Clinicopathological profile of patients diagnosed with coloretal neoplasia from 27 municipalities of Paraná Southwest (2016-2020)

Perfil clinicopatológico de pacientes diagnosticados com neoplasia colorretal de 27 municípios do Sudoeste do Paraná (2016-2020)

Bruna Zibetti, Eduardo Henrique Porfirio Michalak, Francisco Weis, Daniel Rech, Janoário Athanázio de Souza and Carolina Panis*

Programa de Residência Médica em Cirurgia, Universidade Estadual do Oeste do Paraná, Campus de Francisco Beltrão, Paraná, Brasil.

Endereço para correspondência:
Carolina Panis
Universidade Estadual do Oeste do Paraná
Laboratório de Biologia de Tumores
Rodovia Vitório Traiano km 2 - Francisco Beltrão-PR. CEP: 85601-010

E-mail: carolpanis@hotmail.com

Abstract

Colorectal cancer (CRC) represents the neoplasm that affects the segments of the large intestine, with increasing incidence and intense regional variability. In this study, we sought to evaluate the epidemiological and clinical-pathological profile of patients diagnosed with colorectal neoplasia in 27 municipalities attended at the 8th Health Regional of Paraná, according to parameters such as age, size of the primary tumor, lymph node involvement, presence of metastatic disease, tumor staging, among others. To this end, 231 medical records of patients treated at the Francisco Beltrão Cancer Hospital were reviewed, and CRC cases were profiled with subsequent statistical analysis of data. A total of 226 patients were diagnosed with adenocarcinoma. Regarding the tumor's location, it was found that, among individuals with adenocarcinoma, there was a higher frequency in the rectosigmoid region (65.04%). Regarding the staging of patients with adenocarcinoma, most were in stage IIA (T3, N0, M0) (27.43%), and the second-highest percentage was in patients with stage IV (any T or N, M1; 19.03%). A high frequency of adenocarcinoma was observed in patients over 50 years of age, with overweight/obese. Most of these patients did not show evidence of multiple familial polyposes and, in general, they were smokers, alcoholics, and underwent chemotherapy. Despite the regional epidemiologic characteristics concerning pesticides exposure and a high CRC incidence registered in such populations, the disease profile found here is similar to other regions globally, suggesting that other risk factors might be enrolled.
Keywords: Colorectal cancer; epidemiology; clinicopathological data; adenocarcinoma; neoplasm.

Resumo

O câncer colorretal (CCR) representa a neoplasia que acomete os segmentos do intestino grosso, com incidência crescente e intensa variabilidade regional. Neste estudo, buscou-se avaliar o perfil epidemiológico e clínico-patológico dos pacientes diagnosticados com neoplasia colorretal em 27 municípios atendidos na 8ª Regional de Saúde do Paraná, segundo parâmetros como idade, tamanho do tumor primário, acometimento linfonodal, presença de doença metastática, estadiamento do tumor, entre

outros. Para tanto, foram revisados 231 prontuários de pacientes atendidos no Hospital do Câncer Francisco Beltrão e traçados os perfis dos casos de CCR com posterior análise estatística dos dados. Um total de 226 pacientes foram diagnosticados com adenocarcinoma. Em relação à localização do tumor, verificou-se que, entre os indivíduos com adenocarcinoma, houve maior frequência na região retossigmoide (65,04%). Em relação ao estadiamento dos pacientes com adenocarcinoma, a maioria estava no estágio IIA (T3, N0, M0) (27,43%), e o segundo maior percentual estava nos pacientes com estágio IV (qualquer T ou N, M1; 19,03%). Observou-se alta frequência de adenocarcinoma em pacientes acima de 50 anos, com sobrepeso/obesidade. A maioria desses pacientes não apresentava evidências de poliposes familiares múltiplas e, em geral, eram tabagistas, etilistas e faziam quimioterapia. Apesar das características epidemiológicas regionais relativas à exposição a pesticidas e uma alta incidência de CCR registrada nessas populações, o perfil da doença aqui encontrado é semelhante a outras regiões do mundo, sugerindo que outros fatores de risco possam estar envolvidos.

INTRODUCTION

Colorectal cancer (CRC) is a neoplasm that affects the segments of the large intestine (colon, rectum, and anus). It has relevance in global public health since approximately one million new cases and approximately half a million deaths are diagnosed annually due to the disease[1].

According to the National Cancer Institute (INCA), in Brazil, it is estimated that in 2020 around 41,010 new cases of colorectal cancer were diagnosed[2].
Although it is a global condition, there are variations in the incidence of this pathology in terms of geographic distribution in certain areas. About 70% of reported cases of CRC in Brazil occur in the Southeast region and 14.87% in the South region (de Andrade et al., 2019). Together, the Southeast, South, and Midwest regions have the highest rates of the disease[3].

The incidence of CRC varies widely in different regions of the globe. Worldwide, it is the third most diagnosed cancer in men and the second in women, according to WHO data. In Brazil, according to INCA, it is estimated that each year of the triennium 2020-2022, 20,540 cases of colorectal cancer will be diagnosed in men and 20,470 in women. Despite this, the variability of incidence is very high in the country. Since, disregarding non-melanoma skin tumors, CRC cases in men are the second most frequent in the Southeast (28.62/100 thousand) and Midwest (15.40/100 thousand) regions. In the South Region (25.11/100 thousand), it is the third most frequent tumor. While in the Northeast (8.91/100 thousand) and North (5.43/100 thousand) regions, it occupies the fourth position. It is the second most frequent for women in the Southeast (26.18/100 thousand) and South (23.65/100 thousand) regions. In the Midwest (15.24/100 thousand), Northeast (10.79/100 thousand), and North (6.48/100 thousand), it is the third most incident[2].

Differences in incidence between regions suggest not only the occurrence of factors associated with biological or genetic characteristics but also environmental factors and external influences that define people's lifestyles, such as a diet based on animal fats; low intake of fruits, vegetables, and whole grains; alcoholism and smoking; obesity and sedentary lifestyle[4], in addition to specific characteristics inherent to each region.

In this context, the Southwest of Paraná is an area of high incidence for this neoplasm, where 4.3 times more cases are observed than the state and the national average (68.91 new cases/100,000 inhabitants in Southwest Paraná, 16 .08 new cases/100 thousand inhabitants in Brazil and 19.22 new cases/100 thousand inhabitants in Paraná)[5]. This region is predominantly caucasian and is characterized by extensive pesticide exposure, in addition to the high incidence of several other cancers and the occurrence of cultural habits every day in the country's southern

region, such as the consumption of *chimarrão* and smoked red meat[5].

Thus, to search for variables that could explain the high regional incidence. In this context, this study aims to analyze the CRC profile in the population living in the Southwest of Paraná through the characterization of its clinicopathological profile to identify possible parameters associated with its high regional incidence.

METHODOLOGY

The Institutional Ethics Committee approved this retrospective and descriptive study under number CAAE 97411018.6.0000.0107. A total of 231 medical records of patients treated at the Francisco Beltrão Cancer Hospital, Paraná, diagnosed with CRC from January 2016 to December 2020, were consulted. All cases were originated from the municipalities attended at the 8th Health Regional of Paraná.

The study included qualitative variables linked to patient characteristics: age, city of origin, body mass index (BMI), systemic arterial hypertension (SAH), diabetes mellitus (DM), smoking, alcohol consumption, and psychiatric disorder. In addition to tumor-related variables: tumor type, tumor location, surgery performed, TNM classification – primary tumor (T), regional lymph nodes (N), metastasis (M); staging, multiple familial polyposis, chemotherapy, and radiotherapy. The type of tumor was subdivided according to severity into adenocarcinoma and others, including mucinous neoplasia, squamous cell carcinoma, and neuroendocrine neoplasia. Qualitative variables were evaluated according to the type of tumor, thus establishing a profile of patients. Graphical representations were made to complement the profile analysis and logistic regression and visually show how the frequencies of the variables are distributed concerning the types of tumor. Data obtained from 231 patients were tabulated and coded in Microsoft Excel ® spreadsheets. Statistical analyzes were performed in the licensed program XLSTat Version 2017[6]

RESULTS

Among the 231 patients analyzed, 226 (97.83%) had adenocarcinoma, and only 5 (2.17%) were categorized as other types of neoplasms (mucinous neoplasm, squamous cell carcinoma, neuroendocrine neoplasm).

Regarding the tumor's location, it was found that, among individuals with adenocarcinoma, there was a higher frequency in the rectosigmoid region (65.04%; Table 1). Considering the staging in the TNM classification, the primary tumor in patients with more aggressive tumors was more frequent at T3 (53.98%; Table 1), a stage in which the tumor invades beyond the muscularis propria but without subserosa or deperitonized pericolic or perirectal tissues. As for lymph node involvement, there was a higher prevalence of cases with no lymph node involvement (N0). There is a frequency of 80.53% of patients with metastases concerning metastases. About the staging of patients with adenocarcinoma, most were in stage IIA (T3, N0, M0) (27.43%; Table 1); however, the second-highest percentage was in patients with stage IV (any T or N, M1) (19.03%; Table 1).

Even though there was no statistical association with the type of tumor, there was a tendency towards a higher frequency of adenocarcinoma in patients over 50 years of age, overweight/obese, with N0 regional lymph nodes, and positive for metastasis (Tables 1 and 2). Most of these patients did not show evidence of multiple familial polyposis, hypertension,

diabetes, or psychiatric disorder. In general, they were smokers, alcoholics and underwent chemotherapy. Also, most did not undergo radiotherapy (97.35%).

Regarding the municipalities in the southwest of Paraná, the number of individuals with adenocarcinoma from Francisco Beltrão stands out (Figure 1).

Table 1. Age at diagnosis, tumor site, and parameters from TNM staging (primary tumor size, lymphnodal invasion and distant metastasis) according to the type of tumor from CRC patients included in the study.

Variable	Type of tumor	Category	n	5 %
Age (years)	Adenocarcinoma	≤ 50	28	1.,39
		> 50	198	87.61
	Others	≤ 50	1	20.00
		> 50	4	80.00
Tumor site	Adenocarcinoma	Ascending colon	42	18.58
		Transversal colon	18	7.96
		Descendent colon	12	5.31
		Retosigmoid	147	65.04
		Anus	0	0.00
		Vermiform appendix	2	0.88
		Others	5	2.21
	Others	Ascending colon	1	20.00
		Transversal colon	0	0.00
		Descendent colon	0	0.00
		Retosigmoid	2	40.00
		Anus	1	20.00
		Vermiform appendix	0	0.00
		Others	1	20.00
Primary tumor size (T)	Adenocarcinoma	T0	30	13.27
		T1	15	6.64
		T2	29	12.83
		T3	122	53.98
		T4	30	13.27
	Others	T0	3	60.00
		T1	0	0.00
		T2	0	0.00
		T3	0	0.00
		T4	2	40.00
Lymphnodal invasion (N)	Adenocarcinoma	N0	151	66.81
		N1	35	15.49
		N2	40	17.70
	Others	N0	4	80.00
		N1	0	0.00
		N2	1	20.00
Distant metastasis (M)	Adenocarcinoma	Yes	182	80.53
		No	44	19.47
	Others	Yes	4	80.00

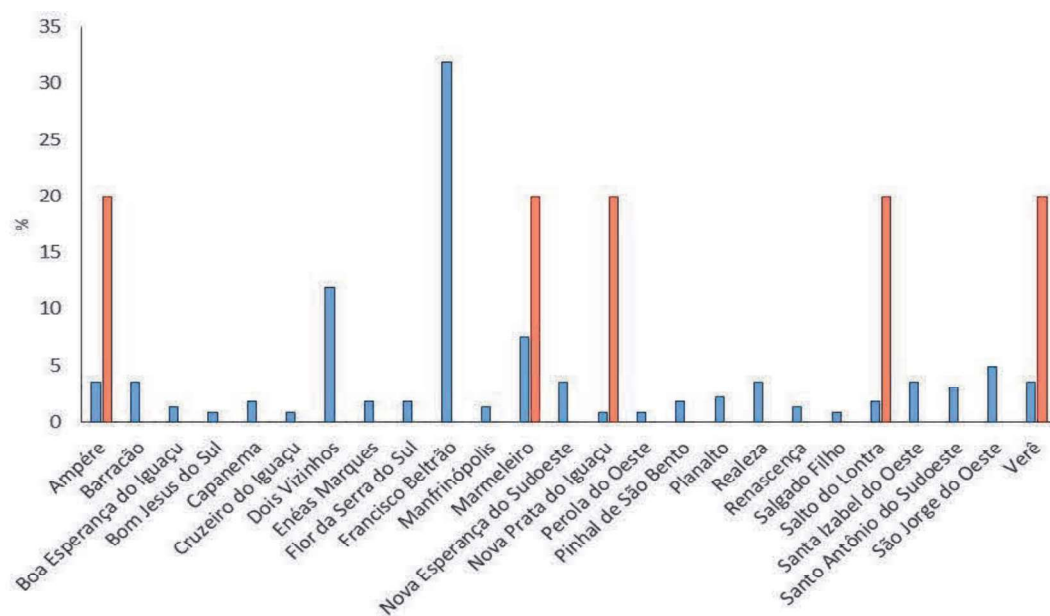|			No	1	20.00
TNM staging		Adenocarcinoma	0	16	7.08
			I	35	15.49
			IIA	62	27.43
			IIB	11	4.87
			IIIA	3	1.33
			IIIB	29	12.83
			IIIC	27	11.95
			IV	43	19.03
		Others	0	3	60.00
			I	0	0.00
			IIA	0	0.00
			IIB	1	20.00
			IIIA	0	0.00
			IIIB	0	0.00
			IIIC	0	0.00
			IV	1	20.00

Figure 1. Distribution of CRC cases among the studied municipalities. Orange bars represent adenocarcinomas, and the blue ones refer to other tumor histology types.

Table 2. Body mass index (BMI), familial history and patients' comorbidities according to the type of tumor from CRC patients included in the study.

Variable	Type of tumor	Category	n	%
BMI (kg/m²)	Adenocarcinoma	Eutrophic	88	38.94
		Overweight/obese	138	61.06
	Others	Eutrophic	1	20.00
		Overweight/obese	4	80.00
Familial polyposis	Adenocarcinoma	No	225	99.56
		Yes	1	0.44
	Others	No	5	100.00
		Yes	0	0.00
Systemic hypertension	Adenocarcinoma	No	173	76.55
		Yes	53	23.45
	Others	No	4	80.00
		Yes	1	20.00
Diabetes	Adenocarcinoma	No	210	92.92
		Yes	16	7.08
	Others	No	5	100.00
		Yes	0	0.00
Psychiatric symptoms	Adenocarcinoma	No	214	94.69
		Yes	12	5.31
	Others	No	4	80.00
		Yes	1	20.00
Smoking	Adenocarcinoma	No	75	33.19
		Yes	151	66.81
	Others	No	2	40.00
		Yes	3	60.00
Alcoholism	Adenocarcinoma	No	13	5.75
		Yes	213	94.25
	Others	No	1	20.00
		Yes	4	80.00
Chemotherapy	Adenocarcinoma	No	66	29.20
		Yes	160	70.80
	Others	No	3	60.00
		Yes	2	40.00
Radiotherapy	Adenocarcinoma	No	220	97.35
		Yes	6	2,65
	Others	No	4	80.00
		Yes	1	20.00

DISCUSSION

Despite the high CRC incidence reported in Paraná Southwest[5], in this study, we observed that the clinical-epidemiological profile of patients corroborates the data seen in the world population[7].

Age is one of the main risk factors for CRC2, and 87.6% of our study population was older than 50 years at diagnosis. There is a worldwide trend of progressive decrease in the age of diagnosis for CRC, and in the next decade, it is estimated that 1 in 10 colon cancers and 1 in 4 rectal cancers will be diagnosed in people younger than 50 years[8]. Among the possible causes for this trend, several hypotheses are suggested, including obesity increase, large-scale use of antibiotic therapy, and westernization of the diet with consequent changes in the intestinal microbiome[9].

In the line of excessive body weight in CRC, our data show that overweight/obese patients represent 61.06% of those affected by colorectal cancer of the adenocarcinoma type and 80% of those diagnosed with other histological subtypes CRC. A meta-analysis of 13 studies reported that weight gain between early adulthood and middle age was associated with a 23% increase in the risk of developing CRC, reinforcing these findings. The risk is lower in middle-aged and elderly patients, 13%, but still significant[10].

Considering the risk habits for CRC, it was observed that most of the patients were smokers at diagnosis. These data are in line with the results of a meta-analysis that evaluated 106 observational studies pointing out a positive correlation between smoking and the incidence of CRC, with an increase of 18% compared to the non-smoking population[11]. Further, we observed that 94.25% of our patients used to ingest alcoholic beverages. Patients who used to drink 2 to 3 alcohol doses per day are reported as a risk of 1.21 (95% CI 1.13-1.28) of CRC, while the risk for heavy drinkers was1.52 (95% CI 1.27-1.81) (12). Regarding comorbidities, people with diabetes were the majority among patients with CRC in this study. Patients diagnosed with type 2 diabetes have an increased risk for CRC of 42% in the male population[13, 14].

About the anatomopathological variations, it was observed that, of the 231 samples from the analyzed patients, 226 (97.83%) presented the histological subtype classified as adenocarcinoma. These data align with the findings presented in the literature since most adenocarcinomas develop from malignancy resulting from a dysplastic process with temporal evolution from adenomatous polyps with initially benign characteristics[7]. Furthermore, it was observed that the most frequent histological pattern was composed of adenocarcinoma, either tubular or with papillary areas, well-differentiated or moderately differentiated, and also that most colon and rectal adenocarcinomas have a well-defined margin of invasion, of the type expansive.

As to the location of the primary tumor, 60% of the patients had the left colon as the primary site. Among these, 40% were of the rectosigmoid portion[15]. In addition to the differences related to the surgical technique, the tumor location possibly represents a prognostic influence in colorectal tumors[16]. A meta-analysis of 66 studies, including 1,427,846 patients with different stages of the disease, conducted by Petrelli, demonstrated that the location of the primary tumor in the left colon (upstream of the splenic flexure) would be associated with a reduced risk of death (RR 0.82, 95% CI 0.79 − 0.84), which was not influenced by stage, adjuvant chemotherapy or other related factors[17]. Some studies attribute this prognostic difference to the fact that right-sided tumors present a more significant number of mutations in genes such as BRAF or KRAS, which is known to be related to greater tumor aggressiveness, which occurs less commonly in left tumors[16]. Regarding the primary tumor, it was observed that most cases (53.98%) had the invasion of the muscular layer propria towards the

pericolorectal tissues, being classified as category T3. It is known that the local extension presents correction with the prognosis of the disease and with the possibility of surgical resection[18].

Considering the aspects of the clinical-epidemiological profile of patients diagnosed with CRC described in the world literature, the Southwest region of Paraná presented a similar clinicopathological profile, despite the notoriously higher documented[5] incidence rates than the rest of the country. The contributing factors in the studied population were smoking and alcohol consumption, but other risk factors not investigated here may have a substantial influence to explain its high incidence in this population, like red meat consumption, pesticide exposure, and genetic inheritance. It reinforces the need for further epidemiological and molecular studies in this region.

REFERENCES

1.Cruz, G. M. G. D, Santana, J. L, Santana, S. K. A. D. A, Constantino, J. R. M, Chamone, B. C, Ferreira, R. M. R. S, Faria, M. N. Z. D. Epidemiology, diagnosis, staging and graduation of colon cancer in 490 patients. Revista Brasileira de Coloproctologia, 27(2), 139-153, 2007.

2.INCA. Disponivel em https://www.inca.gov.br. Acesso em 21/11/2021.

3.Oliveira, M. M. D, Latorre, M. D. R. D. D. O, Tanaka, L. F, Rossi, B. M, & Curado, M. P. Disparidades na mortalidade de câncer colorretal nos estados brasileiros. Revista Brasileira de Epidemiologia, 21, 2018.

4.Lima WCS, Lima, TS. Câncer colorretal: um estudo dos fatores de risco. Anais do I Congresso norte e nordeste da sociedade brasileira de cirurgia oncológica. Blucher medical proceedings.1(3):22, 2014.

5.Panis, C, Alves, V. D, de Borba Cecílio, A. P, Ghedin, C. C, Della Justina, E. Y, Jumes, J. J, de Souza, J. A. O. Localizações primárias de câncer mais incidentes na 8ª Regional de Saúde do Paraná e potenciais fatores de risco regionais. Biosaúde, 18(2): 54-63, 2016.

6.Addinsoft. Software xlstat versão anual 2017.19.02. Licença id 43894 (node-lock).

7.Kovacheva, V. N, Snead, D, Rajpoot, N. M. A model of the spatial tumour heterogeneity in colorectal adenocarcinoma tissue. BMC bioinformatics, 17(1): 1-16, 2016.

8.Collaborative, R. E. A. C. C. T, Zaborowski, A. M, Abdile, A, Adamina, M, Aigner, F, d'Allens, L., Otero, J. Characteristics of early-onset vs late-onset colorectal cancer: a review. JAMA surgery, 156(9): 865-874, 2021.

9.Kuipers, E. J, Rösch, T, & Bretthauer, M. Colorectal cancer screening—optimizing current strategies and new directions. Nature reviews Clinical oncology, 10(3): 130-142, 2013.

10.Karahalios, A, English, D. R, Simpson, J. A. Weight change and risk of colorectal cancer: a systematic review and meta-analysis. American journal of epidemiology, 181(11): 832-845, 2015.

11.Botteri, E, Iodice, S, Bagnardi, V, Raimondi, S, Lowenfels, A. B, & Maisonneuve, P. Smoking and colorectal cancer: a meta-analysis. Jama, 300(23): 2765-2778, 2008.

12.Fedirko, V, Tramacere, I, Bagnardi, V, Rota, M, Scotti, L, Islami, F, Jenab, M Alcohol drinking and colorectal cancer risk: an overall and dose–response meta-analysis of published studies. Annals of oncology, 22(9): 1958-1972, 2011.

13.Hull, M. A, Rees, C. J, Sharp, L, & Koo, S. A risk-stratified approach to colorectal cancer prevention and diagnosis. Nature Reviews Gastroenterology & Hepatology, 17(12): 773-780, 2020.

14.Xi, Y, & Xu, P Global colorectal cancer burden in 2020 and projections to 2040. Translational Oncology, 14(10): 101174, 2021.

15.Ma, Y, Yang, W, Song, M, Smith-Warner, S. A, Yang, J, Li, Y, Zhang, X. Type 2 diabetes and risk of colorectal cancer in two large US prospective cohorts. British journal of cancer, 119(11): 1436-1442, 2018.

16.Loree, J. M, Pereira, A. A, Lam, M, Willauer, A. N, Raghav, K, Dasari, A, Kopetz, S. Classifying Colorectal Cancer by Tumor Location Rather than Sidedness Highlights a Continuum in Mutation Profiles and Consensus Molecular SubtypesmCRC Profile by Location. Clinical Cancer Research, 24(5): 1062-1072, 2018.

17.Petrelli, F, Tomasello, G, Borgonovo, K, Ghidini, M., Turati, L, Dallera, P, Barni, S. Prognostic survival associated with left-sided vs right-sided colon cancer: a systematic review and meta-analysis. JAMA oncology, 3(2): 211-219, 2017.

18.Shepherd, N. A, Baxter, K. J, & Love, S. B. The prognostic importance of peritoneal involvement in colonic cancer: a prospective evaluation. Gastroenterology, 112(4): 1096-1102, 1997.