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Colon cancer: clinical, macroscopic and microscopic aspects

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Abstract

Although in developed countries the incidence of colorectal cancer is decreasing through the introduction of well-designed screening systems, the worrying worldwide increase of the mortality rate by colorectal neoplasm indicates the need for a thorough characterization of this pathology. Clinical, endoscopic, histopathological and immunohistochemical data provide important information for creating categories of patients that can benefit from intensive screening methods and for establishing the prognosis based on these data. Approximately 80% of the colorectal cancer develops from adenomas, which shows that early detection of premalignant lesions is an important step in reducing global incidence and mortality. Our study aims at providing information about the clinical, imaging and histopathological characterization of colorectal neoplasm and premalignant lesions. A total of 98 patients were evaluated, including 72 patients diagnosed with colorectal cancer and 26 with premalignant lesions. Patients underwent colonoscopy with biopsy specimens that were examined histopathologically. From the epidemiological data, we observe a higher incidence in men with a men/women ratio of 2/1, with a median age in colorectal cancer patients of 63.93 years. Different data on signs and symptoms were observed according to the colonoscopy location, with a slight difference between symptoms of patients with premalignant lesions compared to those diagnosed with colorectal neoplasm. Endoscopy showed that the rectum was the most frequent location, followed by the left colon, the tumor having a vegetative aspect in most cases. Histopathology confirms that the most common subtype is adenocarcinoma, described in 67 of the studied cases. The moderate differentiation degree is present in more than half of the cases.

Keywords: colon cancer, adenocarcinoma, colonoscopy, histopathology, premalignant lesions.

Introduction

In 2012, colorectal cancer ranked third in terms of the incidence, being the fourth leading cause of death by cancer in the world, summing up 1.4 million patients recently diagnosed with this disease and causing almost 700 000 deaths [1]. According to GLOBOCAN 2018, colorectal cancer is today the second leading cause of death by cancer after lung cancer, with a total of 881 000 deaths. In terms of global incidence, it maintains its third place after lung and breast cancer, with 1.8 million new cases reported in 2018 [2].

Over the past decade, rapid increases in the incidence and mortality of colorectal cancer have been reported in many countries with a medium to large human development index (HDI), particularly in Eastern Europe, Asia and South America. This worrying rise is due both to the aging process of the population as well as to prolonged exposure to risk factors such as diet changes, obesity or smoking. In contrast, rates of colorectal cancer incidence and mortality stabilize or decrease in a number of states in the USA, Australia, New Zealand and several Western European countries [3].

The downward trend of the incidence of colorectal cancer in some countries has many reasons, one of them being intensive early detection by polypectomy. This was the case with the USA, where colonoscopy screening showed a significant increase from 20% to 48% within eight years [4]. Approximately 80% of colorectal cancers develop from preexisting adenomas, which demonstrates the preventive and curative impact of colonoscopy as a primary screening method [5]. Together with factors that reduced incidence, improved perioperative care as well as chemotherapy and radiotherapy will contribute to the decreasing trend of colorectal cancer mortality rates in many countries with financial resources [6, 7].

By 2030, an increase in incidence and mortality of colorectal cancer of up to 60% is expected, estimating that a total number of 2.2 million patients will be diagnosed with this disease and almost 1.1 million patients will die from this cause [1]. The presented data highlights the need for a thorough study of this pathology, characterizing this pathology clinically, endoscopically, histopathologically and immunohistochemically, in order to assess the data needed to develop new personalized therapies that will become new therapeutic standards.

However, increasing evidence showed that, due to considerable heterogeneity in the clinical presentation of

colorectal cancer, colorectal neoplasm should be subdivided into different prognostic groups by additional prediction factors. Molecular biomarkers are widely used to reflect the pathways of this pathology [8].

There are three molecular targets commonly used as independent prognostic biomarkers in colorectal cancer: expression of mismatch repair (MMR) proteins, Kirsten rat sarcoma viral proto-oncogene (*KRAS*) and B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) genes and their mutations [9]. An important role in selecting the appropriate histological sections for testing and analyzing micro-satellite instability (MSI), *KRAS* and *BRAF* mutations that determine prognosis and subsequent treatment is attributed to pathologists [10].

The highest percentage in immunohistochemical (IHC) colorectal diagnosis is occupied by cytokeratin (CK) 2, CK7 and CK20 markers. Colorectal adenocarcinoma is most commonly characterized as an immunophenotype with CK20 marker positive and CK7 marker negative [11].

Various studies attempted to establish the prognostic value of the association between certain biomarkers, with the aim of dividing into risk groups that are appropriately treated according to the molecular subtype.

Aim

The present study aims to clinically, endoscopically and histopathologically evaluate a group of patients with colorectal neoplasm and premalignant lesions, thereby completing the literature, in order to divide patients into categories that can benefit from extensive screening, hoping that, in the future, colorectal cancer will be detected only in early stages, even in the form of premalignant lesions.

Patients, Materials and Methods

Our study included 98 patients suspected of having colorectal cancer, evaluated between January 2013 and November 2017 at the "Renașterea" Medical Center in Craiova and at the Clinic of Internal Medicine, Emergency County Hospital, Craiova, Romania. All patients underwent colonoscopy with tumor tissue harvesting. The colonoscopy was performed with Pentax® colonoscope GVS308389 / 2009. The tumor fragments were fixed in 10% formalin, included in histological paraffin and specifically stained with Hematoxylin–Eosin (HE) and Goldner–Szekely (GS) trichrome. All these were achieved in "Elana Med" Pathology Private Clinic, Craiova. Out of 98 patients, 72 were diagnosed with colorectal neoplasm of different histopathological (HP) types and 26 with malignant precursor lesions. Data such as the signs and symptoms the patients accused at first presentation, as well as personal data, came from the analysis of the consultation registry. Tumor localization, endoscopic appearance, HP type, degree of differentiation, and the presence of other endoscopic modifications were extracted from the HP results.

For the phenotype characterization of tumor cells, of the biopsy samples there was performed an IHC study using the following antibodies: anti-CK7 (monoclonal mouse anti-human CK7, clone OV-TL 12/30, Dako, 1:50 dilution); anti-CK19 (monoclonal mouse anti-human CK19, clone RCK108, Dako, 1:50 dilution); anti-CK20 (monoclonal mouse anti-human CK20, clone Ks20.8, Dako, 1:50 dilution); anti-MNF116 (monoclonal mouse anti-human cytokeratin, clone MNF116, Dako, 1:100 dilution); anti-Ki67 (monoclonal mouse anti-human Ki67, clone MIB-1, Dako, 1:50 dilution); anti-p53 (monoclonal mouse anti-human p53 protein, clone DO-7, Dako, 1:50 dilution); anti-cluster of differentiation (CD) 34 (monoclonal mouse anti-human CD34 Class II, clone QBEnd10, Dako, 1:50 dilution); anti-vascular endothelial growth factor (VEGF)-A (monoclonal mouse anti-human VEGF-A, clone VG1, Thermo Fisher Scientific, 1:200 dilution); anti-VEGF-C (polyclonal anti-human VEGF-C, Thermo Fisher Scientific, 1:100 dilution).

Results

The patients diagnosed with colorectal neoplasia included in this study were aged between 33 and 82 years old, with a median age of 63.93 years. A total of 48 (66.67%) patients were over 60 years old. The age group distribution includes four (5.56%) patients less than 50 years old, 20 (27.27%) patients aged between 50–59 years old, 25 (34.72%) patients aged between 60–69 years old, 21 (29.17%) patients aged between 70–79 years old and only two (2.78%) patients over 80 years old. The patients diagnosed with malignancy precursors were between 40 and 84 years old, with a mean age of 64 years, the distribution by age group being as follows: four (15.38%) patients less than 50 years old, three (11.54%) patients aged between 50–59 years old, 11 (42.31%) patients aged between 60–69 years old, six (23.08%) patients aged between 70–79 years old and two (7.69%) patients over 80 years old (Figure 1).

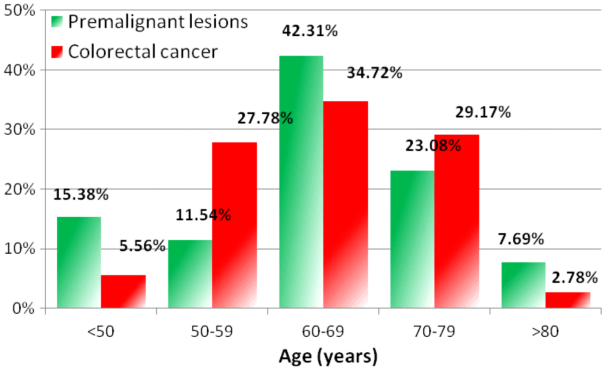

Figure 1 – ***Distribution of lesions according to age groups and lesion type.***

The gender distribution in the group of patients with colorectal neoplasm was 48 (66.67%) men and 24 (33.33%) women, with a men/women ratio of 2/1. Premalignant lesions reported seven (26.92%) cases in women subjects and 19 (73.08%) cases in men, with a men/women ratio of 2.71/1 (Figure 2).

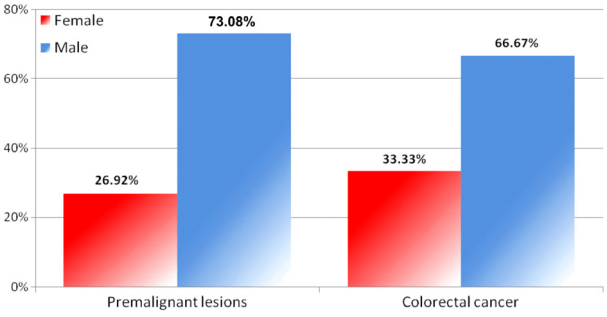

Figure 2 – ***Distribution of the lesions by gender.***

From the epidemiological data, we observed the significant difference in the distribution of the origin of both colorectal cancer patients and patients diagnosed with premalignant lesions, 43 (59.72%) carcinoma patients and 19 (73.08%) patients with premalignant lesions from urban areas compared to 29 (40.28%) patients with colorectal neoplasia and seven (26.92%) patients with premalignant lesions from rural areas (Figure 3).

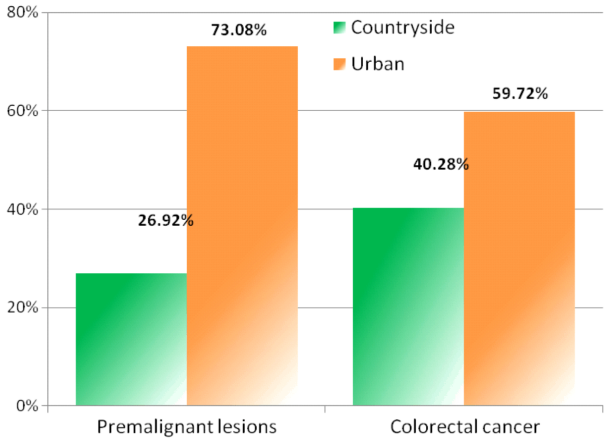

Figure 3 – *Distribution of lesions based on the home environment.*

The signs and symptoms that led to the doctor presentation of patients with colorectal neoplasm was represented by: transit disorders present in 51 (70.83%) cases, anemia in 42 (58.33%) cases, weight loss of at least 10% in the last 3–6 months in 42 (58.33%) cases, rectal bleeding in 33 (45.83%) cases, while abdominal pain was present only in 17 (23.61%) cases. In the group of patients diagnosed with lesions precursor to malignancy, the predominant onset of symptoms was represented by transit disorders in 16 (61.54%) cases, followed by anemic syndrome in six (23.08%) cases and abdominal pain in five (19.23%) cases, rectal bleeding being present in four (15.38%) cases, without recording patients with weight loss.

In attempting to correlate symptoms and signs with the endoscopic location, transit disorders in patients with rectal cancer were reported in 32 (74.11%) cases, representing the main symptom in this location, followed by rectal bleeding with 72.09% (31 patients). Anemia was found in 65.11% (28) of the patients diagnosed with rectal neoplasm followed by weight loss in 41.86% (18 patients).

Patients with left-sided neoplasm accused at the onset weight loss in 19 (82.6%) cases, followed by transit disorders in 18 (78.26%) cases. Abdominal pain was described by 12 of the 23 patients with this localization, representing 52.17%, whereas anemia was found in 34.7% of the patients, being reported in eight cases. Rectal bleeding was described by only one patient as the onset symptom, with a percentage of 4.34%. For tumors located in the right colon, abdominal pain and anemia represent the main onset symptoms with 83.3% (five patients), followed by 66.6% (four patients) weight loss and transit disorders in 16.6% (one patient) of the cases.

Endoscopically, colorectal neoplasm has a more frequent localization reported in the rectum with 59.72% (43 patients), followed by the left colon with 31.94% (23 patients) and the right colon with 8.33% (six patients). Premalignant lesions were detected in 57.69% (15) of the cases in the rectum, followed by the left colon with 42.31% (11) of the cases, without being registered patients with premalignant lesions located in the right colon (Figure 4).

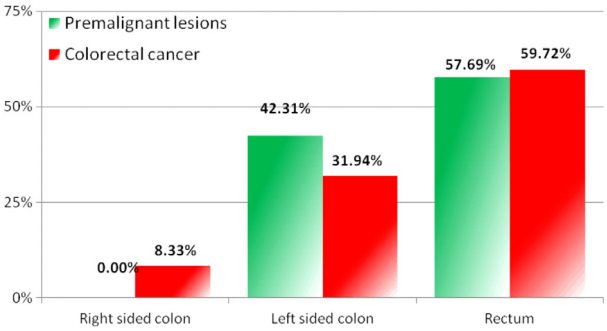

Figure 4 – *Distribution of the lesions according to localization and lesion type.*

The endoscopic appearance was occupied by vegetant tumors (Figure 5) in 54.17% (39) of the 72 patients, while the association of vegetant tumors with ulceration (Figure 6) occupied 26.39% (19 patients). Infiltrative tumors with ulceration zones (Figure 7) were described endoscopically in 9.72% (seven) of the cases, whereas the classical infiltrative aspect was detected in 9.72% (seven) of the cases.

At the HP evaluation, 94.47% (68 cases) of colorectal cancers were adenocarcinomas, 4.16% (three cases) mucinous carcinomas, and only 1.37% (one case) signet ring cell carcinoma. In the premalignant lesions group, high dysplasia polyps were described in a proportion of 65.38% (17 cases), while areas of high dysplasia in 34.62% (nine cases). There were reported 10 (13.88%) cases of colorectal neoplasia associated with concurrent detection of polyps with high-degree dysplasia, two cases of which had sigmoid localization and eight cases of rectal localization. A single case of rectal cancer relapse was described. At the examination of the differentiation degree, we identified 19.44% G1 (Figure 8), 59.72% G2 carcinomas (Figure 9), 13.89% G1 + G2 and 6.94% G2 + G3 carcinomas (Figure 10).

The IHC study showed that all forms of colon adenocarcinomas (G1–G4) presented a negative reaction to the immunomarking with anti-CK7 (Figure 11). The reaction of tumor cells to anti-MNF116 was low and inconstant, showing the presence of various different clones of tumor cells in the structure of colon tumors (Figure 12).

In contrast, the tumor cells were highly positive to the immunomarking with anti-CK19, regardless of the tumor differentiation degree (Figure 13). The immunomarking with anti-CK20 showed quite a varying reaction, from negative to highly positive of tumor cells, irrespective of the tumor grading (Figure 14, a and b).

The evaluation of the ability to multiply of tumor cells was performed by using the anti-Ki67 antibody. In our study, we observed that the cellular proliferation index was correlated with the tumor differentiation degree. Well-differentiated tumors had a much lower proliferation index than the poorly differentiated tumors, which seem to be the most aggressive ones (Figure 15, a and b).

The investigation of tumor protein 53 (*TP53*) gene changes, known as the "genome guardian", was performed by evaluating the p53 protein expression. In our study, the

tumor cells of the colon adenocarcinoma had an extremely varying reaction to anti-p53 antibody, from negative to intensely positive, without any correlation to the cellular differentiation degree (Figure 16, a and b), showing that *TP53* gene is variably affected in colon cancer.

The evaluation of tumor microvascularization was performed by using the anti-CD34 antibody. The microvascular density was quite varied from one tumor to another, and even from one area to another of the same tumor; also, the shape and size of the vessels were quite varied. Nonetheless, there was observed that the moderately and well-differentiated tumors presented richer microvascular networks, in comparison to the poorly differentiated tumors (Figure 17, a and b).

The ability of tumor cells in the colon adenocarcinoma to stimulate the processes of angiogenesis and lymphangiogenesis was investigated by the IHC study of some specific markers, namely of VEGF-A and VEGF-C. The intensity of the IHC reaction of the tumor cells in the two markers varied from negative to highly positive (Figures 18 and 19). Poorly differentiated adenocarcinomas were most often negative or poorly positive, while the moderately and well-differentiated adenocarcinomas presented much more intense reactions.

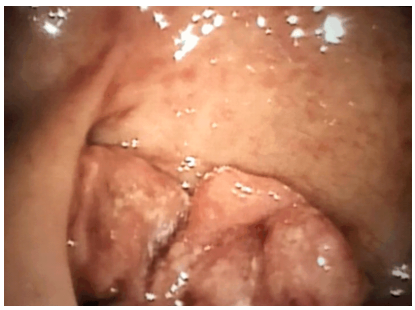

Figure 5 – ***Endoscopic aspect of the vegetant tumor.***

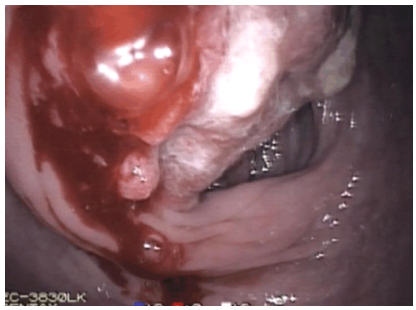

Figure 6 – ***Vegetant tumor with ulceration.***

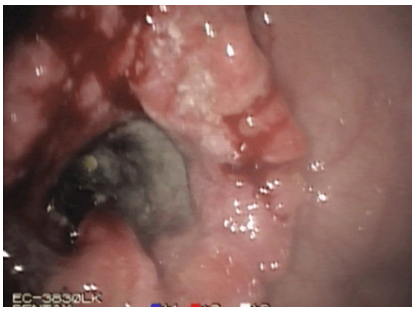

Figure 7 – ***Infiltrative tumor with ulceration.***

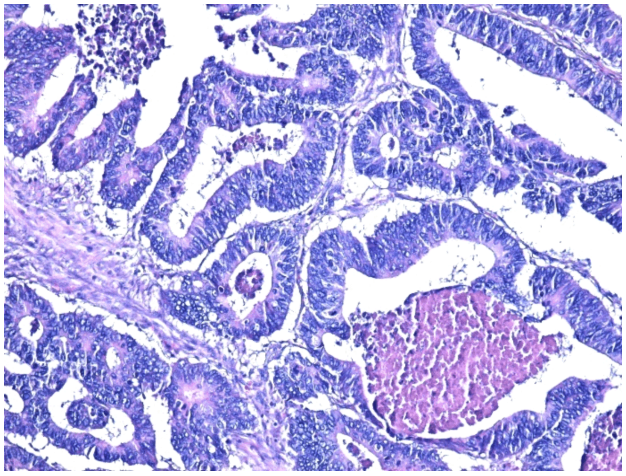

Figure 8 – ***Image of a well-differentiated colon adenocarcinoma (G1) (HE staining, ×100).***

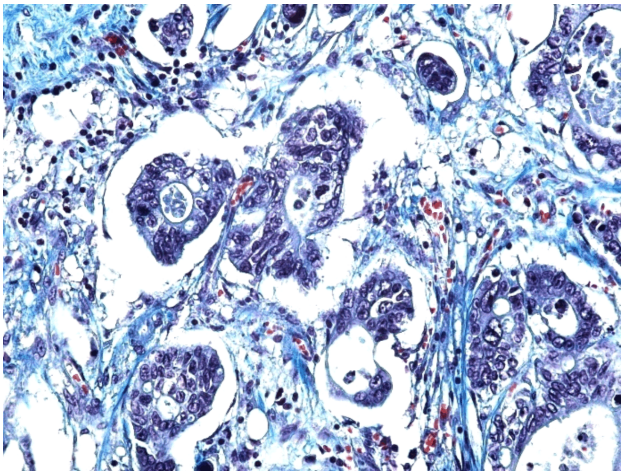

Figure 9 – ***Moderately differentiated colon adenocarcinoma (G2) (GS trichrome staining, ×200).***

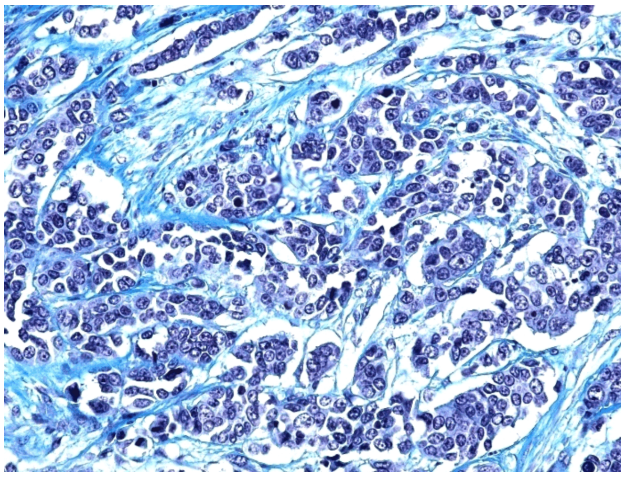

Figure 10 – ***Poorly differentiated colon adenocarcinoma (G3) (GS trichrome staining, ×200).***

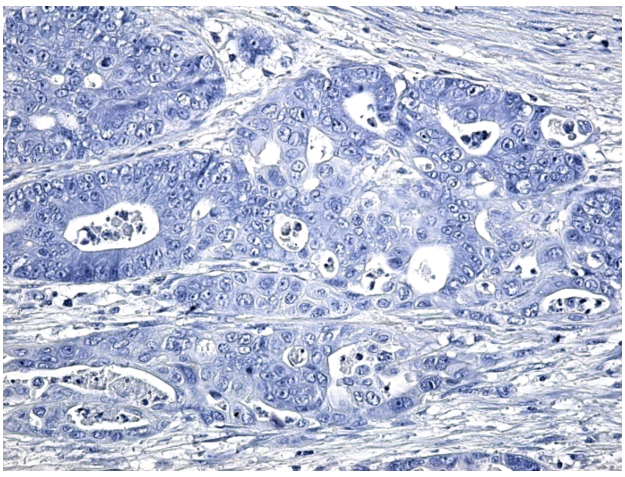

Figure 11 – ***Image of moderately differentiated colon adenocarcinoma with a negative reaction to CK7 (Anti-CK7 antibody immunomarking, ×200).***

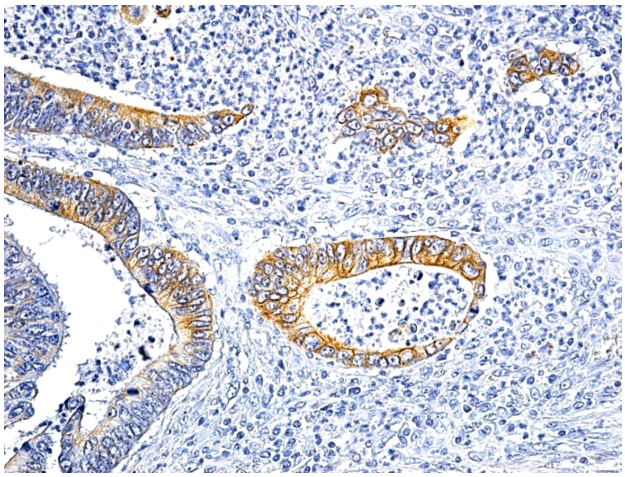

Figure 12 – ***Colon adenocarcinoma with low reaction and inconstant to CK MNF116 (Anti-MNF116 antibody immunomarking, ×200).***

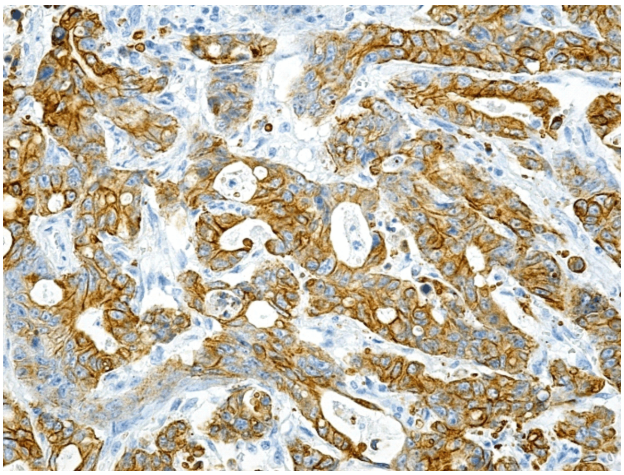

Figure 13 – ***Colon adenocarcinoma with intense positive reaction to CK19 (Anti-CK19 antibody immunomarking, ×200).***

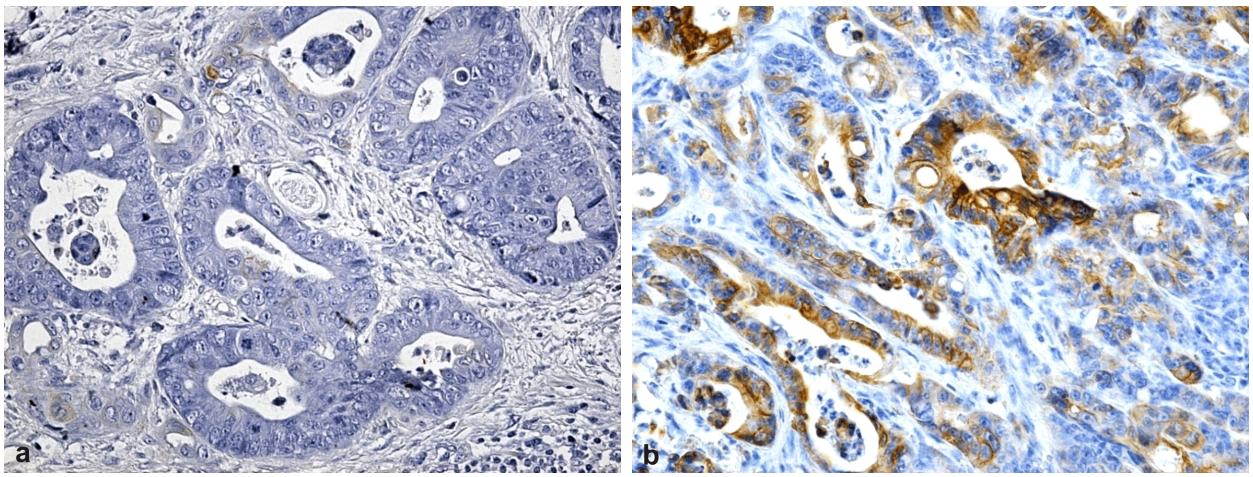

Figure 14 – ***(a) Well-differentiated colon adenocarcinoma (G1) with a negative reaction to CK20; (b) Image of moderately differentiated colon adenocarcinoma (G2) with a positive reaction to CK20 (Anti-CK20 antibody immunomarking, ×200).***

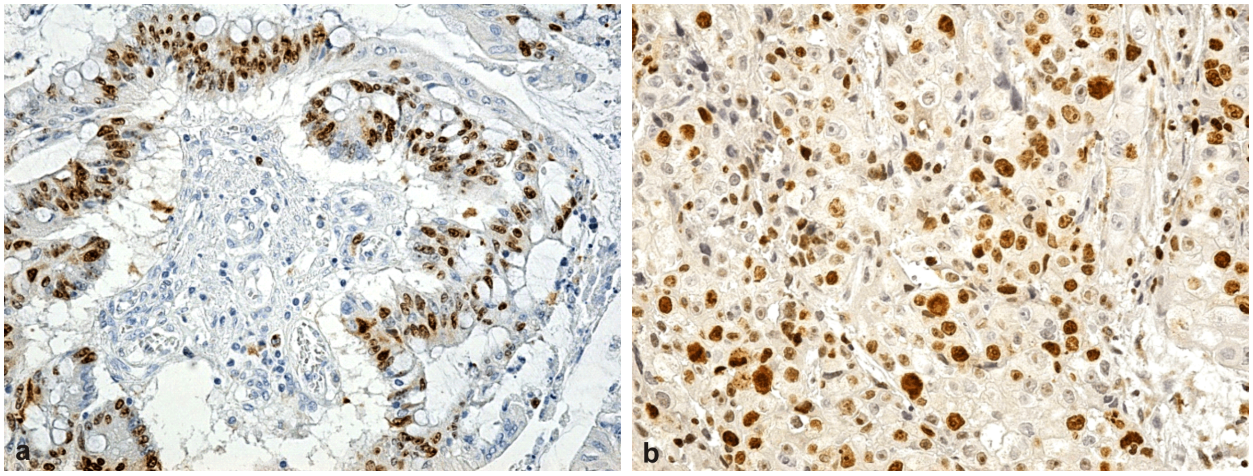

Figure 15 – ***(a) Image of colon adenocarcinoma with a moderate Ki67 proliferation index; (b) Poorly differentiated adenocarcinoma with high Ki67 proliferation index (Anti-Ki67 antibody immunomarking, ×200).***

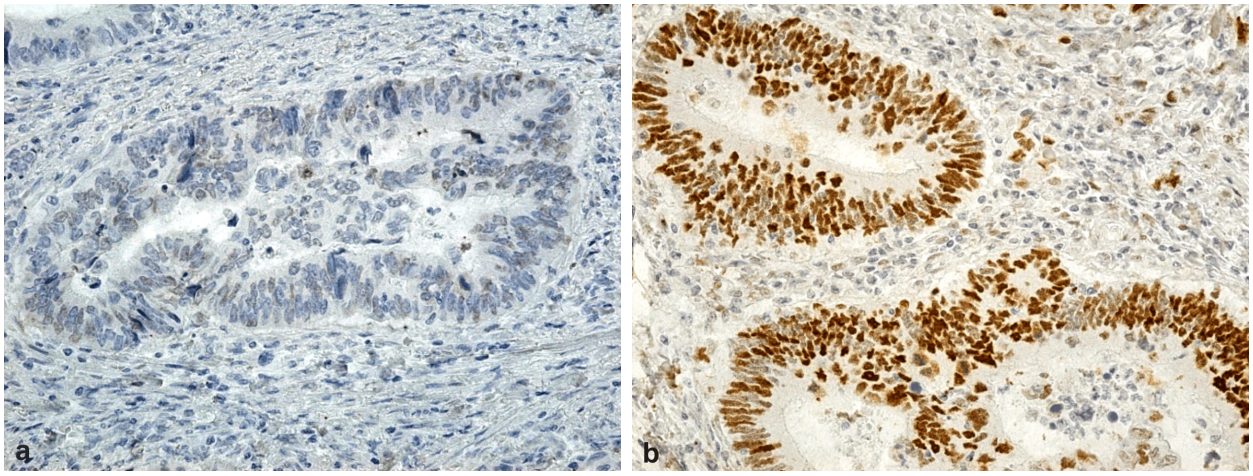

Figure 16 – ***(a) Well-differentiated colon adenocarcinoma with a negative reaction to p53; (b) Well-differentiated colon adenocarcinoma with an intense positive reaction to p53 (Anti-p53 antibody immunomarking, ×200).***

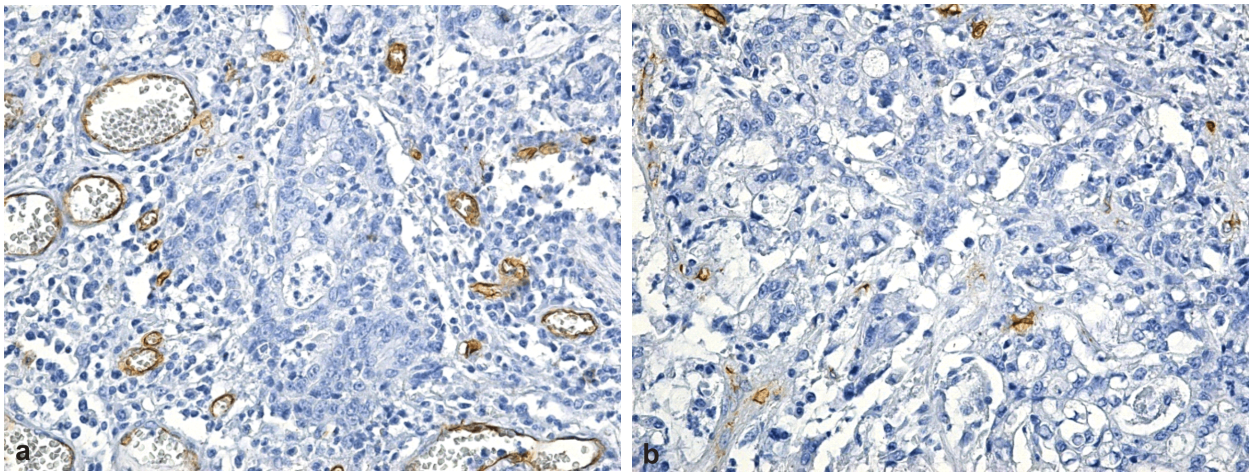

Figure 17 – ***(a) Image of moderately differentiated colon adenocarcinoma, with a well-developed microvascular network; (b) Poorly differentiated colon adenocarcinoma with low microvascular network (Anti-CD34 antibody immunomarking, ×200).***

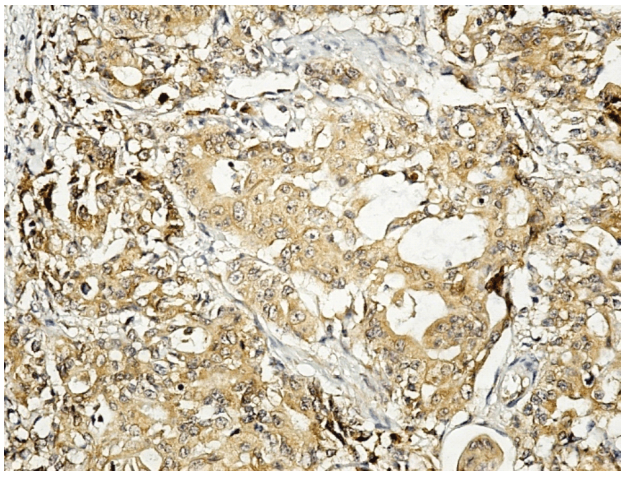

Figure 18 – ***Image of moderately differentiated colon adenocarcinoma with an intense positive reaction to VEGF-A (Anti-VEGF-A antibody immunomarking, ×200).***

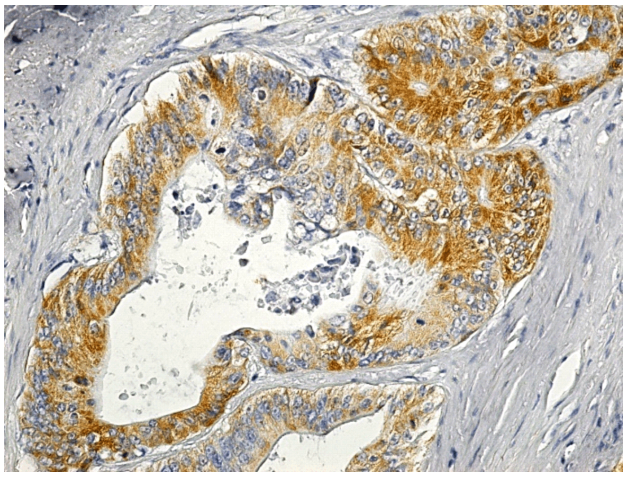

Figure 19 – ***Well-differentiated colon carcinoma with positive reaction to VEGF-C (Anti-VEGF-C antibody immunomarking, ×200).***

Discussions

Worldwide, more than 90% of colorectal cancers occur in people over the age of 50. Our study included patients between the ages of 33 and 84 years old, the average age being 63.93 years in the group of patients with colorectal neoplasm and 64 years in patients with malignancy precursors, in accordance with the epidemiological data described worldwide. The incidence rate has been described as being over 50 times higher in people aged between 60 and 79 years old than in those less than 40 years old. However, colorectal cancer appears to increase among youngsters. In both US men and women in the 20–49 years age group, colorectal cancer is a very common subtype of newly diagnosed carcinoma, being included in the first 10 localizations [12]. In contrast to the decrease in the incidence of colorectal cancer in the elderly, there is an increase in the incidence rate in people less than 55 years old of about 2% per year in the last decade [13].

In terms of gender distribution, the men/women ratio of 2/1 for colorectal cancer patients and 2.71/1 for patients with premalignant lesions recorded in the current study is aligned with data already known worldwide, rates of colorectal cancer incidence being generally higher in men than in women, on all anatomical segments of the large intestine, increasing progressively in the colon, from cecum to rectum. The lower incidence of colorectal cancer observed in women is probably due to the beneficial effect of exogenous and endogenous hormones, woman gender-specific risk factors and a better awareness of the importance of screening in women [14].

The symptomatology that determined the patient's presentation to the physician is varied and although no major differences have been described between the patterns of premalignant lesions and colorectal cancer, however, this differs depending on the location. Therefore, in rectal cancer patients, transit disorders and rectal bleeding are the main symptoms at onset, these being the most common manifestations described in this location. In tumors located in the left colon, weight loss and transit disorders were the most common symptoms described by patients, the obstructive character of the left colorectal cancer manifested by progressive constipation being due to the diminished dimensions of the lumen in this site [3]. Tumors located in the right colon often cause abdominal pain and anemia, followed by weight loss and transit disorders, symptoms described in medical literature as the most common [15]. This is due to the broad lumen of the right colon that allows the long-term development of the tumor process to reach impressive dimensions.

All of these symptoms have been studied in various articles to establish a relationship between onset pattern and prognosis of the disease. Therefore, it has been reported that rectal bleeding was associated with less advanced staging and reduced mortality. Mild anemia at onset, with hemoglobin of 10–12.9 g/dL, was associated with more advanced stagnation and lower mortality [16].

Numerous studies have demonstrated a significant difference regarding the association of tumor, node, metastasis (TNM) staging and specific symptoms, abdominal pain and intestinal transit change being observed in advanced stages of the disease, while rectal bleeding is associated with early stages [15, 16]. Ben-Ishay *et al.* (2013) demonstrated that patients with tumors localized on the left colon manifested a greater percentage of rectal bleeding and changes in intestinal habits more significant than patients with tumors localized on the right colon, as it was confirmed by our study [17].

The non-specific symptoms sometimes create difficulties in the differential clinical diagnosis, at least in the early stages, with other malignant tumors localized in the liver and biliary ways, stomach, pancreas, bladder or woman genital organs [18–21]. In these situations, medical imaging plays a major part in the diagnosis and treatment of colon tumors. Still, colonoscopy remains the most important method of investigating colon tumors at present.

Most studies support the idea that colonoscopy represents the golden standard for diagnosing and monitoring colon cancer, as well as for diagnosing and removal of intestinal polyps [22–24]. Introducing colonoscopy in medical practice led to the reduction of morbidity and mortality caused by colorectal cancer in most developed countries [25–27].

With the help of endoscopy, we were able to describe the location of the tumors, our study including tumors mainly located in the rectum, followed by tumors located in the left colon, the latter being located in the right colon. This ranking also applies to premalignant lesions without being described premalignant lesions in the right colon.

Numerous studies have been conducted to determine whether there is a trend towards increasing the incidence of right colon localization compared to distal location. Several authors have concluded that the distribution of proximal colorectal cancer is on the rise, although Rabeneck *et al.* (2003) concluded that this increase of the percentage of proximal colon neoplasm is not due to the incidence increase of this localization but to the incidence decrease of distal localization of colon cancer and the aging process of the population [28, 29]. However, these data are not supported by other studies, such as that of Gomez *et al.* (2004), which revealed the stable trend of the ratio between proximal and distal localization of colon tumors, without being able to point out this "switch" to the proximal location described by the previously presented authors [30]. This latter study also denies the relationship between advanced ages and proximal localization, idea debated in numerous other studies [29].

The current study completes the global statistical data, confirming adenocarcinoma as the most frequent HP type, being reported in 94% of cases in accordance with the accepted 90% average [31]. Secondly as frequency is mucin carcinoma, followed by signet ring cell carcinoma. Other HP types were not described in the current study. The G2 (moderately differentiated) tumor was the most frequent described, being followed by G1 tumors, G1 + G2 tumors, the latter being described by the G2 + G3 differentiation degree. The tumor degree is generally considered as an independent prognostic factor; therefore, low survival rates have been associated with poorly differentiated tumors [32]. However, we should be aware of the fact that only conventional adenocarcinomas can benefit from this histological classification. MSI status

associated with poorly differentiated tumors changes their prognosis, now being similar to well-differentiated HP tumors.

Although it is well known that signet cell carcinoma is characterized by a more severe prognosis determined by poor histological differentiation, it may have a better prognosis when associated with MSI status [33, 34]. Lynch syndrome is characterized by the presence of a high proportion of MSI tumors that determines favorable prognosis, so mucinous adenocarcinomas occurring in this context behave as low-grade tumor formations [35]. In contrast, microsatellite stability associated with advanced tumors lead to an aggressive phenotype.

However, studies showed that the heterogeneity of colorectal cancer reflects the different pathways of colorectal cancer, with three pathways of pathogenesis: chromosomal instability (CIN), MSI and CpG island methylation pathway [36]. The main biomarkers investigated by researchers in recent decades included *KRAS* mutation, *BRAF* mutation and MSI that are now used as prognostic factors in intrinsic colorectal cancer subtypes [37].

MSI is the result of the failure in repairing the deoxyribonucleic acid (DNA) immediately after replication, and can be defined as a consequence of the repair defect (MMR) deficiency. The epigenetic inactivation of the MutL homolog 1 (*MLH1*) gene and the phenotype of the CpG island is the most common cause of MMR deficiency along with an inherited mutation of *MMR* gene [*MLH1*, MutS homolog 2 (*MSH2*), MutS homolog 6 (*MSH6*), PMS1 homolog 2, mismatch repair protein (*PMS2*)] and Lynch syndrome [38, 39]. MSI occurs in ~ 15% of cases and is accompanied by a much better prognosis than microsatellite stability. The determination of microsatellite status is obtained by IHC evaluation of MMR by *MLH1*, *MSH2*, *MSH6*, and *PMS2* analysis or by MSI testing by chain polymerization reaction [8].

Several studies were conducted to identify the biomarkers categories that give negative prognosis to colorectal cancer. Phipps *et al.* proposed five neoplasm colon models depending on the present molecular subtype, concluding that the molecular subtype with MSI had the best prognosis, being associated with a 40% higher survival rate than microsatellite stability. The most reserved prognostic pattern was the one that associates microsatellite stability/low MSI with positive CpG island methylator phenotype (CIMP), $BRAF^{V600}$-positive mutation and *KRAS* negative [40].

BRAF status was the target of discussion for its prognosis value. Although it was considered to be a predictive factor of low survival, many studies showed the influence of MSI in this case with higher survival rates of patients with *BRAF*-positive status and MSI *versus* those with positive *BRAF* and microsatellite stability [41].

Lack of response to 5-Fluorouracil (5-FU)-based chemotherapy of MSI tumors was observed in many previous studies, seeking optimal therapy for this category of patients. Improved survival using immunotherapy in colorectal cancer with MSI was demonstrated in numerous studies, having as a substrate the presence of multiple neoantigens that are recognized by the immune system, thus explaining the very large amount of tumor-infiltrating lymphocytes (TILs) present in patients with MSI [42].

Immunohistochemistry showed that the typical profile of colorectal carcinoma is CK20 positive and CK7 negative, a pattern seen in 75–95% of the patients. However, in some cases, these markers are not commonly expressed. Numerous studies have tried to establish correlations between marker expression and clinico-pathological aspects. Thus, the CK20 negativity was correlated with the age over 56 years old, with a more frequent localization in the right colon, higher degree of differentiation, increased presence of intratumoral lymphocyte infiltrate, histology mucosal type, advanced stage diagnosis, lymphatic metastasis and lower survival compared to patients expressing positivity for CK20 [43].

In our study, in most adenocarcinomas, the tumor cells were positive and intensely positive to CK19, which shows a high variability of the tumor cell clones. CK19 is the smallest known acid keratin, with a molecular weight of 40 kDa. In the colon, it is present in the proliferative compartment of the epithelium [44]. According to some studies, the cells from the colon epithelium that express CK19 are capable of starting the process of tumorigenesis in certain situations [45]. Other studies showed that CK19 is a tumor marker frequently found in the lymphatic ganglions of the patients with colorectal cancer presenting metastases [46]. Other studies support the idea that the patients with a high CK19 expression have lower survival rates [47]. We consider that, at present, there are few data regarding the phenotype variations of tumor cells and their impact in the prognosis and progression of the disease.

One of the most studied IHC markers in cancer is protein p53, which is involved in the repair of DNA lesions, in the regulation of the cellular cycle, in apoptosis and in cellular aging. In our study, the IHC expression of p53 was extremely varied. According to some studies, p53 presents mutations in approximately 50% of cancers [48, 49]. Low survival rates were registered at patients diagnosed with stage III colon tumors that presented p53 overexpression [50, 51].

The positive expression of VEGF-A and of VEGF-C identified on our samples showed the ability of the tumor cells to synthesize and release biological factors that may facilitate the processes of tumor angiogenesis and lymphangiogenesis. According to some studies, it increases the proliferation and migration of endothelial cells, thus enhancing the formation of blood and lymph vessels [52]. VEGF-A is one of the most important factors of angiogenesis, but it is also involved in the tumor progression, as well as in their metastases [53, 54]. VEGF-C was shown to play a vital part in tumor lymphangiogenesis and in metastases of tumor cells through the lymphatic ways [55–57]. Based on these IHC findings, the growth factors for vascular endothelium have become therapeutic targets.

Conclusions

The alarming increase of colorectal cancer mortality despite the innovative treatments used in personalized colorectal neoplasm therapy shows the need for studying all tumor cell characteristics in order to integrate patients into different prognostic categories and therefore provide the optimal treatment. In conclusion, our study managed

to clinically, endoscopically and histopathologically characterize various cases of colorectal neoplasm and premalignant lesions, without identifying any major differences between clinical data collected from patients diagnosed with premalignant lesions and patients diagnosed with colorectal neoplasm. Our study found that colorectal cancer is most common in 60 years old men, coming from the urban environment, with symptom onset depending on the primary location, the left colon and the rectum being dominated by transit disorders, anemia and weight loss, whereas the tumors located in the right colon having abdominal pain and anemia as primary signs. Colonoscopy described the rectum as the most frequent site for lesions, followed by the left colon. The endoscopic aspects of the tumors were predominantly vegetative processes followed by ulcero-vegetative processes. The HP study confirms that adenocarcinoma is the most common form of presentation, the moderately differentiated degree (G2) representing more than 60%.

Conflict of interests

The authors declare that they have no conflict of interests.

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