Colorectal cancer in patients under age 50: a five-year experience

Câncer colorretal em pacientes com idade inferior a 50 anos: experiência em cinco anos

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A B S T R A C T

Objective: to evaluate the clinical characteristics of patients with colorectal cancer under the age of 50 treated at a public hospital in Brasilia over 5 years. **Methods:** we conducted a longitudinal, retrospective study, with 184 patients undergoing surgical procedures at the Asa Norte Regional Hospital (HRAN), including those who underwent only biopsy, between January 2013 and January 2018. We divided the patients into two groups: under the age of 50 (n=39) and age equal to or greater than 50 years (n=145). We compared the groups as to age, sex, symptoms, time between symptom onset and diagnosis, family and personal history, tumor location, histopathological characteristics, applied surgical management, staging and mortality. **Results:** the group of patients under the age of 50 had more individuals with stage III and IV (p=0.041), more frequent poorly differentiated tumors (10.25% versus 3.52%; p=0.153), and higher incidences of compromised surgical margins (p=0.368), angiolymphatic (p=0.07) and perineural (p=0.007) invasion, which denotes more advanced disease in this group of patients. **Conclusions:** the study showed the low effectiveness of population screening methods for colorectal cancer currently used in this population, given the high incidence of the disease and late diagnosis in both groups.

Keywords: Colorectal Surgery. Neoplasm Staging. Intestinal Neoplasms. Young Adult.

INTRODUCTION

The estimated incidence of colorectal cancer (CRC) is 1.36 million new cases per year worldwide[1]. In Brazil, there were an estimated 36,360 new cases of colorectal cancer between 2018-2019, 17,380 in men and 18,980 in women. These values correspond to a risk of 16.83 new cases for every 100,000 men and 17.90 for every 100,000 women. It is the third most common cancer in men and the second among women[2].

It is well established in the literature that the incidence of CRC increases significantly after the 5th decade of life and continues to increase with advancing age[3,4]. Although the recommended average age for starting screening is traditionally 50 years, more than 1/10 of cases of CRC (11% of colon tumors and 18% of rectal tumors) occur in individuals under 50, and the incidence and mortality have increased in this group[3-8].

In the United States, the incidence of CRC per 100,000 inhabitants in patients under 50 years old ranges from 0.85 (20-24 years old) to 28.8 (45-49 years old). Statistics from the National Cancer Institute reveal that between 1987 and 2006 there was a significant increase in the incidence of CRC in all age groups (grouped into 5-year ranges) between 20 and 49 years. The most significant increase occurred in the group between 40 and 44 years of age, representing 10.7 per 100,000 inhabitants in 1988 and 17.9 per 100,000 inhabitants in 2006[3].

Among CRC patients of all ages, around 15 20% of patients have a family history of colorectal neoplasia[9]. CRC in young patients corresponds to a heterogeneous group of diseases. Genetic and hereditary syndromes are responsible for the minority of cases, the majority of patients in fact having sporadic disease. Genetic and environmental factors are involved in the development of CRC[9,10].

The data are inaccurate in Brazil, but studies have shown the same upward tendency in the incidence of colorectal cancer in young patients[10,11]. There are still

controversies about the characteristics and prognosis of these tumors in this population. The delay in diagnosis and the advanced disease stage were associated with the unfavorable evolution of CRC in young people[6,8,11-16].

Currently, there is no consensus on the screening of young people who do not have a family history of risk for CRC. However, there is an increase in the number of cases among patients under the screening age, especially in underdeveloped countries, while there is a decline in the number of cases in the elderly in developed countries[17].

Regarding the implementation of a population screening method for colorectal cancer, there is evidence of the high effectiveness of population screening in the early diagnosis and reduction of mortality from the disease. It is justified by its high incidence, long time of clinical progression, a recognized and treatable pre-malignant marker, and the high cost of surgical treatment in case of late diagnosis, in addition to the high mortality rates from this cancer[18-20].

In 2018, the American Cancer Society published new guidelines recommending the start of screening for CRC at 45 years of age for asymptomatic patients without specific risk factors[21].

The WHO recommends the systematic screening of people over 50 in those countries with conditions to guarantee all stages of care for patients with the disease. However, it recommends that early diagnosis strategy be implemented with all its components: wide dissemination of warning signs to the population and health professionals, immediate access to diagnostic procedures for suspected cases, which implies expanding the supply of digestive endoscopy services and other diagnostic supports, in addition to access to appropriate and timely treatment[22].

In Brazil, despite the high incidence of colorectal cancer, there is no program for screening asymptomatic patients in the Unified Health System (SUS). Currently, this type of public policy is restricted to breast and cervical cancer. The Ministry of Health (MS) does not currently consider the implementation of population-based screening programs for colorectal cancer feasible and cost-effective in Brazil, and recommends an individual approach for high-risk situations[22].

Thus, the objective of this study is to demonstrate the experience in a public hospital in Brasilia over 5 years, evaluating the epidemiological, histopathological and clinical characteristics of patients with colorectal cancer, comparing the groups of patients aged up to 50 years with those with age over 50 years.

METHODS

We carried out an observational, longitudinal and retrospective study, based on the analysis of medical records of patients diagnosed with colorectal neoplasia between January 2013 and January 2018 treated at the Asa Norte Regional Hospital (HRAN).

We collected data through rigorous review of medical records at the Center for Clinical Pathology. We analyzed all the results of the histopathological examinations processed in the period. In addition to the results corresponding to primary tumors (submitted to surgery or colonoscopy), we also analyzed data on lymph nodes and peritoneal, mesentery and liver lesions. We studied the medical records and included all patients with colorectal cancer who underwent biopsy during the period. The variables assessed were age, sex, symptomatology, time between onset of symptoms and diagnosis, family and personal history, tumor location, histopathological characteristics, surgical management, staging and mortality.

We included 184 patients with colorectal cancer treated at the hospital and who had the histopathological examination during the period, either harvested by surgery or colonoscopy. We excluded six selected patients, whose medical records were incomplete. We carried out outpatient follow-up until the end of 2019.

All surgeries took place in the same hospital, by a homogeneous team. Staging was performed in accordance with the American Joint Committee on Cancer (AJCC) TNM system.

The project of the present study was submitted to the Ethics in Research Committee of the Foundation for Teaching and Research in Health Sciences / FEPECS / SES / DF, which gave a favorable opinion to its realization.

Statistical analysis was done with the software GraphPadPrism 6 and IBM SPSS (Statistical Package for Social Science) version 21.0. The graphs were generated

in GraphPadPrism, and the descriptive analysis, in SPSS. To perform the hypothesis test, we used the software R: The R Project for Statistical Computing, with the aid of the R Commander package. For independent nominal samples, we used the Chi-square test, the Fisher's exact test and the Mann Whitney test in non-parametric and unpaired samples. Samples with multiple variables had the ANOVA analysis of variance as statistical test.

RESULTS

We included 184 patients in the study, of whom 39 (21.2%) were younger than 50 years old (Table 1).

Table 1. *Distribution of patients by age group.*

Age (years)	N	%
20-29	5	2.7%
30-39	12	6.5%
40-49	22	11.9%
50-55	38	20.6%
56-59	14	7.6%
≥ 60	93	50.5%
Total	184	100%

Regarding sex, we found that 43.6% of patients under the age of 50 were male and 56.4% female. Similar results were observed in patients aged 50 years and over, of which 52.4% of the patients were male and 47.6% were female (Table 2).

Table 2. *Relationship between sex and age of the patients evaluated*

Age (in years)	Female		Male		p-value
	N	%	N	%	
25-50	22	24.2	17	18.3	
> 50	69	75.8	76	81.7	0.32
Total	91	100.0	93	100.0	

The distribution was homogeneous between sexes in the different age groups, and in the statistical analysis used, we noted that the variables age group and sex had no degree of association or dependence (p=0.32).

Risk factors

We assessed the presence of the following comorbidities, such as Systemic Arterial Hypertension (SAH) and Diabetes Mellitus (DM), and risk factors described for CRC, such as diagnosis of intestinal polyposis, inflammatory bowel diseases (IBD), lifestyle habits, such as smoking and alcohol consumption, family history of colorectal cancer in first-degree relatives, personal history of cancer (including ovary, uterus, stomach, breast, lung), and obesity.

There were no cases of familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC) diagnosed in the studied population.

Among CRC patients in the group under 50 years of age, there was a greater association between the disease and obesity (p=0.042). In patients over 50 years of age, there was a greater association with SAH and DM (Table 3).

Table 3. *Age-related risk factors for CRC.*

Risk factor	Age < 50 years		Age ≥ 50 years		p -value
	N	%	N	%	
Intestinal polyposis	2	5.1	2	1.4	0.154
IBD	0	0.0	2	1.4	0.460
Obesity	5	12.8	6	4.1	0.042
Smoking	8	20.5	38	26.2	0.466
Alcohol consumption	3	7.7	13	9.0	0.802
SAH	4	10.3	43	29.7	0.013
DM	0	0.0	20	13.8	0.046
Cancer personal history	1	2.6	5	3.4	0.782
CRC family history	5	12.8	8	5.5	0.114

Symptomatology

All patients in the group under the age of 50 were symptomatic at the time of diagnosis. In the group of patients aged 50 years and over, only one patient was asymptomatic and had the diagnosis due to a colonoscopy finding.

In both groups, the most frequent symptom was abdominal pain, followed by weight loss. Abdominal pain was present in 55.2% of participants aged 50 years and over and in 71.8% of patients under 50 years of age. Weight loss was reported by 47.6% of participants aged 50 and 46.2% of participants aged 50 and over.

We performed statistical analysis to assess the association or dependence of the age group with the symptoms and verified that among the analyzed symptoms, only palpable abdominal mass ($p=0.013$), nausea and vomiting ($p=0.024$) and fever ($p=0.014$) were associated with the age group variable, that is, such symptoms were more frequent in patients under 50 years of age.

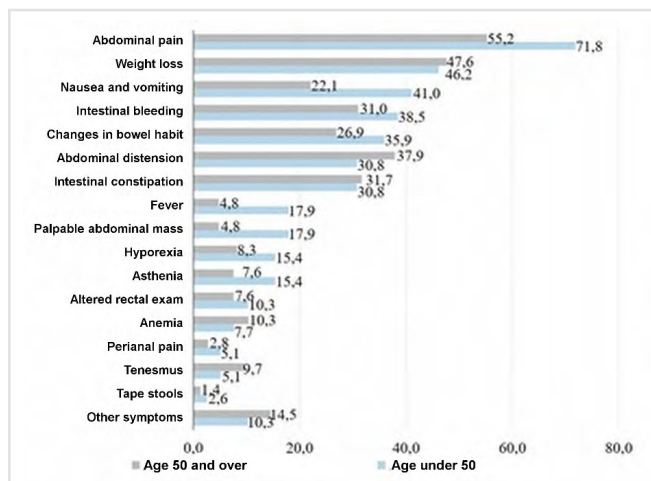Figure 1 shows the incidence of symptoms in both age groups.

Figure 1. *Frequency of symptoms (%) according to age group.*

The average time between symptoms onset and diagnosis was 4.2 months in the group of patients under 50 years, with a standard deviation of 4.6 months. In the group of older patients, the mean time to diagnosis was 4.6 months, with a standard deviation of 8.4 months. In this context, we observed no statistical significant relationship between the age group and the time from symptoms onset to diagnosis (p value > 0.05). The global mean time between symptom onset and diagnosis was 4.5 months, with a standard deviation of 7.9 months.

Tumor location

The location of the most frequent primary tumor was in the retosigmoid in both groups. Figure 2 shows the location of the primary tumor described in both groups. There was no statistical significance for this variable ($p> 0.05$).
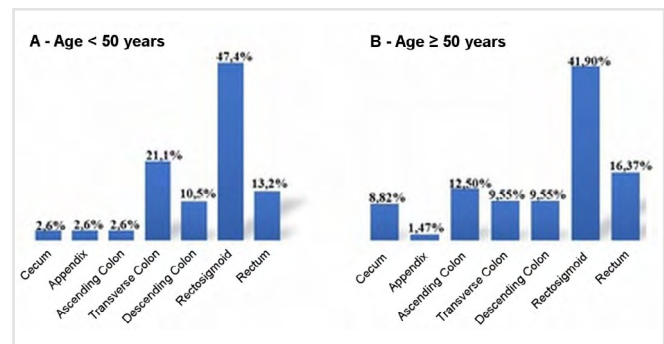

Figure 2. *Location of the primary tumor according to age group.*

Adopted surgical management

We further classified participants according to the applied surgical conduct. The most frequently adopted approach in both groups was rectosigmoidectomy.

In the group of patients under 50 years of age, we found that the number of left hemicolectomies (cancer surgery) was similar to the number of rectosigmoidectomies, both corresponding to 31% of cases. Figures 3 and 4 show the frequency of surgeries performed in each group.

Histopathological characteristics

The most frequent histological type in both groups was Adenocarcinoma ($n=181$). We classified patients according to the level of cell differentiation described in the histopathological examination.

In the group of patients under 50 years of age,

the presence of poorly differentiated tumors (10.25% versus 3.52%) was more frequent - Table 4.
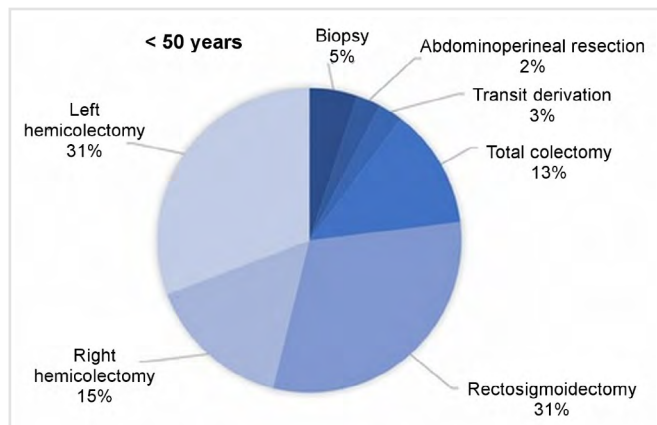

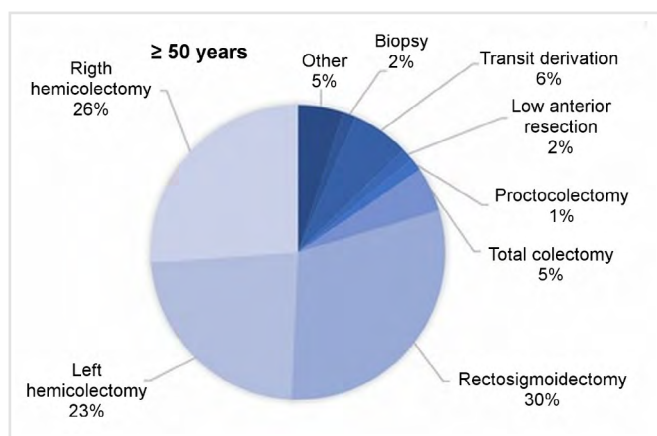**Figure 3.** *Distribution of surgical approaches adopted in the group under the age of 50.*

Figure 4. *Distribution of surgical approaches adopted in the group aged 50 years and over.*

Table 4. *Degree of tumor differentiation according to age group in patients diagnosed with adenocarcinoma.*

| Adenocarcinoma | Age | | | | p-value |
| | < 50 years | | ≥ 50 years | | |
	N	%	N	%	
Well differentiated	5	12.82	34	23.94	
Moderately differentiated	28	71.79	91	64.08	
Poorly differentiated	4	10.26	5	3.52	0.153612
Indeterminate	2	5.13	12	8.45	
Total	39	100	142	100	

We also evaluated the histopathological exams as to surgical margins, presence of angiolymphatic and perineural invasion, multiple tumors, and presence of microsatellite instability. Table 5 shows the distribution of the characteristics studied according to age groups.

There was a higher incidence of perineural invasion (p=0.007) by primary tumors in patients under 50 years of age (Table 5).

Table 5. *Characteristics of the histopathological exams according to age group.*

| Variables | Category | Age < 50 years | | Age ≥ 50 years | | p-value |
			%	N	%	
Surgical Margins	Compromised	3	8.82	6	4.8	
	Free	31	91.18	119	95.2	0.368
	Total	34	100.0	125	100.0	
Angiolymphatic Invasion	No	21	63.64	97	78.9	
	Yes	12	36.36	26	21.1	0.07
	Total	33	100.0	123	100.0	
Perineural Invasion	No	19	57.58	98	80.3	0.007
	Yes	14	42.42	24	19.7	
Multiple Tumors	No	23	95.83	60	90.9	
	Yes	1	4.17	6	9.09	0.441
	Total	24	100.0	66	100.0	
Microsatellite Instability	No	22	88.0	52	76.47	
	Yes	3	12.0	16	23.53	0.2215
	Total	25	100	68	100.0	

The study included the evaluation of the number of lymph nodes isolated in the surgical specimen. Previous studies have recommended the analysis of at least 12 lymph nodes in the surgical specimens for adequate assessment of tumor extension and postoperative follow-up with appropriate adjuvant therapy. This figure is not always achievable. The average number of isolated lymph nodes in all specimens was 11.96, with a standard deviation of 8.3.

In the group of patients under the age of 50, the average number of isolated lymph nodes was 15.35, and in the group of patients aged 50 years or more, 11.01 (Table 4). When analyzing Table 6, one can notice that in 61.29% of cases in the group under the age of 50 years, at least 12 lymph nodes were isolated.

Table 6. Relationship between age and number of isolated lymph nodes in the surgical specimen.

Number of isolated lymph nodes	Age < 50 years		Age ≥ 50 years		p-value
	N	%	N	%	
0 |-- 12	12	38.71	67	60.90	
12 |--	19	61.29	43	39.10	0.02784
Total	31	100.00	110	100.00	

Staging

Regarding clinical staging (CS), among patients under 50 years of age, there was a higher concentration of individuals with more clinically advanced disease, with 75% of cases (p=0.041) with stages III and IV in that group. As for patients over the age of 50, the most frequent stage was II, followed by IV, corresponding to 35.8% and 32.5% of the cases, respectively (Table 7).

Table 7. Clinical staging according to age group.

Clinical staging	Age				p-value
	< 50 years		≥ 50 years		
	N	%	N	%	
CS I	1	3.13	11	9.2	
CS II	7	21.88	43	35.8	
CS III	12	37.50	27	22.5	0.041
CS IV	12	37.50	39	32.5	
Total	32	100.00	120	100.0	

Relapse and Mortality

Regarding tumor recurrence, among patients under 50 years of age, 23.8% had distant recurrence, 14.3% local recurrence, and 61.9% had no report of recurrence. Among patients 50 years and over, 28% had distant recurrence, 6% local recurrence, and 66% did not display recurrence. There was no statistically significant difference between groups (p=0.5125).

The overall mortality in the population with colorectal cancer was 31.5%. When analyzing the association between mortality and age groups, we found that the mortality rate was similar between the two groups, with no statistical association between mortality and age (p=0.29).

DISCUSSION

Colorectal cancer is the most common cancer of the gastrointestinal tract and the third leading cause of cancer-related mortality in the world[1]. This disease is usually diagnosed between the 5th and 6th decades of life[22], which is in line with the results found in this study.

Practically all cases of sporadic colorectal cancer have adenomas as precursor lesions, which are often asymptomatic and can be diagnosed by screening tests. Approximately 25% of men and 15% of women who are screened at age 50 or older have at least one or more adenomatous polyps. The described rate of transformation of these adenomatous polyps into carcinoma is about 0.25% per year, varying according to the polyps' size and histological characteristics. This risk is eliminated with the complete removal of the polyps. For this reason, colonoscopy remains the most important screening modality, a longer interval between exams being possible. For patients at medium risk, without abnormal findings, it is safe to repeat the exam in 10 years[22,23].

Among the patients included in this study, 20.6% are in the 50-55 age group and would probably have benefited if they had undergone screening tests for CRC at 45 and had precursor injuries eliminated.

Several studies have described the increase in colorectal cancer in young people in recent decades, which has been attributed to inadequate screening, increased risk factors related to obesity and diet[2,9,24].

In the present study, there was a statistical association between obesity and the development of colorectal cancer in patients under 50 years of age, which suggests the contribution of changes in lifestyle in increasing the incidence of colorectal cancer in young people.

In the literature, most publications on colorectal cancer in young people refer to patients under 40 years of age. In a comprehensive review on the increase in the incidence of colorectal cancer in young patients, O'Connel et al. (2017) described that between 10.9% and 15% of CRC cases are diagnosed in this age group.

In the present study, the proportion of patients under the age of 40 was 9.2%[9].

Regarding sex, the literature describes a higher risk of developing colorectal cancer in male patients of any age compared with female ones. In this series, there was no statistical difference between sexes.

The comparative analysis regarding the time between symptoms onset and diagnosis did not show any difference between the two groups, a finding also observed by other authors[7,10,25,26].

Regarding symptomatology, the literature presents divergences. In a similar study, Carneiro Neto et al. (2006) described CRC symptoms in patients under 40 years of age. In their series, changes in bowel habits and weight loss were the most common symptoms found, both being present in about 75% of cases, followed by abdominal pain in 62.5% of cases, and hematochezia and anemia in 37.5% of the cases[25]. In the present study, the most frequent symptom in both groups was abdominal pain, followed by weight loss. As to age group, patients under 50 years more frequently displayed a palpable abdominal mass (p=0.013), nausea and/or vomiting (p=0.024) and fever (p=0.014) compared with patients 50 years and older.

Regarding the location of the tumors, the results of the study were consistent with the literature, following the pattern of sporadic CRCs, with a predominance of distal tumors[26].

The prognostic value related to the location of colorectal tumors is uncertain. While many authors propose that the location in the rectum renders higher mortality from the disease[27,28], others have failed to demonstrate any difference attributable to tumor location[26,29,30].

The literature amply describes the worst prognosis for young patients compared with older patients. There is disagreement, however, regarding age-related disease characteristics in CRC. The worst prognosis in young patients is usually attributed to the diagnosis of the disease in more advanced stages. In this regard, most studies have shown that young patients most often have the disease diagnosed in stages III or IV. Other authors, in turn, attribute it to the higher prevalence of mucinous tumors or to a lesser degree of cell differentiation[26,31,32].

The results found in the studied population are in agreement with the literature, since in the group of patients under the age of 50 there was a greater concentration of individuals with stage III and IV (p=0.041), revealing the existence of relationships between age and staging for the patients analyzed.

Regarding the degree of tumor differentiation, the results are also in accordance with those described in the literature, as in the group of patients under the age of 50 years the presence of poorly differentiated tumors was more frequent (10.25% versus 3.52%), although there was no statistical significant relationship (p=0.153).

The present study also described higher incidences of compromised margins (p=0.368), angiolymphatic (p=0.07) and perineural (p=0.007) invasion in younger patients, which denotes more advanced disease in this group. In a similar study, Ganapathi et al. (2011) described a higher frequency of poorly differentiated tumors (43% vs. 16%, p < 0.001), T4 (47% vs. 30%, p=0.005) and with vascular invasion (38% vs. 29%, p=0.13) in patients under 40 years of age. T4 status and vascular invasion were independent prognostic factors for overall survival, and T4 status, an independent factor for disease-free survival[33,34].

The analysis of the number of lymph nodes isolated in the surgical specimen is essential for CRC staging, as it assists in the assessment of the disease extent and in the choice of adjuvant therapy, contributing proportionally to the increase in patients' overall survival. The current literature recommends a minimum analysis of 12 lymph nodes. However, this value is not always achieved, especially in emergency procedures[34].

In the studied population, the average number of isolated lymph nodes in all specimens was 11.96, with a standard deviation of 8.3, that is, close to the ideal. In the group of patients under the age of 50, the average number of isolated lymph nodes was 15.35, a value significantly higher (p=0.027) than that of patients aged 50 years and older.

In a retrospective study, Cisz et al. (2011) described the correlation of age below 50 years as an independent variable with the number of lymph nodes found by the pathologist. This finding can be explained by the greater volume of tumors in such patients, a

more advanced disease, and histopathological indicators showing a greater aggressiveness, which may have contributed to the broader surgical resection on the part of the surgeon, and as a consequence, a greater number of identified lymph nodes[34].

Although patients in the group under 50 years of age had more advanced staging, the overall mortality rate was similar between the two groups. There was also no significant difference regarding recurrence. In a similar study, Schellerer et al. (2012) compared the clinical and histopathological characteristics of 244 patients aged 50 years or less with 1,718 patients aged over 50. They described that, although young patients have more aggressive histological subtypes and more advanced staging, cancer-related survival rates was similar[33,35]. In this regard, we should note that there were limitations of the study as to the length of patients' follow-up, requiring further research in this regard. It was also not possible to analyze specific mortality.

CONCLUSION

The majority of patients with colorectal cancer under the age of 50 years included in this study did not have a disease related to genetic and hereditary syndromes associated with CRC, were symptomatic, and received late diagnosis, mostly with clinical staging III and IV. We also found higher incidences of poorly differentiated tumors with compromised margins, angiolymphatic and perineural invasion in this population, which denotes more advanced disease. Survival was similar in both age groups, although results are limited for survival analysis. More in-depth studies and longer follow-up are needed for this purpose. The study showed the low effectiveness of population screening methods for CRC currently used in this population, judging by the high incidence of the disease both in patients under 50 years old and in patients aged 50 years and over.

R E S U M O

Objetivo: *avaliar o perfil clínico de pacientes portadores de câncer colorretal com idade inferior a 50 anos atendidos em um hospital público de Brasília ao longo de 5 anos.* **Métodos:** *estudo longitudinal e retrospectivo. Foram incluídos 184 pacientes submetidos a procedimento cirúrgico no Hospital Regional da Asa Norte (HRAN), incluindo aqueles que realizaram apenas biópsia, entre janeiro de 2013 e janeiro de 2018. Os pacientes foram divididos em dois grupos: com idade inferior a 50 anos (n=39) e idade igual ou superior a 50 anos (n=145). Os grupos foram comparados em relação às seguintes variáveis: idade, gênero, sintomatologia, tempo entre início dos sintomas e diagnóstico, antecedentes familiares e pessoais, localização do tumor, características anatomopatológicas, conduta cirúrgica estabelecida, estadiamento e mortalidade.* **Resultados:** *no grupo dos pacientes com idade inferior a 50 anos houve maior concentração de indivíduos com estadiamento III e IV (p=0,041), foi mais frequente a presença de tumores pouco diferenciados (10,25% contra 3,52%; p=0,153), foram descritas maiores incidências de margens cirúrgicas comprometidas (p=0,368), invasão angiolinfática (p=0,07) e perineural (p=0,007), o que denota doença mais avançada nesse grupo de pacientes.* **Conclusões:** *o estudo evidenciou a baixa efetividade dos métodos de rastreamento populacional para câncer colorretal atualmente empregados nesta população, visto a elevada incidência da doença e ao diagnóstico tardio em ambos os grupos.*

Palavras chave: *Cirurgia Colorretal. Estadiamento de Neoplasias. Neoplasias Intestinais. Adulto Jovem.*

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