension ≤ 4.5 cm, with more serosal invasion (74.3%, $n = 791$). The majority of patients had no synchronous tumors (97.1%, $n = 1034$). The median of nodes was greater in tumors > 4.5 cm (Md = 13), and in tumors with serosal invasion (Md = 11). The presence of synchronous tumors had no impact in the median of nodes assessed (eleven nodes in both cases).

Histologically, the tumors were mainly adenocarcinoma (84.3%, $n = 898$), and mucinous adenocarcinoma was the second most frequent tumor (11.4%, $n = 121$), followed by invasive adenocarcinoma in 3.4% of cases ($n = 36$). Tumors with signet ring cells and mucinous areas had a small frequency (0.9%, $n = 10$). The median nodes retrieved was greater in mucinous adenocarcinoma (Md = 13), followed by tumors with signet ring cells and mucinous areas (Md = 12) and adenocarcinoma (Md = 10). Invasive adenocarcinoma had the lower median nodes evaluated (Md = 9).

Relatively to tumor extension (T), the majority of tumors are classified as T3 (71.2%, $n = 758$), followed by T2 in 13.9% of cases ($n = 148$). T4 lesions were present only in 5.9% of cases ($n = 63$), followed by the T1 (4.7%, $n = 50$) and Tis in 1.2% of cases ($n = 13$). The higher median nodes was found in T3 and T4 tumors (Md = 11).

Differentiated tumors were more frequent (41.1%, $n = 438$) than undifferentiated (5%, $n = 53$). However, undifferentiated tumors had higher median nodes (Md = 11). Regarding the number of lymph nodes in surgical specimen, 54.7% ($n = 583$) of patients had less than twelve nodes retrieved, whereas in 42.9% ($n = 457$), twelve or more lymph nodes were assessed. In the great majority, 56.9% of cases ($n = 606$), no metastatic lymph node was found, and in 27.1% ($n = 289$) of patients 1–3 metastatic lymph nodes were found. In only 13.6% ($n = 145$) cases, four or more lymph nodes were invaded. In 94.6% of cases ($n = 1007$), there was free surgical margins with no neoplastic lesion, and in 3.4% of cases ($n = 36$) the tumor was intercepted by margins of excision, and median ganglia found in both cases was the same (Md = 11).

More patients had no venous involvement (55.9%, $n = 595$) but most had lymphatic invasion (44.9%, $n = 478$). The median of nodes assessed was greater in the presence of venous and lymphatic involvement (Md = 11). Most patients (56%, $n = 596$) were classified as N0, followed by N1 in 27.5% ($n = 293$) and N2 in 13.9% of patients ($n = 148$). In 77% of cases ($n = 820$) there was no distant metastases. pN2 stage recorded higher median nodes assessed (Md = 13) and the presence or absence of distant metastases (PM0 and pM1) had no influence on this result (Md = 11). The stages II and III were the most frequently observed in 36.8% ($n = 392$) and 34.7% ($n = 369$) of cases, respectively. The stages III and IV were those who reported higher median nodes assessed (Md = 11).

74.2% of patients ($n = 790$) were free of relapses, and the median lymph nodes evaluated was 11, regardless of the existence of recurrences. The majority of patients, 59.6% ($n = 635$), are alive, and the median nodes assessed was higher in this patients (Md = 11). Relating the number of nodes analyzed with several variables (Table 2), significant correlations were found with: age ($p = 0.002$), tumor size ($p = 0.000$), serosal invasion ($p = 0.000$), differentiation ($p = 0.000$), tumor penetration ($p = 0.000$), venous and lymphatic invasion ($p = 0.000$), presence of metastasis ($p = 0.000$) and TNM stage ($p = 0.003$). There were no statistically significant correlations with gender ($p = 0.787$), tumor location ($p = 0.331$); synchronous tumors ($p = 0.921$), histological type ($p = 0.055$), and resection margins invasion ($p = 0.152$).

Figs. 1–3 represent survival curves (for all patients, colon cancer patients and rectal cancer patients, respectively) related with the number of lymph nodes assessed in surgical specimen. Although in the early months after surgery survival is greater in patients with evaluation of twelve or more nodes, this result is not statistically significant ($p > 0.05$).

Table 2 – Relationship between variables and number of lymph nodes examined.

Variable	*n* (%)		*p*
	<12 nodes	≥12 nodes	
Sex			
Female	237 (40.7%)	182 (39.8%)	0.787
Male	346 (59.3%)	275 (60.2%)	
Age (years)			
≤71.5	288 (49.4%)	270 (59.1%)	0.002
>71.5	295 (50.6%)	187 (40.9%)	
Location			
Right colon	70 (24.5%)	50 (23.8%)	0.331
Left colon	134 (46.9%)	111 (52.9%)	
Rectum	82 (28.7%)	49 (23.3%)	
Tumor size (cm)			
≤4.5	389 (68.7%)	201 (45.6%)	0.000
>4.5	177 (31.3%)	240 (54.4%)	
Serous invasion			
Absent	96 (33.6%)	25 (11.9%)	0.000
Present	190 (66.4%)	185 (88.1%)	
Sincrones tumors			
No	276 (96.5%)	203 (96.7%)	0.921
Yes	10 (3.5%)	7 (3.3%)	
Histological type			
Adenocarcinoma	245 (85.7%)	170 (81%)	0.055
Mucinous adenocarcinoma	26 (9.1%)	27 (12.9%)	
Invasive adenocarcinoma	15 (5.2%)	9 (4.3%)	
Signet ring & mucinous cells	0 (0%)	4 (1.9%)	
Histological grade			
Differentiated	268 (95.7%)	167 (81.1%)	0.000
Undifferentiated	12 (4.3%)	39 (18.9%)	
Depth of invasion			
Tis	16 (2.8%)	7 (1.6%)	0.000
T1	38 (6.6%)	8 (1.8%)	
T2	97 (17%)	50 (11%)	
T3	389 (68%)	358 (79%)	
T4	32 (5.6%)	30 (6.6%)	
Resection margins			
Without involvement	280 (98.2%)	200 (96.2%)	0.152
Involved	5 (1.8%)	8 (3.8%)	
Venous invasion			
Absent	198 (71%)	70 (34.7%)	0.000
Present	81 (29%)	132 (65.3%)	
Lymphatic invasion			
Absent	187 (67%)	19 (9.9%)	0.000
Present	92 (33%)	172 (90.1%)	
Stage			
I	112 (19.2%)	54 (11.8%)	0.003
II	220 (37.8%)	170 (37.8%)	
III	188 (32.3%)	175 (38.3%)	
IV	62 (10.7%)	58 (12.7%)	
pM			
M0	266 (93%)	160 (76.2%)	0.000
M1	20 (7%)	50 (23.8%)	

Differentiated, well and moderately differentiated tumors; Undifferentiated, poorly differentiated and undifferentiated tumors; Tis, intramucous/*in situ Ca*; T1, submucous invasion; T2, muscularis propria invasion; T3, subserosous/not peritonized pericolic conjunctive tissue invasion; T4, organs and structures invasion.

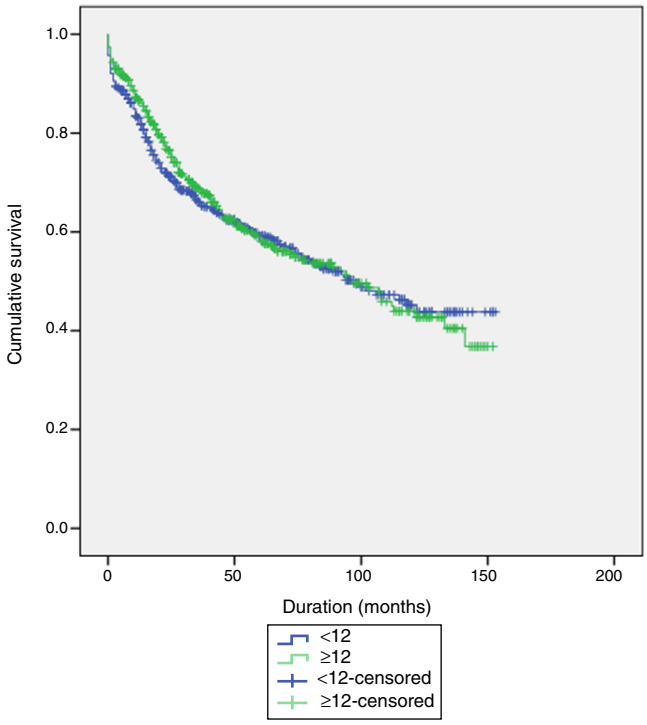

Fig. 1 – Survival curve in function of the number of lymph node evaluated in CRC patients submitted to surgical treatment, assessed by log-rank test ($p = 0.642$).

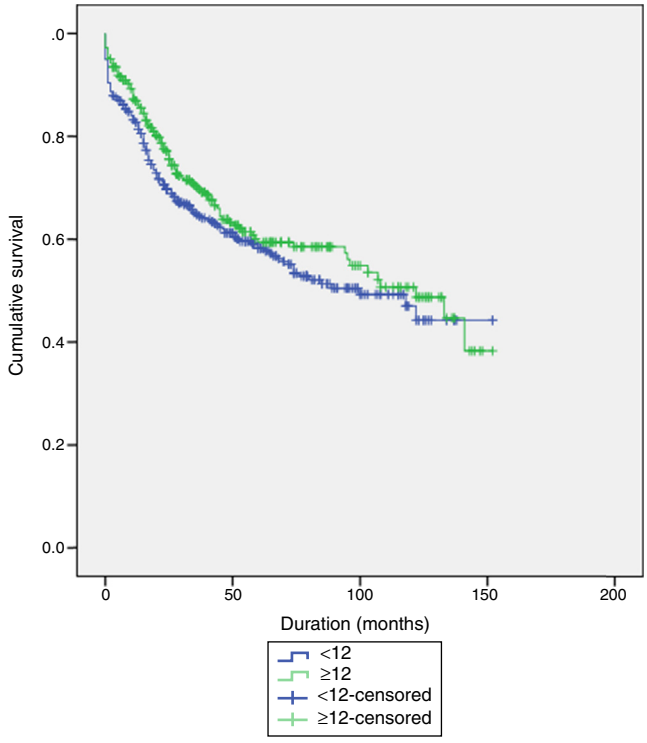

Fig. 2 – Survival curve in function of the number of lymph node evaluated in Colon Cancer patients submitted to surgical treatment, assessed by log-rank test ($p = 0.171$).

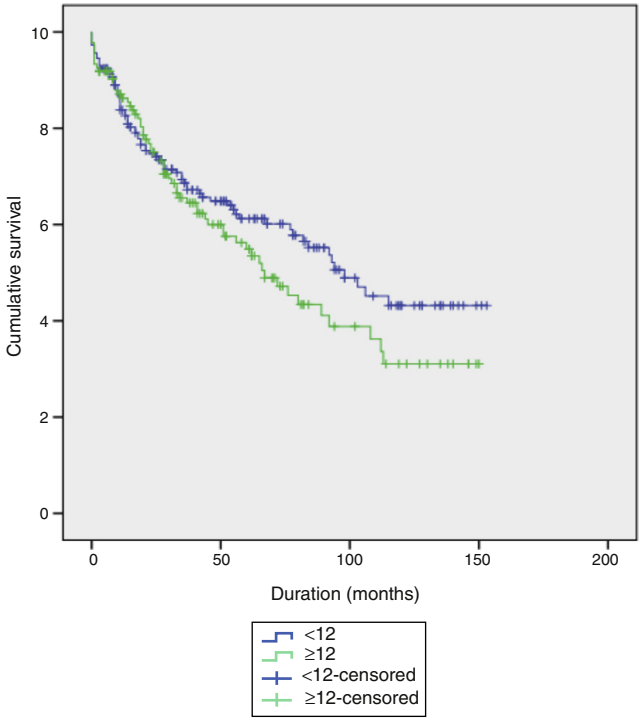

Fig. 3 – Survival curve in function of the number of lymph node evaluated in Rectal Cancer patients submitted to surgical treatment, assessed by log-rank test ($p = 0.204$).

Discussion/Conclusion

Pathological staging is a major prognostic factor for CRC and the regional lymph node metastases are one of the strongest predictors of outcome after surgical resection. Currently, several guidelines suggest a minimum score of 12 lymph nodes assessed in the surgical specimen as a prognostic factor of CRC.[11,34–36]

The results of patient's epidemiological characterization, in this study, coincide with those mentioned by several authors, highlighting this region as an area of high incidence of CRC. In this study, the distribution of CRC by sex and age is well proven, affecting more men than women and noting a higher incidence in individuals aged less than 71.5 years. In this population, colon tumors, left colon in particular, were the most prevalent, and adenocarcinoma was the most common histological type, as documented in the literature.[37–39] Data of countries with high incidence of CRC show that about 20% of patients are diagnosed in stage IV and 25% in stage I,[4,40,41] which coincides with the results obtained.

We observed a significant correlation between the number of nodes evaluated and the variables: age, tumor size, serosal invasion, differentiation, penetration, venous and lymphatic invasion, presence of metastases and TNM stage. This number is lower in older patients, and a possible explanation may be that the number of lymph nodes tends to decrease with age.[42] Larger tumors, with greater penetration tumor (pT) stage and with serosal invasion, venous and lymphatic involvement and presence of metastases are associated with a greater number of nodes assessed. Since the technique of surgical resection and lymphadenectomy are standardized, it is unlikely that

this is due to surgical technique. On the other hand, these factors relate to poor prognosis and can thus be associated with increased nodes dimension and consequently better visualization and collection by the pathologists and also a greater diligence in identification of associated nodes.

This study also demonstrate that factors such as age, location, tumor size, histologic type, venous and lymphatic invasion, and tumor penetration influence the median nodes assessed. This number is higher in tumors ≥ 4.5 cm, right colon tumors, patients aged $\leq$72.5 years, tumors with venous and lymphatic invasion, in mucinous adenocarcinoma and in tumors with invasion of subserous or other organs/structures (higher pT), which goes against the literature.[15] However, sex, resection margins involvement, presence of distant metastases and relapses did not have any influence on the median nodes assessed, unlike reported in various studies.

The results demonstrate that in the case of colon tumors, assessment of twelve or more nodes results in a greater survival. In rectal cancer, it was found that survival decreases after approximately twenty-five months of diagnosis, compared to patients with less than twelve lymph nodes evaluated. However, these results are not statistically significant ($p > 0.05$), and it is not possible to admit the existence of a correlation between survival and the number of nodes assessed be larger or smaller/equal to twelve. The results obtained in this study contradict various studies and current recommendations. This is a controversial topic, and the optimal number of nodes to evaluate, in order to obtain significant results in patients survival, is still highly debated and questionable. One possible explanation for the results of this study lies in the fact that is common practice of the oncologists in this hospital label patients with less than twelve nodes, identified in surgical recession, as "N-positive"; thus, these patients are subjected to adjuvant therapy if their general condition permits. This means that they are overtreated patients who might actually be N0, but are treated as having nodal metastases since less than twelve nodes were retrieved. It is not possible to rule out other factors that also influence survival, including comorbidities, performed treatments and post-surgical mortality. Surgical and pathological techniques should also be taken into consideration in obtaining lymph nodes.[15,16] A more careful resection of mesorectum and a more accurate nodes pathological evaluation contribute to improved staging and therefore more accurate evaluation and patient follow up. Thus, subject patients for adjuvant treatment toxicity, for which this is unnecessary, could be avoided, reducing consequent hospital costs, both economic and humans.

Conflicts of interest

The authors declare no conflicts of interest.

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