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Metastatic Colorectal Cancer: Review of Diagnosis and Treatment Options

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Abstract

Colorectal cancer (CRC) is currently considered the third most common neoplasm in the world according to the World Cancer Research Fund International with 1.4 million cases diagnosed in 2012, and the second malignity as cause of death. Approximately 1/5 of patients present directly with metastatic disease (mCRC), and 30 to 50% develop metastasis after surgical treatment for initially localized disease. The aims of the current study are to review the diagnostic particularities, treatment options and clinical evolution of mCRC. Metastatic process in CRC is long and complex, involving several mechanisms, molecular pathways and cellular types. Advances in medical imaging now allow an early and accurate diagnosis of metastatic lesions no matter their location. The progress of fundamental research in CRC led to understanding the molecular basis of the metastatic process that was further translated into novel chemotherapic and biological agents, thus increasing overall survival and and progression-free survival rates. Resection of liver, lung and brain metastases is crucial for survival when achievable and is more effective when completed by an oncological treatment and rigorous follow-up. All patients with mCRC should be discussed by a multidisciplinary team (surgeon, oncologist, radiologist, and gastroenterologist) in order to identify the most appropriate therapeutic management.

Keywords: Colorectal cancer; Metastasis; Chemotherapy

Introduction

Colorectal cancer (CRC) is currently considered the third most common neoplasm in the world according to the World Cancer Research Fund International with 1.4 million cases diagnosed in 2012, and the second malignity as cause of death [1]. In Romania, CRC registered an incidence of 17.74 cases/100.000 inhabitants in 2000, and was responsible for 19.05 deaths/100.000 inhabitants in 2002, while 8240 new cases have been diagnosed in 2006 [2].

Age greater than 50, alcohol abuse, reduced physical activity, obesity, unbalanced diet (poor in fibers, rich in fats), personal or familial history of polyps, and inflammatory bowel disease are known risk factors for the development of CRC. Histopathologically, 95% of the CRC are adenocarcinomas [3].

Approximately 1/5 of patients present directly with metastatic disease (mCRC), and 30 to 50% develop metastasis after surgical treatment for initially localized disease [4,5]. Metastatic disease involves in the order of frequency the liver, the peritoneum, the lungs, the bone and the brain, other locations being extremely rare (ovary, pancreas etc.). An advanced stage of the primary lesion with lymphatic or vascular invasion at the moment of diagnosis, high levels of the carcinoembryonic antigen (CEA), gene mutations (18q) and aggressive cellularity are important risk factors for metastatic disease [6]. The median survival interval of the mCRC without treatment is of less than 8 months, with longer intervals in case of patients with a limited number of metastases in a single organ (liver) [7]. Some metastases can be addressed surgically, but chemotherapy (single or combined with biological agents) remains the only valuable treatment in patients with inoperable metastases (most cases with mCRC). With the advance of pharmacological research, mortality from mCRC has decreased over the past decades. The aims of the systemic therapies are to increase survival rate, and to offer a good life quality. The most commonly used drugs in mCRC adjuvant therapy are the chemotherapics 5-fluorouracil (5-FU), oxaliplatin, irinotecan, capecitabine and the biological agents bevacizumab, panitumumab, cetuximab that act either against angiogenesis (bevacizumab) or inhibit the endothelial growth factor receptor (EGFR) (panitumumab, cetuximab). These drugs can be used in different combinations depending on patient's general condition, tumor histopathological and immunohistochemical characteristics, and drug availability, leading to variable survival rates [8,9].

Metastases in CRC can be syncronous (detected prior/during surgery of the primary tumor or within 3-12 months since initial intervention) or metachronous (discovered more than 1 year after surgical resection of the primary tumor). According to Slesser et al. a distinctive approach is mandatory as synchronous metastases usually are associated with a locally advanced CRC, a greater metastatic burden and a poor outcome [10]. On the other hand, metachronous metastases occur mostly in patients already treated with adjuvant chemotherapy and are more prone to be chemo resistant compared to synchronous metastases thus compensating the worse initial prognosis of synchronous metastases.

The aims of the current study are to review the diagnostic particularities, treatment options and clinical evolution of mCRC.

Metastatic Spread in CRC

The cellular and molecular pathways of metastatic process in CRC have been extensively analyzed over the last decades, and their understanding was materialized in the form of a new generation of anti-tumoral drugs like bevacizumab, an anti-VEGF antibody that has been proved to increase survival rate.

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Liver Metastases

The liver is most frequently involved organ in mCRC and often the single site of metastasis in CRC, both at the time of initial diagnosis (20–25% of cases) or after resection of the primary tumor (40% of cases) [11].

Liver metastatic process in CRC involves a series of steps such as [6,12,13]:

- **Lysis of the extracellular matrix**: enzymes produced by cancer cells alter the extracellular matrix and allow cancer cells to leave the primary tumor. Cancerous cells can ignore integrin signaling and survive without contact to the extracellular matrix;
- **Cellular adhesion**: cancerous cells express adhesion molecules (cadherins, integrins, carcinoembryonic antigen - CEA) that favor their adhesion to the extracellular matrix;
- **Angiogenesis**: some CRC have an increased expression of the vascular endothelial growth factor (VEGF) and the platelet derived growth factor (PDGF), important angiogenic factors associated with a poor prognosis. The vascular network whose formation was induced by tumor cells is poorly effective, fragile and hemorrhagic. VEGF and PDGF together with fibroblastic growth factor (FGF) and hepatocyte growth factor (HGF) also promote lymphangiogenesis by circulating endothelial progenitors derived from the bone marrow. Cancerous cells adapted to the mechanical forces of the circulatory system and attach to platelets thus forming tumoral emboli, and are able to bypass immunosurveillance by an overexpression of protective acute phase proteins [8,14,15];
- **Dissemination, invasion and colonization of distant organs with subsequent growth**: the liver is the most involved organ because of the portal circulation, and the morphology of the fenestrated sinusoid network.

According to Paschos, liver metastases formation is a 4 stages process:

1) Microvascular infiltration with tumoral cells,
2) Interlobular micrometastasis phase,
3) Angiogenetic micrometastasis phase and
4) Established liver metastasis phase [6].

Cancerous cells adhere to sinusoidal endothelial cells (SEC) and resist this way to the blood stream forces [6]. Kupffer cells are able to identify and destroy tumor cells, but this is a two-ways interaction: as cancerous cells attached to Kupffer cells are arrested in the liver, Kupffer cells eventually become saturated and cancerous cells start to divide and grow inside the liver. Hepatic stellate cells (HSC) that lie in the space of Disse can be activated by cancerous cells through citokines and promote liver angiogenesis. Some members of the tumor necrosis factor (TNF) family expressed by cancerous cells make them able to resist apoptosis, and the gene for the chemokine receptor CXCR4 regulates their migration. The epidermal growth factor (EGF) is also overexpressed in mCRC and is a target for chemotherapics [16]. Formation of macroscopic metastases takes weeks or months, and cancerous cells may rest in dormancy state for a long period of time.

Peritoneal Metastases

Peritoneal metastases, detected in 7-10% of patients at the initial presentation, occur in 4-19% after surgical resection of the primary tumor. Survival rates in these cases range from 5 to 24 months [17]. Peritoneal metastases develop secondary to intraperitoneal spread caused by full thickness invasion of the colonic wall or secondary to rupture of a mucus-producing appendix cystadenocarcinoma (pseudomyxoma peritonei). Peritoneal spread may also occur during surgery under the form of tumor cells or emboli that freed from dissected vessels or bowel lumen.

Lung Metastases

Lung metastases in CRC occur in 10 to 30% of all cases at 5-60 months after resection of the primary tumor. Tumor cells reach the lungs through haematogenous dissemination (colon – portal vein – inferior vena cava – pulmonary artery) or, less frequent, through lymphatic dissemination [18]. Contrary to the liver, the lungs are the single organs involved in only 2-4% of cases [19]. Mediastinal adenopathies occur through lymphatic spread from a nearby lesion in 3.5% to 16.7% of cases [20].

Bone Metastases

The incidence of bone metastases in CRC varies from 6% to 10.4% depending on the study, with a median time of detection of 11-21 months after resection of the primary tumor. In all the reviewed studies, bone metastases were associated to lung and/or liver metastases [21-23]. Metastatic lesions, usually multiple, occur secondary to hematogenous dissemination, and most frequently involve the axial skeleton and the proximal segments of the limbs. In decreasing order, they are located in the dorsal and lumbar spine, sacrum, pelvis, ribs, sternum, proximal femur and humerus and cranium. Metastatic bone destruction is not caused by tumor cells, but by osteoclasts activated by tumor cells that secrete an osteoclast activating factor. Mundy et al. divided this process into 4 stages [21,22]: tumor cells adhere to the basement membrane; tumor cells produce proteolytic enzymes that alter the basement membrane; tumor cells migrate through the basement membrane; tumor cells stimulate osteoclasts' activity.

Brain Metastases

Brain metastases occur in 2-12% of patients with CRC during the course of the disease, and median survival rate ranges from 2.8 to 6 months without surgery and from 6 to 10 months after metastasis resection [24]. Brain metastases occur through hematogenous spread and they may locate in the cerebrum (80%), cerebellum (15%) and the brainstem (5%) [25].

Clinical Diagnosis

A series of symptoms like pain in the right upper quadrant, significant weight loss, anorexia, jaundice, nausea suggest the presence of an advanced form of CRC with a high probability of liver metastases, especially if these symptoms are associated with an elevated CEA [20]. Patients with peritoneal metastases present with nonspecific symptoms like abdominal discomfort, increased abdomen size, nausea, vomiting, weight loss, cachexia, and fatigue, symptoms indistinguishable from those that generally occur in advanced CRC [17]. By contrast, lung metastases are frequently asymptomatic and incidental radiographic findings with the exception of bronchial lesions that occur rarely and can present with cough, dyspnea, or repeated infections [18,19]. Apparition of vertigo, headache, blurred vision or hemiparesis suggests the possibility of brain metastases [24].

Diagnostic Imaging in mCRC

The purposes of medical imaging in mCRC are to quantify the number and extent of secondary lesions, to evaluate the liver prior to liver resection (residual volume), to assess tumoral response to chemotherapy and conversion of initially unresectable lesions into resectable ones, to exclude local or distal recurrence or any associated pathology [26]. Despite the multitude of available imaging methods, there is no international consensus concerning the most appropriate method for assessing recurrent disease on the operated liver.

Chest X-ray

Chest X-ray, routinely performed as part of preoperative evaluation, of limited use in detected lung metastases as small lesions (< 1 cm), is either missed or invisible.

Ultrasound (US)

Abdominal US are the most accessible and widely available imaging method. US is able to diagnose most liver metastasis >1 cm (20% sensitivity rate for metastases < than 1 cm) but its sensitivity is limited by user's experience, technical performances of the US device, and patient's characteristics (obesity, particular conformation, steatosis). Typically, CRC liver metastases present as solid lesions with a hypo echogenic halo, but iso echogenic lesions (difficult to detect) and hyper echogenic ones (differential diagnosis with hemangiomas) have also been reported. Intravenous contrast agents are not used for ultrasound examination in Romania despite the fact that their use could increase sensitivity rate to up to 87% [2,26]. Conversely, intraoperative US are used in many Romanian clinics for detecting liver lesions prior to metastasis resection.

Computed Tomography (CT)

Currently, CT is a widely available low cost method of choice for metastases screening in patients with known CRC. CT with intravenous contrast (three phase's examination–non-contrast, late arterial and portal venous) is mandatory for preoperative cancer staging in all cases except for patients with absolute contraindications to iodinated contrast material when other methods like MRI, chest X-ray, PET should be considered. In late arterial phase, liver metastases may present a rim enhancement but they are more conspicuous in the portal venous phase. Liver metastases typically present as hypovascular lesions, and CT is able to detect up to 85% of all liver metastases with false negative/positive results in case of small, indeterminate, hypo-enhancing lesions (cysts mistaken for metastases or metastases mistaken for cysts) [27]. Evaluation of vascular invasions and a liver volumetric study are mandatory when liver metastasis resection is planned. Infiltration of both portal veins and the three principal hepatic veins contraindicates liver resections. Vascular invasion of portal or hepatic veins of a single lobe does not contraindicate surgery but is associated to a poor prognosis [28].

Lung metastases are easily detected by CT, but false positive results may occur in case of benign lung nodules (non-calcified granulomas, hamartomas with low fat content or without calcifications, etc.). If the patient underwent a previous CT examination, a comparative study is mandatory for differential diagnosis.

CT is also the method to use for postoperative or adjuvant therapy follow-up according to the revised Response Evaluation Criteria in Solid Tumors (RECIST) revision 1.1, the gold standard for evaluating tumor progression [7].

Magnetic Resonance Imaging (MRI)

MRI is not the first method to be used for metastases screening except for brain metastases, due to its high costs, the length of the examination, and the necessity of repeated breath holds and long period of immobility. Despite its limitations, MRI has the advantage of a more accurate characterization (sensitivity and specificity rates of 85% and 100% respectively) of liver lesions compared to CT, especially in patients with steatosis or small lesions (MRI can precisely identify pure liquid lesions). The new diffusion sequences and the apparent diffusion coefficient (ADC) allow a better identification of metastases due to limited diffusion of water molecules in the extracellular space of tumoral tissue [26,27]. In the western world a series of liver-specific contrast agents have been introduced but they are of very limited availability in Romania.

Positron Emission Tomography (PET) with or without a CT Acquired at the Same Time (PET-CT)

PET using F-18-fluorodeoxyglucose (FDG) as a radiopharmaceutical is, taken by itself, of limited use in liver metastases diagnosis but when associated with CT (PET-CT) it can anatomically map all lesions with an increased metabolic rate. Reviewed studies report sensitivity and specificity rates inferior to MRI (71% and 93.7% respectively) in case of liver metastases. In case of CT detected lung nodules, the PET adds the metabolic information thus facilitating the differentiation between benign and malignant lesions [26,27].

Therapeutic Management

Surgical Treatment

Liver Metastases: Addition of new, multidisciplinary techniques and therapies like systemic or local chemotherapy, radiofrequency ablation (RFA), cryotherapy and radiotherapy improves the rate of liver metastases resectability but currently there is no gold standard concerning the optimal treatment of synchronous liver metastases. Neoadjuvant chemotherapy may convert up to 15% of liver metastases from inoperable to operable by tumor shrinkage and producing free margins. In case of small lesions that disappear after chemotherapy, it is still necessary to remove the containing liver as most lesions are not sterilized [29].

According to clinical studies, 10-25% of patients with hepatic metastases may be candidates for surgical resection, while the recurrence rate ranges from 60 to 80%. Historically, extrahepatic metastases were considered as a contraindication to liver resection but recent studies proved that patients undergoing both lung and liver resection (usually first pulmonary resection and then liver resection) register 5-year survival rates superior to 30% [30]. The presence of extrahepatic disease is associated to mix patterns of dissemination that lead to new metastatic foci after surgical resection.

The purpose of the surgical treatment for liver metastases is to remove all lesions with a free margin of 1 cm and to leave sufficient liver parenchyma (at least two liver segments in continuity) in order to ensure 25% of total functional liver or a remnant liver volume to body weight ratio superior to 0.5%. The residual liver has to be supplied by a portal vein, a main hepatic vein, a hepatic artery and a bile duct that can be anastomosed to the gut [29,30]. Complete metastasis resection (R0) increases 5-year survival rate to 25-40% depending on the study. Small survival intervals are expected if there are more than four metastases or involved lymph nodes at the moment of primary tumor resection or if metastases occur less than 1 year after removing the CRC [31].

Sectional medical imaging (CT, MRI) is necessary to calculate the volume of the future residual liver prior to surgery. 25% of the initial liver volume is sufficient only in patients free of cirrhosis, steatosis and hepatic disease due to chemotherapy. In cirrhotic patients, a minimum of 40% remnant liver volume has been recommend in order to prevent liver failure [27]. As most patients underwent prior chemotherapy, leaving just ¼ of total liver volume is associated to a high rate of complications and an increased postoperative mortality. Two techniques have been used in such cases, separately or combined: staged resection at one-month interval and portal vein embolization (determines atrophy of the affected lobe and hypertrophy of the healthy lobe) with resection of the embolised lobe [29,30].

Garden et al. have proposed some guidelines for resection of mCRC liver metastases. According to these guidelines, patients with mCRC should have a preoperative CT of the abdomen and pelvis, and ideally of the thorax as well (a chest X-ray may also be accepted). The entire colon has to be examined prior to surgery in order to assure that there is no recurrent disease at this level. CEA levels also have to be

determined prior to surgery. In most cases, primary tumor resection and liver metastasectomy are not to be performed at the same time, but in selected cases with superficial, small metastases, combined, synchronous resection may be considered. Recurrent liver lesions could be treated in the same way as the initial liver metastases [32].

Anatomical vascular variants should always be assessed prior to surgery, as hepatic arteries originating from the left gastric artery (left hepatic artery) or the superior mesenteric artery (right hepatic artery) together with multiple hepatic arteries require additional steps. In case of right lobe resection, the middle and left hepatic veins are to be preserved in order to prevent venous congestion or ischemia of the remnant liver. For left lobe resection, the right and middle hepatic veins should be preserved. Similarly, the presence of accessory hepatic veins requires additional surgical times. In case of trifurcation of the portal vein (the right anterior portal vein originates directly from the main portal vein), resection of the left portal vein proximal to the origin of the right anterior portal vein could lead to a compromise of the portal perfusion of the anterior segments of the right lobe (V and VIII) and of segment IV. Portal vascularization of segment IV must be accurately assessed as it can originate from the any of the two portal veins. Bile leakage may occur when resection is extended to segments I and IV. A triple confluence of hepatic ducts (right, left, a division of the right anterior and posterior ducts with the left one) occurs in up to 15% of individuals, and in 8% of individuals a right sectorial duct may confluence with the left hepatic duct. Rarely (2%) a right posterior sectorial duct joins the neck of the gallbladder. All these variants increase the risk of biliary complications [33].

When synchronous liver metastases are diagnosed, the sequence of surgical procedures remains controversial. The order of tumor resection, liver metastases or primary colorectal carcinoma first, is an issue that surgeon has to deal with taking into account the impact of new chemotherapics on tumor size, the role of portal vein embolization in increasing liver volume, and the possible association of liver resection with ablation techniques.

Traditionally, colorectal primary tumor is resected first, followed by postoperative chemotherapy for 3-6 months and liver surgery in a second stage. This approach has a significant prognostic impact as survival rate is determined by the presence of liver metastases, and the presence of postoperative complications (ex. anastomosis dehiscence) could delay the onset of chemotherapy and second stage liver surgery. In case of locally advanced rectal cancer, neoadjuvant radio-chemotherapy could be applied thus delaying second stage liver surgery with subsequent progression of metastases.

Single stage resection of both primary tumor and liver metastases seems like the perfect approach as it is associated with less physical and psychological stress, lower costs, shorter hospitalization, and faster recovery. The disadvantages are represented by the cumulative risk of two surgical procedures with increased morbidity and mortality [34].

A "liver-first" approach has been proposed by several teams [34-36] in order to prevent complications associated with liver surgery in the context of chemotherapy-associated steatohepatitis (CASH), to perform a curative R0 liver resection that could become impossible after several months of chemotherapy, and to reduce the delay between surgical and oncological treatment. Despite its advantages, this approach carries the risk of bowel occlusion.

In selected cases (patients who are not eligible for resection, recurrences, small liver metastases, or need for major liver resection), several down staging techniques (chemotherapy, portal vein occlusion, local ablation) can be used as part of a single-stage or two-stage hepatectomy. Portal vein occlusion (by embolization or ligation) triggers the atrophy of the correspondent lobe and hypertrophy of the noninvolved lobe thus increasing the size of the future remnant liver volume (FRLV) and allowing lobe resection. Local ablation (radiofrequency, cryotherapy, steam thermonecrosis, microwave coagulation) can be combined to hepatic resection in order to treat metastases less than 5cm in diameter (3cm for a better control rate). Anatomic location of liver metastases can limit the use of down staging techniques like radiofrequency ablation that cannot be applied to lesions close to large vessels (heat sink effect increases the risk of incomplete ablation) or main biliary structures (risk of thermal injury).

Concerning metastases reduction chemotherapy, a French study showed similar prognosis in patients that underwent metastasis resection of initially resectable liver metastases compared to patients with initially unresectable lesions converted to resectable ones after chemotherapy [37]. The presence of < 1 cm free margins and of extrahepatic disease is the most important predictive factor of recurrence after liver metastasectomy. Characteristics of the primary tumor like lymph node involvement, grade of differentiation and location (rectum) still are considered independent prognostic factors of survival and recurrence [38,39].

Lung Metastases: Lung is the second most involved organ in mCRC after the liver, and up to 20% of lung metastases are not detectable prior to surgery [18]. The aim of the surgical treatment is complete removal of metastases without extensive lung resection. Operative approach is chosen based on the size and location of metastases. Lung metastases are most frequently located peripherally in the lower lobes thus allowing ease wedge resection. Lobectomy and pneumonectomy are avoided because of the high postoperative morbidity and mortality. Patients with adequate cardiopulmonary reserve, without extrathoracic disease except the primary tumor or with resectable extrathoracic disease, are candidates to lung resection for metastasis. Authors like Lizasa et al. consider that the number and size of lung nodules represent independent prognostic factors for survival, and that multiple or bilateral lesions can be excised [40]. Several studies have proved that preoperative carcinoembryonic antigen (CEA) is an important prognostic factor for survival after lung resection for metastasis. According to Rama et al., patients with completely resected single nodules, a disease free interval of more than 3 years prior to lung metastasis discovery, and a normal preoperative CEA register the higher survival rates [34]. A 21-63% 5-year survival rate has been registered in patients who have undergone lung resection [41]. Radiofrequency ablation (RFA) is preferred in patients with insufficient cardiopulmonary reserve, but it is not widely available.

Peritoneal Metastases: Peritoneal metastases were classically considered as a contraindication for surgery in CRC cancer and a terminal condition. However recent studies revealed that cytoreductive surgery (CRS) with peritonectomy, peritoneal resection associated with Hyperthermic Intraperitoneal Chemotherapy (HIPEC), and Early Postoperative Intraperitoneal Chemotherapy (EPIC) has promising results in selected patients. Complete CRS is achievable in patients with a Peritoneal Cancer Index (PCI) score inferior to 10, no extra-abdominal disease, a maximum of 3 small, resectable, liver metastases, no enteric or biliary obstruction, no gross mesenteric involvement [36,42]. CRS aims to completely remove macroscopic disease using visceral resection and peritonectomy procedures and can be combined to HIPEC.

Brain Metastases: Treatment recommendations from brain metastases are similar to brain primary tumors. The resection is usually indicated in case of single metastases in the absence of important comorbidities and uncontrolled disease. Surgical resection may also be performed in case of multiple (mostly double) lesions if neurological symptoms cannot be controlled with radiotherapy and steroids alone. Surgery is combined with radiotherapy and steroid administration in 1/3 of cases, improving overall survival up to 11-12 months [24,25].

Focal Therapies

Radiofrequency Ablation (RFA): RFA is indicated for patients with unresectable lesions, small recurrent metastases, severe comorbidities contraindicating extensive surgery, and as a complement to hepatic resection. RFA is restricted to a maximum of 3 metastases measuring less than 3cm [43]. Lesions located close to large vessels, extrahepatic organs or major biliary ducts cannot be treated by RFA due to the heat sink effect and the risk of thermal injury. In patients with resectable lesions and no contraindications to major surgery, RFA should not be used.

Cryotherapy: Liquid nitrogen introduced into the metastases through thin metallic probes freezes the tissue with subsequent tumor necrosis. This method is not as popular as RFA due to the risk of hemorrhage from parenchymal lesions and intravascular coagulation [43].

Stereotactic Body Radiotherapy (SBRT): SBRT can be used to treat liver, lung, lymph nodes, spinal and adrenal metastases, and postoperative pelvic recurrence. SBRT involves irradiating metastases with hypofractionated high-dose (10-20 Gy per fraction) radiation while sparing the surrounding normal tissue with a 2-year local control rate of up to 80% [44].

Stereotactic Radiosurgery: Stereotactic radiosurgery using Gamma Knife, Cyberknife or Linac can achieve control of both single and multiple brain metastases by focally applying high-dose radiation (minimum 18 Gy) with a recurrence rate of 39-52%. The procedure can be repeated if a new lesion appears and is as efficient as classical surgical resection (level I evidence) [45]. Adjacent cerebral tissue and cerebral functions are preserved.

Percutaneous Ethanol Injection (PEI): Although PEI proved to be efficient in treating small hepatocellular carcinoma, is not effective in case of CRC metastases but the only studies have been performed more than 20 years ago [46].

Microwave Ablation (MWA): MWA uses microwave frequencies of more than 900 MHz that induce coagulative necrosis similar to RFA but due to its recent availability there is a lack of extensive studies that evaluate the efficiency of this method [43].

Thermonecrosis with overheated steam implies laparoscopic or open surgery injection of overheated steam into metastases that induces coagulative necrosis similar to MWA and RFA with promising results [47].

***In Situ* Chemotherapy via the Hepatic Artery**

In case of unresectable liver metastases, chemotherapic agents (5-FU, leucovorin, oxaliplatin, irinotecan) may be administered direct into the hepatic artery with higher response rates (40-50%) compared to systemic chemotherapy, according to Lorenz [48]. This type of treatment can also be used after hepatic resection in order to prevent the recurrence of the disease. Kemeny has reported a 1-year free of disease rate of 90% in case of in situ chemotherapy after liver metastasectomy compared to 60% in case of metastasectomy alone [28]. Due to the toxicity of the chemotherapic drugs, elevated liver enzymes (transaminases, alkaline phosphatase, and bilirubin), hepatic artery thrombosis, gastritis and biliary sclerosis may occur. Also, the catheter must be left in place for 14 days and may dislodge.

Transarterial Chemoembolisation (TACE)

TACE involves supraselective injection of chemotherapeutic agents emulsified in a viscous carrier like lipiodol into the feeding artery of the tumor followed by definitive embolization with polyvinyl alcohol particles or spheric embolic agents. The aim of this procedure is to achieve a high concentration of chemotherapeutic drugs combined with tumor necrosis due to arterial occlusion. Currently, this procedure is being replaced by injection of microspheres impregnated with chemotherapeutic agents (drug-eluting beads transarterial chemoembolization) which, compared to lipiodol, allows progressive drug delivery for a long period of time [49].

Radiation Therapy

Palliative or definitive radiation therapy is indicated in metastatic or locally advanced rectal cancer. 45 to 50 Gy may be administered in 1.8 Gy fractions for 4-5 weeks. Radiation therapy cannot be used in case of patients with antecedents of ulcerative colitis, Crohn disease or prior pelvic radiation therapy for another cancer [3]. As side effects, radiation enteritis and colitis, radiation cystitis and incontinence are frequently cited. Preferably, radiation therapy is to be performed after chemotherapy, 5-FU being proved to make tumors more radiosensitive.

Adjuvant Chemotherapy

The usual cytotoxic drugs used for chemotherapy in mCRC that can be administered single or in combination: fluoropyrimidines, oxaliplatin, and irinotecan.

Fluoropyrimidines (5-fluorouracil) (5-FU) were the first ones discovered by Heidelberger in 1957who observed that cancerous tissues utilize uracil for nucleic acids synthesis. He substituted an atom in the 5th position of the uracil molecule thus acting towards division of tumor cells. Decades later, leucovorin (LV) has been associated to 5-FU as its biomodulation increases 5-FU activity with amelioration of survival rates [50].

Microsatellite instability (MSI) diminishes the chemosensitivity to 5-FU that requires a functional MMR system. Chemotherapeutic agents like oxaliplatin and LV have been added to the 5-FU in the FOLFOX regimen in order to circumvent this mechanism of 5-FU resistance [51].

In the years 2000s, oxaliplatin, and irinotecan have been added to the arsenal used to treat mCRC with increase of survival rates from 12 months (5-FU + LV) to 20 months. Oxaliplatin is platinum derivate that inhibits DNA replication and transcription, and irinotecan is a semisynthetic analogue of the natural alkaloid camptothecin that prevents DNA from unwinding by inhibition of topoisomerase 1. Irinotecan improves the median survival period from 6.5 months to 9.2 months and the 1-year survival rate (from 14% to 34%) in patients refractory to 5-FU [9].

A succession of two sequences has been proposed by the Groupe Cooperateur Multidisciplinaire en Oncologie (GERCOR): FOLFOX (oxaliplatin + 5-FU + LV) followed by FOLFIRI (irinotecan + 5-FU + LV). A special regimen using all three drugs at a time (FOLFOXIRI) has been reserved to patients with a good general status (notably a good liver function) and to patient's candidate to metastasectomy as it is highly toxic. Recently, chemotherapic drugs have been associated with monoclonal antibodies in a regimen called XELOX that involves administration of oxaliplatin and capecitabine together with monoclonal antibodies that bind to VEGF and to EGFR [4,5].

Biological Agents

In addition to first and second line chemotherapics, molecular targeted agents like antibodies towards fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), mast/stem cell growth factor receptor (KIT) and epidermal growth factor receptor (EGFR) have been developed [14].

VEGF is a diffusible glycoprotein that regulates both physiological and pathological angiogenesis. The recombinant antibody targeting VEGF, Bevacizumab (Avastin, Roche, Bale, Switzerland), is used to inhibit VEGF function and thus tumor angiogenesis, indispensable

to growth and metastasis. Randomized trials have proved that adding bevacizumab to chemotherapy regimens both in first and second-line treatment slows disease progression and increases survival rates with 4.7 months in case of first-line treatment and 2.1 months in second-line treatment. When bevacizumab was added to chemoteraphy regimens, median overall survival (OS) increased from 15.6 to 20.3 months and progression–free survival (PFS) increased from 6.2 to 10.6 months compared to chemotherapy alone [38,52]. Side effects occur rarely, are dose dependent and consist of gastrointestinal bleeding and perforation, thromboembolic events, hypertension and proteinuria.

A mutation that occurs early both in adenoma-carcinoma sequence and in colorectal cancer metastatic spread is the activation of Kras (Kirsten rat sarcoma viral oncogene homologue), a small intracellular GTPase (guanosin triphosphate cleaving enzyme) which is the main transduction pathway for EGFR. Kras mutations are present in 30-60% of colorectal cancers and confer resistance to anti-EGFR antibody therapy [40]. Cetuximab (Erbitux, Merck, Darmastadt, Germany) and panitumumab (Vectibix, Amgen, Thousand Oaks, CA) are monoclonal antibodies against EGFR and can be used use in tumors that express a specific molecular marker, namely wild-type Kras and are chemotherapy refractory.

The BOND study has proved that by adding cetuximab it is possible to overcome irinotecan resistance with an increase of PFS from 1.5 to 4.1 months and of OS from 6.9 to 8.6 months. The CRYSTAL trial performed on 1198 patients with EGFR-positive tumors that were randomly assigned to receive FOLFIRI with or without cetuximab has showed that cetuximab prolonged PFS with a median of 1.5 months and OS with 3.5 months. Studies analyzing panitumumab showed similar results [52].

Several trials argued against the association of anti-angiogenetic and anti-EGFR drugs: in the CAIRO study, the addition of cetuximab to a regimen including bevacizumab leaded to a decrease of PFS by 1.3 months, results further confirmed by the PACCE trial. The mechanisms behind the negative interaction of these drugs are not known [9].

Antibodies against FGF, PDGF, and KIT are still in research and not yet approved for general use neither in USA nor in Europe.

Prognostic Factors in mCRC

Survival rate in mCRC significantly increased from the 1950s (12 months) to the 2010s (60 months) when a combination of surgery, chemotherapy and biological agents is used [31].

Traditionally, tumor size (pT), positive surgical margins, lymph node involvement (pN), lymphovascular invasion, carcinoembrionar antigen (CEA) level, poor histological differentiation (G3 grade) and tumor budding were considered the most important prognostic factors both in CRC and in mCRC.

In the last 2 decades, many studies have analyzed the survival prognostic factors in mCRC with disparate results [31,39,53]:

1983 - Lahr indicates elevated alkaline phosphatase, serum bilirubin, the presence of bilateral hepatic metastases, the number of involved lymph nodes, depressed serum albumin and the presence of an unresectable primary tumor as negative prognostic factors for survival;

2005 – Schindl adds the Dukes Stage, the number of metastases and the serum CEA levels to the list of prognostic factors;

2009 – Luo states that increased histopathological grade and CEA level are associated with an unfavorable prognosis;

2010- Zacharakis reports that combination chemotherapy and an improved performance status lead to an increase in survival rates, and that increase C-reactive protein, influenced performance status, anemia, cachexia, anorexia, hypoalbuminemia, necessity of blood transfusions indicate unfavorable survival.

High CEA levels indicate an advanced disease and a high risk of recurrence after metastasectomy. Liver metastasectomy with a > 1 cm free margin led to a 5-year survival rate of approximately 40% that has increased to 50% when combination chemotherapy (5-FU, irinotecan, oxaliplatin, biological agents) has been added. Chemotherapy alone is associated with significantly lower survival rates at 5 years (25%) [31].

However, traditional factors are unable to predict the outcome in case of advanced CRC and therefore additional markers have to be evaluated in order to improve therapeutic management.

Histological Factors

Mucinous adenocarcinomas represent 4-19% of CRC and are commonly encountered in older patients and in the right colon. These tumors are often microsatellite-unstable and associated to a poor prognosis.

Signet ring-cell carcinomas represent almost 1% of CRC, occur most commonly on the right side, and are associated with a lymphatic invasion and poor differentiation, markers of a poor survival.

Micropapillary adenocarcinomas are very rare, have an infiltrative pattern and are associated with lymphovascular and perineural invasion. The presence of a micropapillary adenocarcinoma indicates a poor survival [54].

Tumor infiltrating inflammation corresponds to host antitumoral response, the presence of lymphocytic and macrophagic infiltrate predicting high recurrence and poor survival both in hepatocellular carcinoma and in CRC with liver metastases [55,56].

Dedifferentiation represents clusters (buds) of undifferentiated cancer cells located at the tumor invasive front and is associated with an increased recurrence rate of liver metastases in CRC [56,57]. Dedifferentiation presents a desmoplastic reaction and important neovascularization thus increasing tumor invasiveness.

Lymph and blood-vessel invasion are considered major prognostic factors in CRC and are associated to an increased risk of liver metastases [54].

Cell Proliferation Indices

Immunohistochemical methods allow detection of antibodies that bind to nuclear proteins associated with tumor proliferation and are a marker of malignity. Proliferating cell nuclear antigen (PCNA), Ki-67, Mib-1, MCM-2, Bcl-2 have been investigated in order to evaluate their role as prognostic factors and proved to indicate the development of lymph node metastases. On the other hand, no association was found between their expression and distant metastasis [58].

p53, a tumor suppressor gene, is involved in cell cycle regulation and its abnormal nuclear accumulation can be detected by immunohistochemical methods. Overexpression and abnormal nuclear accumulation of p53 are associated with an advanced T stage, lymph node metastases, and local recurrences in the liver and decreased survival rate [58].

Angiogenesis

Angiogenesis is crucial to metastasation process and VEGF is the main angiogenic stimulator. VEGF expression can be assessed by immunohistochemical methods with anti-VEGF antibodies or by mRNA analysis. VEGF expression holds an independent prognostic role and is associated to an increased metastatic spread and a poor prognosis.

Genetic Factors

Microsatellite Instability (MSI) is present in 15% of CRC and involves inactivation of the Mismatch Repair Genes. This anomaly is found in hereditary CRC and some sporadic forms. MSI predicts 5-FU resistance in mCRC [59]. Currently, routine evaluation of MSI is still a subject of debate with no general consensus.

Recent studies demonstrate that right-sided CRC follow different molecular pathways of carcinogenesis compared to left-sided CRC and are more prone to MSI, diploidy and gene mutations. Left-sided CRC mostly involve chromosomal instability and aneuploidy. Overall and progression-free survival rates are better in patients with left-sided tumors, and bevacizumab is less efficient in case of right-sided tumors [60].

The genotype of the primitive tumor also holds a significant impact on mCRC prognosis. Patients with Kras mutations (30-60%) do not respond to monoclonal antibody treatment and this pattern is maintained by CRC metastases [61]. On the other hand, the presence of a special genotype called wild type-Kras is associated with a good response to cetuximab and panitumumab therapy. Identifying such patients could lead to a reduction of hepatotoxic chemotherapics administration and avoidance of additional side effects. BRAF mutations are rare (only 10% of all CRC) and associated with diploid, microsatellite-unstable tumors that carry a poor prognosis. Almost 30% of patients with mCRC present a CpG island methylator phenotype (CIMP), exhibiting promoter methylation at multiple sites. This phenotype contributes to CRC progression and is associated to Kras/BRAF mutations. CIMP-High tumors that are MSI and BRAF mutation positive have a good prognosis compared to MSI negative tumors which are positive for CIMP and BRAF mutation and carry a poor prognosis [59].

Conclusions

CRC metastatic spread is long and complex, involving several mechanisms, molecular pathways and cellular types. Advances in medical imaging now allow an early and accurate diagnosis of metastatic lesions no matter their location. The progress of fundamental research in CRC led to understanding the molecular basis of spreading process that was further translated into biological agents like anti-VEGF and anti-EGFR antibodies. The combination of classic and recent chemotherapies and biological agents increased OS and PFS rates.

Resection of liver, lung and brain metastases is crucial for survival when achievable and is more effective when completed by an oncological treatment and rigorous follow-up.

All patients with mCRC should be discussed by a multidisciplinary team (surgeon, oncologist, radiologist, and gastroenterologist) in order to identify the most appropriate therapeutic management.

Conflict of interests

Authors have no conflict of interests to disclose.

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