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Review

Colorectal Cancer Liver Metastasis—State-of-the-Art and Future Perspectives

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Abstract: The current management of colorectal cancer liver metastasis (CRCLM) patients involves a multidisciplinary approach, with surgical resection remaining the primary curative option. The advances in liver surgery have improved outcomes, enabling more patients to undergo surgery successfully. In addition, the development of imaging software has improved the preoperative planning and patient selection for surgery and other interventions. Systemic therapies, such as targeted therapies and immunotherapies, have enhanced the chances of complete resection. Targeted agents, in combination with chemotherapy, have shown efficacy in downstaging tumors and increasing resectability. The algorithm approach for these patients continues to evolve, driven by a deeper understanding of the underlying biology. Personalized medicine, guided by molecular profiling and the potential of liquid biopsies in this field, may lead to more tailored treatment strategies. A greater understanding of the immune microenvironment in CRLM may unlock the potential for immune checkpoint inhibitors and novel immunotherapies to become more prominent in the treatment landscape. This review explores the current state-of-the-art treatment of CRCLM and discusses promising future perspectives.

Keywords: colon cancer; metastasis; liver neoplasms; review literature

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1. Overview of Colorectal Cancer

The high incidence and prevalence rates of colorectal cancer (CRC) translate into an elevated healthcare burden, making this issue and the research around it highly important.

Currently, CRC is the third most commonly diagnosed cancer and the second most common cause of cancer death in the world, with a lifetime risk of approximately 2–5% [1–4].

In 2020, CRC accounted for 10% of the total cancer diagnoses, with 1,931,590 new cases, and 9.4% of total cancer deaths, with 935,173 deaths.

In the same year, the incidence rates were 52.3%, 26.9% and 9.3% in Asia, Europe and North America, respectively [5].

In the past 20 years, the CRC incidence in older populations has decreased with a corresponding mortality reduction; however, the incidence among adults younger than 50 years continues to increase, and the CRC global burden has been predicted to increase by 60% with more than 1.1 million deaths and 2.2 million novel cases expected by 2030 [6,7].

Therefore, it is important to optimize the CRC approach, and the most cost-effective one is prevention.

Prevention can be optimized by avoiding the modifiable risk factors and by effective and periodic screening tests.

More than half of all CRCs are attributable to modifiable lifestyle factors.

An unhealthy diet appears to be associated with a higher risk of CRC. A meta-analysis of prospective observational studies highlighted an association between higher CRC risk and low intakes of calcium, yogurt, and dietary fiber and high consumption of red meat [8]. The anthropometric characteristics appear to have some impact on CRC risk, on the one hand, associated with the lifestyle that results in higher body weight, fat mass and body mass index but also due to the pro-inflammatory state present in obese people [9].

Tobacco smoking has consequences in the oxidative stress pathway with consequent damage to cellular DNA, promoting cancer [10].

Another clear and modifiable risk factor is alcohol consumption. Several studies confirm that more than one alcoholic beverage per day has a relationship with the development of colon polyps and CRC [8].

There are some drugs associated with prevention. Aspirin and non-steroidal anti-inflammatory drugs appear to be associated with a decreased incidence of colorectal cancer. In fact, a study published in 2020, with a more than 90,000 patient sample, proved that those who started using aspirin on a daily basis before the age of 70 had a decreased risk of CRC [11]. Multiple studies have also mentioned this association, and a recent Clinical Practice Update from the American Gastroenterological Association recommended the use of aspirin for the prevention of CRC in specific cohorts based on their age and cardiovascular risk profile [11–13].

According to the population-attributable fraction, about 50% of CRC cases in the United States and the United Kingdom were estimated to be attributable to the aforementioned modifiable risk factors.

With respect to nonmodifiable risk factors, the best approach is through an attempted screening. Gender, race and ethnicity are some of those. Although the lifetime incidence between men and women is approximately equal, the prevalence of preneoplastic lesions is higher in men, with 1.77 times more risk of finding adenomas during colonoscopy screening [14,15]. Racial and ethnic differences are difficult to study due to group heterogeneity and the inherent factors associated with lifestyle factors and genetics.

Genetics is a well-known nonmodifiable risk factor. About 20–30% of CRC patients have a family history of CRC, and only 5% are understood by Mendelian inheritance [16].

The hereditary polyposis syndromes are familial adenomatous polyposis (FAP), serrated polyposis syndrome, MYH-associated polyposis (MAP), polymerase proofreading-associated polyposis (PPAP), juvenile polyposis syndrome, and Peutz-Jeghers syndrome [17], Hereditary non-polyposis colorectal cancer syndrome (HNPCC), or Lynch syndrome, is associated with an increased risk of malignancy that can occur with or without precursor polyps [18].

2. CRC Liver Metastasis

The major causes of CRC fatality are the metastatic processes associated with the disease, with the liver being the most common metastatic site (accounting for 70% of all CRC patients with metastatic cancer) and reported as the leading cause of death in CRC patients.

As we know, 20–25% of CRC cases have LM at the time of diagnosis, and about 50% and 10–15% of CRC patients will develop LM and lung metastasis during the course of the disease [7].

These metastatic state decreases the overall 5-year survival rate to 4–20% [19,20]

Even in the case of radical liver resection, approximately 30–50% of the patients will experience a recurrence, and more than 50% of them will die due to disease progression [7].

The target therapy and immunotherapy as well as the improvement of surgical procedures and the availability of different local ablative treatment, have already changed the approach algorithm of these patients and increased the overall survival rates which is now about 30 months; however local or systemic recurrence of CRC still remains a problem [21]

The underlying mechanisms of CRC metastasis have not yet been fully understood, and that is the focus of every CRC researcher, as the molecular mechanism of CRC metasta-

sis will determine the development of novel therapies against it and improve survival rates of metastatic patients.

One of the reasons why it is so difficult to obtain a complete understanding of the metastatic process is due to the complex interactions involved in the process, making it difficult to reproduce. Cancer and its metastatic processes not only depend on tumor biology but are also a result of the tumor and host interaction, resulting in a unique microenvironment in the primary tumor location as well as in the metastatic site.

In addition, the previously accepted progression sequence of the tumors, in which primary tumors first seeds lymph node metastasis and then further seed distant metastases is no longer a reality. The distant metastasis and the lymph nodes ones appears to have independent origins [22].

The intratumor heterogeneities and the relationships among CRC different omics have not been fully integrated as we can already determine the point of mutation in a certain patient through a genome sequency analysis; however, most of the time, we cannot know the phenotypic and transcriptomic consequences. The RNA sequencing allows us to compare the gene expression differences between the primary and the metastatic tumors, but this transcriptomic result may just be a reflection of other factors during the metastatic process.

3. CRCLM—Information about the Primary Tumor

The prognostic information that the tumor–node–metastasis (TMN) staging system provides is well-known. In addition, there is other important information that we need to consider when approaching these patients:

- Tumor location: Right-sided primary colon tumors have worse survival rates and present *RAS*, *BRAF* and *PIK3CA* gene mutations more frequently [23]. Left-sided tumors are characterized by chromosomal instability and activation of the epithelial grown factor receptor pathway [24].
- Histology: The different histological subtypes of CRC are associated with different tumor aggressiveness and the tendency to metastasize. The mucinous carcinoma, present in 10% of cases, as well as signet-ring cell carcinomas, present in 1% of cases, have a high incidence of deficient mismatch repair (dMMR), which is associated with microsatellite instability (MSI) and *BRAF* mutations. These genetic statuses are recognized to have poor prognosis in stage IV CRC, and therefore, histological subtype may be used as a prognostic factor without the need for genetic analysis [25,26].
- Grading: Histologic grade is a subjective analysis that reflects the degree of tumor differentiation and is a feature that has consistently been demonstrated to be a stage-independent prognostic factor. All three guidelines (American Society of Clinical Oncology—ASCO; National Comprehensive Cancer Network—NCCN and European Society for Medical Oncology—ESMO) consider poorly differentiated histology to be an adverse feature, resulting in cancers that are more likely to grow and spread quickly, increasing the risk of metastasis [27,28].
- MMR status: Mutations in DNA mismatch repair genes occur in 15% to 20% of sporadic colon cancers and in hereditary nonpolyposis CRC [29]. Tumors that are MMR deficient (microsatellite unstable (MSI-H)) are associated with longer survival despite being often poorly differentiated [30–32]. In addition to the better prognosis of MMR deficiency tumors, adjuvant FU-based chemotherapy (ChT) is less beneficial in these patients.
- The lymph vascular invasion is an important and independent adverse prognostic factor [17,18,33,34]. It is one of the clinicopathologic factors that is included in the definition of "high-risk" stage II colon cancer from ASCO, NCCN and ESMO, and its presence influences the use of adjuvant treatment. The perineural invasion is another clinicopathologic factor included in the definition of "high-risk" stage II by ASCO, NCCN and ESMO, as their presence is associated with poor prognosis.

- Tumor budding is defined as single cells or clusters of up to four cells at the invasive margin of colorectal cancer [35]. High levels of tumor budding are associated with an increased risk of metastasis [36,37].

4. CRCLM—The Role of Imaging

A radiological assessment of liver metastasis provides several important pieces of information that go beyond staging. Its use has gained recent interest as a possible tool to improve the tailored approach.

The definition of resectable CRC liver metastases is simple: a tumor that can be resected completely, leaving adequate liver remnants [38]. To select a patient for resection, most surgeons require radiographic evidence of the hepatic artery, major bile ducts, main portal vein or celiac/paraaortic lymph nodes, and an adequate predicted remaining functional liver. To decide what surgical technique to choose, there is other important information to consider.

Contrast-enhanced preoperative liver magnetic resonance imaging (MRI) is the preferred first-line imaging study for evaluating CRC liver metastasis as it identifies more hepatic lesions, which are visualized by computer tomography, especially in the presence of background fatty liver change.

The number, size and lobar distribution have been the focus of attention, and multiple studies have reported cutoffs to select patients for surgical resection. The previous rule was that patients should not be considered for surgery if presenting with more than three lesions or bilobar distribution, or if it is not possible to achieve a 1 cm margin, but this rule is no longer valid. Studies referring to number, size and lobar distribution are addressed further in this article.

A modern multidisciplinary consensus defines CRC liver metastasis as resectable if R0 resection can be achieved while leaving a functional residual liver volume. The American Hepato-Pancreato-Biliary Association, the Society for Surgery of the Alimentary Tract, and the Society of Surgical Oncology in 2006 state that the feasibility of hepatic resection should be based on three criteria: (1) the ability to preserve two contiguous hepatic segments; (2) preservation of adequate vascular inflow and outflow as well as biliary drainage; (3) the ability to preserve adequate future liver remnant (FLR) (>20% in a healthy liver; >30% after chemotherapy/or in liver steatosis) [39].

Another important utility of liver images is to evaluate the treatment response to chemotherapy. For patients with resectable liver metastasis, particularly for the synchronous lesions, initial chemotherapy is followed by reevaluation. The standard response evaluation classification is based on the RECIST (response evaluation criteria in solid tumors) criteria, which may not be applicable to biologic agents such as bevacizumab. This classification predicts pathologic response and, therefore, is also a prognostic tool.

Radiomics is defined by the analysis of grey patterns of radiologic images to derive clinical and pathological information [40]. It is an area of increasing interest, given the association of images with tumor biology and the fact that images are already part of the routine of oncologic patients. It has been studied in MRI, CT scan and PET-CT images and may help to stratify the risk of recurrence and predict responses to systemic treatment and overall survival (OS) [41,42]. Radiogenomics is another associated concept that defines the possibility of predicting gene expression or polymorphisms through radiomic features [43]. Some studies are difficult to interpret given the fact that they include both chemo-naïve and pre-treated patients and the lack of standardization of the analytical techniques. Nevertheless, it is definitely a promising prognostic tool in the era of computational analysis.

5. Serum Markers/Liquid Biopsy

There are some substances found in the blood that can provide valuable information about the presence and progression of liver metastasis. These markers play an important role in the prognostics and monitoring of CRC with liver metastases. The carcinoembryonyonic antigen (CEA) is a widely used serum marker for CRC and other solid tumors. The CEA is considered a proangiogenic molecule, and it is associated with changes in the

sinusoid microenvironment, promotion of the expression of adhesion molecules and malignant cell survival, and protection of metastatic cells from death. Elevated CEA levels can indicate the presence of liver metastasis and are an important marker to monitor during the treatment and follow-up of these patients. It is a promising target biomarker for multiple biotechnological applications [44].

However, the CEA has low sensitivity, and the adjunctive monitorization of carbohydrate antigen 19-9 (CA 19-9) may improve its sensitivity [45].

Although high CA 19-9 levels are known to be associated with poor prognosis in stage IV CRC patients, routine measurements of CA 19-9 in colon cancer are not recommended by ASCO guidelines due to insufficient evidence [46].

However, some authors still defend its role in the evaluation of treatment response or even in predicting the response to chemotherapy. A study by Ma et al. reported that CA 19-9 levels were higher in patients with disease that had responded to chemotherapy than in the group of patients that did not respond to the treatment [47]. Zhou et al. performed a retrospective study with over 300 patients with stage III CRC who underwent curative resection followed by adjuvant ChT with oxaliplatin and capecitabine, where they determined that high levels of preoperative CA 19-9 indicated a worse prognostic outcome [48]. These patients may benefit from a different and more strict follow-up protocol for an early determination of recurrence.

Other markers that provide information about liver damage or impairment due to metastatic involvement are the serum markers of liver function, including ALT (alanine aminotransferase)/AST (aspartate aminotransferase) and bilirubin.

The enzyme lactate dehydrogenase is a marker of cancer-cell division and tissue damage, and it is considered in metastatic CRC patients as a marker of disease activity and response to treatment.

All of the previously mentioned markers are routinely measured in CRC patients; however, there are other informative serum markers that can be present in several other tumors as they reflect cellular proliferation and angiogenesis.

Hepatocyte growth factor (HGF) and vascular endothelial growth factor (VEGF) are some examples of molecules that can be elevated in the serum of CRC with liver metastasis [49,50].

Other important data that can be found in serum samples are the microRNA profiles. Many researches show that these data play important roles in the development and metastasis of various tumors [51–53].

Noncoding RNAs (NcRNAs) are molecular regulators of metastatic development and have been used as biomarkers. The NcRNAs include microRNAs (MiRNAs), circular RNAs (CircRNAs) and long non-coding RNA (LncRNAs). The MicroRNAs (miRNAs) are a class of small non-coding RNAs with 22–24 nucleotides in length that affect the gene expression levels via targeting messenger RNA (mRNA)and have gained interest as a potential therapeutic target [54–57]. Changes in miRNA expression may affect the extent of target regulation and thus influence cell homeostasis. These changes can be detected in serum samples and are associated with cancer progression.

Its influence on gene expression and robust presence in bodily tissues and fluids makes them an ideal biomarker.

CircRNAs play important biological roles in cell proliferation, migration and invasion, and their high conservation and cytoplasm stability leads to special functions in transcriptional regulation and post-transcription gene expression [58].

LncRNAs are untranslated transcripts of more than 200 nucleotides, and although they do not have a protein-coding function, they are involved in regulating the expression of almost all protein-coding genes in cells [59].

NcRNAs are abnormally expressed in metastatic cancer cells and are crucial for colon cancer liver metastasis development.

The analysis of circulating tumor cells (CTCs) originating from primary or secondary tumors and the DNA fragments (circulating tumor DNA (ctDNA)) in the blood can be used

for the early detection of invasive cancer (micrometastasis), as well as a prognostic tool for evaluating the response to chemotherapy [60–62].

Isolated ctDNA from plasma carries genetic and epigenetic changes originating from the primary tumor and enables the molecular analysis of mutations, but the main challenge of ctDNA analysis is the low concentration compared to the total DNA present in serum [63]. Clinically, it can be used as a biomarker for patient stratification, therapy selection, and real-life information about the effectiveness of the therapy [64–66].

It appears to be possible to detect CTC in 80 to 90% of the patients in the pretreatment window and after surgical or chemotherapy [67]. The retrospective studies have described a concordance of over 90% between RAS status in matched tumor and ctDNA samples and that the *RAS* status of the ctDNA has high specificity (90–100%) but suboptimal sensitivity (89–96%) [65,68]. The Unicancer Prodige-14 trial investigated the variation of *KRAS* mutated ctDNA in 92 patients and showed that the drop of *KRAS* mutational load after four cycles of neoadjuvant ChT was associated with higher rates of R0/R1 resection, and the presence of detectable ctDNA before surgery was associated with shorter survival versus undetectable presurgical ctDNA [69]. Another use of liquid biopsy is to evaluate the minimal residual disease after resection of CRCLM [70,71].

The liquid biopsy is a minimally invasive technique for detecting molecular biomarkers that uses an analysis of liquid biological material [72]. It has the great advantage of the availability of material for diagnosis; however, adequate and widely available technology and the standardization of the process are needed. There are some available commercial tests based on liquid biopsy and ctDNA analysis: Guardante360, FoundationOne Liquid CDx, Colvera, BEAMing and Signatera [73–76]. These molecular assays can be useful in determining genomic alterations for monitoring disease progression, disease recurrence or relapse, as well as monitoring the response to immune-check-point inhibitors for patients with CRC [77].

Properly designed prospective trials are eagerly awaited to explore these potential applications so they can be used in clinical practice.

6. Genetic Markers

Several genetic markers and mutations have been identified that increase the risk of developing colon cancer. Some of the most well-known genetic markers and mutations associated with colon cancer include the following.

The *KRAS* mutation present in 25–52% of cases is associated with an invasive and more aggressive behavior, more likely in right-sided primary tumors, a higher rate of extrahepatic disease at the time of resection and a decreased likelihood of achieving a major pathologic response [78]. CRCs with a *KRAS* mutation have a disease-free survival (DFS) of 10.8 months and OS of 19.6–55 months. Some studies suggest that *KRAS* mutational status may influence the choice of surgical technique because some data suggested that removing major vascular branches that facilitate the spread of tumor cells to adjacent liver segments reduces the risk of liver disease in *KRAS* mutation tumors that appear to mimic cholangiocarcinoma behavior [72,73]. Other studies reported that surgical margins had no impact among patients with *KRAS*-mutated tumors [79–81] The *KRAS* status is already defined as part of the metastatic CRC approach.

The *BRAF* is a component of the *RAS* pathway and is equally associated with a more aggressive biology. Its mutation is more common in females and right-sided tumors. It is present in 8–12% of CRC patients and in up to 4% of patients undergoing metastasectomy, which means that it is present more frequently in unresectable disease or multiorgan involvement [82]. Its negative prognostic impact is even more pronounced when considering that the burden of the *RAS* mutation meant that liver resection was discouraged for many years in this subgroup [83,84]. However, more recent studies favor the use of preoperative ChT in these patients [85].

The *TP53* tumor suppressor gene mutations are associated with an increased risk of CRC and, when present, are linked to a more aggressive disease and a high risk of metastasis. It is reported in 50–75% of CRC cases [86].

HER2 (human epidermal receptor growth factor 2) amplification is present in about 2–3% of mCRC patients and characterizes a subgroup of patients with worse prognosis and resistance to anti-EGFR therapies [87,88]. Raghav et al. even suggested that *RAS/BRAF* wild-type mCRC patients should be screened for HER2 amplification before anti-EGFRab treatment [89]. The results of a DESTINY-CRC01 multicenter non-RCT trial demonstrated the safety of transtuzumab deruxtecan (T-DXd, an antibody–drug conjugate of a humanized anti-HER2 monoclonal antibody linked to a topoisomerase I inhibitor) in *HER2*+ mCRC patients, and 2 years later, Yoshino et al. reported an OS benefit of 5 months longer in HER2+ mCRC patients treated with T-DXd [90,91].

The DESTINY-CRC02 trial, addressed to evaluate the safety and efficacy of two different T-Dxd doses in *HER2*+ mCRC, showed anti-tumor efficacy irrespective of *RAS* status and in those with prior anti-HER2 therapy [92].

SMAD (small mothers against decapentaplegic)4 is a gene involved in the TGF-beta signaling pathway with a tumor suppressor role [93]. Its loss of expression is reported in over 50% of CRC, which is associated with lymph node metastases [94]. Some studies also reported that *SMAD-4* expression levels are correlated with a response to 5-FU [95–97].

In a recent study, Kawaguchi et al. show that, in addition to *RAS*, mutations in *TP53* and *SMAD-4* are independent negative prognostic factors for survival in patients undergoing resection of CRLM [98]. These authors also demonstrated that the combination of these triple mutations was associated with worse survival than patients with only one or two of these, as well as patients with wild-type mutations.

Therefore, a comprehensive mutational tumor profiling shall be performed in trials and in clinical practice to properly stratify the patient's prognosis and tailor therapy accordingly.

Microsatellite instability (MSI-H) is reported in a rather low frequency (4–8% of metastatic CRC), making it difficult to establish definitive conclusions [99,100]. However, the well-known sensitivity of these tumors to immune checkpoints has improved the prognostic of these patients, and a recent retrospective study showed that liver resection after immune checkpoint inhibitors is associated with a higher rate of pathological complete response long-term-term survival [101].

PD-1 and its respective ligand molecule (*PD-L1*) are immune checkpoints that deliver co-inhibitory signals that suppress exaggerated immune responses [102].

Patients with MSI-high or MMR-deficient CRC exhibit improved responses to PD-1/PD-L1 immunotherapy and improved OS rates [103].

Since 2017, Pembrolizumab has been in use for the treatment of MSI-high metastatic CRC if the disease progresses following treatment with 5-FU, oxaliplatin or irinotecan-based regimens [104]. In these same patients, the ChekMate-142 trial also showed that nivolumab may adequately control the disease [105].

Results from a KEYNOTE-158 study showed that Pembrolizumab, as an immune checkpoint, is effective in various types of cancers with tumor burden (defined as the number of mutations in cancer cells' DNA, reported as mutations per megabase) $\geq$10 mut/Mb, particularly solid cancers [106]. Later, the same study reported that pembrolizumab administration improved outcomes in patients with non-resectable MSI-high non-CRC following the failure of standard therapy [107].

Mutations in the *CTNNB1* gene can activate the Wnt signaling pathway and are more common in adenomas than in invasive cancer (12.5% vs. 1.4%) but can be found in preliminary stages of CRC and plausibly substitute *APC* (adenomatous polyposis coli) mutations in cancer onset and progression [108].

PIK3CA mutations are present in up to 20% of mCRCs [109]. It is associated with the activation of the *PI3K-Akt* pathway, which can promote cancer growth and metastasis and may influence treatment decisions.

A retrospective meta-analysis concluded that *PIK3CA* is a poor prognostic factor and predictive of decreased response to anti-EGFR therapy in patients with mCRC [110].

A rare mutation, the *SMARCB1* loss, with an incidence of less than 1%, is associated with a higher histological grade, larger tumor size, lower survival, MSI and *BRAF V600E* status. It is associated with a subtype of CRC, small cell carcinoma, which tends to have a poor prognosis and high metastatic potential [111].

The molecular factors have been the focus of researchers in recent years to achieve the ultimate goal of personalized medicine using gene signatures to achieve better risk stratification and therapy selection.

Three multi-gene prognostic signatures have already been developed—the OncotypeDX (12 genes), the coloPrint (18 genes) and the colon cancer DSA (ColDx, with 634 genes) [112], and the validation study is still ongoing in Stage II and III CRC patients in the United States, Asia and Europe [113].

Two other molecular pathological classifications for CRC are described. The cancer genome atlas (TCGA) classified CRC into two groups using integrated molecular analysis: the first group consisted of hypermutated tumors (~16%), and the second group consisted of non-hypermutated tumors (~84%), microsatellite stable (MSS) tumors with a high frequency of DNA somatic copy number alterations (SCNAs) and dysregulated Wnt pathway with frequent mutations in genes, including *APC, KRAS, PIK3CA, SMD4* and *TP53* [109].

The group study by Guinney et al. described the four consensus molecular subtypes (CMS) of CRC: CMS1 (MSI-immune) was associated with a very poor OS rate after relapse; CMS2 (canonical) and CMS3 (metabolic) had better survival rates after relapse, and CMS4 (mesenchymal) had the worse prognostic [114]. This genetic classification has been stated as the most robust but requires fresh tissue and is not ready for widespread application.

Finally, another genetic marker must be considered in the algorithm approach of CRC patients—dihydropyrimidine dehydrogenase (*DPYD*) gene polymorphisms.

DPYD is a main enzyme in the biochemical functions of the antimetabolite 5-FU, as well as capecitabine, and the tumor response rate to these drugs and the adverse events depend on *DPYD* levels [115,116].

The *DPYD* gene variations are present in 5–7% of the population and account for 23% of life-threatening toxicity cases from fluoropyrimidine-based chemotherapy [117,118].

Chemotherapy resistance remains one of the greatest challenges in metastatic cancers, and the DPD expression level is inversely associated with chemosensitivity [119].

However, upfront genotyping is not mandated by most well-known guidelines. In 2020, the European Medicines Agency (EMA) recommended testing for DPD deficiency prior to 5-FU treatment. The NCCN and the ASCO have not yet provided recommendations for universal pretreatment genotyping, but the NCCN reports strong links between *DPYD* variants and toxicity risk as well as the potential benefits of testing [120–123].

It is important to note that the presence of these genetic markers alone may not be sufficient to predict the development of liver metastasis in an individual patient. The interplay of multiple factors, including the tumor stage, location, and other clinical variables, must also be considered when assessing the risk of metastasis in colorectal cancer.

7. CRCLM—Prognostic Tools

Prognostic tools are fundamental in CRC patient management since tumor recurrence and metastases are the main issues in patients' survival.

R0 surgical resection is a curative treatment with a reported 5-year overall survival of 20–45% [124].

The treatment options for these patients are systemic treatment, surgery and/or local ablative techniques, such as thermal ablation (TA) or stereotactic body radiotherapy (SBRT), which may be added to surgery to achieve a complete treatment or provide an alternative to resection if inoperable due to frailty or poor anatomical location for resection.

The treatment selection criteria depend on patient characteristics as well as technical and prognostic criteria.

Patient characteristics include performance status, age, previous treatments and patient preferences (QoL and expectations).

The technical criterion is not just a question of technicality but rather a functional criterion, which considers if the tumors may be resected while leaving sufficient liver remnant (30–40% depending on the basal function). In cases where this is not possible, liver transplant may be considered by some authors.

The prognostic factors are those that represent the tumor biology and have a true impact on disease-free survival. These factors include the tumor burden (number, size of lobar distribution), the timing of metastatic disease presentation (synchronous versus metachronous), the primary tumor location and proof of time (response after systemic treatment), and the molecular profile, including *RAS/BRAF* status and dMMR/MSI.

The patient selection to approach CRCLM has been based on clinical risk scores, the most widely used is the Fong clinical score present in 1999 (disease-free interval <12 months, node-positive primary, more than one liver metastasis, largest lesion > 5 cm in diameter, and serum carcinoembryonic antigen (CEA) level > 200 μg/L) [125]. This score does not take into consideration the knowledge of tumor biology. There are more recent scores that incorporate genetic and molecular markers.

In recent years, other scores have surged, such as the MD Anderson-modified CRS (mCRS), the RAS Mutation Clinical Risk Score and the Genetic and Morphological Evaluation (GAME) score. The last two have been externally validated and appear to be superior to Fong's [126,127].

A recent study demonstrated that the GAME score has superior discriminatory capacity compared to both the Fong score and mCRS score [128].

Other isolated prognostic parameters have been analyzed. A large multicenter study with a sample of 1643 used a statistical technique previously described by Allen et al. to define optimal cut-off values for the three most commonly employed prognostic factors: 2.95 cm for tumor size, 1.5 for tumor number and 6.15 ng/mL for CEA levels [129].

The inclusion of our actual knowledge concerning molecular and genetic markers in the decision-making process for these patients is our next step in optimizing existing prognostic tools.

8. CRCLM—Therapeutic Approach

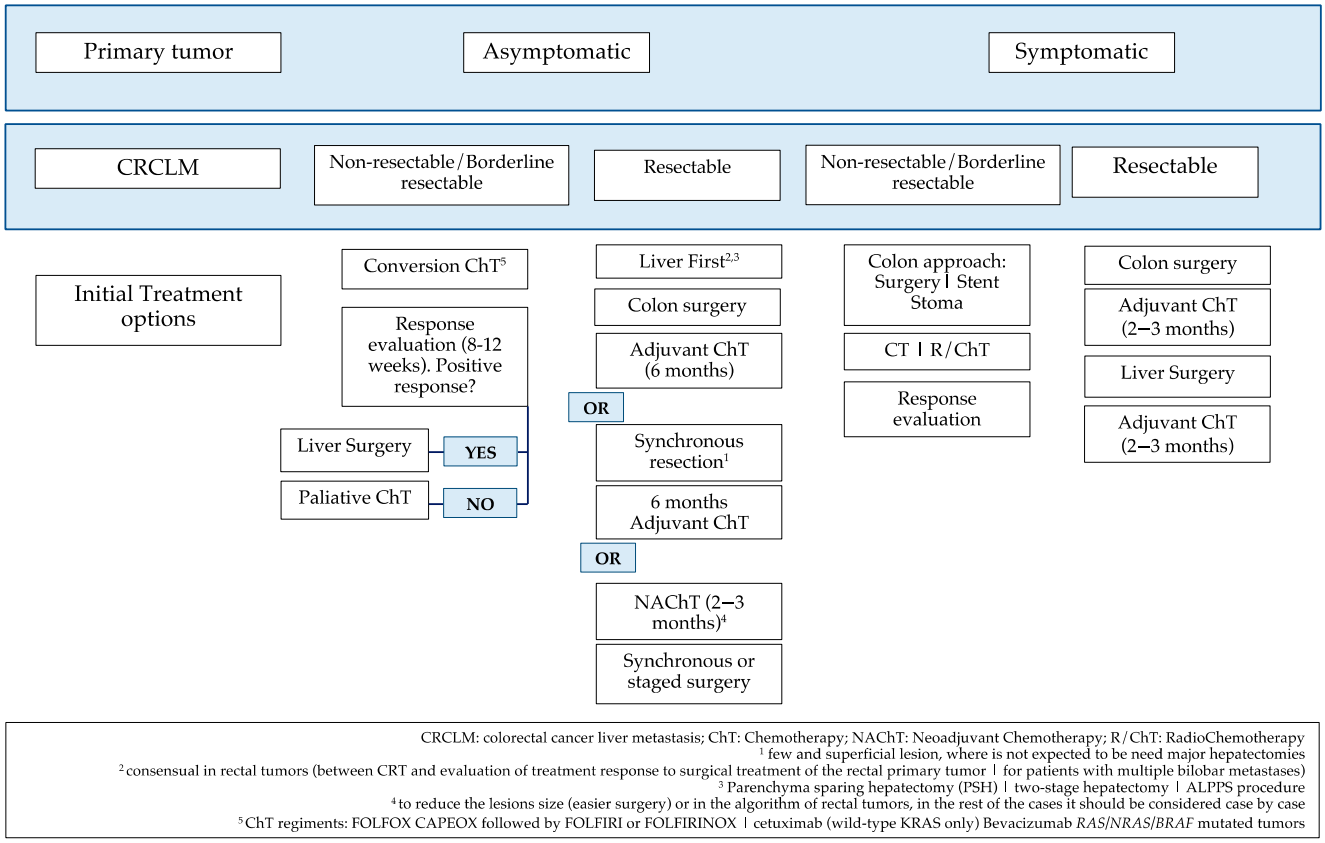
In the case of CRC with irresectable LM, there is some consensus on starting systemic treatment as a conversion therapy. The patients must be re-evaluated every 8–12 weeks with a maximum of 6 months to achieve the maximum response. If some response is present and liver resection is feasible, yielding at least 30% liver remanent, the 5-year OS rates in retrospective studies range from 25 to 58% [130] (Schemes 1 and 2).

Nearly 70% of patients will develop recurrent disease in 2 years, and up to 50% will experience a recurrence within the liver alone [131].

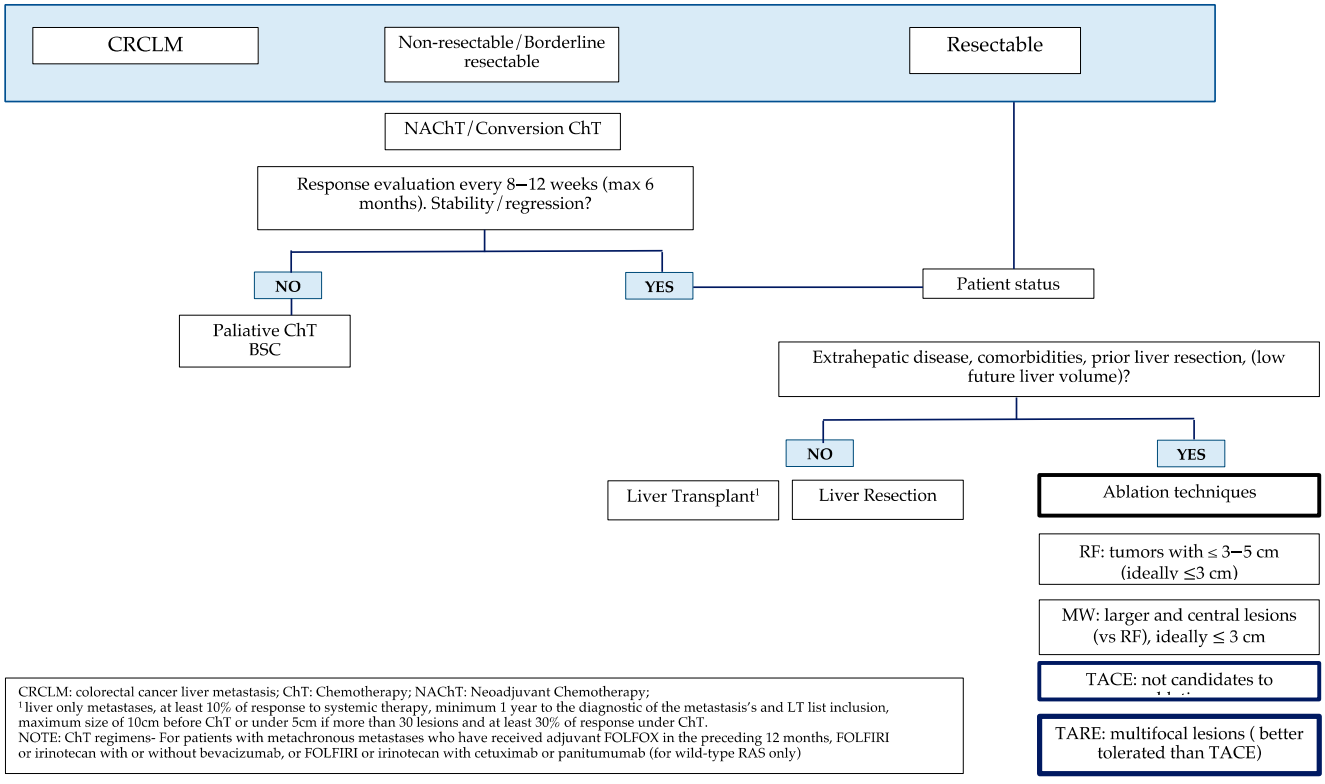
The NCCN guidelines provide three treatment options for patients with CRC and synchronous and resectable LM: (1) synchronous or staged colectomy with resection of metastatic disease followed by 6 months of adjuvant ChT; (2) neoadjuvant ChT (NAChT) (2–3 months) followed by synchronous or staged colectomy and resection of the metastatic diseases supported by a remaining 3–4 months of adjuvant therapy; (3) colectomy followed by ChT (2–3 months) and staged resection of liver disease with 3–4 months remaining adjuvant ChT.

In fact, both American and European Guidelines recognize the role of chemotherapy and recommend the use of 6 months of an oxaliplatin-based regimen in addition to surgery [29,30,56]. However, the timing of this treatment remains unclear, and both perioperative and post-operative treatments offer potential advantages and disadvantages.

The ChT drugs preferred are FOLFOX or CAPEOX followed by FOLFIRI or FOLFIRINOX. Besides the double or triple schemes, the addition of a target agent leads to a more effective treatment. Patients with *RAS* mutant CRC should be treated with bevacizumab.



Scheme 1. Algorithm approach of synchronous liver metastases from colorectal cancer.



Scheme 2. Algorithm approach of Metachronous Liver metastases from colorectal cancer.

The main advantages and limitations of each treatment option approach will be mentioned below.

8.1. CRCLM—Neoadjuvant ChT

The increasingly effective systemic drugs have prompted interest in preoperative or neoadjuvant treatment prior to liver resection. Neoadjuvant ChT is not questionable as conversion therapy in cases of borderline resectable lesions, which will make the liver resection feasible in the case of unresectable ones or easier by reducing the lesion size or in the algorithm of rectal tumors. In the rest of the cases, it should be considered case-by-case.

For patients with R0 resectable and favorable oncological criteria with up to four lesions, metachronous presentation and liver-only site, there is no level 1 evidence to support the improved survival with upfront ChT, and upfront surgery should be performed. Some centers will administer neoadjuvant ChT for nearly all patients with resectable CRCLM to select who will benefit most from resection, particularly in patients with a synchronous presentation of metastatic disease.

The ideal selection criteria, specific drug scheme and duration of neoadjuvant chemotherapy, and the best way in which chemotherapy should be interdigitated with surgery in patients who present with synchronous metastatic disease have not been well defined.

A randomized controlled trial showed some benefit to disease-free survival but no benefit of overall survival if neoadjuvant ChT with FOLFOX was used in upfront resectable LM [132,133]. Other retrospective studies showed no benefits [134].

The European Organization for Research and Treatment of Cancer trial of 40,983 patients showed no improvement in OS or DFS when compared with patients summited to six cycles of FOLFOX pre-operatively and six cycles post-operatively versus surgery alone [133].

In patients with bad biology, a preoperative ChT for no more than 2 months with fluoropyrimidine and oxaliplatin should be proposed, and liver resection should be delayed at least four weeks after completion of ChT (FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) or FOLFIRI (5-fluorouracil, leucovorin, and irinotecan)—6–8 weeks if bevacizumab was used.

Currently, three biologic agents—bevacizumab, cetuximab, and panitumumab—are approved for first-line treatment of metastatic colorectal cancer. There are no clear advantages to the addition of monoclonal antibodies binding to VEGF or to the epidermal growth factor receptor (EGFR) in the neoadjuvant setting of resectable LM, and there are conflicting data regarding the use of FOLFOX + cetuximab in patients who have potentially resectable liver metastases. Its use is established for unresectable lesions, with bevacizumab being the only biologic agent approved for *RAS/NRAS/BRAF*-mutated tumors.

The main concern about upfront ChT is that the small lesions may disappear and be missed during the surgery yet still active in terms of the presence of tumor cells. This effect and the liver toxicity induced by ChT increases the risk of liver surgery complications as well as the possibility of progression besides resection, leading to unresectable situations.

The guidelines that support NAChT consider it as a possibility of early treatment of micrometastasis and a "proof of time" that translates the tumor biology, as the response to chemotherapy may prevent unnecessary surgery for those who present early disease progression. In addition, the tumor downsizing allows liver preservation and more manageable tumors, which typically result in better surgical outcomes. The 5-year OS in patients that progressed after NAChT even when an R0 resection is obtained is 8% vs. 30–37% in cases of stable or partial response [135].

To specifically address this issue, the CHARISMA trial is an ongoing multicenter randomized phase III clinical trial evaluating the impact on OS of neoadjuvant chemotherapy in patients with resectable CRC liver metastases and a high clinical risk score (Fong score 3–5) [136].

8.2. CRCLM—Best Surgical Algorithm Approach

The management of colorectal cancer with synchronous liver metastasis typically involves a multidisciplinary approach that may include surgery, chemotherapy, and other treatment modalities. The choice of the best surgical approach depends on several factors, including the location and size of the primary colorectal tumor, the number and size of liver metastases, the overall health of the patient, and the potential for achieving curative or palliative goals [21,123].

A controversial issue is the timing of hepatic resection in patients who have liver metastases at initial presentation. The primary tumor resection is clearly indicated in symptomatic primary tumors (obstruction or hemorrhage) [123,137].

In the cases of asymptomatic CRC and synchronous liver metastasis, the liver-first vs. synchronous resection varies between expert groups. First, synchronous can only be considered in patients with few and superficial lesions, wherein it is not expected to require major hepatectomies given the consideration that major liver resections may increase the risk of colorectal anastomosis due to Pringle times and the risk of post-operative complications [138–141].

The liver-first approach appears to be consensual in the cases of rectal tumors in the window between the completion of chemoradiotherapy and the ensuing evaluation of the treatment response before surgical treatment of the primary rectal tumor [142].

Despite these concerns, some groups state that approaching the most prognostic impact disease should be the first step. In a recent study, Giuliante et al. analyzed the results of 7360 patients from the LiverMetsSurvey database and proposed a tumor burden-driven strategy: for patients with multiple bilobar metastases, a liver-first approach has a clear survival advantage; in cases of solitary lesions or multiple unilobar lesions, the staged procedure showed to be equivalent regarding survival [143].

A recent meta-analysis including 6417 patients operated between 2000 and 2021 suggested that simultaneous and staged strategies are similar regarding long-term survival, although the length of hospital stay and post-operative mortality may differ between groups. The simultaneous resection was associated with a shorter length of stay (median of 4 days shorter), and although there were no differences in general complication rates, the risk of post-operative mortality was higher in the resection group [144].

A retrospective multicentric analysis with 1116 patients demonstrated, after a propensity match analysis, a comparable 90 days mortality as well as a similar 3-year OS, between simultaneous resection versus staged resection of the colorectal liver metastases, although simultaneous resection had a higher incidence of overall and severe surgical complications [139].

Sijberden et al. reported a retrospective study from an international database with 766 patients with synchronous CRCLM submitted to different types of liver and colorectal resection. They concluded that synchronous resection should be reserved for CRCLM patients in whom minor liver resection would suffice and those requiring a left-sided colectomy [145].

A unique RCT with 105 patients showed that perioperative complications did not differ between both strategies (49% and 46% (p = 0.70) in simultaneous- and delayed-resection groups, respectively, and DFS tends to be superior in simultaneous resection after a median follow up of 47 months (p = 0.05) [146].

On the other hand, a large multicenter study with more than 23,000 patients reported that 30-day morbidity was higher among patients treated with simultaneous resection even after controlling for confounding factors such as extent or risk of the procedure [138].

Careful patient selection remains paramount when determining the optimal surgical approach in patients presenting with colorectal cancer and synchronous liver metastasis.

8.3. CRCLM—Surgical Options

There are several options to surgically remove liver disease: major or minor hepatectomy, two-stage hepatectomy and liver transplant.

Liver R0 resection and or ablation offers the only possibility of a cure for patients with CRCLM with a reported 5- and 10-year OS of 55–71% and 25%, respectively. However, up to only 20% of the patients are eligible for intervention, and a substantial proportion of these do not benefit from surgery, as approximately half of them develop systemic disease within 3 years of resection [147,148].

Liver surgery should be considered 5–12 weeks after the previous ChT or at least 5 weeks after ChT if bevacizumab has been used, according to NCCN guidelines, while ESMO guidelines recommend the optimal operation time of 6–8 weeks after NaChT [137,149].

The optimal timing is still controversial. Some groups defend that a longer interval before surgery can increase the rate of tumor downstaging and the rate of pathological complete response, and other authors suggested that a longer interval might increase the difficulty of surgery and reduce the quality of the results, and for that reason, it should be performed as soon as the lesions become technically resectable.

A recent propensity match analysis compared two groups: an early resection subgroup ($4 \leq$ TTS < 6) and a delayed resection subgroup ($6 \leq$ TTS ≤ 8) and concluded that the early surgical resection subgroup had better OS and DFS [150]. Other studies have also suggested that surgical resection more than 6 weeks after NA ChT can lead to regrowth of potential resistant tumor cell population [151,152].

Due to the advances in FLR grow strategies and the downstaging/conversion therapy, the number of patients considered eligible for CRCLM continues to increase (from 1–2% to 15–30%), which offers a 5-year OS rate of 25–44% in different series, but up to two-thirds will recur and 15% will die within a year [135,148,153].

The parenchyma sparing hepatectomy (PSH) was described by Gold et al. who demonstrated that wedge uni- or bilobar resections have no impact on oncological outcomes if R0 is completed [154]. The authors reported a similar DFS and OS when comparing standard or extended hepatectomies. Besides the absence of impact on the oncological outcome, the benefits of PSH include the lower complications associated with liver surgery with shorter intensive care units, lower liver failure rate, low decrease in cases (because more patients received adjuvant ChT) and the possibility of performing a salvage rehepatectomy, which is very important given the recurrence rate of the disease.

However, the PSH strategy does not fit all cases. In the past 20 years, some new surgical strategies have appeared to increase the rate of resectable patients, e.g., the two-stage hepatectomy. It was described in 2000 by Adam et al. and consists of two separate surgeries: in the first intervention, the liver parenchyma is transected along the intended line of resection, the FLR is cleaned by partial resections or ablation from all tumor tissue, and a portal vein embolization or ligature is associated. The second surgery is performed afterward, and the deportalized liver is removed completely for a resection [155].

The ALPPS procedure (associating liver partition and portal vein ligation for stage hepatectomy) was described in 2012, and the long-term oncologic results of this technique were first published in 2020 from a cohort from 22 international centers. The 3- and 5-year cancer-specific survival rates after ALPPS were 59% and 33%. Regardless of prognostic factors, the response to neoadjuvant ChT was the strongest independent predictor of short and long-term oncologic outcome, and the T4 stage, the right-side location of the primary tumor and *KRAS* mutation were negative predictor factors [156].

The selection criteria for these procedures are not uniform and vary between groups, and the results are difficult to compare given the heterogeneity of the cohorts.

Liver transplant (LT) is an acceptable option in certain hepatic malignancies such as HCC and hilar cholangiocarcinoma.

Although it is also acceptable for some cases of secondary lesions, such as neuroendocrine tumors, with a 5 y OS of 52%, the poor outcomes reported in the cases of unresectable CRCLM make the LT a controversial option in these cases [157,158].

As reported before, only about 20% of the patients are eligible for surgery, and for the ones unsuitable for complete resection, palliative ChT is the only option, which achieves a 5-year OS of less than 10%.

The Norwegian RCT (SECA-I) showed a 5-year OS of 60%, and the Toso et al. retrospective study showed a 5 y OS of 50 ± 16% [159,160].

Another study comparing the SECA-I with those who received ChT (NORDIC VII trial) showed a significant difference in OS in favor of LT (5 y OS of 56% versus 9% [161]).

The SECA-II included patients with liver-only metastases, at least 10% response to systemic therapy, minimum 1 year to the diagnostic of the metastasis's ant LT list inclusion, maximum size of 10 cm before ChT or under 5 cm if more than 30 lesions and at least 30% response under ChT. The OS at 1, 2 and 5 years was 100%, 83% and 83%, respectively [162].

There are several ongoing trials to confirm these results. The TRANSMET (Liver Transplantation in Patients with Unresectable Colorectal Liver Metastases Treated by Chemotherapy—NCT02597348) trial is a multicenter randomized trial comparing the 5-year survival of chemotherapy followed by LT versus chemotherapy alone; the SECA-III (NCT03494946) is an RCT comparing LT and chemotherapy/TACE/SIRT or other treatment options. Results will be expected in 2027 [163,164]. There is also an Italian multicenter RCT, COLT (improving outcome of selected patients with non-resectable hepatic metastases from colorectal cancer with liver transplantation) comparing LT after chemotherapy to chemotherapy alone in a cohort of patients with the RAS and BRAF WT and MSI tumors (NCT03803436) and the Swedish study SOULMATE NCT04161092 with only BRAF wild-type and MSI patients [165].

The shortage of deceased organ donors is the main problem associated with the use of grafts in patients without the conventional indications. In order to overcome this issue, other transplant options have emerged, namely the RAPID (resection and partial liver segment 2/3 transplantation with delayed total hepatectomy) and LIVER-T(W)O-HEAL.

At the time of transplantation, segments 1 to 3 are resected in the patient and orthotopically replaced by allograft at segments 2 to 3. Portal inflow is modulated (portal vein pressure below 20 mm Hg). A second-stage hepatectomy is performed as soon as the graft has regenerated to reach at least 0.8% of the recipient's body weight or 35–40% of standardized total liver volume [166,167].

This hybrid of the auxiliary LT and the ALPPS procedure concept has the advantage of not reducing the liver donor pool. There is a prospective ongoing study in Oslo University Hospital as well as a North American transplant center [168].

8.4. CRCLM—Ablation Techniques

When the patient criteria do not allow for surgical intervention, or in cases of unclear prognostic situations or require a pause or delay in systemic treatment, there are several ablative techniques available that provide an opportunity for curative intent. These local treatment options can be curative, as 20–45% of the patients can undergo a complete A0 of their metastasis [169].

The objective of ablation in resectable patients is similar, i.e., to achieve complete local control A0 [135].

Local treatment techniques have a particular interest in oligometastatic disease. Currently, there is no consensus on the number and location of the metastatic lesions; however, most clinical protocols and clinicians accept the definition of oligometastatic disease as 1–3 or 1–5 metastatic lesions, up to 2–3 sites of metastasis and a controlled primary tumor. Here, it is highlighted that this definition does not include the tumor biology, so care must be taken to select the therapeutic options for these patients.

Local metastasis therapies include the radiofrequency (RF), microwave ablation, transarterial chemoembolization (TACE), and more recently, stereotactic body radiation therapy (SBRT). Factors that conditioned the selection of these techniques are size, location and the *RAS* status.

Some studies have reported OS similar to those of hepatectomy for some of the ablation techniques (up to 55% at 5 years) [170,171].

The RF is the old one and the most common form of thermal ablation used in liver tumors, applicable in tumors with ≤5 cm (ideally not larger than 3 cm), allowing as much as 94% of local control and a 5-year OS of up to 40% for small solitary CRCLM.

A recent meta-analysis showed, however, that RF had a higher recurrence rate and lower OS at 1, 3 and 5 years for CRCLM. In addition, a study reported that there was no difference between RF and liver resection at 10 years of DFS. In these reports, the tumor size (more than 3 cm), old age, primary node-positive and metachronous metastasis were independent factors of survival [172].

Two recent meta-analyses recognized a superiority in OS and DFS with reduced local recurrence favoring the surgical resection, even in lesions with less than 3 cm [173,174].

These conclusions should be analyzed with caution since most of the studies that considered that surgery is superior to RF included a heterogenous group of patients to compare. The RF group included more patients with extrahepatic disease, comorbidities, prior liver resection and higher values of CEA.

The LAVA trial was a multicenter RCT with the goal of comparing thermal ablation with liver resection in high-risk surgical patients that was stopped after 1 year, and the COLLISION trial is an ongoing RCT that aims to compare RF with liver resections for patients with lesions under 3 cm [175].

When we search for RF versus ChT alone, there are some studies, including RCTs, that show a longer survival in favor of RF [176].

In conclusion, RF is a valid option as a minimally invasive treatment with low complicated rates that can be repeated to treat progression or new lesions and does not require prolonged interruption of chemotherapy. For these reasons, there is growing interest in the possibility that RF could reach the same oncologic results as surgery [177].

Cryoablation with liquid nitrogen or argon gas has fallen out due to the higher complication rate and recurrence compared with RF [178].

Microwave ablation is a percutaneous procedure that uses electromagnetic signals to generate heat through molecular friction. It is indicated for patients considered not fit for surgery or that have unresectable lesions. It allows for the treatment of larger and more central lesions than RF, and the 5-year OS is 37% [141].

TACE transarterial chemoembolization consists of a shutdown of blood flow and the simultaneous release of high doses of the drug through the administration of embolic particles mixed with a chemotherapeutic drug. It is an option in patients not fit for surgery, candidates not applicable for ablation or when the ChT fails. It has significant toxicity and a 5-year OS of 6% [141].

Transarterial radioembolization (TARE) or selective internal radiotherapy with yttrium-90 (SIRT) is a type of intra-arterial brachytherapy that targets hypervascular nodules with a 2.5 mm range of tissue penetration. This allows the safe administration of high doses of radiation to the tumor. It is an indication for palliative patients with multifocal irresectable lesions. It is better tolerated than TACE [179].

SBRT stereotactic body radiation therapy delivers precise external beam radiation using 4D imaging and appears to allow for the treatment of liver metastasis with ablative intent while significantly limiting the dose to the healthy liver and surrounding tissues. There is no clear advantage over ablation or ChT and the OS reported varies between 24–27 months [141]. The retrospective and prospective clinical studies refer to it as a safe and effective technique with minimal and promising OS [180,181]. The majority of the studies have treated one to three liver lesions, but multiple liver metastases can be treated with sequential SBRT with a 5-year OS of 57%.

9. After CRCLM Resection—The Role of Histopathological Growth Patterns and the Immune System

Histopathological growth patterns (HGP) play a crucial role in the diagnosis, prognosis, and management of liver metastasis of colorectal cancer. These growth patterns reflect the interaction between tumor cells and the host in a particular microenvironment, provide

valuable insights into the behavior of the metastatic lesions and can guide treatment decisions.

There are three described patterns associated with different responses to QT and, consequently, different rates of relapse and prognosis: replacement (rHGP), pushing (pHGP), also classified as non-desmoplastic (ndHGP) and desmoplastic (dHGP)—the latter being associated with better prognosis (OS of up to 80% at 5 years) [182–184].

In 2015, R. L. Eefsen et al. showed higher R0 resection rates for dHGP, suggesting that the different recurrence rates after surgery could be explained by HGP [185]. The same author concluded that some characteristics of the tumor microenvironment (TME) differ between HGP but only in those patients not undergoing neoadjuvant therapy [186].

The main limitation of this information is the fact that they can only be accessed after surgical resection, which is too late as more aggressive HGP may require aggressive strategies such as NAChT or, in a more extreme case, liver resection. The radiomics is being developed to try to overcome this handicap (see below), but a better correlation with primary tumor characteristics and liquid biopsies are needed.

The immune system plays a crucial role in the growth and metastasis process. With the introduction of immune checkpoint inhibitors into clinical practice, the interest of the scientific community in the study of the TME has been growing.

Pagès et al. reported that MHCCR are characterized by high levels of CD3+, CD8+ and CD45R0 lymphocytes, with their distribution being asymmetrical and greater on the periphery of the lesions, and that dHGP have a higher density of CD8+ cells, a finding later reproduced by others [187].

D. J. Höppener et al. evaluated the TME of MHCCR from chemo-naïve patients, comparing dHGP with ndHGP [188]. The greater infiltration of CD8+ T lymphocytes associated with dHGP corroborates what was previously described: patients with ndHGP have a higher risk of recurrence after surgical treatment [189].

Last year, G. Garcia-Vicién et al. mentioned an immunosuppressive microenvironment in MHCCR with ndHGP and an antitumor immune microenvironment in MHCCR with dHGP, a fact that reinforces the better prognosis associated with encapsulating metastases [190].

While T cells are gaining notoriety in this field, little is known about the impact on the prognosis of B cells [191,192]. It is believed that the release of cytokines by B cells can increase the antitumor response of T and J cells. Hof et al. suggested that high infiltration of CD79A+ B cells may be an indicator of a favorable prognosis after surgery [193].

A 2022 prospective study has taken a step further in the characterization of CRC liver metastasis as they characterized 60 different T-cell populations in tumor and peri-tumor liver tissue that were also subdivided according to their HGP. They reported that the immune microenvironment within CRC liver metastasis lacks infiltrated lymphocytes and presents an immunosuppressive profile compared to the non-tumor samples. They also correlated the metastasis size with the percentage of IL-17-producing cells present in tumor samples and identified an increase in cells with antitumor activities ($CD8^+$ $CD185^+$ cells and effector $CD8^+$ T cells), which can be new targets for CRC LM [194].

Later, they also found that tumor samples with a desmoplastic growth pattern exhibited a significantly decreased percentage of CD274 (PD-L1)-and CD206-positive cells, which are proteins associated with poor prognosis and disease progression; therefore, reinforcing the role of dHGP as predictors of better outcome. They found a correlation between a lower expression of CD206 or CD274 on classical, intermediate, and non-classical monocytes and increased disease-free survival, which points to a better prognosis for these patients [195].

In summary, the tumor microenvironment, particularly the innate immune system, seemed to play a crucial role in the progression of CRCLM, and its study is essential for a better understanding of the pathophysiology of CRCLM and further treatment planning. There is a possibility in the future to correlate these TME characteristics with peripheral blood analysis. Once again, liquid biopsies appear to have an important role in the CRC patients' future algorithm.

10. After CRCLM Resection—The Role of Liver Margin

Reaching an R0 resection is considered the most important factor associated with better prognosis in terms of 5-year OS: 55% in R0 patients vs. 26% in R1 patients; p = 0.017 [196]. Multivariate analysis has identified R1 resection (p = 0.03) as a factor independently associated with worse survival [197].

The width-of-margin has a well-known importance, yet the research has evolved from the 1 cm to 1 mm rule, confirming that margin width does not affect the outcome as long as a negative margin is achieved [198].

An "incomplete resection" or "microscopically positive margin" that defines the R1 resection can still provide symptomatic relief and local tumor control; it is associated with a higher risk of local recurrence and poorer long-term outcomes. In these cases, adjuvant treatments may be considered.

Furthermore, there is an additional distinction that should be made, i.e., R1 parenchymal resection and R1 vascular resection, because Vigano et al. demonstrated that R1 vascular resection guaranteed the same local control as R0 parenchymal resection [199].

In the literature, an R1 resection varies between an involved margin (width = 0 mm) or a margin width less than 1 mm, and the absence of a universally adopted definition can mislead the interpretation of different research results that reported R1 as a worse OS with significance as a predictor of survival [200].

Some concerns have equally been raised in relation to the margin width and the HGP since patients with non-desmoplastic HGP are at higher risk of a positive resection margin [182,201].

In conclusion, R1 resections are associated with local recurrence and worse long-term results but are still a better option than no resection [200]. We believe that the future challenge in the field of surgical resection of CRLM is to integrate the disease biology in the resection margins.

11. CRCLM—Adjuvant Chemotherapy

Adjuvant chemotherapy aims to eradicate micrometastatic disease, reduce recurrence and prolong OS after an R0 resection with curative intent. If there is a clear OS benefit from resection in patients with limited hepatic metastases from CRC, the role of systemic or regional therapy following metastasectomy is far less certain.

Some RCTs have studied this question: The French FFCD trial recruited 173 patients who had undergone R0 CRCLM. The patients were stratified according to LM size, number of lesions and time of metastasis diagnosis. The 2- and 5-year DFS was 50.4% and 33.5% for those treated with chemotherapy, and 38.1% and 26.7% for the surgery-only group, respectively (p = 0.028). The OS favored the ChT arm, but the results did not reach statistical significance (p = 0.13) [202].

The EORTC (European Organization for Research and Treatment of Cancer) trial evaluated the results of perioperative FOLFOX (six cycles preoperatively, six post-operatively) versus observation alone in patients with initially resectable CRCLM and reported an improved 3 y OS when ChT was used [132]. However, the 5-year OS update showed no differences [133].

The EPOC study evaluated the benefit of perioperative (12 weeks pre and 12 weeks post) oxaliplatin plus fluoropyrimidine chemotherapy with or without cetuximab in patients with initially resectable liver and concluded that the addition of cetuximab was associated with significantly worse progression-free survival [203].

Despite the paucity of the data regarding OS benefit, the NCCN guidelines recommended a total of 6 months of perioperative ChT for patients who have undergone CRCLM resection. The FOLFOX or CAPEOX appears to be the preferred regimen for this group of patients [137,204]. There is no place for biologic agents in the adjuvant setting of initial resectable CRCLM.

Hepatic artery intra-arterial chemotherapy (HAI) is used as an adjuvant treatment combined with systemic chemotherapy to reduce the risk of recurrence. Its concept has

evolved in the past 30 years and is now accepted as the first line of treatment in some countries for unresectable cases or as adjuvant therapy

The technique expertise and knowledge requirement to manage treatment is the main reason this is infrequently used. The four early RCTs compared adjuvant HAI with either systemic therapy or no treatment, revealing mixed results [27,205–207].

A report from the 2017 Memorial Sloan Kettering Cancer Center revealed an increase in the OS from 44 months to 67 months ($p < 0.01$) for patients treated with HAI versus adjuvant systemic chemotherapy alone [204].

The ongoing PUMP trial plans to evaluate the efficacy of adjuvant HAI in low-risk patients, and the PACHA-01 trial is comparing adjuvant systemic FOLFOX and Oxaliplatin + systemic 5-FU in patients with four or more resected lesions and R0 or R1 resection and/or thermal ablation [208,209].

This liver-directed therapy with HAI can target residual micrometastatic disease to reduce the risk of hepatic recurrence and improve survival. In patients with unresectable lesions, HAI can be used to increase response rates even in patients after progression on the first and second line of ChT [210].

12. CRCLM—Future Directions

Liver metastasis from colorectal cancer is a significant clinical challenge, but there have been several new perspectives and advances in the management of this condition.

An ongoing research focus is the development of non-invasive, highly sensitive biomarkers to allow for an early detection of CRCLM. The areas of imaging technologies and liquid biopsies are definitely the future.

The advances in genomics and molecular profiling have led to a deeper understanding of the genetic and molecular characteristics of colorectal cancer. This knowledge allows for the identification of specific mutations and biomarkers that can guide treatment decisions, allowing for a more tailored treatment strategy.

Immunotherapy has a long way to go. Immune checkpoint inhibitors is still a growing field based on new targets that are discovered every day. We believe that personalized immunotherapeutic approaches that boost the immune system's response against metastatic lesions will be a major player in the future.

Radiology and intervention radiology may play a more interventive role in the CRCLM approach. We believe that the future may bring us image-guided interventions for precise tumor removal. The development of a more complex image system that allows us to predict tumor biology is also definitively in the near future and will have a role in individualized medicine.

The systemic drugs available and drug delivery systems have huge potential for optimization. The role of nanomedicine for direct liver metastasis treatment has been reported with better drug efficacy and reduced side effects.

The use of liquid biopsies is gaining importance in the monitoring of treatment response and detecting the emergence of resistance mutations. As said before, it allows real-time monitoring, and thus, a more dynamic view of the disease progression. Optimization of this analysis is necessary to be widely used in clinical practice.

Artificial intelligence (AI) and machine learning are scary yet have potential. The possibility of utilizing AI algorithms to analyze medical images and identify metastatic lesions at an early stage and the development of predictive models to assess the risk of liver metastasis in CRC patients can change the known therapeutic decision process.

In addition to all of these promising advances, there is an area that we need to improve that does not necessarily depend on medical advances: the quality of life of these patients. Focus on supportive care and palliative measures, incorporating psychological and emotional support into the treatment process of the patients and families, must be a key part of this process because we perform research to treat people.

Another crucial part of the future of CRC patients' approach is knowledge sharing. It is important to develop global health initiatives promoting collaboration between medical institutions, researchers and pharmaceutical companies to accelerate progress and

expand access to CRC screening, diagnosis and treatment in underserved regions, as these collaborative efforts may reduce the global burden of CRCLM.

Advances in these areas aim to improve patient outcomes, enhance the understanding of the disease, and provide more effective treatment options.

13. Discussion

The approach to CRLM has witnessed remarkable progress with increasing curative potential. Multidisciplinary strategies, encompassing surgical innovations, systemic therapies, and advanced imaging, have collectively improved the algorithm approach.

The future holds exciting possibilities with a focus on precision medicine and immunotherapy, providing hope for a brighter outlook for these patients.

As we look ahead, the emphasis on precision medicine, liquid biopsy technologies and a deeper understanding of the immune microenvironment offers prospects for earlier detection, more effective treatments, and long-term control of CRLM. However, these promising avenues require ongoing research and clinical trials to translate potential into reality.

In summary, the management of colorectal cancer liver metastases is evolving rapidly, and its future is filled with optimism. The collaborative efforts of clinicians, researchers and innovative technologies are paving the way for improved patient outcomes and a brighter future for those facing this challenging condition.

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