Original Article

Incidence of angiolymphatic invasion in colorectal cancer

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ABSTRACT: Angiolymphatic invasion (ALI) in colorectal cancer (CRC) is considered as an important independent prognostic factor and may influence therapeutic decisions. **Objective:** This aim of the study is to find the incidence of ALI in histopathological reports of surgical specimens from patients who underwent surgical treatment of colorectal adenocarcinoma. **Results:** One hundred and twenty seven patients were male (50.6%) and the mean age was 60 years old. The overall incidence of ALI was 44.6%, and there was a significant association with age (p=0.016), lymph node involvement (N) (p<0.00001) and tumor differentiation (p=0.0039). **Conclusion:** There was a higher probability of finding ALI in younger patients, with a higher number of lymph node metastases and a lower tumor differentiation.

Keywords: neoplasm invasiveness; colorectal neoplasms; prognosis; survivorship.

RESUMO: A invasão angiolinfática (LVI) no câncer colorretal (CCR) é considerada um importante marcador independente de prognóstico e pode influenciar em decisões terapêuticas. **Objetivo:** Encontrar a incidência de LVI através de laudos histopatológicos de peças operatórias de pacientes submetidos a tratamento cirúrgico de câncer colorretal, por adenocarcinoma. **Resultados:** A média de idade encontrada foi de 60,08 anos. Cento e vinte sete pacientes eram do sexo masculino (50,6%). A incidência global de LVI foi de 44,6% e houve associação significativa com a idade (p=0,016), o grau de acometimento linfonodal (N) (p<0,00001) e o grau de diferenciação (p=0,0039). **Conclusão:** Há uma maior probabilidade de encontrarmos LVI em pacientes mais novos, com um número maior de linfonodos acometidos e um menor grau de diferenciação celular.

Palavras-chave: invasividade neoplásica; neoplasias colorretais; prognóstico; sobrevida.

INTRODUCTION

Colorectal cancer (CRC) represents one of the most common malignant neoplasms in Brazil and in the world, taking the fourth position in our country. It is only topped by lung, breast and prostate tumors. Its death rates reach the third position among women and the fifth among men[1,2].

Due to its varied etiology, which involves genetic and environmental factors such as diet, the incidence of CRC is heterogeneous in different countries, and it is more prevalent in richer and more industrialized nations. High rates have been observed in North America, Europe and Oceania, and lower rates in South America, India and Equatorial Africa[3,4].

The increasing number of deaths caused by CRC in Brazil is closely connected to the increase in life expectancy, since most patients are older than 50 years at the time of diagnosis. For 2050, it is estimated that this relation will be of one to five all over the world, and of one to three in developed countries[5-7].

Generally, there is a slight prevalence among the male gender, and the most affected site is the rectum, even though recent studies have shown variations of these data. Symptoms from colorectal cancer may present in the following forms: diarrhea, dysentery, constipation, abdominal pain, meteorism, localized abdominal pain, blood and mucus in stool, anemia, palpable mass, and symptoms that result from abdominal com-

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plications, such as bowel obstruction, intestinal perforation with peritonitis, and fistulae to other organs. It is important to remember that these manifestations depend very much on the location of the tumor[8,9].

Many factors have been cited as indicators of prognosis and survival, among which are age, perineural invasion, angiolymphatic invasion (ALI), tumor differentiation, presence of metastasis, parietal invasion and the presence of metastasis in regional lymph nodes. The last three factors mentioned still represent the main base to predict survival and criterion to recommend adjuvant therapy. The TNM classification is mentioned, and is the current guideline of the American Joint Committee, which is the most used staging system in the world[10-12,13].

Due to these factors, the anatomopathological stage of the surgical specimen represents the main tool that is clinically available in order to infer on prognosis and survival of patients with CRC[10,12,14,15].

Many authors have demonstrated that ALI can be an independent factor to determine the prognosis and potential predict result in these patients, and also response to surgical treatment, incidence of lymph node metastases, and response to adjuvant treatment[16-19]. The American College of Pathologists (CAP), in the 1999 consensus, reviewed the available literature and established that "blood or lymphatic vessel invasion" is in category I, as a definitively proved factor of prognostic importance based on evidence of many published studies with statistical significance[10].

Besides, patients with colorectal adenocarcinoma and without lymph node compromise and negative ALI have a five-year survival significantly higher in comparison to patients with positive ALI[21,22]. Therefore, patients identified with ALI and absence of positive lymph nodes could benefit from adjuvant therapy.

The criteria used to identify ALI in microscopy, using hematoxylin and eosin staining (H&E), include: presence of tumor cells in a vascular space; erythrocytes around the tumor cell; the identification of endothelial cells in overlay cells; presence of an elastic membrane around the tumor; and fixation of tumor cells to the vascular wall[20]. However, it is important to mention that the number of analyzed slides and the cutting levels in each tissue block can present significant variability to diagnose and observe ALI in different institutions. Therefore, pathologists may or may not use auxiliary staining, such as elastin or immunohistochemical staining, to help the assessment of ALI[16].

The prognostic value of ALI is controversial, but its importance is mostly emphasized[10,13,16-19,23-25], even though some researchers have not observed such influence[26,27].

Therefore, this study aims to evaluate the incidence of ALI and associate it with other variables of important prognostic value, in order to find possible significant associations and strengthen its relevance.

METHODS

A cross-sectional study was conducted based on the analysis of secondary data in anatomopathological reports.

The population of the study was all anatomopathological reports obtained from surgical resections of patients who underwent surgery at *Hospital Nossa Senhora da Conceição* (HNSC), diagnosed with colorectal adenocarcinoma from 2000 to 2010. The convenience sample was constituted by reports obtained from surgical specimens.

Patients underwent surgical treatment that met the conventional standards of resections according to the oncologic principles, which include the access to the abdominal cavity with lymph node excision and, in cases of rectal tumor, intact mesorectal resection.

Patients with CRC associated with inflammatory bowel disease, those who underwent neoadjuvant therapy and patients submitted to resection of the CRC by videolaparoscopy were excluded.

The presence or absence of ALI was associated with age, gender, tumor location, level of tumor invasion (T), lymph node involvement (N), and tumor differentiation.

Data collection was performed in a laboratory of pathological anatomy in the city of Tubarão, in Santa Catarina, Brazil. Data were obtained from filed reports (secondary data source) from this laboratory. Data collection began after the study was approved by the Research Ethics Committee of *Universidade do Sul* (UNISUL), in Santa Catarina, registration number 10.696.4.01.III. Because of the characteristics of this study, only data from anatomopathological reports were analyzed, with no contact with the patient.

All data were catalogued in a data base and inserted in the program Epidata® 3.1 and transferred to the statistical analysis of SPSS®, version 16.0.

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Descriptive epidemiology was used to present the data in terms of absolute and relative values. Statistical analysis was performed using SPSS 16.00, and the χ^2 test was used for categorical variables.

RESULTS

Two hundred and fifty one patients were submitted to CRC resection from 2000 to 2010, and the mean age was 60 years old, (+/– 15 years). ALI was present in 112 patients, which corresponds to a global incidence of 44.6%.
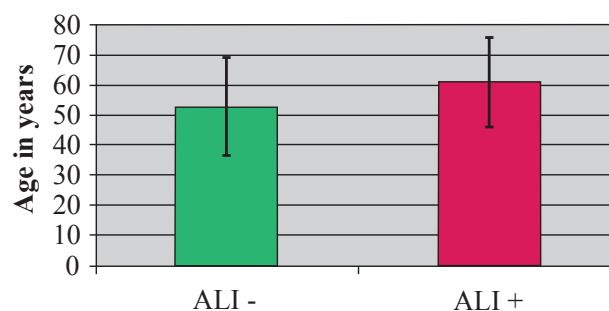
Table 1 shows the data associated with the following variables: gender, anatomic position, tumor

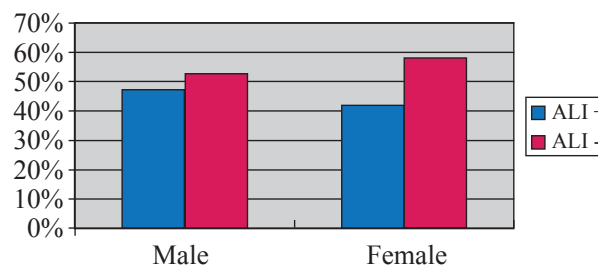*Table 1. Incidence of angiolymphatic invasion in colorectal cancer in Tubarão (SC). Analyzed variables.*

Variable	n	%
Gender		
Male	127	50.6
Female	124	49.4
Anatomic location		
Right colon (RC)	66	26.3
Transverse colon (TC)	15	6.0
Left colon (LC)	29	11.6
Rectosigmoid (RS)	141	56.2
Tumor invasion (T)		
T0	1	0.4
T1	9	3.6
T2	17	6.8
T3	197	78.5
T4	27	10.8
Lymph node involvement (N)		
N0	125	49.8
N1	78	31.1
N2	47	18.7
N3	1	0.4
Presence of perineural invasion		
Yes	22	8.8
No	229	91.2
Tumor differentiation		
Well differentiated	184	73.3
Moderately differentiated	50	19.9
Poorly differentiated	15	5.9
Undifferentiated	2	0.7

invasion (T), lymph node compromise (N), presence of perineural invasion and tumor differentiation. The most common anatomic location (56.2%) was the rectosigmoid. Around 91% of the patients did not present with perineural invasion, 49.8% were lymph node negative (N0) and the majority of tumors were well differentiated.
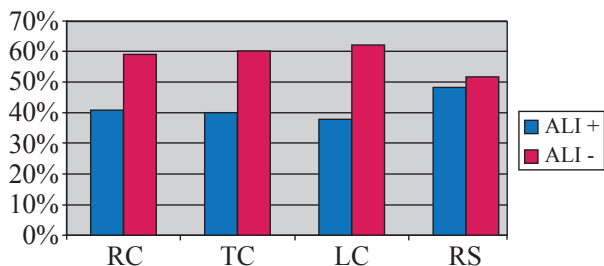
Figure 1 shows that the perineural invasion were significantly associated with patients age. Figure 2 demonstrates there was no association between the ALI and gender, as well as Figures 3 and 4, which show that ALI was not associated with the anatomic location and the tumor invasion (T), respectively. However, we observe that, in Figure 5, there was an association between ALI and lymph node compromise, as well as in Figure 6, which demonstrates that ALI was associated with tumor differentiation.

Figure 1. Incidence of angiolymphatic invasion in colorectal cancer in Tubarão, Santa Catarina. Association of angiolymphatic invasion (ALI) versus age: p=0.016.
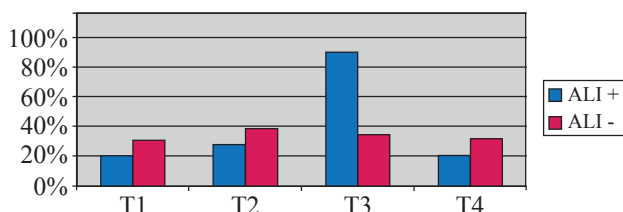

Figure 2. Incidence of angiolymphatic invasion in colorectal cancer in Tubarão, Santa Catarina. Association of angiolymphatic invasion (ALI) versus gender: p=0.398.

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DISCUSSION

Colorectal cancer is one of the most frequent tumors, corresponding to 9.4% of all cases of cancer in the world. Its incidence is higher in rich and industrialized countries. In Brazil, the South and Southeast regions lead the number of cases in the national ranking[1]. The pathological staging of the surgical specimen after tumor resection is essential to inform us on the prognosis and survival of these patients[10,11]. Age, TNM classification, tumor differentiation and other clinical factors, such as ALI, are important variables that help us to evaluate a less favorable clinical situation[13,17-19,24].

Our results were similar to prior reports in the literature. The prevalent gender was male, with 50.6% of the cases and mean age of 60 years old. The T3 stage was prevalent, with 78.5%, and of the absence of lymph node involvement N0 represented 49.8%. The rectosigmoid location was the most affected one, in 67.7% of the cases, and the most prevalent histological type was well differentiated adenocarcinoma in 184 patients, 73.3%.

Out of the 251 analyzed reports, ALI was found in 112 cases, compounding a global incidence of 44.6%. A national study that analyzed 320 patients with CRC showed a venous invasion rate of 14,1%[21], however, these numbers can range from 12.5 to 40.9%[28,29]. Such range can be explained due to the fact that there is great variability among observers to differentiate small lymphatic vessels from postcapillary venules. Therefore, venous invasion is analyzed together with lymphatic invasion. It is worth mentioning that the number of analyzed slides and the cutting levels of each paraffin block also influence the observation of ALI[16].

It is a known fact that CRC affects the older population, however, it has been increasingly diagnosed in younger patients. An American study conducted in California[30] analyzed the characteristics of 204 patients with CRC by comparing two groups, one with patients aged 40 years old or less, and the other with patients aged 60 years old or more. They observed that the advanced stage (T3 and T4) was present in 87.8% of the younger group, and in 63% of the older patients (p=0.002, *odds ratio* – OR 4.08). The conclusion was that the younger population presented a more advanced stage and a more aggressive tumor. In the current study, ALI was significantly associated with
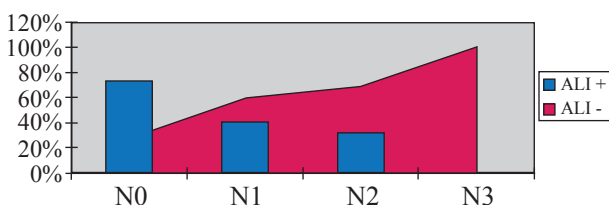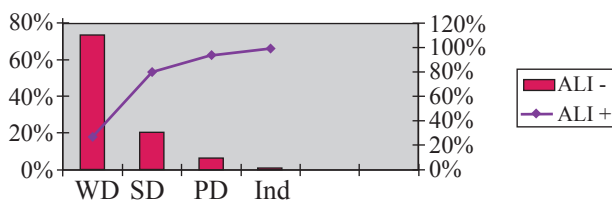

RC: right colon; LC: left colon; TC: transverse colon; RS: rectosigmoid.

Figure 3. *Incidence of angiolymphatic invasion in colorectal tumor in Tubarão, Santa Catarina. Association of angiolymphatic invasion (ALI) versus anatomic location: p=0.623.*

Figura 4. *Incidence of angiolymphatic invasion in colorectal tumor in Tubarão, Santa Catarina. Association of angiolymphatic invasion (ALI) versus tumor invasion (T): p=0.851.*

Figura 5. *Incidence of angiolymphatic invasion in colorectal tumor in Tubarão, Santa Catarina. Association of angiolymphatic invasion (ALI) versus lymph node involvement (N): p<0.00001.*

WD: well differentiated; Ind: indeterminate; MD: moderately differentiated; PD: poor differentiated.

Figura 6. *Incidence of angiolymphatic invasion in colorectal tumor in Tubarão, Santa Catarina. Association of angiolymphatic invasion (ALI) versus tumor differentiation: p=0.0039.*

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age. Patients with positive ALI presented a mean age of 57.50 years old (SD+/-15.42), versus 62.16 years old (SD+/-14.61) in patients without ALI (p=0.014). Thus, we can consider the possibility of finding this less favorable histological characteristic in younger patients.

This study found a significant association between ALI and lymph node involvement (N). Patients without lymph node involvement had positive ALI in 26.4%. Patients with N1 lymph node involvement presented four times more chances of positive ALI (OR=4.01), and those with N2 had almost six times more chances (OR=5.95), when compared to N0 (p<0.00001). Moreira et al.[31] analyzed 144 patients, 66 females (52%) with mean age of 65 years and correlated the fraction of metastatic lymph nodes with staging, identifying prognostic factors. At the univariate analysis, age <60 years old, poor differentiated tumors, lymphovascular invasion and lymph node positivity were associated with worse prognosis. Kuhnen and Kock[9] analyzed 132 patients with initial diagnosis of colorectal carcinoma, with mean age of 58.69 years old. The most common neoplasm was among females (75 cases – 56.8%), well differentiated tumors (70 cases), and those classified as T3 (75%). The presence of metastasis in regional lymph nodes has been associated with tumor differentiation (p=0.00011) and to gender (p=0.001), and there was no relation with tumor size (p=0.11).

Like lymph node involvement (N), the tumor differentiation was also associated with ALI. The histological Broder's classification[27] consistent with undifferentiated or poor differentiated tumors had four times more risk of positive ALI (relative risk – RR=4.32; confidence interval – 95%CI 1.45–12.91; p=0.0039). The relevance of this finding is reinforced in an American study[19], which concluded that patients with CRC who had submucosal invasion, with at least one of the following factors – lymphatic invasion, mild or poor differentiated budding tumor – present high risk for lymph node metastasis.

Likewise, looking for this same association with level of tumor invasion (T classification), we did not find significant results. However, the importance of tumor invasion for the prognosis of CRC is clear, as demonstrated by Mehrkhani et al.[24], who evaluated and followed-up a total of 1090 patients (68% of men and 32% of women) with the objective to determine the prognostic factors that affect the survival of patients with CRC after surgical resection. Mean age was 50.5 years old, and mean survival was 42.8 months. In five years, the survival rate was 84% for stage I, 50% for stage II, 20% for stage III and 6.4% for stage IV. In a univariate analysis, only age (p=0.016), stage (p=0.001) and tumor differentiation (p=0.008) were significant.

As observed in the previous study, gender has no positive value on survival of patients with CRC. This is also noticed when we associate gender with ALI, since no significance was found.

The incidence of ALI was 44.6% and it was more frequent to find in patients with younger age, higher number of lymph node involvement (N) and poor tumor differentiation.

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