

## Clinical and epidemiological evaluation of patients with colorectal cancer from Rio Grande do Sul

Michelle Fraga Eisenhardt<sup>1</sup>, Fabrine Huwe<sup>1</sup>, Marcelo Luis Dotto<sup>2</sup>, Cátia Severo<sup>3</sup>, Juliana Jornada Fontella<sup>3</sup>, Andreia Rosane De Moura Valim<sup>4</sup>, Helen Tais Da Rosa<sup>5</sup>, Cézane Priscila Reuter<sup>6</sup>, Lia Gonçalves Possuelo<sup>4</sup>

<sup>1</sup>Academician, School of Pharmacy, Universidade de Santa Cruz do Sul (UNISC) – Santa Cruz do Sul (RS), Brazil.

<sup>2</sup>Oncologist, Centro de Oncologia Integrado, Hospital Ana Nery – Santa Cruz do Sul (RS), Brazil. <sup>3</sup>Nurse, Centro de Oncologia Integrado, Hospital Ana Nery – Santa Cruz do Sul (RS), Brazil. <sup>4</sup>Post-Graduation Program of Health Promotion, Universidade de Santa Cruz do Sul (UNISC) – Santa Cruz do Sul (RS), Brazil. <sup>5</sup>Academician, Course of Biological Sciences, UNISC – Santa Cruz do Sul (RS), Brazil. <sup>6</sup>Pharmacist, attending postgraduate program (master's degree) in Health Promotion, UNISC – Santa Cruz do Sul (RS), Brazil.

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**ABSTRACT:** Colorectal cancer has a high incidence in Brazil, with the South and Southeast regions presenting the largest number of cases. **Objective:** Identify the epidemiological characteristics and the regimens used as first-line treatment of patients with colorectal cancer treated at a cancer center in Santa Cruz do Sul (RS, Brazil) from 2006 to 2011. **Methods:** The records of 130 patients were retrospectively evaluated. Clinical and epidemiological characteristics, such as age, gender, ethnic group, stage of disease, primary site of disease and first-line treatment, were evaluated. The association of significance was evaluated using the chi-square and Fischer exact tests. The confidence interval used was 95% ( $p < 0.05$ ). **Results:** The mean age of patients with colorectal cancer in this study was 60.8 years, with higher incidence of the disease in men. At diagnosis, 40% of the patients had advanced disease stage IV. The regimen of 5-fluorouracil/folic acid (68.5%) was used as first-line treatment. **Conclusion:** This study showed high prevalence of colorectal cancer in patients of advanced age with the diagnosis made in the later stage of the disease. This fact demonstrates the importance of prevention campaigns that encourage periodic examinations in patients over 50 years of age.

**Keywords:** colorectal neoplasms; incidence; drug toxicity; 5-fluorouracil/folic acid.

**RESUMO:** No Brasil, o câncer colorretal apresenta uma elevada incidência, sendo as Regiões Sul e Sudeste as com maior número de casos. **Objetivo:** Identificar as características epidemiológicas e os esquemas terapêuticos utilizados como primo-tratamento dos pacientes portadores de câncer colorretal atendidos em um centro especializado em oncologia em Santa Cruz do Sul (RS) no período de 2006 a 2011. **Método:** Foram avaliados retrospectivamente 130 prontuários de pacientes portadores de câncer colorretal. Características clínicas e epidemiológicas como idade, sexo, cor da pele, estágio da doença, sítio primário da doença e primo-tratamento foram avaliadas. A associação de significância foi avaliada pelos testes do qui-quadrado e exato de Fischer. O intervalo de confiança utilizado foi de 95% ( $p < 0,05$ ). **Resultados:** A idade média dos pacientes encontrada neste estudo foi de 60,8 anos com incidência maior da doença entre os homens. No momento do diagnóstico, 40% dos pacientes estavam com a doença no estágio IV. Como primo-tratamento o esquema terapêutico mais utilizado foi o 5-fluoracil/ácido folínico (68,5%). **Conclusão:** Este estudo ratificou a alta prevalência do câncer colorretal em pacientes com idade mais avançada, com o diagnóstico realizado na fase mais avançada da doença. Esse fato evidencia a importância da realização de campanhas de prevenção que estimulem a realização de exames periódicos nos pacientes com idade acima de 50 anos.

**Palavras-chave:** neoplasias colorretais; incidência; toxicidade de drogas; 5-fluoracil/ácido folínico.

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## INTRODUCTION

Colorectal cancer (CRC) is one of the most common types of cancer worldwide, with predominance in more industrialized and economically richer countries. In Brazil, CRC has a high incidence, with the South and Southeast regions presenting the largest number of cases<sup>1,2</sup>. CRC is a disease that predominates in individuals over 50 years of age, only 10% of people with CRC are under 50 years old, with 2% to 10.6% of the diagnoses made in patients under 40 years old and only 2.4% of the diagnoses made in patients under 30 years old<sup>3,4</sup>.

CRC is a disease that can be treated and frequently healed; with the treatment usually involving surgery, radiotherapy and chemotherapy. Surgery is the main type of treatment, which, alone or combined with chemotherapy, can offer long survival and, consequently, healing, since diagnosed in its early stage<sup>5</sup>. The treatment selection is basically dependent on the tumor size, location and extension, and the patient's general health, and the different forms of treatment can be used individually or combined<sup>6</sup>. Adjuvant chemotherapy is habitually used in the treatment of high-risk stage III and stage II CRC to reduce recurrences after the initial treatment with surgery, eliminating residual tumor cells and increasing the number of patients that obtain long-term disease-free survival and increased overall survival (OS)<sup>7</sup>.

The chemotherapeutic treatment for CRC has become increasingly complex in the last years<sup>8</sup>. The combination of 5-fluorouracil and folic acid (5-FU/LV) became the standard treatment for CRC many years ago, and remains as the standard treatment for stage II CRC and one of the options for stage III CRC<sup>9-11</sup>. However, stage III e IV CRC may be treated with different therapeutic regimens that incorporate new agents, such as irinotecan and oxaliplatin<sup>12,13</sup>. Examples of these combinations include: irinotecan, 5-FU (continuous bolus infusion) and folic acid (FOLFIRI) and oxaliplatin, 5-FU (continuous bolus infusion) and folic acid (FOLFOX)<sup>13</sup>. These therapeutic regimens present different toxicity profiles, but both are considered first-line therapeutic options for the treatment of advanced CRC<sup>14-16</sup>.

Before the introduction of these regimens, the combination of irinotecan, 5-FU (bolus) and folic acid

(IFL) was largely accepted as the first-line treatment for the metastatic colorectal cancer (mCRC), producing better results than those obtained with 5-FU/LV<sup>17</sup>.

When selecting the therapeutic regimen, an effective, well-tolerated and convenient therapy is desirable<sup>18</sup>. Goldberg et al.<sup>19</sup> demonstrated that FOLFOX presents significantly lower rates of nausea, vomiting, diarrhea, febrile neutropenia and dehydration when compared to IFL. And, when compared to FOLFIRI, the occurrence of diarrhea and febrile neutropenia is also higher in patients treated with IFL<sup>20</sup>. The regimen of 5-FU/LV is associated with adverse drug reactions (ADRs), such as diarrhea, leukopenia, neutropenia, mucositis and vomiting, but at significantly lower rates than IFL<sup>21</sup>.

The fact that innumerable pharmacological agents are not effective in the treatment of advanced CRC or present high toxicity raises an important question about what really constitutes the standard treatment for this disease and about how the active agents for such disease should be combined<sup>22,23</sup>.

Thus, the purpose of this study was to identify the epidemiological characteristics of patients with CRC treated at a cancer center in Santa Cruz do Sul (RS) and the main therapeutic regimens used as the first-line treatment and their ADRs.

## METHODS

### Study design and data collection

A retrospective descriptive study was conducted, which analyzed patients with CRC treated at the Centro de Oncologia Integrado (COI) at the Hospital Ana Nery, in the city of Santa Cruz do Sul, 155 km from the State capital, Porto Alegre, in the central region of the State of Rio Grande do Sul. Hospital Ana Nery is a hospital of medium complexity, with a cancer center that is a reference to Vale do Rio Pardo and Centro-Serra, a region of 458,238 inhabitants.

### Selection of patients and data collection

The medical records of patients over 18 years of age diagnosed with CRC confirmed by biopsy between March 2006 to April 2011 were evaluated. The patients' data were collected between October 2010 and December 2011.

During the analysis of medical records, clinical and epidemiological data were evaluated and transcribed to a previously elaborated data form. The epidemiological data included age, gender, occupation, marital status and ethnic group. The clinical data included disease stage, primary site of the disease, metastases at the diagnosis, lymph node invasion, chemotherapeutic regimen adopted as the first-line treatment, ADRs and therapeutic response.

### Ethical considerations

This study was approved by the Research Ethics Committee of the Universidade de Santa Cruz do Sul (UNISC), under protocol number 2.523/10.

### Statistical analysis

Clinical and epidemiological data were stored and analyzed in a database created with the software *Statistical Package for the Social Science* (SPSS, Chicago, IL), version 18.0. The association of significance was evaluated using the chi-square and Fisher exact tests. The confidence interval used was 95% ( $p < 0.05$ ). Descriptive statistics were calculated and univariate comparisons were performed.

## RESULTS

### Characteristics of patients

The medical records of 130 patients were analyzed; 53 (40.8%) of them were of patients from the city of Santa Cruz do Sul. This number refers to the total patients treated at COI in the studied period; 125 (96.2%) of them were treated under the government's Unified Health System (SUS). Table 1 shows the epidemiological characteristics of patients. The mean age of patients at the diagnosis was 60.8 years ( $\pm 12.6$ ), with 6 (4.6%) patients under 40 years of age. In terms of gender, 71 (54.6%) were male patients, but the difference between male and female patients was not statistically significant ( $p = 0.29$ ). Regarding the tumor site, 85 (65.4%) patients had colon cancer and 45 (34.6%) had rectal cancer.

Regarding the TNM staging system, at the diagnosis, 52 (40%) patients presented stage IV CRC, 32 (24.6%) stage III CRC and 42 (32.3%) stage II CRC and, regarding the lymphatic invasion, 67 (51.5%) patients did not present metastasis in regional lymph

**Table 1.** Epidemiological characteristics of patients with colorectal cancer treated at the Oncology Center at the Hospital Ana Nery from 2006 to 2011.

Characteristics	Total n=130* (%)	p-value
Mean age	60.8 ( $\pm 12.6$ )	-
Gender		
Male	71 (54.6)	0.29
Female	59 (45.4)	
Marital status		
With a companion	97 (74.6)	<0.001
Alone	32 (24.6)	
Skin color		
White	128 (98.5)	<0.001
Other than white	2 (1.5)	
Occupation		
Retired	39 (30)	0.83
Housewife	30 (23.1)	
Agriculturist	30 (23.1)	
Others	31 (23.8)	
Medical care		
SUS (public system)	125 (96.2)	<0.001
Private medical care	5 (3.8)	

\*The difference in percentage is due to the number of cases without such information in the patient's records.

SUS: Unified Health System (public system).

nodes. In this group of patients, the most frequent metastatic site at the diagnosis was the liver (23.8%).

### Chemotherapeutic treatment

Regarding the chemotherapeutic treatments, the most frequent first-line treatment was 5-FU/LV (68.5%). The second most frequent treatment was IFL, used by 13 (10%) patients, followed by FLOX (5-FU bolus infusion, LV and oxaliplatin), used by 9 (6.9%) patients. Table 2 correlates the most frequent therapeutic regimen with the patients' clinical characteristics.

The regimen of 5-FU/LV was used in the treatment of 40 (95.2%) patients with stage II CRC and 27 (84.4%) patients with stage III CRC. Sixty-nine patients (71.9%) that used this regimen had moderately differentiated tumors. The level of carcinoembryonic antigen (CEA) above 5 ng/mL before starting the treatment was observed in 50 (83.3%) patients.

**Table 2.** Clinical characteristics of patients associated with the therapeutic regimen adopted as the first-line treatment.

Characteristics	5FU/LV n=89 (%)	Others** n=41 (%)	Total n=130 (%)	p-value
Primary tumor site				
Rectum	31 (68.9)	14 (31.1)	45 (34.6)	0.90
Colon	58 (68.2)	27 (31.8)	85 (65.4)	
TNM stage system*				
II	40 (95.2)	2 (4.8)	42 (32.4)	<0.001
III	27(84.4)	5 (15.6)	32 (24.6)	
IV	21 (40.4)	31 (59.6)	52 (40)	
Pathology				
Well differentiated	3 (75)	1 (25)	4 (3.1)	<0.001
Poorly differentiated	69 (71.9)	27 (28.1)	96 (73.8)	
Moderately differentiated	6 (85.7)	1 (14.3)	7 (5.4)	
CEA baseline*/***				
<5 ng/mL	50 (83.3)	10 (16.7)	60 (46.2)	<0.001
>5 ng/mL	13 (48.1)	14 (51.9)	23 (20.8)	
Metastatic site*				
Liver	8 (25.8)	23 (74.2)	31 (23.8)	<0.001
Others	81 (81.8)	18 (18.2)	17 (13.1)	
Lymph node invasion				
Yes	39 (61.9)	24 (38.1)	63 (48.5)	0.17
No	50 (74.6)	17 (25.4)	67 (51.5)	
Death*				
Yes	30 (56.6)	23 (43.4)	53 (40.8)	0.026
No	59 (76.6)	18 (23.4)	77 (59.2)	
ADR*				
Yes	46 (71.9)	18 (28.1)	64 (49.2)	0.23
No	9 (52.9)	8 (47.1)	17 (13.1)	
Purpose of treatment*				
Adjuvant	77 (89.5)	9 (10.5)	86 (66.2)	<0.001
Palliative	12 (27.9)	31 (72.1)	43 (33.1)	
Response rate*				
Complete remission	5 (71.4)	2 (28.6)	7 (5.4)	0.059
Partial remission	3 (75)	1 (25)	4 (3.1)	
Stable disease	26 (86.7)	4 (13.3)	30 (23.1)	
Progressive disease	14 (53.8)	12 (46.2)	26 (20)	

\*The difference in percentage is due to the number of cases without such information in the patient's records; \*\*IFL: 13 (10%) patients, FLOX (5-FU bolus infusion, LV and oxaliplatin): 9 (6.9%) patients, capecitabine: 7 (5.4%) patients, FOLFOX: 6 (4.2%) patients, XELOX (capecitabine and oxaliplatin): 3 patients (2.3%), imatinib mesilate: 2 (1.5%) patients and BFOL to only 1 (0.8%) patient. \*\*\*CEA baseline refers to the level of CEA in the beginning of the treatment, with cutoff between normal and altered 5ng/mL. 5FU/LV: 5-fluorouracil/folic acid.

The purpose of the 5-FU/LV treatment was to act as an adjuvant therapy for 77 (89.5%) patients, while the other therapeutic regimens were used in only 9 (10.5%) patients with the same purpose (p<0.001).

The patients who, according to the analyzed medical records, reported any ADR during the chemotherapeutic treatment totaled 64 (49.2%). Forty-six (71.9%) of these received the 5-FU/LV treat-

ment. Reported ADRs included diarrhea (62.3%), mucositis (50.8%), leukopenia (7.5%), thrombocytopenia (11.7%), nausea (11.3%), neutropenia (10.5%) and vomiting (7.5%).

Regarding the treatment response rate, the disease remained stable in 30 (23.1%) patients, 26 (86.7%) of them were treated with 5-FU/LV. Complete remission occurred in only 7 (5.4%) patients and partial remission in 26 (20%) patients, 14 (53.8%) of them were treated with 5-FU/LV. The analysis of medical records identified 53 (40.8%) deaths, 30 (56.6%) of them were treated with 5-FU/LV as the first-line treatment.

## DISCUSSION

CRC is usually affects men more often, regardless of their age<sup>24-27</sup>. In this study, the disease frequency in male patients was 54.6%, in agreement with the world tendency<sup>4</sup>. In the United States and the European Union, the disease is diagnosed in patients over 70 years old<sup>26</sup>. In this study, the mean age at the diagnosis was 60 years old, in agreement with other studies described in the literature<sup>27,28</sup>. In addition, the risk of cancer increases with the age – 50% of the cases affect individuals over 60 years old<sup>1</sup>.

Regarding the ethnic origin, most patients with CRC are known to have a Caucasian origin, also in agreement with this study, as 98.5% of the patients were white<sup>12,29</sup>.

Colon was the primary tumor site in 65.4% of the analyzed patients, confirming what has been demonstrated by other investigators<sup>12,27</sup>. On the other hand, the rectum is more frequently indicated in other studies as the primary tumor site<sup>18,30</sup>.

Today, the CRC staging at the diagnosis is considered an important factor of prognosis, as it is directly related to OS. Once the disease staging is known, it is possible to define the best therapy. Through the TNM system, proposed by the Union for International Cancer Control (UICC), the analysis observed that 40% of the patients had stage IV CRC at the diagnosis. This is the most severe stage, which may indicate delayed diagnosis in most patients, who, for this reason, presented more advanced neoplasms, making prognosis more difficult<sup>28</sup>. Unlike this study, other authors show stages II and III as the most frequent at the diagnosis<sup>31</sup>. In this study, the site most frequently affected by metastasis was

the liver, which is in agreement with the studies conducted by Roits et al.<sup>27</sup> and Adachi et al.<sup>4</sup>.

The cellular differentiation degree is the most frequent histological variable in association with the TNM staging system, attributing a more careful prognosis to little differentiated adenocarcinomas<sup>32</sup>. In this study, only 3.1% of the tumors were well differentiated, which agrees with findings reported in previous studies<sup>28,30</sup>.

Evidences show that the presence of metastatic lymph node invasion at the diagnosis is related to factors of worse prognosis, such as advanced disease and presence of distant metastasis<sup>33</sup>. Such identification is extremely important for the prognosis, but the macroscopic access to lymph nodes is not viable, as a considerable part of lymph node metastasis (more than 30%) have maximum diameter of 3 mm<sup>34</sup>. In this study, most patients (51.5%) did not present lymph node metastasis at the diagnosis, just as demonstrated by other authors<sup>33,34</sup>.

Only 23 (20.4%) patients presented levels of CEA above 5ng/mL at the diagnosis. These values confirm the idea that this antigen does not have a diagnostic value, it is beneficial only for prognosis and treatment monitoring<sup>28-30</sup>.

Regarding the occurrence of ADRs during the chemotherapeutic treatment, 64 (49.2%) patients mainly had diarrhea, mucositis and leukopenia, but some medical records (37.7%) did not have information about ADR occurrences, making the analysis and calculation of ADR frequency in oncological patients more difficult.

In terms of first-line chemotherapeutic treatment, the 5-FU/LV regimen is indicated by two meta-analyses as the treatment of option to patients with stage II CRC<sup>10,11</sup>. In this study, 95.2% of the patients in this stage received 5-FU/LV as adjuvant therapy.

In this study, 27 (84.4%) stage III patients received 5-FU/LV, which is considered by some authors a generally well-tolerated adjuvant regimen and effective for the treatment of CRC<sup>35,36</sup>. The study conducted by Twelves et al. demonstrated that oral capecitabine is a highly effective alternative to 5-FU/LV for the treatment of stage III CRC, with disease-free survival equivalent to that of 5-FU/LV with less ADRs<sup>18</sup>. On the other hand, the study conducted by Van Cutsem et al. shows capecitabine as

an alternative to mCRC treatment<sup>37</sup>, where it was used as the first-line treatment by 7 (5.4%) patients, all with stage IV CRC.

Other therapeutic options to treat stage II and III CRC were considered by Twelves et al., Thierry et al. and Cassidy et al. better than 5-FU/LV, as they significantly increase the overall survival of patients, such as XELOX, FOLFOX and FLOX<sup>9,18,38</sup>. In this study, these therapeutic options were used in 5 (15.6%) patients, and the regimens were FLOX and FOLFOX.

The therapeutic regimen used as the first-line treatment of 21 (40.4%) stage IV patients was 5-FU/LV. The other stage IV patients (59.6%) received other therapeutic regimens, including the IFL, used by 13 (10%) patients. For the treatment of the disease at a more advanced stage, FOLFOX and FOLFIRI, in the presence or absence of monoclonal antibodies – bevacizumab (an anti-VEGF antibody) or cetuximab (an anti-EGFR antibody) – are considered first-line treatment for mCRC, as both regimens offer similar OS and disease-free survival, with different toxicity profiles<sup>14,15</sup>. However, XELOX, FOLFOXIRI, 5-FU/LV and capecitabine are also considered alternatives to first-line treatment for mCRC<sup>37-40</sup>.

Regarding the utilization of IFL regimen, studies have demonstrated that FOLFIRI, FOLFOX and 5-FU/LV are related to less ADRs, such as neutropenia and gastrointestinal effects, when compared to IFL<sup>18-20</sup>. However, the adoption of chemotherapeutic regimens that use 5-FU in continuous infusion, such as FOLFIRI and FOLFOX, require the implantation of a long-term catheter (Port-A-Cath). As a result, typical complications of this type of device occur, especially thrombosis of superior vena cava and infection, both very serious and with risk of death. However, as demonstrated in this study, IFL is used as the first-line treatment for mCRC.

As described above, there are many treatment options for CRC, but the selection of the best treatment to each patient is made by the oncologist based on international regulations, such as the *National Comprehensive Cancer Guideline*. However, this selection is many times limited, as most patients are treated under SUS, which has specific

protocols. But, regardless of the therapeutic regimens available, the treatment option should be always selected on an individual basis, considering the best to each patient, based on his/her clinical characteristics. In addition, it should be noted that, in stage IV CRC, as the treatment is usually palliative, it is not always interesting to use the whole therapeutic arsenal in the first intervention. Not using a drug in the first-line treatment may represent the possibility of using it in the future, as the second- or third-line treatment, depending on the response rate expected to alleviate the symptoms caused by the disease.

## CONCLUSION

The epidemiological characteristics showed higher frequency of CRC in male patients, over 60 years of age. This study demonstrated that the most frequent primary tumor site is the colon, and that patients are diagnosed with CRC at a more advanced clinical stage of the disease, which leads to lower possibility of healing and more indefinite prognosis.

Regarding the first-line treatment, the most frequent therapeutic regimen was 5-FU/LV. The treatment selection is based on international protocols, according to the patient's clinical characteristics and the availability of the therapeutic regimen at the hospital. Most patients (49.2%) reported, at one point of the treatment, any type of ADR, regardless of the therapeutic regimen. And the most frequent ADRs were diarrhea, mucositis and leukopenia.

This study demonstrates the importance of prevention campaigns that encourage periodic examinations to prevent the disease development through the identification of CRC precursor lesions.

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**Correspondence to:**

Lia Gonçalves Possuelo  
Avenida Independência, 2293, bloco 35, sala 3504  
CEP: 96815-900 – Santa Cruz do Sul (RS), Brazil  
E-mail: liapossuelo@unisc.br