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Genetic and serological markers in colorectal cancer surgery

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ABSTRACT

Colon cancer is relatively asymptomatic in the early stages, the manifestations appearing and intensifying with the evolution of the disease, especially when associated with local and/or systemic complications. In such cases, surgical interventions are often emergency and involve more extensive operations (on metabolically and immune-stressed organisms), so that an early diagnosis (endoscopy, tumor markers, etc.) remains not only desirable but even a priority, especially in predisposed patients (genetic factors, lifestyle, etc.). As a consequence, the involvement of tumor markers in colon neoplasms has become more and more investigated in recent times. This review investigates the roles of serological and genetic markers in the management of patients with colon cancer, focusing on carcinoembryonic antigen, mismatch repair deficiency (dMMR), as well as KRAS and BRAF mutations. As a preliminary conclusion, tumor biomarkers seem to have a significant contribution to the diagnosis, decisions related to operative management, prognosis and postoperative follow-up of colon cancer, both in the categories of patients from high-risk groups and those without a clear predisposition to this condition.

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Introduction

Colon cancer is the third most common cancer worldwide, responsible for approximately 800,000 deaths annually [1]. In addition to this mortality rate, the condition involves high costs due to the specific complementary treatments during and after the surgical intervention, without which the morbidity and mortality rates would be even higher [2]. In 10-40% of cases, the first evaluation of a patient by a doctor is an emergency procedure due to the late presentation, which is usually manifested by symptomatology often given by complications such as perforation, occlusion or hemorrhage. The first two complications are associated with lower survival rates both in the perioperative period and in the medium and long term [3]. Numerous researches have been carried out on the topic of colon cancer, especially related to the etiopathogenesis of the disease (at the cellular and molecular level), the risk factors involved, which are the most effective methods for early detection, as well as how all this data can be monitored during oncological treatment. (all this with the primary goal of increasing the survival and quality of life of patients with complicated colon cancer) [4]. Currently, many cellular pathways such as EGFR, CIMP, BRAF, can be influenced by antitumor molecules, while some mutant genes (which often appear in aberrant

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cell metabolism) can be used as positive or negative prognostic factors (in terms of colon cancer complications, response to treatment and also to predict long-term survival) [2]. The objective of this review is to update the knowledge related to the occurrence of colon cancer, positive or negative prognostic factors, the main surgical complications of colon cancer, as well as anatomical, demographic, histopathological and genetic factors that can generate and support the evolution of this condition.

Discussions

Pathogenesis

Regarding the pathogenesis of colon cancer, a number of factors are being investigated as leading to its appearance; thus, there are sporadic cases, familial cases and those involving a complete genetic association [5]. Sporadic cases are the most common, representing up to 70% of cases and are considered to be largely a cumulative action of environmental factors (low fiber intake, smoking, obesity, etc.) [6]. The proportion of cases with a familial component rarely reaches 25%, being characterized by more than 2 individuals suffering from such cancer, while those involving a certain genetic component usually do not exceed 5% [5]. Among patients with colon cancer, it has been observed that there are genetic and epigenetic changes that cause the transformation of normal epithelium into tumor-type epithelium. It will later progress with the invasion of subepithelial structures, a process that takes place in several stages. In all these stages, genetic changes accumulate, which lead to the overexpression of oncogenes, thus resulting in genetic instability at the cell level [7].

Through genetic and functional analysis of colorectal cancer cells, genetic instability was observed to affect chromosomal instability (CIN), microsatellite instability and CpG island phenotype (CIMP) pathways [8]. Chromosomal instability (CIN) is characterized by the appearance or loss of a significant part of a chromosome and is the most common genetic alteration in colorectal cancer, accounting for over 85% of cases [9]. Secondarily, a number of changes occur, such as activation of oncogenes such as BRAF and KRAS, inactivation of APC and TP53, occurrence of aneuploidy or loss of heterozygosity of the long arm of chromosome 18 [5].

The sequence that can lead to the malignant transformation of normal cells begins with the inactivation of APC, followed by mutations of the KRAS gene that lead to adenomatous growth, and subsequently (through the loss of 18q and TP53 inactivation) the process of malignancy takes place [10,11]. The transition to a specific histopathological and clinical form of colorectal cancer (adenocarcinoma/mucin-rich cell, etc.) occurs through the alteration of other cell proliferation pathways, such as TGF-B/PI13KCA, which are specific to adenocarcinoma [12]. Genomic analysis of malignant cells of the colonic mucosa identified significant karyotype changes, such as loss of the short arm of chr. 1, 17, 20 [13,14], as well as the addition of chromosomal fragments on the long arm of chr. 1, 8, 13, 20 [13-15], suppressing the activity of genes that inhibit proliferation and thus favoring the initiation of neoplastic processes [5,12-14].

The main changes that occur in chromosomal instability involve alteration of the adenomatous polyposis coli (APC) gene, the TP53 gene, and loss of heterozygosity of the long arm of chromosome 18. The APC gene encodes a multidomain protein that interacts with a variety of cellular processes, including cell migration, apoptosis, adhesion, proliferation, and differentiation. Mutations in APC occur in most adenomatous structures in the colon, leading to the development of familial adenomatous polyposis and Turcot syndrome; these are premalignant conditions with familial association and increased risk of developing colorectal cancer at an early age [16]. The APC gene inhibits the transition from the G0/G1 phase of the cell cycle to the S phase, and through interaction with the Wnt-Tcf pathway, stem cells are activated. If there is an alteration of the APC protein, it also associates the activation of the Wnt pathway, leading to the transcription of oncogenes and thus to cell proliferation, differentiation and invasion [17]. Other cell proliferation pathways can be stimulated in the case of a mutated APC gene, such as cyclin D1, which is significantly expressed in early stages of colon cancer, or Myc, which promotes the transition from G1 to S phase and controls cell apoptosis [5].

The TP53 gene is mutated or completely absent from the genome of malignant cells in colorectal cancer, with a variable proportion between 50-75%. Control of cell proliferation is mediated by potent suppressors of cell replication such as BubR1 and WAD-1 [18]. Phosphorylation of p53 by Adenosine monophosphate-activated protein kinase (AMPK) leads to cell cycle arrest, resulting in overexpression of cyclin-dependent kinase inhibitor 1A (p21). A decrease in p21 activity and cyclin D1 has been observed in colorectal cancer, with negative prognostic implications for survival rate [19].

Loss of heterozygosity in the 18q region may be involved in the onset of colorectal cancer, being associated with a poor prognosis. It leads to the appearance of altered genes promoting malignancy such as DCC, SMAD2 and SMAD4, the latter two also being implicated in lymphatic metastasis [5].

Microsatellite instability (MSI) is a characteristic of neoplastic diseases, where there is an instability loci due to insertions or deletions of nucleotide bases, a fact described in both non-hereditary and hereditary non-polypoid colon cancer [5]. Loci such as MSH3, ActRIIB, TGF-βR2, Bax, SEC63, AIM2, EBP1 can be affected by this process. The poly-adenine subunit of TGF-BR2 is mutated in colorectal cancer in about 85% cases, but other genes can also be

affected (such as Bax), thus leading to an aberrant proliferation pathway secondary to inhibition of cell apoptosis [20]. In colorectal cancer without familial aggregation, MSI most commonly affects the BRAFV600E gene compared to hereditary non-polypoid colon cancer. In hereditary cases, the major occurrence of cancer is through MMR with the appearance of Lynch syndrome, in which cells from the colonic mucosa or polyps involve several genes in oncogenesis, such as MLH1, MSH2, MSH6, PMS2. The transition between normal colon wall architecture and the appearance of polyps is not driven or influenced by MMR mutations. Conversely, in cases where such sessile/pedunculated formation has occurred and one of the MLH1, MSH2, MSH6, PMS2 genes is mutated, colorectal cancer usually appears in less than 3 years [21].

The EGFR pathway stimulates cell growth, proliferation, and survival by activating several intracellular factors such as RAS/RAF/MEK/ERK, PI3K/JAK/STAT3, being affected in distinct neoplastic pathologies to different degrees [22]. For colorectal cancer, activation of the RAS-RAF pathway via EGFR has been observed, leading to the phosphorylation of mitogen-activated protein kinase (MEK) and activation of extracellular signal-related kinase (ERK) [23]. Proteins can also be activated through the KRAS and BRAF pathways, having the same effects in enhancing cancer cell survival. The most frequent mutation in the KRAS pathway is that of codon 12, which leads to the replacement of aspartate with glycine, resulting in conformational changes of the protein and its hyperactivation, evident in 58% of all colon cancer cases [24].

The CIMP pathway is characterized by alterations in gene expression, but without modifications in the sequence of DNA bases in a specific DNA strand. In most cases, processes of DNA methylation or histone modifications are altered. Thus, methylation of a gene leads to its inactivation and loss of function, with the development of alternative/ substitution mechanisms, but the quality of this alternative path may be poorer than the substituted one [25]. In colorectal cancer, APC and MLH1 can be affected by this process [26].

Clinical Presentation Forms in Colon Cancer

Symptoms associated with colon cancer are initially non-specific and usually become suggestive when complications occur or when the tumors are large. As an example, most often patients accuse changing of the bowel habits, diffuse or localized abdominal pain, and pallor or fatigue secondary to chronic neoplastic anemia [27].

Intestinal obstruction is the most frequent complication of the colon cancer (especially for the left colon), being associated with increased rates of mortality and morbidity [28]. The clinical manifestations of the patient depend by the degree of obstruction caused by the tumor, by competency of the ileocecal valve, and the time elapsed since the inability to pass through the stenotic area. Thus, in the early stages of obstruction, patients present with abdominal distension associated with acute constipation or its worsening in the last months or weeks. Subsequently, symptoms of dehydration appear, secondary to vomiting and fluid migration into the interstitial space [29]. In the advanced stage of an obstructive syndrome, peritoneal irritation syndrome may occur (with or without fever) due to bowel perforation, which may be located at the level of the tumor or at the cecal level in the case of a competent ileocecal valve. Both situations are associated with an increased risk of perioperative mortality through sepsis. Other consequences of intestinal obstruction are represented by the occurrence of respiratory failure due to distension of the intestines, the diaphragm thus having limited movements. In addition, increased permeability of the colonic mucosa to toxins and pathogens leads to a marked inflammatory-infectious syndrome [28]. Treatment for this life-threatening complication is an emergency surgical procedure. Such procedures consist of resection of the affected colonic segment (with/without stoma formation), stoma formation upstream of the stenotic area (without tumor removal), internal derivations, or an endoscopic procedure (in selected cases) with the placement of a metallic stent, which can only solve the acute obstructive complication [30,31]. Medical treatment aims to stabilize the patient in the pre- and postoperative period, in order to correct various hydroelectrolytic, hemodynamic and metabolic imbalances [28].

Perforation is another complication of colon cancer and occurs as the first manifestation of the disease in about 2.6 and 10% of cases [32]. It most often occurs either at the level of the sigmoid colon in 47.3% of cases (by tumor necrosis), or at the level of the cecum (secondary to its marked distension). It is considered that patients with such a perforation have a higher ASA score compared to other causes of perforation of the large intestine (such as acute diverticulitis). In addition, mortality in such cases is higher (between 8-33%), even in patients who benefit from prompt medical and surgical treatment [33]. The location of the perforation can determine outcomes in terms of survival and local recurrence rate. If the perforation is placed at a distance from the tumor, the patient usually presents with diffuse fecaloid peritonitis and sepsis, hemodynamic instability, alteration of the state of consciousness, and a high risk of mortality in the first 24 hours [34]. When perforation occurs at the site of the tumor, localized peritonitis most often occurs in association with a mild inflammatory syndrome [35]. The clinical manifestations of the perforated colon tumor depend to a great extent on the patient. Manifestations can thus vary from abdominal pain, fever, possible muscle defense at the site of tumor perforation, to very serious

manifestations due to multiple organ failure caused by septicemia [32]. The management of such a patient differs depending on the clinical manifestations and the location of the perforation. For perforation at the tumor site, resection of the tumor and formation of a stoma or anastomosis is recommended. If there is diastatic perforation, either the lesion and the site of perforation are resected simultaneously (if the general condition of the patient allows), or a stoma is formed at the site of the perforation [35].

Gastrointestinal bleeding secondary to colon cancer is relatively common, but is often small and self-limiting, rarely requiring surgery to stop the bleeding. Most often, it takes the form of occult bleeding, associated with symptoms of chronic anemic syndrome (asthenia, fatigue, weight loss, loss of appetite) or changes in stool appearance (fresh blood or melena), which alarm the patient to go to the doctor [36]. The therapeutic management of these patients consists of administration of blood products or derivatives, rehydration, administration of electrolytes. After the bleeding has stopped, the source of the bleeding can be identified and treated, using endoscopic/ angiographic methods or surgical procedures [37]. Surgical interventions can also be performed as an emergency if the patient is hemodynamically unstable, needs more than 6 units of blood, or in case of failure of other treatment procedures [38].

Prognostic and Predictive Markers in Colon Cancer

Tumor markers in colon cancer can have both predictive roles on survival and in terms of choosing the best therapeutic approach. Currently, available therapeutic options include not only conventional surgical and chemotherapy treatments, but also immunotherapy represented by monoclonal antibodies, immune checkpoint inhibitors, etc. Such biomarkers (MSI/MMR, KRAS, BRAF and CEA) that offer individualized treatment alternatives are associated with improved prognoses compared to other populations of colon cancer patients undergoing only conventional treatment [39]. The main markers for choosing oncologic and/or immunotherapeutic treatment include deficiency in mismatch repair (dMMR), KRAS mutations, BRAF mutations, CEA levels, toxicity determined by irinotecan or UGT1A1 [38-40].

Mismatch repair deficiency is used in stratifying the risk of chemotherapy response, being a negative prognostic marker for the patients with stage II and III colonic cancer (whose treatment is mainly based on fluorouracil). Studies have shown that patients with stable microsatellite cells had a longer disease-free survival compared to the others [40,41]. High microsatellite instability is a positive prognostic factor in colon cancer that can be cured, unlike stage IV that is associated with low survival rates and resistance to 5-FU administration. These results are explained by the high mutational capacity that determines a marked antitumor response. Unfortunately, this antitumor response is diminished by the local expression of inhibitory messages (such as PD-1 or PD-L1), but which can be targeted by immunotherapy [42].

KRAS is a gene from the RAS family that has mutations in 40-50% of colon cancer cases (with various variants), resulting in a poor response to anti-EGFR treatment (and thus a negative impact on the patient's prognosis). The presence of the native gene led to a better response to cetuximab, while patients with mutated genes showed poor therapeutic responses (having a median disease-free survival of only 1.9 months compared to 3.7 in the group of patients with the native gene) [43]. Metastatic disease does not contraindicate the administration of anti-KRAS immunotherapy. Panitumumab is a a monoclonal antibody that led to an increase in survival without progression of the disease in patients with the wild form compared to those with the mutant form, thus being a treatment of choice in the case of patients with metastatic disease but also for end-stage diseases [39]. Anatomical location of colic tumors (right vs. left) can be both a prognostic and predictive marker. Groups of patients who have tumor formations on the cecum, transverse or ascending colon generally have a lower survival rate compared to those who have tumors located in the left colon. In the latter, an increased response to treatment with EGFR pathway inhibitors was observed. In addition, in left colon tumors the KRAS mutation is less frequent (both in the initial stages and in the metastatic stage), having greater benefits after immunotherapy [44].

BRAF V600E mutation in colon cancer leads to a 50% decrease in survival rate compared to patients with non-mutant genes, especially in sporadic colon cancers with high microsatellite instability [45,46]. The disease-free period for patients with mutant form is 6.2 months, compared to 7.7 months for the wild gene type [45]. Administration of anti-BRAF treatment in combination with anti-EGFR and anti-mitogen-activated protein kinase (MEK) therapy resulted in a response rate of 21% in patients with metastatic colon cancer, in comparation with the control lot where no anti-BRAF treatment was administered [47].

Carcinoembryonic Antigen (CEA) has low sensitivity and specificity in colon cancer, but it is useful in detecting post-surgical and post-immunotherapeutic recurrences. Serum levels above 5 ng/dL led to a significant decrease in postoperative survival rate, as well as a higher risk of acute presentation to emergency room for recurrence of colon cancer and complications [48].

Irinotecan is a topoisomerase inhibitor used in the treatment of metastatic colon cancer, either as first-line or secondary therapy for 5-FU-refractory cases (but has higher side effects, such as severe neutropenia and diarrhea). Mutations in the UGT1A1 gene, which metabolizes irinotecan, lead to drug accumulation with more frequent side effects and reduced overall survival in

patients with metastatic cancer. The UGT1A1 mutation may be considered a useful marker to identify toxicity and the risk of major hematological adverse reactions [39].

Other markers that can be used for prognosis and prediction of survival for colon cancer patients include CpG island methylator phenotype (CIMP), DNA aneuploidy, presence of stem cell markers and circulating DNA. CIMP is characterized by a process of gene inactivation through hypermethylation, which can be identified at the pathways that controls the cell proliferation (CIMP-H) or other tumor-related metabolic pathways (CIMP-L) [49]. Clinical and histopathological analysis has shown that CIMP-H tumors mostly affect women and the right colon, while microscopic examination has shown predominance of mucinous type with poor cell differentiation due to alterations in BRAF genes and genetic repair deficiency. Colon cancer with CIMP-H is associated with lower survival rate compared to CIMP-L [39,50]. Analysis of CIMP/BRAF/MSI-positive cancer leads to a better prognosis compared to CIMP/BRAF/MSI-negative neoplasia (with greater impact on survival), being largely related to the absence or presence of microsatellite instability [50].

A new hypothesis suggests that a small population of stem cells with malignancy characteristics are responsible for dimensional growth, metastasis, and resistance to anti-proliferative treatment, thus leading to recurrence [51]. For colon cancer, several markers such as CD 44, BMI-1, CD24, CD29, CD133, CD144, CD166 and cXCR4 have been studied. CD 44 is a transmembrane protein with role in cell interaction, adhesion, and migration. The isoforms created by mRNA modifications, especially CD44v6, lead to more aggressive disease with poorer prognosis. CD44v6 is involved in the migration of tumor cells and their adhesion to the liver by interacting with hepatocyte growth factor, leading to epithelial-mesenchymal transition with increased cell motility and invasiveness. Accordingly, especially CD44v6 but also CD44 can be used as prognostic markers and treatment targets in colon cancer, especially in metastatic disease [52].

The presence of circulating genetic material can be used in diagnosis, as well as a marker of therapeutic efficacy and prognosis in cancer patients. Circulating DNA can be used to detect micrometastatic disease in surgically treated patients. Related to the dosage of the circulating genetic material, their short half-life (1-2 minutes) must be taken into account, allowing detection only in real time of the amount of neoplastic cells [53]. An increased quantity of tumor genetic material is associated with lower recurrence-free survival and overall survival [54]; the same data have been observed for patients with advanced disease [39].

Sarcopenia is defined as muscle deficiency or inefficiency, which can be confirmed by testing the muscle strength, muscle quality, and overall physical performance. In colon cancer, it is found that up to 50% of non-metastatic cases are sarcopenic, while for the metastatic disease 70% of patients are in this condition [55]. The presence of this syndrome is a negative prognostic marker, leading to lower rates of recurrence-free survival and overall survival, compared to non-sarcopenic patients [56]. The negative effects result from a higher incidence of postoperative septic syndrome, the need for more transfusions, and a higher risk of anastomotic fistula [55].

Influence of Biomarkers on Clinical Presentation

Several factors can be considered in predicting the risk of emergency presentation secondary to complications for colon cancer. These factors are represented by tumor location, size, TNM stage, and anatomopathological features (tumor type, degree of differentiation, lymphovascular and perineural invasion, etc.) [57]. The anatomical characteristics of the tumor can influence the appearance of various complications, and can therefore be considered risk and prognostic factors. Thus, a tumor with a diameter of more than 5 cm leads to an increased frequency of obstructive syndrome, tumor perforation, or bleeding, regardless of whether it is located in the right or left colon [58].

TNM staging may influence the possibility of emergency presentation; the more advanced the stage, the higher the risk of complications [59,60]. The appearance of obstructive syndrome as the initial clinical presentation occurs for stages I-III in 7-29% of cases, reaching up to 40% for stage IV, especially if the tumor associates an aggressive histological pattern [61]. Tumors exceeding stage T3 have a higher rate of perforation, especially if the number of positive lymph nodes on histopathological examination was at examination greater than 4 [60].

Regarding histological markers influencing the mode of surgical emergency presentation in colon cancer, factors such as histological type, tumor circumference, lymphovascular or perineural invasion, degree of differentiation, and the presence or absence of necrosis and/ or microperforation are largely involved [57]. The most frequent histopathological type of colonic tumors consists in adenocarcinoma (in more than 80% of cases), while the rest forms are represented by mucinous or signet-ring cell type [62].

Given the increased incidence of adenocarcinomas, these are more frequently associated with emergency presentation. For cases where the presence of mucinous cells was observed, the clinical presentation was predominantly as an acute obstruction/bleeding, while for cells with a signet-ring appearance, it was associated especially with perforation and obstruction [63].

Lymphovascular, arterial, venous, and neural invasion are negative prognostic factors in colon cancer, being associated with a poor prognosis. For patients whose emergency room presentation was as a complicated form

of colon cancer, these histopathological characteristics were present in varying proportions. Thus, in patients operated electively, the rate of perineural invasion reaches 21.8%, while for those operated on urgently, it reached 33.7%. Vascular invasion was also more common for those treated emergently, with rates of 39.6% versus 29.1% for those treated electively [64].

Other factors contributing to the emergency diagnosis of colon cancer were represented by demographic and socio-economic data. Thus, patients over the age of 79 are twice as likely to undergo emergency surgery compared to those aged 18-54, with women in particular at a 23% higher risk [65]. This phenomenon can be explained by the decreased immune capacity associated with aging, as well as due to associated comorbidities [66]. Other socio-economic factors, such as the distance from the patient's home to the nearest hospital or diagnostic center, as well as the net income/year may also influence the presentation of patients with complicated colon cancer to emergency. Thus, the greater the distance and the lower the income, the more likely they are to present late and with severe forms (poor diet, lack of information about the disease, limited access to screening programs or early treatment, etc.). [67].

Conclusions

Colon cancer poses a significant health problem, characterized by nonspecific symptomatology that often becomes clinically relevant upon the occurrence of complications or with the advancement of the disease. Understanding the clinical presentation forms of colon cancer is crucial for timely diagnosis and effective management. A comprehensive understanding of the interplay between clinical presentation forms, complications, and biomarkers is essential for improving the management and outcomes of patients with colon cancer. Incorporating this knowledge into clinical practice enables tailored approaches that address individual patient needs, ultimately enhancing overall patient care and prognosis. Further research and advancements in diagnostic and therapeutic modalities are warranted to continue improving outcomes in colon cancer management.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. Informed consent was obtained from all subjects involved in the study.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

References

1. Lannagan TR, Jackstadt R, Leedham SJ, Sansom OJ. Advances in colon cancer research: in vitro and animal models. *Curr Opin Genet Dev*. 2021;66:50-56. doi:10.1016/j.gde.2020.12.003
2. Yang KM, Jeong MJ, Yoon KH, Jung YT, Kwak JY. Oncologic outcome of colon cancer with perforation and obstruction. *BMC Gastroenterol.* 2022;22(1):247. doi:10.1186/s12876-022-02319-5
3. Chen TM, Huang YT, Wang GC. Outcome of colon cancer initially presenting as colon perforation and obstruction. *World J Surg Oncol*. 2017;15(1):164. doi:10.1186/s12957-017-1228-y
4. Hafez N, Gettinger S. Oligometastatic Disease and Local Therapies: A Medical Oncology Perspective. *Cancer J*. 2020;26(2):144-148. doi:10.1097/PPO.0000000000000439
5. Bogaert J, Prenen H. Molecular genetics of colorectal cancer. *Ann Gastroenterol.* 2014;27(1):9-14.
6. Le Marchand L, Wilkens LR, Hankin JH, Kolonel LN, Lyu LC. A case-control study of diet and colorectal cancer in a multiethnic population in Hawaii (United States): lipids and foods of animal origin. *Cancer Causes Control*. 1997;8(4):637-648. doi:10.1023/a:1018406716115
7. Malki A, ElRuz RA, Gupta I, Allouch A, Vranic S, Al Moustafa AE. Molecular Mechanisms of Colon Cancer Progression and Metastasis: Recent Insights and Advancements. *Int J Mol Sci*. 2020;22(1):130. Published 2020 Dec 24. doi:10.3390/ijms22010130
8. Pino MS, Chung DC. The chromosomal instability pathway in colon cancer. *Gastroenterology*. 2010 Jun;138(6):2059-72. doi: 10.1053/j.gastro.2009.12.065
9. Markowitz SD, Bertagnolli MM. Molecular origins of cancer: Molecular basis of colorectal cancer. *N Engl J Med*. 2009; 361(25):2449-2460. doi:10.1056/NEJMra0804588
10. Baker SJ, Fearon ER, Nigro JM, et al. Chromosome 17 deletions and p53 gene mutations in colorectal carcinomas. *Science.* 1989; 244(4901):217-221. doi:10.1126/science.2649981
11. Thiagalingam S, Lengauer C, Leach FS, et al. Evaluation of candidate tumour suppressor genes on chromosome 18 in colorectal cancers. *Nat Genet.* 1996;13(3):343-346. doi:10.1038/ng0796-343
12. Markowitz S, Wang J, Myeroff L, et al. Inactivation of the type II TGF-beta receptor in colon cancer cells with microsatellite instability. *Science*. 1995;268(5215):1336-1338. doi:10.1126/science.7761852
13. Hao S, Tong J, Jha A, et al. Synthetical lethality of Werner helicase and mismatch repair deficiency is mediated by p53 and PUMA in colon cancer. *Proc Natl Acad Sci U S A*. 2022;119(51):e2211775119. doi:10.1073/pnas.2211775119
14. Jasmine F, Rahaman R, Dodsworth C, et al. A genome-wide study of cytogenetic changes in colorectal cancer using SNP microarrays: opportunities for future personalized treatment. *PLoS One*. 2012; 7(2):e31968. doi:10.1371/journal.pone.0031968
15. Baudis M. Genomic imbalances in 5918 malignant epithelial tumors: an explorative meta-analysis of chromosomal CGH data. *BMC Cancer*. 2007;7:226. doi:10.1186/1471-2407-7-226
16. Kinzler KW, Vogelstein B. Lessons from hereditary colorectal cancer. *Cell*. 1996;87(2):159-170. doi:10.1016/s0092-8674(00)81333-1
17. Pronobis MI, Rusan NM, Peifer M. A novel GSK3-regulated APC:Axin interaction regulates Wnt signaling by driving a catalytic cycle of efficient βcatenin destruction. *Elife.* 2015;4:e08022. Published 2015 Sep 22. doi:10.7554/eLife.08022
18. Colussi D, Brandi G, Bazzoli F, Ricciardiello L. Molecular pathways involved in colorectal cancer: implications for disease behavior and prevention. *Int J Mol Sci*. 2013;14(8):16365-16385. Published 2013 Aug 7. doi:10.3390/ijms140816365

19. Pasz-Walczak G, Kordek R, Faflik M. P21 (WAF1) expression in colorectal cancer: correlation with P53 and cyclin D1 expression, clinicopathological parameters and prognosis. *Pathol Res Pract*. 2001;197(10):683-689. doi:10.1078/0344-0338-00146
20. Boland CR, Goel A. Microsatellite instability in colorectal cancer. *Gastroenterology*. 2010;138(6):2073-2087.e3.
21. O'Brien MJ, Yang S, Mack C, et al. Comparison of microsatellite instability, CpG island methylation phenotype, BRAF and KRAS status in serrated polyps and traditional adenomas indicates separate pathways to distinct colorectal carcinoma end points. *Am J Surg Pathol*. 2006; 30(12):1491-1501. doi:10.1097/01.pas.0000213313.36306.85
22. Zanetti-Domingues LC, Bonner SE, Iyer RS, Martin-Fernandez ML, Huber V. Cooperation and Interplay between EGFR Signalling and Extracellular Vesicle Biogenesis in Cancer. *Cells*. 2020;9(12):2639. Published 2020 Dec 8. doi:10.3390/cells9122639
23. Constantin VD, Silaghi A, Epistatu D, Dumitriu AS, Paunica S, Bălan DG, Socea B. Diagnosis and management of colon cancer patients presenting in advanced stages of complications. *J Mind Med Sci*. 2023;10(1):51-65. doi:10.22543/2392-7674.1388
24. Kosmidou V, Oikonomou E, Vlassi M, et al. Tumor heterogeneity revealed by KRAS, BRAF, and PIK3CA pyrosequencing: KRAS and PIK3CA intratumor mutation profile differences and their therapeutic implications. *Hum Mutat*. 2014;35(3):329-340. doi:10.1002/humu.22496
25. Koulis C, Yap R, Engel R, et al. Personalized Medicine-Current and Emerging Predictive and Prognostic Biomarkers in Colorectal Cancer. *Cancers (Basel)*. 2020;12(4):812. doi:10.3390/cancers12040812
26. Al-Sohaily S, Biankin A, Leong R, Kohonen-Corish M, Warusavitarne J. Molecular pathways in colorectal cancer. *J Gastroenterol Hepatol*. 2012;27(9):1423-1431. doi:10.1111/j.1440-1746.2012.07200.x
27. Argilés G, Tabernero J, Labianca R, Hochhauser D, Salazar R, et al. Localised colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020;31(10):1291-1305. doi:10.1016/j.annonc.2020.06.022
28. Muldoon RL. Malignant Large Bowel Obstruction. *Clin Colon Rectal Surg*. 2021;34(4):251-261. doi:10.1055/s-0041-1729922
29. Webster PJ, Aldoori J, Burke DA. Optimal management of malignant left-sided large bowel obstruction: do international guidelines agree?. *World J Emerg Surg*. 2019;14:23. doi:10.1186/s13017-019-0242-5
30. Tudosie MS, Pauna A, Stefani C, Staicu IM. Diet and Food chemicals increasing the risk of colorectal cancer – literature review. *J Mind Med Sci*. 2022;9(1):118-124. doi: 10.22543/7674.91.P118124
31. Lee HJ, Hong SP, Cheon JH, et al. Clinical Outcomes of Self-Expandable Metal Stents for Malignant Rectal Obstruction. *Dis Colon Rectum*. 2018;61(1):43-50. doi:10.1097/DCR.0000000000000910
32. Otani K, Kawai K, Hata K, et al. Colon cancer with perforation. *Surg Today*. 2019;49(1):15-20. doi:10.1007/s00595-018-1661-8
33. Zamaray B, van Velzen RA, Snaebjornsson P, et al. Outcomes of patients with perforated colon cancer: A systematic review. *Eur J Surg Oncol*. 2023;49(1):1-8. doi:10.1016/j.ejso.2022.08.008
34. Yang XF, Pan K. Diagnosis and management of acute complications in patients with colon cancer: bleeding, obstruction, and perforation. *Chin J Cancer Res*. 2014;26(3):331-340. doi:10.3978/j.issn.1000-9604.2014.06.11
35. Pisano M, Zorcolo L, Merli C, et al. 2017 WSES guidelines on colon and rectal cancer emergencies: obstruction and perforation. *World J Emerg Surg*. 2018;13:36. doi:10.1186/s13017-018-0192-3
36. Korsgaard M, Pedersen L, Sørensen HT, Laurberg S. Reported symptoms, diagnostic delay and stage of colorectal cancer: a population-based study in Denmark. *Colorectal Dis*. 2006;8(8):688-695. doi:10.1111/j.1463-1318.2006.01014.x
37. Baer C, Menon R, Bastawrous S, Bastawrous A. Emergency Presentations of Colorectal Cancer. *Surg Clin North Am*. 2017;97(3): 529-545. doi:10.1016/j.suc.2017.01.004
38. Silaghi A, Gaspar BS, Epistatu D, Bălan DG, Păunică I, Dumitriu AS, Paunica S, Socea B, Constantin VD. Upper gastrointestinal bleeding in the COVID-19 pandemic; particularities of diagnosis and therapy. *J Mind Med Sci*. 2022;9(2):276-284. doi:10.22543/2392-7674.1363
39. Kuznetsova O, Fedyanin M, Zavalishina L, Moskvina L, Kuznetsova O, et al. Prognostic and predictive role of immune microenvironment in colorectal cancer. *World J Gastrointest Oncol*. 2024;16(3):643-652. doi:10.4251/wjgo.v16.i3.643
40. Grant M, Haydon A, Au L, et al. Immunohistochemistry testing for mismatch repair deficiency in Stage 2 colon cancer: A cohort study of two cancer centres. *Int J Surg*. 2018;51:71-75. doi:10.1016/j.ijsu.2018.01.020
41. Sinicrope FA, Foster NR, Thibodeau SN, et al. DNA mismatch repair status and colon cancer recurrence and survival in clinical trials of 5-fluorouracil-based adjuvant therapy [published correction appears in J Natl Cancer Inst. 2011 Nov 2;103(21):1639. Kim, George P [added]]. *J Natl Cancer Inst*. 2011;103(11):863-875. doi:10.1093/jnci/djr153
42. Gelsomino F, Barbolini M, Spallanzani A, Pugliese G, Cascinu S. The evolving role of microsatellite instability in colorectal cancer: A review. *Cancer Treat Rev*. 2016;51:19-26. doi:10.1016/j.ctrv.2016.10.005
43. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med*. 2008;359(17):1757-1765. doi:10.1056/NEJMoa0804385
44. Hsu WH, LaBella KA, Lin Y, et al. Oncogenic KRAS Drives Lipofibrogenesis to Promote Angiogenesis and Colon Cancer Progression. *Cancer Discov*. 2023;13(12):2652-2673. doi:10.1158/2159-8290.CD-22-1467
45. Venderbosch S, Nagtegaal ID, Maughan TS, et al. Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies. *Clin Cancer Res*. 2014;20(20):5322-5330.
46. Nazemalhosseini Mojarad E, Farahani RK, Haghighi MM, Aghdaei HA, Kuppen PJ, Zali MR. Clinical implications of BRAF mutation test in colorectal cancer. *Gastroenterol Hepatol Bed Bench*. 2013;6(1):6-13.
47. Corcoran RB, André T, Atreya CE, et al. Combined BRAF, EGFR, and MEK Inhibition in Patients with BRAFV600E-Mutant Colorectal Cancer. *Cancer Discov*. 2018;8(4):428-443. doi:10.1158/2159-8290.CD-17-1226
48. Baqar AR, Wilkins S, Staples M, Angus Lee CH, Oliva K, McMurrick P. The role of preoperative CEA in the management of colorectal cancer: A cohort study from two cancer centres. *Int J Surg*. 2019;64:10-15. doi:10.1016/j.ijsu.2019.02.014
49. Socea B, Silaghi A, Rebegea LF, Balan DG, Balalau C, Tenea-Cojan TS, Mihai DA, Paunica I. Diabetes mellitus: interdisciplinary medical, surgical and psychological therapeutic approach. *J Mind Med Sci*. 2023;10(2):217-236. doi:10.22543/2392-7674.1445
50. Murcia O, Juárez M, Rodríguez-Soler M, et al. Colorectal cancer molecular classification using BRAF, KRAS, microsatellite instability and CIMP status: Prognostic implications and response to chemotherapy. *PLoS One*. 2018;13(9):e0203051. Published 2018 Sep 6. doi:10.1371/journal.pone.0203051
51. Motofei IG. Biology of cancer; from cellular and molecular mechanisms to developmental processes and adaptation. *Semin Cancer Biol*. 2022; 86(Pt 3):600-615. doi:10.1016/j.semcancer.2021.10.003
52. Todaro M, Gaggianesi M, Catalano V, Benfante A, et al. CD44v6 is a marker of constitutive and reprogrammed cancer stem cells driving colon cancer metastasis. *Cell Stem Cell*. 2014;14(3):342-356. doi:10.1016/j.stem.2014.01.009

53. Kustanovich A, Schwartz R, Peretz T, Grinshpun A. Life and death of circulating cell-free DNA. *Cancer Biol Ther*. 2019;20(8):1057-1067. doi:10.1080/15384047.2019.1598759
54. Basnet S, Zhang ZY, Liao WQ, Li SH, Li PS, Ge HY. The Prognostic Value of Circulating Cell-Free DNA in Colorectal Cancer: A Meta-Analysis. *J Cancer*. 2016;7(9):1105-1113. Published 2016 Jun 4. doi:10.7150/jca.14801
55. Vergara-Fernandez O, Trejo-Avila M, Salgado-Nesme N. Sarcopenia in patients with colorectal cancer: A comprehensive review. *World J Clin Cases.* 2020;8(7):1188-1202. doi:10.12998/wjcc.v8.i7.1188
56. Nakanishi R, Oki E, Sasaki S, et al. Sarcopenia is an independent predictor of complications after colorectal cancer surgery. *Surg Today*. 2018;48(2):151-157. doi:10.1007/s00595-017-1564-0
57. Golder AM, McMillan DC, Horgan PG, Roxburgh CSD. Determinants of emergency presentation in patients with colorectal cancer: a systematic review and meta-analysis. *Sci Rep*. 2022; 12(1):4366.
58. Yang Z, Wang L, Kang L, et al. Clinicopathologic characteristics and outcomes of patients with obstructive colorectal cancer. *J Gastrointest Surg*. 2011;15(7):1213-1222. doi:10.1007/s11605-011-1563-1
59. Jones AN, Scheurlen KM, Macleod A, Simon HL, Galandiuk S. Obesity and Inflammatory Factors in the Progression of Early-Onset Colorectal Cancer. *Cancers (Basel)*. 2024;16(7):1403. Published 2024 Apr 3. doi:10.3390/cancers16071403
60. Okuda Y, Shimura T, Yamada T, et al. Colorectal obstruction is a potential prognostic factor for stage II colorectal cancer. *Int J Clin Oncol*. 2018;23(6):1101-1111. doi:10.1007/s10147-018-1307-2
61. Boeding JRE, Ramphal W, Crolla RMPH, et al. Differences in Metastatic Pattern in Patients Presenting With or Without Obstructing Colorectal Cancer: A Retrospective Observational Study of 2595 Patients. *Ann Surg Oncol*. 2020;27(4):1048-1055. doi:10.1245/s10434-019-08119-8
62. Pruitt SL, Davidson NO, Gupta S, Yan Y, Schootman M. Missed opportunities: racial and neighborhood socioeconomic disparities in emergency colorectal cancer diagnosis and surgery. *BMC Cancer*. 2014;14:927. Published 2014 Dec 9. doi:10.1186/1471-2407-14-927
63. Sibio S, Di Giorgio A, D'Ugo S, et al. Histotype influences emergency presentation and prognosis in colon cancer surgery. *Langenbecks Arch Surg*. 2019;404(7):841-851. doi:10.1007/s00423-019-01826-6
64. Amri R, Bordeianou LG, Sylla P, Berger DL. Colon cancer surgery following emergency presentation: effects on admission and stage-adjusted outcomes. *Am J Surg*. 2015;209(2):246-253. doi: 10.1016/j.amjsurg.2014.07.014
65. Sullivan J, Donohue A, Brown S. Colorectal Oncologic Emergencies: Recognition, Management, and Outcomes. *Surg Clin North Am*. 2024;104(3):631-646. doi:10.1016/j.suc.2023.12.003
66. Simon AK, Hollander GA, McMichael A. Evolution of the immune system in humans from infancy to old age. *Proc Biol Sci*. 2015;282(1821):20143085. doi:10.1098/rspb.2014.3085
67. Askari A, Nachiappan S, Currie A, et al. Who requires emergency surgery for colorectal cancer and can national screening programmes reduce this need?. *Int J Surg*. 2017;42:60-68. doi:10.1016/j.ijsu.2017.04.050