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Diagnosis and management of colon cancer patients presenting in advanced stages of complications

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ABSTRACT

Colorectal cancer is an important health problem with a significant impact on the individual and society. Malignancy (including colorectal cancer) is usually slightly symptomatic in its initial stages. This causes cancer to be discovered in some patients accidentally (either through screening tests in predisposed individuals or during routine investigations for other diseases), while in other patients the colorectal cancer is discovered in late stages, when the symptoms are much more intense due to complications. Unfortunately, such advanced cases of the disease have high rates of morbidity and mortality even with treatment. Current treatment methods are usually complex, interdisciplinary, causing significant suffering (physical, mental) to the individual, while the cost of treatment per patient seems to be extremely high. Until finding therapeutic methods that are effective and accessible to most patients with advanced colorectal cancer, several methods of prophylaxis and early diagnosis should be considered, to reduce as much as possible the devastating impact of this disease. The purpose of this review is to present literature data regarding the current methods of diagnosis and treatment of patients presenting to the doctor with colorectal cancer in advanced stages of complications.

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Introduction

Tumors have been described since ancient times. For example, in some mummies found in the Middle East and South America, anthropologists have found metastases of an osteosarcoma [1]. As for colon cancer, it was originally studied and described by Hippocrates, who considered that excess black bile was the cause of its occurrence. At that time, in the absence of analgesia and anesthetics, treatment was primarily dietary and symptomatic (administration of tinctures that can relieve pain and/or a mixture of figs and charcoal to stimulate peristalsis in case of occlusive syndrome) [2].

Important steps in understanding the evolution of cancer were made in the following centuries, through the development of a theory according to which the spread of digestive cancers (especially colon cancer) is mainly via the lymphatic route, a fact later demonstrated by Waldayer [3]. Examining cancer cells under an optical microscope, Muller was later able to differentiate between normal and malignant cells based on their different-looking cell nuclei [4]. With the development of technology, a better understanding of the pathophysiology of cancer and how it metastasizes has been achieved, which has led to the implementation of several surgical and medical therapeutic approaches.

Initially, many substances that were supposed to inhibit the growth and spread of cancer cells (such as mustard gas and lead compounds) were tried for therapeutic purposes [5]. The first effective chemotherapy agent was fluorouracil (discovered in 1957), and the first successful operation was performed by Jacques Lisfranc on a 45-year-

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old patient with a rectal tumor [6]. Technological advances have enabled the development of new research theories and models. Thus, nuclear abnormalities were identified in cancer cells, so scientists linked carcinogenesis to DNA mutations. Such mutations would cause not only the appearance of cancer, but also a predisposition of subjects to develop various malignancies, including colon cancer.

All these efforts over the centuries have been driven by an increasing incidence/detection of colon cancer in the general population (being in the top 3 most common cancers in the adult population, both in men and in women), with over 1 million cases currently diagnosed annually [7].

In many cases, symptomatology is nonspecific at onset, such as fatigue and asthenia if the tumor is located on the right colon, while diarrhea and constipation (or their alternation) are more common in patients with tumors of the left colon and rectum. Clinical manifestations are more extensive in the presence of complications (loco-regional invasion with the formation of large tumors that change the relief of the abdominal wall and can be palpated, perforation, hemorrhage, occlusive syndrome or their associations) that determine high rates of morbidity and mortality [8,9].

Colonoscopy is the main diagnostic tool for colon cancer. Due to the low cost of use and increased accessibility, this method can now be used either for the screening of malignant diseases of the rectum and colon, or as a diagnostic and therapeutic method [10]. Current treatments for most patients include surgical resections, with or without adjuvant or neoadjuvant (radio/chemo/immuno-) therapy. For specific cancer forms, targeted genetic and immunological therapies or nanomedicine based on chemotherapeutic agent particles incorporated into various systems (including malignant cells) can also be used, alone or in combination [11]. Regarding complicated colon cancer (hemorrhage, perforation or occlusion), the patient is in a critical general condition (severe anemia, marked inflammatory syndrome with sepsis, etc.), so management is mainly operative and in emergency conditions, with the main goal of saving the patient's life [12].

The aim of the present study is to review the specialized literature on methods of diagnosis and management of patients with colorectal cancer in advanced stages of complications at admission.

Discussions

Epidemiology

Colon cancer is the second most common malignancy in countries with high living standards, causing approximately 50,000 deaths annually in the USA and over 950,000 globally [13,14]. Incidence in the global population tends to be 9.5% of cancers in women and 10.1% in men [15]. The population most prone to develop colorectal cancer is the one with a high economic status, where sedentary lifestyle, obesity and smoking have a high prevalence in the population. Instead, the highest mortality was found in developing countries, as lifestyles are rapidly approaching the Western pattern, while screening programs and access to advanced treatments are still very limited [16].

The stage and type of complications by which colon cancer is discovered significantly influence survival. Thus, patients with small tumors and no lymph node invasion (stage I or II) have a 5-year survival rate of approximately 90% [17]. In contrast, patients presenting in emergency with a complication have a median survival of 59 weeks from the acute event, with perioperative mortality ranging from 5 to 34% and 5-year survival between 12 and 30% [18,19]. The lifetime risk of developing colon cancer varies by sex. The male population has a 0.65% risk, while the female population has a 0.45% lifetime risk of developing colon cancer [20].

Complicated colon cancer can take 3 major clinical forms: perforation, occlusive syndrome, and hemorrhage. Hemorrhage can manifest itself in the form of simple chronic anemia through the constant loss of small amounts of blood, dark-colored stools, or in the form of freshly excreted blood [21]. The complicated form of colon cancer occurs in almost one third of all cases, in which there is usually loco-regional invasion and distant dissemination. They cause a higher rate of tumor recurrence and a higher 5-year mortality rate compared to cases detected in early forms [22]. In perforated forms of colon cancer, the rate of hematogenous metastases is much higher than in other forms of the disease, even if they present the same stage and histological type [23].

As for the risk of developing colon cancer, it is given by two types of factors. Individual/genetic factors cannot usually be modified, while environmental factors can lead to either a decrease in the degree of risk or an increase in it (depending on their nature and action).

Factors that cannot be modified are represented by: age, the 60-79 year group having a 50 times greater risk of developing colon cancer compared to the population under 40 [24]; the presence of inflammatory bowel diseases (both Crohn's disease and ulcerative colitis lead to a risk more than 10 times higher than in the general population, due to inflammation that is localized in the mucosa or the entire wall of the colon) [25], colon history of cancer or adenomatous polyps in the family and the genetic component [26].

The genes involved in the occurrence of colon cancer are represented by MLH1 and MSH2 mutations, which are associated with non-polyposis colon cancer (which represents between 2 and 6% of the entire colon cancer population) but also with other neoplasms such as the

pancreas, kidneys and uterus [27]. APC is a suppressor gene that controls beta-catenin and also interacts with E-cadherin, thereby inhibiting cell growth. When mutated, APC leads to the appearance of familial adenomatous polyposis, characterized by the appearance of numerous colonic polyps that can become malignant; the risk of developing colon cancer during life is 100%, since their malignant transformation begins in the first two decades of life [26].

Environmental factors that can influence the occurrence of colon cancer are largely represented by food. Preparations based on meat or animal fat (prepared at high temperatures) can be degraded by bacterial flora into N-nitroso compounds, polycyclic amines and aromatic hydrocarbons, which have carcinogenic effects [28,29]. Physical activity has a protective role by accelerating the rate of defecation, while smoking predisposes to the appearance of adenomatous polyps which are precursors of colon cancer [30]. Excessive alcohol consumption can induce malignant transformation of cells through its metabolites (acetaldehyde), especially in association with nicotine [31].

The most studied factors that can be influenced are diet and physical activity, which are closely related. By increasing the intake of fiber, fruits and vegetables, there is a reduction in the risk of developing cancer by up to 70% [32]. This effect is obtained due to the increased content of antioxidants, the most important of which are phenols, flavonoids and sulfur products. Such compounds can neutralize free radicals formed as a result of fermentation processes, can influence different cellular or metabolic transmission pathways increasing primary cellular immunity, or can induce apoptosis of premalignant cells [33,34]. Another protective factor against colorectal cancer is the increased intake of whole milk and products derived from it, which can reduce the risk of colon cancer by up to 26% if consumed daily in proportion of 500g/day [35]. It is probably an effect of the increased calcium content that acts as a ligand, trapping saturated fatty acids and bile acids, thus reducing the degree of inflammation in the colonic mucosa [36].

Diagnosis

In the initial stages of the disease, the symptomatology associated with colon cancer is usually nonspecific and of low intensity (in the form of abdominal pain, changes in stool and transit, and/or weight loss). Later, when the disease becomes more advanced, bleeding may occur in association or not with the stool, as well as the palpation of a tumor formation in the abdomen [36]. For a prompt and reliable diagnosis, an anamnesis is necessary (if there are relatives who have suffered from this disease, at what age the cancer started and the cause of death, if there are cases of Lynch syndrome or familial adenomatous polyposis), after which a colonoscopy with biopsy is necessary to obtain a definite histopathological result [37].

Currently, the gold standard for diagnosis is colonoscopy and biopsies from suspected tissue, which may also be a useful method of treatment for malignantly transformed adenomatous polyps [38]. Because it is an intervention that must be performed by an operator with extensive training, deep learning methods have been developed to help the operator recognize possible tissue abnormalities that require biopsies. The rates of misdiagnosis or non-diagnosis appear to be much lower when software associated with the endoscopy method is used [39].

Endocytoscopy is a relatively new method that evaluates the appearance of the mucosa and submucosa with high resolution by obtaining microscopic images of both cells and even nuclei. It is a method that involves the application of methylene blue, being able to highlight some cellular characteristics such as: the arrangement of the cells, their size and shape, as well as the number of nuclei (or if there is any atypical nucleus) [40]. Regarding cytoendoscopic examination in colon cancer, it has a sensitivity and specificity approaching 95% [41]. Compared to the traditional method of diagnosis with colonoscopy and histopathological examination, there are no differences in lesions larger than 5 mm [42]. In association with artificial intelligence, the sensitivity obtained was over 90% and the specificity over 98% in a group of 200 patients [43].

High-resolution microendoscopy (HRME) is an effective method for investigating the mucosa and submucosal tissue, but it is not yet widely available at present. From a technical point of view, a probe can be placed on the working channel of the endoscope that approaches the tissue to be investigated and histological images are obtained, highlighting the nuclear number, shape and pleomorphism [44]. Regarding colon cancer, HRME has a much higher sensitivity and specificity for detecting potentially malignant adenomatous polyps compared to standard white light endoscopy (94% and 95%, vs. 65% and 39%) [45].

Blood tests, urine and stool samples have the advantage of being easy to collect and without creating a pronounced discomfort for the patient, so numerous methods have been developed to identify patients with colon cancer (some of them with an even very accurate large, similar to pathological examination). APC, K-ras, p53, Bcl-2 Cyclin D1, E1 and microRNA/DNA can be identified in stool, blood, urine, even in breath via volatile products [46,47].

One of the new diagnostic markers developed for colon cancer is circulating DNA as a result of cell apoptosis. Most of the time, the sizes of these chains of nitrogenous bases reach the number of 180, while in patients with cancer of any type the fragments are larger [48]. By

forming a ratio between the number of long and short DNA chains, the integrity of cellular DNA can be identified. A 25- to 50-fold increase in the ratio is observed in colon cancer patients compared to the healthy population [49]. Thus, quantitative PCR analysis of DNA microchains has a sensitivity of 73.1% and a specificity of 91.8% [50]. Unlike DNA, RNA chains of about 20 bp are more stable, being harder to degrade endogenously and can withstand variable pH values [51]. Thus, various batteries have been developed for the recognition of circulating mircoRNA, including the colorectal cancer, which can reach sensitivities of over 90%. The association of Mi-24, Mi-320a and Mi-423-5q (preformed RNA sequences) leads to a sensitivity of 92.8% and a specificity of 70.8% in the diagnosis of colorectal cancer [52].

Another type of markers that can be used in colorectal cancer are hypoxia-inducible factor (HIF) and 1-alpha-antisense RNA-1, which have high specificity, establishing the diagnosis in 151 cases out of 160 [53].

Colorectal neoplasia differentially expressed-h (CRNDE-h) is a marker that can diagnose colon cancer. Comparing with CEA marker, it can better differentiate the suspected patients from the healthy individuals and can also be used as a prognostic marker. Its increased values are associated with lymph node metastases, and with a lower 5-year survival compared with those who have borderline levels [54].

Slit-Like 2 is a transmembrane protein (also known as Vasorin) that can be found in aortic smooth muscle fibers, as well as in breast, hepatocellular or prostate cancers, where it has a role in promoting tumor growth and invasion [55,56]. In colon cancer, high levels of this marker were found compared to the control group, the higher values being correlated with advanced disease. Values between 75.54 ± 5.70 pg/mL occur in the normal population, while values between 252.81 ± 76.82 pg/mL are frequently found in patients with tumors placed on the colon [57].

Although they have lower specificities and sensitivities, non-invasive tests collected from faecal matter have the advantage of being fast, cheap and easy to use even by patients. The first of the stool-collected tests was the Guaiac stool test, which can identify small amounts of blood in the stool, reducing mortality by 10-20% in tested patients by faster detection of colon tumors [58]. Unfortunately, the sensitivity and specificity of this test are around 40% [59], being not able to differentiate between human and animal heme or whether the hemorrhage is above or below the Treitz angle [60]. An improvement of this test was the faecal immunochemical test which recognizes human hemoglobin only in very small amounts (only one test being required) so that bleeding lesions (adenomatous polyps, diverticula, etc.) can be identified [61].

Apart from the presence of blood in the stool as a result of an adenomatous polyp or a tumor lesion, another diagnostic element can be represented by the presence of genetic material in the form of DNA/RNA. About 0.1% of the DNA in the stool is from the colonic mucosa, the rest being bacterial or from food [62]. The Cologuard test is the only test that recognizes tumor DNA and is currently used as a screening method in colorectal cancer. It has much better sensitivity and specificity than faecal occult blood tests [63].

Alteration of cellular metabolism in a neoplastic patient can lead to waste products that can be gaseous at room temperature and can be detected in the various eliminated products of patients, such as urine, exhaled air or feces [64]. Urine from cancer patients was examined by gas chromatography and field asymmetric ion mobility spectrometry, and degradation products with molecular masses up to 1500 daltons were identified [65]. These methods have a sensitivity between 68 and 89% and a specificity of 60% when used in association.

Regarding the volatile products emanated through feces, in colon cancer hydrogen sulfide is involved in carcinogenesis through direct effects on the cells of the colonic mucosa and via the alteration of the microbiota at this level [66,67]. Other volatile products identified in patients with colon cancer are those derived from acetone such as propan-2-ol and hexan-2-one resulting as a reaction between ethanol and 3-methylbutanoic [68], methyl mercaptan which was found in large quantities in those who had advanced stages of the disease as a result of the reaction between amino acids with sulfur and lactic acid produced by cancer cells [69].

Regarding the volatile products emitted by feces, in colon cancer hydrogen sulfide is involved in carcinogenesis through direct effects on the cells of the colonic mucosa and by altering the microbiota at this level [67]. Other volatile products identified in colon cancer patients are those derived from acetone, such as propan-2-ol and hexan-2-one, which result from the reaction between ethanol and 3-methylbutanoic acid [68]. Methyl mercaptan has been found in large amounts in those with advanced disease stages as a result of the reaction between aminoacids with sulfur and lactic acid produced by cancer cells [69].

Numerous volatile compounds can be eliminated through breathing, colon cancer patients being more easily identified by changing the ratio of these volatile products. Thus, gas chromatography found higher levels of ethyl acetate compared to the healthy population and identified lower levels of 4-methyloctane, with a sensitivity of 85% and a specificity of 95%, with an accuracy of 91% [70]. Secondary to these results, gas chromatographic examination of breath can be used as a future screening method for colorectal cancer, the only drawbacks being the lack of a universal protocol for device calibration and the limited availability of the necessary equipment [66].

Treatment of complicated forms of colon cancer

Occlusion and hemorrhage are the most common surgical complications/ emergencies of colon cancer. If the general condition of the patient is good and there is no dissemination (local or distant), curative surgical oncological treatment should be performed [71,72]. From an anatomical point of view, the occlusion of the colon can be proximal (if the formation is on the transverse or ascending colon, up to the splenic flexure) or distal (if the tumor is located on the descending and sigmoid colon). These tumors placed on distinct segments of the colon have different treatments, due to distinct embryological and anatomical characteristics. Stenotic tumors occur more frequently in the left colon because it is smaller in diameter and the stool is generally solid (due to greater water absorption), so the occlusive complication is more common in the left colon [73]. In contrast, the right colon is much larger in diameter and the contents are semisolid. Tumors placed at this level are frequently voluminous and invade adjacent structures, the most frequent complication of tumors located on the right colon being hemorrhage.

Surgical treatment in the case of obstructive tumors of the right colon is represented by right hemicolectomy, with ligation at the origin of the ileo-colic arteries, of the right colic arteries, and of the right branch of the middle colic artery, followed by the restoration of digestive continuity through ileo-colic anastomosis. If the tumors are placed distally on the right colon, an extended right hemicolectomy with ligation of the middle colic artery at the origin is required, which would involve extensive resection and more distal anastomosis [18]. Postoperative complications that may occur in emergency patients are higher, with the rate of post-anastomotic fistulas estimated to be between 2.8 and 4.6% compared to 1-2% in elective operations [74].

Minimally invasive laparoscopic treatment of obstructive colon cancer can achieve the same oncological standards in terms of complication rate and survival. The 30-day mortality of patients who underwent laparoscopic resections was better than those who underwent the classical surgical approach, while oncological outcomes were similar. Comparing the number of nodes removed, the recovery rate, and the amount of blood lost, the outcome was much more favorable in the case of the laparoscopically treated group [75].

Distal occlusion is more clinically evident because the consistency of fecal chyme is greater and the diameters at this level are smaller, so a small tumor can cause intestinal obstruction in relatively early stages of the disease. Therapeutic modalities in this case vary, from continuous colostomy, Hartman resection, resection with anastomosis, colonic stenting, etc. [18].

Regarding the placement of the continuous colostomy, it can be performed either as a definitive treatment (in advanced cases) or as an intermediate therapeutic stage (in which the patient must first be rebalanced and stabilized). After stabilization, the patient is treated by oncological methods, to transform the tumor into a resectable stage. Afterwards, the tumor is resected and the continuity of the digestive tube is restored. It is a simple treatment method that can be performed even with local anesthesia, but the rates of peristomal complications are relatively high (due to the risk of prolapse or parastomal hernia, especially when performed as an emergency) [76].

Resection of the tumor placed in the left colon, followed by colostomy at the proximal end and closure of the distal end is known as the Hartman operation (a type of surgical procedure commonly performed for obstructive tumors of the distal colon) [77]. Currently, there are no significant differences in the long-term evolution of patients in the colostomy group compared to those who followed a sequential therapy, in the latter case, however, the time spent in the hospital being longer [78]. The main disadvantage of this intervention is the presence of residual stoma, which leads to a decrease in the quality of life secondary to local complications. In 20% of cases, the restoration of normal digestive transit is not performed by closing the colostomy, because there is a high risk of morbidity and mortality, as well as a higher risk of local recurrence [79].

The indications for the Hartmann procedure are aimed at patients with high anesthetic risk scores in whom the time of presentation to the hospital is late (the evolution of the disease being associated with significant distension of the colon), and patients with high operative risk in whom a staged surgical approach could lead to the decompensation of some severe systemic (cardiac, pulmonary, renal, hepatic, etc.) comorbidities [80-82].

In the case of obstructive colon cancer, it is therefore preferable for the patient to undergo a unique surgical intervention (resection with anastomosis), thus maintaining the quality of life as before the operation. For a long time, it was considered risky to perform an anastomosis in the case of patients with occlusive tumors, due to the marked distension of the digestive segments associated with an altered state of nutrition. These factors predispose to the occurrence of anastomotic fistulas (with high morbidity and mortality rates), which can cause prolonged hospitalization that delays the initiation of chemotherapy [18]. Currently, it is considered that the method of resection and anastomosis in the same time should be applied only to well-selected patients, in order to reduce the large number of surgical interventions secondary to complications [76]. Such factors that influence the possibility of performing an anastomosis in emergency cases are: age >70 years, high anesthetic risk (ASA III-IV), if the disease is in an advanced phase, the presence of preoperative renal insufficiency or other

systemic comorbidities. When several such unfavorable factors are associated, it is necessary to perform a colostomy or a Hartmann-type surgical procedure [83].

Another therapeutic option in the case of stenotic tumors is represented by the installation of metal stents in the affected area, being used either as a palliative method (in cases of unresectable tumors), or as a transitional therapy until the patient is stabilized in order to have an optimal (local and general) operator status [84].

Some authors recommend avoiding the placement of stents as a temporary treatment, as there are suspicions that it could negatively influence the long-term outcome. By installing the dilating stent, there could be microperforations in the colon wall that would lead to transparietal spread and thus a higher risk of peritoneal dissemination and carcinomatosis. Another possible consequence of the mechanical action of the stent would be the migration of tumor cells through the microcirculation with hematogenous dissemination [85-87]. However, the morbidity and mortality rates of patients with preoperative stent placement appear to be similar to those of electively operated patients, with the rate of anastomosis being relatively comparable [84]. Another advantage of this minimally invasive treatment is the lower rate of performing colostomies, while the number of nodes harvested for histopathological evaluation was similar to that corresponding to scheduled surgical interventions [88].

From a technical point of view, difficulties may arise in terms of stent placement and functionality, especially if the stenotic portion exceeds 8 cm and its placement requires the installation of a guide system to reach the area of stenosis [89].

Cancer placed in the rectum and causing an occlusive syndrome has the same principles of treatment as the tumor located in the left colon. Thus, a colostomy can be done for decompression, but this involves sacrificing a few centimeters of intestine that would be necessary in the case of a low anastomosis. An alternative to this inconvenience is the formation of an ileostomy, but with the risk of creating an isolated loop if the ileo-cecal valve is competent [18]. Another option for patients with stenosing formations at the level of the recto-sigmoid junction or in the upper rectal region is the Hartman procedure. This has curative potential, but with the risk of putting the patient in the situation of a definitive colostomy, because restoring the continuity of the digestive tube through anastomosis is very rare. Metal stents can be mounted as a palliative method also at the level of the rectum, but this maneuver is risky due to the increased peristalsis at this level that can lead to the migration of the metal device and the induction of rectal wall lesions [90].

Another complication that can develop in the evolution of colon cancer is represented by the perforation of the colon wall (secondary to the ischemia and necrosis of the tumor tissue) or by distant (diastatic) perforation due to the upstream phenomenon of distension of the colon [91]. Such colonic perforations lead to acute fecaloid peritonitis, a clinical entity with high mortality that can reach up to 50% (secondary to septic shock with multiple organ failure) [92]. One of the factors that influence mortality in the case of peritonitis by perforation of a tumor is the blood pressure value, a value below 80 mmHg (especially in the elderly) being a negative prognostic factor [18].

The clinical features of this complication are those of an acute abdomen, so the strategy must be based on a surgical intervention aimed at controlling/ treating the lesion. This is possible by performing a laparotomy/ laparoscopy, with identification of the perforated area followed by resection of the affected segment. Even if there is no data to suggest a preoperative diagnosis of malignancy, surgery will be performed (where possible) according to the principles of oncological surgery. If resectable liver metastases are present, they can be resected only if the general condition of the patient allows extensive surgery. In most cases, the anastomosis cannot be performed, the ileostomy being the final result of the intervention. If an attempt is made to restore the continuity of the digestive tract during the first operative time, an upstream protective stoma is recommended [93].

Diastatic perforation of the cecum occurs secondary to severe vascular disorders, caused by the massive distension of this digestive segment as a result of a stenotic tumor located downstream. In this case, a subtotal or even total colectomy is performed excluding both lesions of the digestive tract with stoma formation, or with ileo-colic or ileo-rectal anastomosis if the patient is not in a high-risk group [94].

Minimally invasive treatment for perforated colon cancer can also be performed through laparoscopic procedures. Patients operated with this method had a shorter hospital stay, a quick return to activities, less blood loss, all with oncological results relatively similar to open surgery but with a longer operative time. After the creation of pneumoperitoneum, several factors can intervene and complicate the therapeutic approach (massive contamination of the peritoneal cavity with dilated intestinal loops and multiple adhesions, which makes it difficult to assess the location of the perforation even using an effective peritoneal lavage). Consequently, especially for surgical teams that are not as well trained as for elective interventions, the expected results may not be as good as those in centers of excellence. For this reason, it is recommended that laparoscopy be used only by trained teams (with at least 20 previously operated cases, who can easily overcome any technical difficulties that may arise), to lead to the best postoperative therapeutic results [95].

Lower gastrointestinal bleeding is a syndrome characterized by the passage of fresh or partially digested

blood in the stool. Colon cancer can present this form of complication in 3-11% of cases [96]. Most of the time, lower gastrointestinal bleeding is small, self-limited, which can alarm patients early, bringing them to the doctor at an early stage of the disease [97]. The initial management of this syndrome is represented by stabilizing the patient, correcting his various biochemical abnormalities such as coagulopathy, dyselectrolytemia and, subsequently, finding the source of the bleeding [21]. This can be done by endoscopic methods, but in an emergency situation (with an unprepared colon) the source can only be identified in 74-89% of cases [98]. The advantage of colonoscopy is that this method can be used not only to identify, but also to treat the cause of bleeding. Among the endoscopic treatment methods listed in the literature are devices that use thermal energy to achieve coagulation with or without contact, radiofrequency ablation, endoloops, injection of various sclerosing or hemostatic agents, and hemospray [99].

The thermal methods that assume direct contact with the tumor are by far the most used, through which a good local hemostasis is achieved initially, especially if it is associated with the local administration of norepinephrine. Approximately 30 days after the intervention, bleeding can reappear with rates that can reach up to 80%, thus being a useful therapeutic method especially for the preparation of a subsequent surgical intervention [100].

The injection of sclerosing or procoagulant substances was the first endoscopic method of performing hemostasis, being used even today in the control of upper digestive hemorrhages or in the case of hemorrhagic colon tumors. The most used agent is adrenaline as a solution with a dilution of 1:10,000, having both vasoconstrictor and thrombogenic effect [101]. The use of other agents, such as alcohol, appears to be correlated with high rates of ischemic necrosis and tumor perforation [102].

Angiography is an intervention capable of identifying the source of bleeding and treating it by selectively embolizing the vessels that supply blood to the respective tumor. Different hemostatic agents such as vasopressin or gelatin particles are used for injection, methods that have success rates of approximately 70% [103]. The main disadvantage of this method is the increased risk of ischemia and necrosis. Consequently, angiography is mainly used as a diagnostic method, or as a therapeutic method for cases where there are distant metastases and multiple comorbidities, thus preventing laparotomy (for bleeding control) that would delay the administration of chemotherapy [98].

The natural evolution of colon cancer is aggravated by the occurrence of distant metastases, the most frequently affected organs being the liver, peritoneum, lung and brain (either by lymphatic or hematogenous route). The appearance of two colonic tumors can be considered metastasis if the respective tumors have the same cellular/molecular characteristics [104]. Through a multimodal treatment (surgery, chemotherapy, radiotherapy, immunotherapy, genetic, biological support, etc.), colon cancer can be completely eliminated in some patients even in advanced stages, thus obtaining appreciable survival rates at 5 years. All this can be achieved by a complete evaluation of patients with genomic evaluation of tumor cells, including RAS and BRAF gene status [105].

Liver metastases often occur in patients with colon tumors whose cells overexpress genes encoding MMP-1, MMP-2, COX-2, TIMP-1, VEGF [106,107]. Resection of these metastases without preoperative chemotherapy is recommended, as this therapy has no benefit in terms of patient survival at 5 years, while complication rates appear to be higher in patients who received the chemotherapy regimen [108].

If liver metastases are discovered at the same time as the primary tumor, there are several therapeutic options. When the tumor is symptomatic (complicated by either occlusive syndrome or bleeding) and the metastases are resectable, emergency surgical procedure is required only to treat the local complication. It is followed by systemic chemotherapy, and finally the surgeon proceeds to resect the remaining liver metastases. Regarding occlusive rectal cancer where radiotherapy plays an important role, a colostomy can be performed initially, after which the oncological treatment is initiated which is finally followed by the resection of the liver metastasis [105].

For asymptomatic colon tumors with hepatic metastases, a 6-course cycle of chemotherapy can be initiated, after which the colon tumor and remaining hepatic metastases are resected in the same surgical procedure [109]. The postoperative course is without major complications or an increased mortality, if the surgical intervention does not involve major liver resections [110].

The criteria for resection of liver metastases elaborated by the American Hepato-Pancreato-Biliary Association are represented by the absence of tumor cells in the resection margin of the tumor, the preservation of liver function, the limited presence of extrahepatic disseminations (which can eventually be resected), lack of disease progression during chemotherapy, as well as the ability of the patient to be fit for major surgery [111]. If the patients are at the limit of a possible liver resection, chemotherapeutic treatment can be administered beforehand, thus transforming the initial oncological stage into a stage much more favorable for surgical intervention. These complex therapeutic approaches result in a 5-year survival of 50%, with perioperative mortality rates below 3% [112].

Regarding the surgical treatment of choice, most operators opt for partial hepatectomy [113]. Limited resections are associated with lower rates of postoperative

complications and morbidity, a shorter length of time spent in the intensive care unit, and a lower rate of liver failure [114,115].

For advanced cases with large or disseminated tumors in both liver lobes, hypertrophy of the remaining liver parenchyma can be done by so-called two-stage hepatectomy. It is an intervention associated with high risks, but it can be performed in experienced centers. In the first stage, all tumor formations in segments 2 and 3 are resected, then the right portal branch is ligated, which causes hypertrophy of the remaining parenchyma for 6-12 months. Subsequently, a second resection is performed, which removes all other metastatic formations [116]. In the period of controlled hypertrophy of the liver parenchyma, it is important to follow the growth rate, because an increase of more than 2% per week is a negative impact factor for the second intervention (higher risks of liver failure) [117]. Completion of second-stage resection leads to an increase in median survival of approximately 11 months (37 vs. 16) [118].

Regarding the laparoscopic approach to liver metastases, several studies have compared this minimally invasive method with classical open surgery. Patients who were included in the laparoscopic group had a lower rate of postoperative complications (19% vs. 31%), with lower rates of hospitalization (53h vs. 96h) and less need for narcotics for pain control. The time spent in the operating room was approximately equal, but with a lower blood requirement in the laparoscopically treated group. The cost of the interventions was higher in the case of laparoscopic interventions, but with a better postoperative recovery and a shorter length of hospital stay, thus reaching an approximately equal total cost per patient [119]. After surgery, patients were evaluated for several factors that could predict long-term surgical success, so quality of life was better in the laparoscopically treated group in many respects. This comparison included emotional, physical and social aspects [120]. Recurrence rates ranged between 62-67% in both cohorts of patients with lung, liver and peritoneal metastases, with the factors considered leading to recurrence being the presence of extrahepatic metastases and lymph node invasion [119].

The synchronous approach to both the primary tumor and liver metastases can be done by classical or laparoscopic methods. In a meta-analysis performed in dedicated centers in France, Spain, Israel, UK, Italy, South Korea, survival, feasibility and patient risks were analyzed. Similar rates were obtained in terms of blood loss rates and transfusion, but with longer operating times in the case of laparoscopic operations. Out of the total of 20 laparoscopic interventions, only one was converted to classical surgery, the reason being the appearance of technical defects and intraoperative incidents. Major preoperative complications were encountered in 20% of cases, with no difference in the mortality rate (only 4 deaths out of 490 patients were recorded). Length of hospital stay ranged from 6 to 16 days for both cohorts. At 3 years post-intervention, no differences in survival rates were observed between the 2 cohorts, which means that, from an oncological point of view, the laparoscopic approach is similar to open surgery, but with better results in terms of safety, survival rates, bleeding and postoperative complications. Not all patients were approached laparoscopically, as this type of approach was used mostly for antero-lateral resections compared to posterior ones [119].

Metastasis of colon cancer at the peritoneal level occurs in 11% of patients [121], the last stage of the disease being the appearance of peritoneal carcinomatosis. It is considered a final stage that requires palliative and supportive nutritional treatment for the patient. Most of the time, it is associated with dissemination to other organs, and if more than 2 sites of metastasis are involved, the prognosis is severe, as they generally show BRAF gene mutations much more frequently [122].

Thus, the average survival time without treatment varies between 5.2 and 12.6 months [123], and with treatment it can reach 12.7 months. With an average duration of 5.8 months without disease progression [124], biological treatments can be administered (bevacizumab, cetuximab) which have proven their effectiveness by obtaining better survival rates [125].

The first therapeutic method described for peritoneal dissemination of malignant disease is an association of hyperthermic intraperitoneal chemotherapy with cytoreductive treatment, which aims at the resection of all visible tumors along the visceral and parietal peritoneum associated with complete peritonectomy [126]. Cytoreductive surgery is associated with a significant rate of mortality and morbidity [127], has an average duration of 7–10 hours and involves 12–17 days of hospital stay [128]. Good patient selection is required, and despite this, approximately half of subjects develop rapid disease progression, reaching up to 70% within the first 2 years of disease [129].

Regarding the surgical point of view, the interventions start with the resection of the greater omentum, peritoneum from the left and right quadrants along with the resection of the small omentum, the gallbladder, but also the resection of the pelvic peritoneum, and in selected cases a splenectomy can be required [126]. After the resections, 3 liters of normal saline solution are introduced at a temperature of 42.5 degrees Celsius together with a chemotherapeutic agent: Mitomycin c 40 mg for 90 minutes [130]. The results of the associated treatment are favorable, a combined therapy offering a survival rate of nearly 22.3 months but associated with high risks [131].

Lung metastases are quite rare in the evolution of colon cancer but slightly more frequent in rectal cancer (whose cells express markers such as RAS and CXCR7, while at

the cellular level there is an increased activity of the WNT pathway) [132]. In the occurrence of pulmonary dissemination, the prognosis is poor (most patients do not survive beyond 24 months), with a 5-year survival rate of 1.9%. If extrapulmonary metastatic sites are also present, the patient's prognosis is much worse. In selected cases, surgical treatment with resection is attempted, with survival reaching up to 56% [133] with this management mode, but the recurrence rate after 2 years tends to be 80% [134]. Resection of pulmonary metastases is done with the intention of preserving as much functional parenchyma as possible (atypical resections), and in most cases lymphadenectomy is performed only in the case of suspicious and large nodes that can cause compression phenomena [135].

Conclusions

Colon cancer has a continuously increasing incidence, due to changes in lifestyle that tend to favor the appearance and development of the disease. An early detection of colorectal cancer through appropriate screening methods at the population level (which must be cheap, accessible, but including modern diagnostic and treatment technologies) could lead to a decrease in the level of mortality and morbidity in the case of colon cancer and rectum.

One of the most feared complications of colorectal cancer (in terms of survival, morbidity, and mortality) is perforation, which is associated with high perioperative complications/risks and a very high recurrence rate. Intestinal obstruction must be recognized early by the patient, being manifested by the progressive decrease in transit followed by the absence of stool for several days (signs that should alarm the patient and prompt him to see a doctor as soon as possible). Bleeding from colorectal tumors, although not as severe as upper gastrointestinal bleeding, should be a compelling enough sign to prompt the patient to see a doctor. Even colorectal cancer detected in advanced stages (loco-regional dissemination and distant metastases) should prompt the patient to follow a specific treatment, because recent advances made and implemented in the form of modern treatments can favorably manage such cases, offering good rates of survival and a satisfactory level of quality of life.

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.

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.

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