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Relationship between the presence of liver metastases with histological grading, depth of invasion and nodal involvement in sporadic adenocarcinoma of the large intestine

Relação entre presença de metástases hepáticas com grau histológico, profundidade de invasão e envolvimento nodal no adenocarcinoma esporádico de intestino grosso

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ABSTRACT

Introduction: Large intestine adenocarcinoma (LIA) is the most common cancer of the gastrointestinal tract, and corresponds to the fifth most common malignancy in Brazil. The main prognostic factors related to LIA are depth of tumor invasion and perivisceral lymph nodes status. **Objective:** To estimate the relationship between pathological findings and the presence of liver metastases (LM) in LIA cases. **Method:** We evaluated 51 cases of LIA, previously submitted to surgical resection, in order to determine the following variables: topography, tumor size, macroscopic appearance, degree of differentiation, depth of invasion, nodal status, and presence of LM. **Results:** The average age was 64.8 years, with predominance of men (n = 26/51.0%) and lesions in the sigmoid colon (n = 18/35.3%). The main general characteristics of the sample were ulcerative-vegetative lesions (n = 20/39.2%), no annular tumors (n = 3/64.7%), moderately differentiated tumor (n = 44/86.3%), absence of mucinous areas (n = 40/78.4%), and mesocolon invasion (n = 29/56.9%). LM were found in 14 cases (27.5%), and is associated with presence of nodal metastases (p = 0.005). Tumor size (p = 0.72), macroscopic appearance (p = 0.362), histological grade (p = 0.147), and depth of invasion (p = 0.195) showed no association with LM presence. **Conclusion:** LIA has a wide anatomical and pathological heterogeneity. In this study, the presence of LM associated with LIA was related to perivisceral lymph nodes status, with no relation to tumor size, degree of differentiation, and depth of invasion, which suggests that identifying neoplastic angiolymphatic invasion is a possible predictor of liver involvement.

Key words: adenocarcinoma; neoplastic metastasis; colorectal cancer; pathology; prognosis.

INTRODUCTION

The primary adenocarcinoma of the large intestine is among the ten most common types of cancer worldwide, and it is also the most common form of malignancy of the gastrointestinal tract. It corresponds to the third leading cause of death in women and the fifth among men in Brazil, although these rates are higher in North America and Europe[1-3]. A progressively higher incidence over the last 15 years have been observed; however, the distribution of colorectal cancer in relation to gender and age has remained constant[1-4]. The risk for developing this cancer increases after the age of 40 for both men and women, and this risk doubles with each subsequent decade. Family history is a risk factor for colorectal carcinoma, especially in patients younger than 50 years, the prevalence of adenomas of the colon in relatives of patients with colorectal carcinoma is 39%[1-4].

Colorectal adenocarcinoma may present polypoid, vegetative, ulcerative, ulcerative-vegetative, and infiltrative macroscopic forms. Histologically, it can be classified into grades based on tubular architectural pattern of neoplastic cells[2, 3, 5]. Although poorly differentiated and mucinous neoplasms are

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associated with lower disease-free survival rates, the two most important prognostic factors are the depth of invasion and the presence of metastases in regional lymph nodes. Besides these latter, the metastases may involve the lungs and bones, but as a consequence of the venous drainage of the colon, the liver is the most common location for metastatic lesions[2, 3, 5]. About 25% of patients with colorectal cancer may present liver metastasis at the time of primary tumor diagnosis, and 50% of patients may show liver metastases during the course of the disease[2, 3, 5].

In this study, the authors assessed the relationship between liver metastases and anatomopathological findings of colorectal adenocarcinoma, as topography, tumor size, macroscopic appearance, degree of differentiation, presence of mucinous areas, depth of invasion, and in periviscerais lymph nodes metastasis.

METHOD

This is a cross-sectional retrospective study involving patients with large intestine adenocarcinoma (LIA), who had undergone previous surgical resection and staging. Initially, 51 different LIA cases were selected for the study, previously analyzed in the Pathology Laboratory of the Grupo Hospitalar Conceição (GHC) in Porto Alegre (RS). Data collection was carried out between March 2014 and October 2014, and was approved by the Ethics Research Committee (ERC) of GHC, project nº 14-001. We included in the sample only those cases histologically classified as primary large intestine adenocarcinoma according to World Health Organization criteria. All other histological types of primary benign or malignant neoplasm of the large intestine and cases of metastasis or secondary involvement of the organ were excluded.

The demographic characteristics (age and sex) were collected from the medical records. Each case was previously fixed in 10% formalin, stained with hematoxylin-eosin (HE), and the following anatomopathological data were reviewed and described:

1) anatomical position: cecum, ascending colon, sigmoid colon, transverse colon, and rectum;

2) tumor size: is in centimeters, in the longer axis of the lesion;

3) macroscopic appearance: infiltrative, ulcerative, ulcerative-infiltrative, ulcerative-vegetative and vegetative;

4) presence of annular or no annular lesion;

5) degree of differentiation: well-differentiated, moderately-differentiated and poorly-differentiate;

6) presence of mucous producing area;

7) depth of invasion: mucosa, submucosa, muscle, perivisceral tissue, serous and adjacent organ invasion;

8) surgical margins status: free or positive;

9) presence of lymph nodes metastases.

The evaluated cases were also grouped by TNM staging system; T: tumor, N: lymph node, M: metastasis. Data were recorded and analyzed in a Microsoft Excel 2007 spreadsheet. Quantitative variables were expressed as mean and standard deviation (DP) or median and interquartile range. Categorical variables were described by absolute and relative frequencies. To compare means between groups we used the Student-*t* test; in case of asymmetrical distribution, we used the Mann-Whitney test; Pearson chi-squared tests or Fisher's exact test were used for the difference between proportions; in case of significance, the adjusted residual test was applied. The significance level was 5% ($p \leq 0.05$), and analyzes were performed in SPSS software version 21.0.

RESULTS

The group of patients analyzed had a mean age of 64.8 years, predominantly male. The prevalence of liver metastasis was 27.5% (confidence interval [CI] 95%: 15.2%-39.8%). **Tables 1** and **2** show the results obtained by the research.

The number of lymph node metastasis ($p = 0.005$) and group N of TNM system ($p = 0.015$) were associated with the presence of liver metastases. The pathological variables, such as anatomical position ($p = 0.242$), tumor size ($p = 0.722$), macroscopic appearance ($p = 0.362$), degree of differentiation ($p = 0.147$), presence of mucous producing area ($p = 0.251$), depth of invasion ($p = 0.195$), and positive resection margins ($p = 0.478$), had no significant association with the presence of liver metastasis.

TABLE 1 – LIA: sample characterization

Variables	Total ($n = 51$)	Metastatic liver ($n = 14$; 27.5%)	No metastatic liver ($n = 37$; 72.5%)	p value
Age (years) – mean ± SD	64.8 ± 12.2	70.7 ± 13.8	62.6 ± 10.8	0.032
Sex – n (%)				
Male	26 (51.0)	9 (64.3)	17 (45.9)	0.392
Female	25 (49.0)	5 (35.7)	20 (54.1)	

LIA: large intestine adenocarcinoma; SD: standard deviation.

TABLE 2 – LIA: comparison between groups regarding the variables

Variables[#]	Total (n = 51)	Presence of metastatic liver (n = 14; 27.5%)	Absence of metastatic liver (n = 37; 72.5%)	p value
Anatomical position				
Cecum	6 (11.8)	1 (7.1)	5 (13.5)	
Ascending colon	7 (13.7)	2 (14.3)	5 (13.5)	
Sigmoid colon	19 (37.3)	4 (28.6)	15 (40.5)	0.242
Transverse colon	9 (17.6)	2 (14.3)	7 (18.9)	
Rectum	10 (19.6)	5 (35.7)	5 (13.5)	
Tumor size	5.33 ± 2.49	5.13 ± 1.99	5.41 ± 2.68	0.722
Macroscopic configuration				
Infiltrating	7 (13.7)	3 (21.4)	4 (10.8)	
Ulcerative	7 (13.7)	2 (14.3)	5 (13.5)	
Ulcerative-infiltrative	7 (13.7)	0 (0.0)	7 (18.9)	0.362
Ulcerative-vegetative	20 (39.2)	7 (50.0)	13 (35.1)	
Vegetative	10 (19.6)	2 (14.3)	8 (21.6)	
Annular				
Yes	18 (35.3)	7 (50.0)	11 (29.7)	0.204
No	33 (64.7)	7 (50.0)	26 (70.3)	
Tumor grading				
Well-differentiated	3 (5.9)	2 (14.3)	1 (2.7)	
Moderately-differentiated	44 (86.3)	12 (85.7)	32 (86.5)	0.147
Poorly-differentiated	4 (7.8)	0 (0.0)	4 (10.8)	
Mucous producing areas				
Yes	11 (21.6)	1 (7.1)	10 (27.0)	0.251
No	40 (78.4)	13 (92.9)	27 (73.0)	
Depth of invasion				
Mucosa	0 (0)	(0)	0 (0)	
Submucosa	0 (0)	(0)	0 (0)	
Muscle	14 (27.5)	2 (14.3)	12 (32.4)	
Adjacent organs	1 (2.0)	0 (0.0)	1 (2.7)	0.195
Serous	7 (13.7)	4 (28.6)	3 (8.1)	
Perivisceral tissue	29 (56.9)	8 (57.1)	21 (56.8)	
Margins of resection				
Yes	2 (3.9)	1 (7.1)	1 (2.7)	0.478
No	49 (96.1)	13 (92.9)	36 (97.3)	
Metastatic lymph nodes				
Yes	19 (37.3)	10 (71.4)	9 (24.3)	0.005
No	32 (62.7)	4 (28.6)	28 (75.7)	
Average of lymph nodes isolated in the surgical specimen	13 (10-20)	10 (9-19)	15 (12-21)	0.267
T – TNM classification				
2	11 (21.6)	2 (14.3)	9 (24.3)	
3	29 (56.9)	7 (50.0)	22 (59.5)	0.298
4	11 (21.6)	5 (35.7)	6 (16.2)	
N – TNM classification				
0	31 (60.8)	4 (28.6)	27 (73.0)*	
1	1 (2.0)	0 (0.0)	1 (2.7)	
1[a]	6 (11.8)	5 (35.7)*	1 (2.7)	
1b	5 (9.8)	2 (14.3)	3 (8.1)	0.015
1c	2 (3.9)	0 (0.0)	2 (5.4)	
2[a]	4 (7.8)	2 (14.3)	2 (5.4)	
2b	2 (3.9)	1 (7.1)	1 (2.7)	

*[#] variables expressed as mean ± SD, median (25-75 percentile) or n(%); * statistically significant association by adjusted residual testing to 5% of significance; LIA: large intestine adenocarcinoma; SD: standard deviation; TNM: tumor, lymph node metastasis.*

DISCUSSION

Colorectal carcinoma is among the ten main types cancers in Brazil, affecting both sexes in similar prevalence. The age profile of colorectal carcinoma has dramatic increase in incidence from 40 years for women and 50 years for men. It is estimated that, in 2014, in Brazil, 32,600 cases of colorectal carcinoma were found, 15,070 men and 17,530 women[6]. In this study, data of age group was equivalent to those from the literature. The study population consisted of an age average of 64.8 years, ranging 12.2 years, in 26 male (51%) and 25 female (49%). Oliveira *et al*. analyzed 129 cases of colorectal carcinoma and determined that the mean age of patients was 56.9 years, ranging 25-87 years, of which 51.2% were female patients (51.2%, $p > 0.05$)[7]. Torres Neto *et al*. evaluated 355 cases of colorectal cancer, which was more frequent in women, the age ranged from 5-98 years, mean age of 60.2 years[8].

Colorectal adenocarcinoma may grade in well-differentiated, moderately-differentiated, poorly-differentiated and undifferentiated lesions. The infiltrating edge of adenocarcinomas may have rounded or spiculated tumor growth and, in its progression, the adenocarcinoma gradually invades the intestine layers. During this mural progression of the cancer, there may be angiolymphatic invasion in cancer and potential spread and tumor implantation in regional lymph nodes and distant organs[1, 2, 4, 9, 10]. In this study, the anatomopathological variables, such as anatomical position ($p = 0.242$), tumor size ($p = 0.722$), macroscopic appearance ($p = 0.362$), the presence or absence of annular lesion ($p = 0.204$), degree of differentiation ($p = 0.147$), presence of mucous producing area ($p = 0.251$), depth of invasion ($p = 0.195$), and presence of positive surgical margins ($p = 0.478$), were not associated with the presence of liver metastases. Madeira *et al*. analyzed 50 LIA cases and reported that there was no association between the presence of nodal metastases and age, sex, microscopic edge, presence of mucous producing areas, degree of differentiation, and tumor size[2]. Fujimoto *et al*. reported that the presence of liver metastases on 122 cases with clinical five years follow-up, was significantly associated with tumor size, degree of differentiation, depth of invasion, presence of neoplastic angiolymphatic invasion and presence of metastases in regional lymph[11]. Kitajima *et al*. investigated the depth of submucosa invasion in 865 cases of invasive colorectal carcinoma and concluded that nodal metastasis rates are associated with depth of submucosa lesion[12]. Inoue *et al*. compared the depth of submucosa lesion in 118 cases of colorectal carcinomas sessile and superficial type, which were resected endoscopically, and total depth was significantly higher in sessile type[13].

The liver is the most common site of distant metastases of LIA, found in up to 25% patients at diagnosis[1-3, 5-7, 11]. The prevalence of liver metastases in our study was 27.5%. The average age of the group with liver metastasis was significantly higher than the group without metastasis. Fernandes *et al*. analyzed 749 LIA cases and determined that the main sites of metastases were liver (64.51%), peritoneum (19.35%), and lungs (9.67%). Among metastases associated with colorectal cancer, the liver was also the most affected organ (54.11%)[14]. Murad *et al*. reported that in a sample of 49 patients with liver metastases from colorectal adenocarcinoma, 31 cases (63.2%) had already had hepatic involvement in the initial surgical procedure or presence of metastasis within six months of initial diagnosis. In 18 cases (36.8%), the appearance of metastasis occurred six months after colorectal surgery[9]. Ambiru *et al*. determined that the survival of 168 patients with liver metastases associated with colorectal carcinoma was 42% in three years and 26% in five years. The main prognostic factors included nodal status of the initial resection of the primary tumor, surgical margin status, number of liver metastases, and adjuvant chemotherapy[15]. Arru *et al*., among the 297 cases of resected liver metastases associated with colorectal carcinoma, determined that the time period of disease-free survival was associated with the degree of differentiation, serum level of carcinoembryonic antigen, tumor size greater than 5 cm and time period of metastasis detection after initial surgical treatment[16]. Ohji *et al*. selected 120 cases of advanced colorectal carcinoma, including liver metastases in 60 cases and determined that the presence of nodal metastasis, and the immunohistochemical expression of neprilysin (CD10) and vascular endothelial growth factor (VEGF) are associated with the development of metastatic lesions[17]. Ueno *et al*. reported that the degree of differentiation was associated with groups T and N of the TNM system, the serum levels of carcinoembryonic antigen, the presence of liver, lung and peritoneal metastases, the number of liver metastases and survival time after hepatectomy[18]. Lin *et al*. determined that in cases of colorectal adenocarcinoma, the presence of tumor deposits in perivisceral tissues was associated with liver and nodal metastasis, perineural invasion and disease-free interval after resection of the primary tumor[19]. Adachi *et al*. reported that the presence of liver metastases in adenocarcinoma colorectal cancer was associated with primary tumors with size equal or greater than 6 cm, presence of serosal invasion, neoplastic angiolymphatic invasion, and metastasis to regional lymph nodes[20].

In our study, the presence of regional lymph node metastasis ($p = 0.005$) was associated with the presence of liver metastasis. Kuhen *et al*. analyzed 132 patients undergoing surgical treatment

for colorectal cancer resection, and the presence of nodal metastases was associated with the degree of differentiation[21]. Fonseca *et al*. assessed 521 surgical specimens of patients operated for colorectal cancer and the average of lymph nodes affected by metastases corresponds to 2.57 ± 5.34 lymph nodes[22], while Santo *et al*. found an average of 3.4 ± 3.3 metastatic lymph node from 51 specimens examined (42.8%/*n* = 119)[23]. Homma *et al*. analyzed 65 patients with colorectal adenocarcinoma invading the submucosa or the muscle propria, and concluded that the resection of the affected regional lymph nodes by metastases reduced the local recurrence rate of these carcinomas[24]. In another study Homma *et al*. determined that sex, histologic grade, neoplastic angiolymphatic invasion or nodal status were not significantly associated with tumor recurrence[25]. Ahmadi *et al*. analyzed 824 patients with colorectal carcinoma and found that the right colon tumors are more often associated with nodal metastases, and were also associated with age[26]. Toh *et al*. investigated 207 cases of adenocarcinoma colorectal and demonstrated that the radial extent of the tumor and submucosal invasion area can predict the regional nodal status[27].

CONCLUSION

LIA has good anatomopathological heterogeneity, and the depth of invasion and lymph node status are considered important prognostic factors. In this study, the presence of liver metastases determined by LIA was associated with the status of perivisceral lymph nodes, with no relation to tumor size, degree of differentiation, and depth of invasion, suggesting that identifying neoplastic angiolymphatic invasion by microscopic examination is a potential predictor of liver involvement.

RESUMO

Introdução: *O adenocarcinoma de intestino grosso (AIG) é o tumor maligno mais frequente do trato digestivo e corresponde à quinta neoplasia maligna mais comum no Brasil. Os principais fatores prognósticos do AIG são profundidade de invasão neoplásica e* status *dos linfonodos periviscerais.* ***Objetivo:*** *Estimar a relação entre achados anatomopatológicos e presença de metástases hepáticas (MH) em casos de AIG.* ***Método:*** *Foram avaliados 51 casos de AIG, previamente submetidos à ressecção cirúrgica, e determinadas as seguintes variáveis: topografia, tamanho tumoral, conformação macroscópica, grau histológico, profundidade de invasão,* status *nodal e presença de MH.* ***Resultados:*** *A média de idade correspondeu a 64,8 anos, com predomínio de homens (*n = *26/51,0%) e lesões do cólon sigmoide (*n = *18/35,3%). Lesões ulcerovegetantes (*n = *20/39,2%), tumores não anelares (*n = *3/64,7%), neoplasias moderadamente diferenciadas (*n = *44/86,3%), ausência de áreas mucoprodutoras (*n = *40/78,4%) e invasão do mesocólon (*n = *29/56,9%) foram as principais características gerais da amostra. MH foram encontradas em 14 casos (27,5%), estando associadas à presença de metástases nodais (*p = *0,005). Tamanho tumoral (*p = *0,72), configuração macroscópica (*p = *0,362), grau histológico (*p = *0,147) e profundidade de invasão (*p = *0,195) não apresentaram associação com a presença de MH.* ***Conclusão:*** *O AIG apresenta heterogeneidade anatomopatológica ampla. No presente estudo, a presença de MH associadas ao AIG esteve relacionada com o* status *dos linfonodos periviscerais, não havendo relação com tamanho tumoral, grau de diferenciação e profundidade de invasão, sugerindo que a identificação de invasão neoplásica angiolinfática é possível fator preditivo do envolvimento hepático.*

Unitermos: *adenocarcinoma; metástase neoplásica; neoplasias colorretais; patologia; prognóstico.*

REFERENCES

1. Nadal LRM, Adachi CT, Nunes MAA, et al. Evolução do carcinoma colorretal, comparando doentes com idades acima e abaixo de 40 anos, quanto à diferenciação tumoral e ao estádio do tumor. Rev Bras Colo-proctol. 2009; 29(3): 351-7.

2. Madeira B, Pêgas K, Zettler C, Cambruzzi E. A relação entre metástases em linfonodos regionais e fatores prognósticos no adenocarcinoma esporádico de intestino grosso. Rev Bras Colo-proctol. 2009; 29(4): 472-8.

3. Costa SRP, Lima OAT, Cunha TMR, Soares AF. Hepatectomia direita ampliada com ressecção parcial da veia cava para metástase colorretal: relato de caso. Rev Bras Colo-proctol. 2010; 30(2): 232-6.

4. Loy TS, Kaplan PA. Villous adenocarcinoma of the colon and rectum: a clinicopathologic study of 36 cases. Am J Surg Pathol. 2004, 28: 1460-5.

5. Nahas SC, Marques CFS, Araújo SA, et al. Colonoscopia como método diagnóstico e terapêutico das moléstias do intestino grosso: análise de 2.567 exames. Arq Gastroenterol. 2005 Jun; 42(2): 77-82.

6. Instituto Nacional de Câncer. Tipos de câncer [Internet]. [citado em 18 maio 2015]. Available at: http://www.inca.gov.br/wps/wcm/connect/tiposdecancer/site/home/colorretal/definicao.

7. Oliveira RG, Faria FF, Lima Junior ACB. Cirurgias ênteros-colorretais: abordagem cirúrgica de 129 pacientes do SUS no Programa de Pós-Graduação Sensu Lato em coloproctologia. Rev Bras Colo-proctol. 2010; 30(3): 333-43.

8. Torres Neto JR, Teixeira FR, Prudente ACL, Silvino CJ, Arciere JS, Vieira Filho MC. Estudo demográfico do câncer de cólon e reto no estado de Sergipe. Rev Bras Colo-proctol. 2008; 28(2): 215-22.

9. Murad JC, Ribeiro-Jr U, Corbetti CE, et al. Análise de fatores clínicos e histopatológicos em metástases hepáticas de adenocarcinoma colorretal. ABCD, Arq Bras Cir Dig. 2007; 20(4): 241-4.

10. Henrique-Filho C, Bromberg SH, Barreto E, Godoy AC, Mattosinho-França LC. Valor prognóstico do grau de diferenciação celular, da presença de muco e do padrão de crescimento da margem invasiva em adenocarcinomas colorretais Dukes B. Arq Gastroenterol. 2004 Set; 41(3): 185-9.

11. Fujimoto Y, Nakanishi Y, Sekine S, et al. CD10 expression in colorectal carcinoma correlates with liver metastasis. Dis Colon Rectum. 2005 Oct; 48(10): 1883-9.

12. Kitajima K, Fujimori T, Fujii S, et al. Correlations between lymph node metastasis and depth of submucosal invasion in submucosal invasive colorectal carcinoma: a Japanese collaborative study. J Gastroenterol. 2004 Jun; 39(6): 534-43.

13. Inoue Y, Ohki T, Nakagawa R, Yamamoto M. Depth of submucosal invasion in the sessile ans superficial types of submucosal invasive colorectal carcinoma: objective versus subjective measurement. Hepatogastroenterology. 2013 Nov-Dec; 60(128): 1916-21.

14. Fernandes GMM, Leme CVD, Ruiz-Cintra MT, Pavarino EC, Netinho JG, Goloni-Bertollo EM. Clinical and epidemiological evaluation of patients with sporadic colorectal cancer. J Coloproctol. 2014; 34(4): 216-23.

15. Ambiru S, Miyazaki M, Isono T, et al. Hepatic resection for colorectal metastases: analysis of prognostic factors. Dis Colon Rectum. 1999 May; 42(5): 632-9.

16. Arru M, Aldrighetti L, Castoldi R, et al. Analysis of prognostic factors influencing long-term survival after hepatic resection for metastatic colorectal cancer. World J Surg. 2008 Jan; 32(1): 93-103.

17. Ohji Y, Yao T, Eguchi T, et al. Evaluation of risk of liver metastasis in colorectal adenocarcinoma based on the combination of risk factors including CD10 expression: multivariate analysys of clinicopathological and immunohistochemical factors. Oncol Rep. 2007 Mar; 17(3): 525-30.

18. Ueno H, Konishi T, Ishikawa Y, et al. Prognostic value of poorly differentiated clusters in the primary tumor in patients undergoing hepatectomy forcolorectal liver metastasis. Surgery. 2015 May; 157(5): 899-908.

19. Lin Q, Wei Y, Ren L, et al. Tumor deposit is a poor prognostic indicator in patients who underwent simultaneous resection for synchronous colorectal liver metastases. Onco Targets Ther. 2015 Jan; 8: 233-40.

20. Adachi Y, Inomata M, Kakisako K, et al. Histopathologic characteristics of colorectal cancer with liver metastasis. Dis Colon Rectum. 1999 Aug; 42(8): 1053-6.

21. Kuhnen RB, Kock KS. Número de gânglios dissecados em peças operatórias de pacientes submetidos à ressecção cirúrgica de câncer colorretal: retrospectiva de 10 anos HNSC – Tubarão, SC. Rev Bras Colo-proctol. 2007; 27(4): 417-22.

22. Fonseca LM, Quites LV, Cabral MMD, Silva RG, Luz MMP, Lacerda Filho A. Câncer colorretal: resultados da avaliação patológica padronizada de 521 casos operados no Hospital das Clínicas da UFMG. Rev Bras Colo-proctol. 2011; 31(1): 17-25.

23. Santo GFE, Aguilar-Nascimento JE, Kishima MO, Takiuchi A. Correlação de fatores anatomopatológicos com a sobrevida de pacientes operados por adenocarcinoma colorretal. Rev Col Bras Cir. 2008; 35(3): 82-187.

24. Homma Y, Hamano t, Otsuki Y, et al. Severe tumor budding is a risk factor for lateral lymph node metastasis in early rectal cancers. J Surg Oncol. 2010 Sep; 102(3): 230-4.

25. Homma Y, Humano T, Otsuki Y, et al. The total number of lymph node metastases is a more significant risk factor for poor prognosis than positive lateral lymph node metastasis. Surg Today. 2015 Feb; 45(2): 168-74.

26. Ahmadi O, Stringer MD, Black MA, McCall JL. Influence of age and site of disease on lymph node yield in colorectal cancer. N Z Med J. 2014 Jun; 127(1395): 31-40.

27. Toh EW, Brown P, Morris E, Botterill I, Quirke P. Area of submucosal invasion and width of invasions predicts lymph node metastasis in pT1 colorectal cancer. Dis Colon Rectum. 2015 Apr; 58(4): 393-400.

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