Review

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Multimodal treatment of colorectal liver metastases: Where are we? Current strategies and future perspectives

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SUMMARY: Despite the continued high prevalence of colorectal cancer in the Western world, recent years have witnessed a decline in its mortality rate, largely attributable to the sustained advancement of multimodal treatment modalities for metastatic patients. One persisting issue is lack of consensus between different centres and multidisciplinary teams regarding definition of resectability, the duration of chemotherapy treatment, and surgical strategy. This narrative review outlines current multimodal treatment of patients with colon cancer metastatic to the liver and/or lung in different clinical scenarios. Currently, there are multiple multimodal strategies that can be employed to enhance resectability in these patients. These include novel and sophisticated target therapies (such as novel immunotherapeutic modalities and micro RNAs), complex resections utilising parenchyma-sparing techniques, liver transplantation, and cytoreductive strategies in patients for whom a curative option is not feasible. It is the responsibility of the scientific community to establish standardised protocols across different centres, based on the most recent evidence, while maintaining a high degree of personalisation of treatment for each individual patient. It seems likely that artificial intelligence (AI) will play a significant role in achieving this goal.

Keywords: liver metastases, colorectal cancer, multidisciplinary approach, surgical strategy

1. Introduction

Colorectal cancer represents the third most prevalent cancer diagnosis globally and is the second leading cause of cancer-related mortality (*1*), although there has been a gradual improvement in survival for these patients over the last few decades (*2*). In fact, there have been remarkable advances in the management of metastatic colorectal cancer (mCRC). These developments can be attributed to several factors, including the evolution of liver surgery techniques with a reduction in mortality and morbidity, the introduction of new procedures that enhance the future liver remnant (such as portal vein embolization, two-stage hepatectomy [TSH], and associated liver partition and portal vein ligation for staged hepatectomy [ALPPS]), and the enhanced efficacy of chemotherapy (*3-5*). In addition, the selection criteria for resection of colorectal liver metastasis (CRLM) have changed significantly, becoming less stringent regarding the number and size of metastases, the presence of extrahepatic disease (EHD), patient age limits and resection margins (*6*).

Despite being the only potentially curative strategy for CRLM, surgery remains underused (*7*). This is probably in part because there are still misconceptions about the distinction between resectable and unresectable disease, and it can be difficult to identify ideal windows for surgery that fit with the multimodal management of these patients (*8*). The majority of patients with metastatic disease are seen exclusively by medical oncologists for systemic therapy to manage metastatic disease, which often means that the oncologist is the only specialist to review the resectability of the disease (*9,10*). Furthermore, there is frequently a lack of agreement on strategy and decision-making even among experienced hepatobiliary surgeons themselves (*11*).

So much remains to be done to optimize multimodal treatment of these patients, with protocols that are as standardised as possible, but at the same time tailored to each individual patient. It is not easy, and it is precisely by reviewing evolution of thinking in CRLM treatment that we can understand future prospects.

2. Metachronous CRLM

According to a recent European multi-societal consensus (*12*), "early metachronous metastases" are those absent at presentation but detected within 12 months of the primary tumor, while "late metachronous metastases" are those detected after 12 months.

Currently, there is no absolute evidence on whether or not neoadjuvant treatment is indicated in all cases of metachronous CRLM. In a 2010 study by Adam *et al.* on a multicenter cohort of 1,471 patients with metachronous CRLM who underwent liver resection (LR) with or without neoadjuvant chemotherapy, univariate analysis showed that preoperative chemotherapy did not affect overall survival (OS) (60% at 5 years in both groups); however, postoperative chemotherapy was associated with better OS (65% *vs.* 55% at 5 years, $p < 0.01$) (*13*). In the ESMO Clinical Practice Guidelines, the metachronous onset of CRLM could be an oncological contraindication to upfront surgery (*14*), and in fact, historically, metachronous onset has been considered a biological predictor of poor prognosis (*15*). However, some studies in the literature suggest that upfront resection should be considered in cases of a single small nodule that does not require major hepatectomy or indicate high morbidity (*16*).

3. Synchronous CRLM

3.1. Defining resectability

Each clinical case of a patient with CRLM should be presented to a multidisciplinary team at the time of initial diagnosis (*17*) to assess resectability and determine a precise multimodal treatment pathway (*18*). The criteria for R0 resectability of CRLM (the only way, apart from liver transplantation, to cure the disease after effective chemotherapy) depend on technical and oncological (prognostic) criteria and experience of the multidisciplinary team (MDT). Considerations when assessing resectability must include an assessment of disease burden (*i.e.*, size, number and distribution of CRLM) (*19*), impression of the disease biology (*i.e.*, rate of disease progression, suspicion of EHD, timing of presentation in relation to primary colorectal tumor, sidedness of primary colorectal tumor, RAS/BRAF mutation status, microsatellite instability [MSI] status) (*20*), and technical aspects. Over the years, different definitions of resectability have been given in the case of CRLM (*21-25*) and Table 1 summarizes them according to their temporal evolution. Evolution of the definition reflects the progressive technological and technical-surgical development (three-dimensional study of the liver, increasingly effective hepatic hypertrophy techniques, more accurate imaging, *etc.*) and the appearance of effective chemotherapies, which have pushed the limits of surgical indication. Surgical thinking has progressively evolved: from the indication only in cases with a number of CRLM < 4, absence of extrahepatic metastases and obtaining an R0 margin of at least 1 cm (*26*) up to increasingly less stringent criteria in terms of number of metastases (*27*), surgical margin (*28*) and presence of resectable extrahepatic disease or vascular infiltration. Currently, it is considered resectable if complete resection with tumor-free margins is possible, with preservation of at least 20-30% of total liver volume, adequate vascular inflow and outflow, and effective biliary drainage (*29*). Technically, therefore, resectability is not limited by number, size or bilobar metastatic involvement if tumors can be resected leaving sufficient residual liver (*14*).

Patients defined as initially unresectable could undergo a reassessment of resectability, preferably within 2-3 months of starting therapy, as proposed by an expert consensus (*30*).

3.2. Patients with unresectable CRLM

In the case of initially unresectable liver metastasis, chemotherapy is the only viable treatment option. While traditional chemotherapy has historically demonstrated efficacy in suppressing tumor growth, the advent of novel chemotherapy agents and molecularly targeted drugs has led to a paradigm shift in the treatment landscape. These new agents have been shown to induce tumor shrinkage and, in selected cases, complete remission. Consequently, liver metastasis that was initially deemed unresectable may become resectable through the use of chemotherapy, a process known as conversion therapy.

Bismuth *et al.* first reported the possibility that chemotherapy may convert unresectable disease to resectable disease (*31*). It is estimated that approximately 15% of patients undergoing systemic chemotherapy and 30-50% of those undergoing regional chemotherapy are converted to resectable status (*32-35*). A study by Sugiyama and colleagues identified patients with specific clinical profiles, including a left-sided primary tumor, absence of extrahepatic metastases, H1 or H2 grade, and treatment with molecularly targeted agents, who were potential candidates for conversion hepatectomy with the goal of cytoreduction, and they demonstrated favorable outcomes (*36*).

The question of how long a patient should remain on downstaging chemotherapy prior to resection is still open to debate within the medical community. Some proponents of this approach advocate for surgical intervention as soon as the patient is deemed resectable (*37*), while others advocate achieving highest tumor response (with a median duration of approximately four months) (*38*). A recent review on optimal duration of chemotherapy in colorectal cancer according to indications posits that when the objective is a conversion strategy, a relatively limited number of cycles (four to six cycles) should be administered, with re-staging and

Table 1. The anatomical definition of "resectability" in the case of CRLMs, according to different studies in different time periods

Author, Year (*Ref.*)	N patients	Country	Anatomical definition of resectability
Ekberg *et al*., 1986 (*26*)	72	Sweden	Resectable if < 4 lesions, absence of extrahepatic metastases, possibility of obtaining a surgical margin of at least 1 cm
Charnsangavej C, *et al*., 2006 (*26*)	-	USA	Resectable if is possible to preserve two contiguous hepatic segments, preservation of adequate vascular inflow and outflow as well as biliary drainage, and the ability to preserve adequate FLR > 20% in a healthy liver). *(The presence of extrahepatic disease should no longer be considered an absolute contraindication to hepatic resection.)*
Rees M, *et al*., 2008 (*19*)	929	United Kingdom	Complete resection of all CRLM, regardless of size, number, distribution, or width of resection margin, while preserving a sufficient volume of FLR 25-30% in case of normal liver
Adam R, *et al*., 2012 (*29*)	-	International Consensus	Potential for complete resection with tumor-free margins (R0 resection), with preservation of at least two disease-free liver segments with viable vascular inflow, outflow, and biliary drainage and an FLR volume of 30%.
Worni M, *et al*., 2014 (*21*)	-	USA	Appropriate medical candidate for surgery; possibility to plan R0 resection irrespective of size and multiplicity; sufficient FLR *Note*: The presence of limited extrahepatic disease that is amenable to resection is a relative contraindication.
Viganò L, *et al*., 2015 (*27*)	849	Italy, Switzerland	Surgical indication even if > 8 metastases in the absence of risk factors (good response to chemotherapy, absence of extrahepatic disease, non-rectal location)
Phelip JM, *et al*., 2016 (*22*)	26	France	Borderline resectable: number of metastases ≤ 8 and/or ≤ 6 segments of liver involved whatever the size of the metastases, without infiltration of any hepatic veins and without infiltration of both hepatic arteries or both portal vein branches; absence of more than 2 potentially resectable extrahepatic (*e.g.*, pulmonary) metastases, and at least one metastasis measurable by CT scan or MRI.
Allard MA, *et al*., 2017 (*28*)	12,406	Multicentre	Even in cases with CRLM > 10, with R0/R1 resection we obtain better survival rates than with chemotherapy alone.
Pietrantonio F, *et al*., 2017 (*25*)	31	Italy	Borderline resectable: tumor involvement of > 1 hepatic vein, or > 4 hepatic segments, need for 2-stage hepatectomy or radiofrequency ablation, and/or biologically (high risk): ≥ 4 metastatic nodules, or synchronous metastases.
Huiskens J, *et al*., 2019 (*27*)	181	Netherlands	The ability to obtain a complete resection of all lesions in one single surgical procedure (*i.e.,* excluding 2-stage resections and/or use of portal vein embolization) by resection only (i.e. excluding the use of additional ablative treatments or other local methods), leaving an estimated FLR of 25-30% in uncompromised livers, or 35-40% in compromised livers.
Ichida H, *et al*., 2019 (*23*)	245	Japan	Resectable: ≤ 3 lesions, tumor size <5 cm; absence of extra-hepatic metastases; FLR > 30%. Borderline resectable: > 4 lesions; tumor size > 5 cm; presence of resectable extra-hepatic metastases. FLR < 30%
Nieuwenhuizen S, *et al*., 2020 (*24*)	-	Netherlands	Easily resectabile: ≤ 3 adjacent segments removed; FLR > 40%; < 1 hepatic vein involved; contralateral portal pedicle and inferior caval vein free form tumor. Difficultly resectable: >3 adjacent segments removed; FLR < 40%; perihilar resections or biliary and/or vascular resection required; involvement of contralateral portal pedicle and inferior caval.
Dijkstra M, *et al*., 2021 (*20*)	520	Netherlands	CRLM are resectable at the discretion of the performing oncological or hepatobiliary surgeon.
Cervantes A, *et al*., 2022 (*28*)	-	European Society for Medical Oncology (ESMO)	Resectability is not limited by number, size or bilobar metastatic involvement, if tumours may be resected leaving sufficient FLR > 30%.

Table 1 The anatomical definition of 'resectability' in the case of CRLMs, according to different studies in different time periods. CRLM: colorectal liver metastasis; FLR: future liver remnant.

re-evaluation for surgery as soon as possible in most cases (*39*). Shortly before, a retrospective work on a multicentre court of 2,793 patients with unresectable CRLM undergoing conversion chemotherapy that aimed to assess systemic treatment characteristics impacting outcome after hepatectomy, revealed that short (< 7 or < 13 cycles in 1st or 2nd line) preoperative chemotherapy duration was independently associated with longer OS (HR: 0. 85, $p = 0.046$), DFS (HR: 0.81, $p = 0.016$) and hepatic-specific relapse-free survival (HR: 0.80, $p = 0.05$) (*40*).

Thus, what is currently emerging in the literature is that an excessive duration of chemotherapy can be disadvantageous and does not increase patients' OS, may instead lead to liver toxicity (*41,42*). Prospective studies may define optimal duration in terms of the balance between conversion to resectability, short duration (to reduce cytotoxic effects and prevent missing metastasis) and maximum biological effect.

According to latest ASCO guidelines (*43*), it is recommended that doublet backbone chemotherapy (FOLFOX or FOLFIRI) be offered as a first-line therapy for patients with initially unresectable MSS or pMMR CRLMs. In selected cases, triplet backbone chemotherapy (FOLFOXIRI) may also be offered as a first-line therapy. For patients with a right-sided mCRC, in the first-line treatment bevacizumab is recommended, an anti-vascular endothelial growth factor (anti-VEGF) antibody. This is typically used in conjunction with FOLFOX or FOLFOXIRI, which has been shown to produce high rates of pathologic responses and necrosis of CRLM (*44,45*). First-line therapy with pembrolizumab should be offered to patients with MSI-H or dMMR CRLM (*46*), while first-line therapy with anti-EGFR therapy plus doublet chemotherapy should be offered to patients with MSS or pMMR left-sided RAS wild-type mCRC (*47,48*). Finally, new target therapies are emerging for mCRC with RAS mutation, sometimes associated with anti-EGFR, such as Adagrasib or Divarasib, which are starting to show promising results (*49*).

3.3. Patients with resectable CRLM

Adjuvant chemotherapy during the perioperative period can confer survival benefits to patients with resectable CRLM (*50*). A 2015 consensus from the EGOSLIM group strongly recommended the use of neoadjuvant chemotherapy in these cases, reiterating the fact that synchronous CRLM has less favorable cancer biology and lower expected survival rates than metachronous CRLM (*51*). The value of neoadjuvant treatment is also evident in more recent series, particularly in patients with high-risk metastases. It is, therefore, necessary to identify a subgroup of patients who may benefit more from neoadjuvant treatment than others with resectable disease. A retrospective study of 322 patients conducted in 2022 demonstrated that neoadjuvant treatment can enhance OS in patients with resectable CRLM and high clinical risk scores, as proposed by Fong *et al.* (*52*). In a more recent study by Ninomiya *et al.* on a multi-institutional cohort, CRLM were classified into three grades (A, B and C) based on the combination of the H-stage (H1: ≤ 4 lesions and ≤ 5 cm, H2: ≥ 5 lesions or > 5 cm, H3: ≥ 5 lesions and > 5 cm), the lymph node status of the primary tumor (pN0/1: ≤ 3 metastases, pN2: ≥ 4 metastases), and the presence of resectable extrahepatic metastases. The findings of this study indicate that patients with synchronous grade B/C CRLM may be suitable candidates for neoadjuvant chemotherapy (*53*). On the contrary, a recent meta-analysis from 2024, which included 24 studies on 8,700 patients, indicated favorable OS in the upfront surgery group (OR 1.21, 95% CI: 1.06-1.38) and favorable disease-free survival in the upfront surgery group (OR 1.71, 95% CI: 1.38-2.12). These findings suggest that neoadjuvant chemotherapy offers no additional benefit for resectable colorectal cancer with liver metastases. Consequently, upfront surgery should be considered the preferred treatment option (*54*). Another recent review (*55*) on the use of neoadjuvant chemotherapy (NAC) in CRLM points out that the available literature does not really show a clear superiority of NAC over upfront surgery when considering endpoints such as OS and disease free survival (DFS) in resectable CRLM. However, NAC certainly offers advantages in controlling micrometastases (*56*), increasing the rate of R0/R1 resections (*57*) or in selecting patients who progress during systemic treatment (cases in which surgery may be futile). Thus, in the near future, we will probably tend to stratify more resectable CRLM patients according to risk (*58,59*), for example by analysing circulating tumour DNA (*60,61*) as well as by evaluating validated clinical risk scores (*52,62*). The aim is to identify patients at diagnosis with resectable forms of CRLM who may benefit from preoperative short NAC in terms of OS, DFS, increased chance of curative resection RO/R1 or other patient benefits. Further prospective studies on this topic are needed.

3.4. Synchronous lung metastases

It is becoming increasingly common for patients with colorectal cancer to present with advanced disease, including synchronous liver and lung metastases. Studies available in the literature show a five-year survival rate ranging from 40 to 70% in cases of liver and lung metastases (both synchronous and metachronous) undergoing surgery with radical intent (*63,64*); so the general concept that emerges is that with complete resection we gain an oncological advantage for these patients (*65*).

In cases of peripheral and resectable lung localizations, a simultaneous approach is recommended,

if feasible, utilizing a single abdominal incision to initially resect the liver metastases, followed by a transdiaphragmatic approach for resection of the lung metastases (*66*). This approach has been described in the literature as superior to staged resection in terms of blood loss and costs with a similar impact on survival (*67*). According to the authors, the transdiaphragmatic approach is associated with a number of advantages, including avoidance of two separate anaesthesia episodes and two separate hospital admissions. Furthermore, it eliminates the need for a thoracic incision to resect the lung metastasis. An additional benefit of the transdiaphragmatic approach is that surgeons are able to palpate tiny lung metastases and localise them more accurately than with the video-assisted transthoracic approach, which lacks this capability. In 2021, Jalil *et al.* also proposed a single-port approach with transdiaphragmatic videoassisted thoracoscopy, with less invasiveness and functional impact on the diaphragm but identical ability to achieve R0 resection (*68*). The transdiaphragmatic approach to pulmonary metastases is recommended in the literature also in cases of laparoscopic liver resections, still ensuring an aggressive approach with less invasiveness (*69*).

Although it is the most widely supported oncological strategy, the combined resection rate remains low in the few studies available in the literature. In a recent Swedish study based on a national register, 1923 patients with liver and lung metastases from colorectal cancer registered between 2008 and 2016 were considered. Of these, complete resection of all tumour sites (colon, liver and lung) was performed in only 44 patients. These patients who underwent simultaneous resection were the youngest in the cohort and presented more frequently with right-sided colon cancer than those who were resected only in the liver. In addition, those who were operated on exclusively on the primary more frequently had a higher American Society of Anaesthesiologists (ASA) score. According to the authors of this study, the low rate of combined resection is again to be attributed to a different understanding of resectability between oncologist and surgeon and to heterogeneity in assessment of the MDT (*70*). An aggressive surgical strategy is therefore proposed in strictly selected patients, which is why in the context of oncology recommendations an attempt was made to identify additional predictors of prognosis in these multimetastatic patients. In a 2017 Korean study, a single-centre experience of combined surgical resection of liver and lung metastases in 66 patients who had already undergone resection of the primary tumour, it emerged that the timing of presentation (synchronous or metachronous, within or after 3 months from colonic resection, ed.) is not a negative prognostic factor as it has no impact on OS unlike the number and location of hepatic localizations (*71*). And further studies have been conducted over the years on this subject by identifying prognostic factors as CEA, rectal primary cancer, bilateral lung metastasis and multiple metastases (*72,73*).

Another frequently observed scenario involves patients presenting with resectable liver metastases and innumerable, thus unresectable, lung metastases. In such patients, the natural history of mCRC is determined by the progression of liver metastases rather than lung metastases. Such patients rarely present with symptoms of respiratory distress or other pulmonary complications. Moreover, lung metastases can be effectively managed with alternative chemotherapy regimens.

A recent study examined the efficacy of surgical intervention in patients with synchronous liver and lung metastases and compared three treatment modalities: resection of liver metastases only, resection of liver and lung metastases, and palliative chemotherapy. The patients who underwent resection of liver metastases only exhibited an intermediate survival rate between those who underwent resection of both liver and lung metastases and those who underwent palliative chemotherapy (*74*). This suggests that in the clinical scenario of inoperable lung metastases, resection of liver lesions alone may offer a survival benefit over chemotherapy alone.

A randomized controlled trial (LUNA, liver resection with unresectable pulmonary nodules for colorectal adenocarcinoma; NCT02738606) is ongoing to objectively determine the benefit of LR alone in these patients (*75*).

3.5. Liver-first?

According to an international consensus (*51*), if both the primary tumor and metastases are resectable, synchronous resection can be performed in selected patients undergoing limited hepatectomy. An even more recent consensus (*12*) recommends that when upfront synchronous LR is to be performed together with colectomy, the LR component should be a minor hepatectomy.

For rectal tumors, preoperative radiotherapy is the standard of care, but not for high rectal tumors or T2 tumors, and single-stage surgery should not be performed (*51*).

In a retrospective analysis of 7,360 patients (4,415 primary-first, 552 liver-first, and 2,393 simultaneous resections) from the LiverMetSurvey registry (*76*), the liver-first approach is associated with longer survival than the alternative approaches (3-year survival 65.9% *vs.* primary-first 60.4%: hazard ratio [HR] 1.321, $p = 0.031$; *vs.* simultaneous resections 54.4%: HR 1.624, $p < 0.001$).

The liver-first approach is recommended when there are specific liver-related criteria, such as borderline resectability, that favor hepatectomy first after systemic chemotherapy. A retrospective study of 217 patients by the Strasbourg group identifies synchronous CRLM, right colon tumors, persistently high preoperative CEA

levels and lack of adjuvant treatment as prognostic factors associated with limited survival when comparing patients undergoing primary-first and simultaneous resection approaches (*77*). In a more recent paper on 658 patients, comparing simultaneous, liver-first, and colorectal-first strategies for the surgical treatment of synchronous colorectal liver metastases, a simultaneous approach was not associated with worse OS or morbidity compared with a liver-first approach (*78*).

Determining the optimal surgical strategy for each patient with CRLM is a complex process. A multitude of critical factors must be considered, including the location and extent of the primary tumor and liver metastases, the patient's performance status, the presence of symptoms, and the presence of underlying comorbidities. It is important to note that not all patients are suitable for all treatment options (*51*).

3.6. Adjuvant treatment

Adjuvant chemotherapy following curative liver resection of CRLM is not a standard protocol in all medical centres (*79*) and the data provided by the literature considered are incomplete, as the patients analysed are often not stratified according to risk categories. Some randomised controlled trials on adjuvant chemotherapy after CRLM resection have recently demonstrated an extension in the duration of DFS, although no such extension has been observed in OS (*80,81*). On the other hand, there are some studies showing that both OS and DFS are improved in patients with synchronous CRLM in the adjuvant chemotherapy group (*79,82*). In any case, there is a benefit for the patient, as long as the duration is not excessive (with an associated increase in toxicity). In a clinical trial on however a small number of patients (no. 28), a 3-month treatment with CAPOX appears to be safe and effective (*83*). Indeed, the actual duration of the treatment still remains unclear. So even if there is no real difference in OS, a better DFS still has a beneficial impact on the patient, so adjuvant chemotherapy continues to be recommended by the guidelines. It is the opinion of experts that, in the absence of prior chemotherapy for metastatic disease, the recommendation is for chemotherapy (low level of evidence – expert opinion), with options being FOLFOX or CAPOX, unless patients have been recently (< 6-12 months) exposed to oxaliplatin-based adjuvant chemotherapy for stage II or III colorectal cancer (*84,85*).

In the context of metachronous liver metastases, a retrospective study of 75 patients who underwent curative resection of metachronous CRLM revealed that survival at 10 and OS were enhanced when adjuvant chemotherapy was administered post-surgery (*86*), but there are actually no consistent results in the literature. Certainly, the identification of risk scores as proposed by Chinese colleagues could help us in this regard (*87*): the prognostic score was based on five clinical factors such as lymph node spread of the primary tumour, size of the largest metachronous focus > 5 cm, presence of multiple liver metastases, preoperative CEA level > 200 ng/mL and recurrence-free interval from the time of resection of the primary tumour to the appearance of the metachronous metastasis of less than 12 months. The findings revealed that there was no significant difference in 3-year recurrence-free survival (RFS) and OS between the adjuvant chemotherapy and observation groups. However, when patients were stratified according to risk, 3-year RFS and OS were comparable between the groups in patients with the lowest risk. A similar result was demonstrated by Nakai *et al.* (*88*).

Probably in the future, circulating tumor DNA (ctDNA)-based molecular residual disease will help us to stratify patients as candidates for systemic treatment after curative resection (*89*).

4. Systemic Therapy

Novel therapies; The recent open-label, multicenter, randomized, phase III study (CAIRO5) from the Dutch Colorectal Cancer Study Group corroborates the findings of previous studies that FOLFOXIRI-bevacizumab is the preferred treatment for patients with initially unresectable CRLM, provided that the primary tumor is right-sided or mutated at the RAS or BRAFV600E level. In patients with a left-sided tumor and wild-type RAS and BRAFV600E, the addition of panitumumab to FOLFOX or FOLFIRI demonstrated no clinical benefit over bevacizumab but was associated with increased toxicity. These treatments have the potential to reduce tumor size and render the tumor amenable to curative treatment (*45*).

The emergence of *novel immunotherapeutic modalities*, including cancer vaccines and adoptive cell transfer therapies, has begun to transform the landscape of CRLM treatment (*90*). In a phase II clinical trial of a dendritic cell (DC) vaccine in colon cancer liver metastasis patients with disease-free resection margins, Rodriguez *et al.* observed a clear tendency for the DC group to exhibit a reduction in tumor recurrence and an extension in disease-free survival compared with the control group. The median disease-free survival for the DC group was 9.53 months, compared with 25.26 months for the control group (*91*).

Chimeric antigen receptor T-cell (CAR-T) therapy may represent a promising approach for the treatment of CRLM. A phase I trial of CAR-T therapy targeting CEA in patients with mCRC has yielded encouraging results (*92*).

Furthermore, the potential therapeutic role of *microRNAs* (miRNAs) in CRLM is becoming increasingly evident. Prior research has demonstrated the potential of miRNAs as prognostic biomarkers for CRLM patients (*93,94*).

Although the evidence is still preliminary, there are also data indicating that the addition of a *fecal microbiota*

transplantation (FMT) to a treatment regimen may be beneficial for patients with mCRC (*95*). A phase II trial is currently underway to assess the efficacy of FMT in combination with either pembrolizumab or nivolumab (programmed death-1 pathway (PD-1) inhibitors) in mCRC patients who have not responded to anti-PD-1 therapy (NCT04729322).

Recently, research has also shown that *nanosystems* can effectively deliver anticancer drugs to target mCRC. A study conducted in 2021 demonstrated successful synthesis and characterization of a nanocarrier capable of recognizing mCRC cells in secondary organs (*96*).

5. Surgical Strategies

In the 1980s, indications for resective liver surgery were very limited, and less than 10% of patients were candidates for surgery.

The expansion of technical indications for LR is based on three key factors: the improvement of the efficacy of systemic chemotherapy, the improvement of liver surgery techniques and the expansion of knowledge about liver regeneration (*97*). Patients with extensive disease, including those with synchronous disease, bilobar disease, and extensive numbers of nodules, are now eligible for aggressive surgical intervention (*98*). It is now widely accepted that the number and lobar location of metastases are less important in determining resectability than the presence of adequate inflow, outflow and a functional liver remnant (*99*). Any discussion of optimal timing and candidates for surgical intervention should involve a multidisciplinary team comprising medical oncologists, surgical oncologists, radiologists, pathologists, interventional radiologists, radiation oncologists, and geneticists. This approach goes beyond simply considering the technical feasibility of a given procedure.

Furthermore, there is considerable variation in the hospital and surgeon practice patterns regarding the definition of resectability (*100*).

5.1. ALPPS, TSH and LVD

As progress continues, expanded indications are giving way to new operative strategies, including TSH and ALPPS. Recently, an interventional radiology technique has also emerged with the aim of hypertrophying the future liver remnant (FLR): liver venous deprivation (LVD).

The TSH, with a portal vein ligation or portal vein embolisation (PVE) in the first stage, has been developed to facilitate resection in patients with an inadequate FLR (*4,101*). Typically, the desired degree of hypertrophy is not reached for a period of 4-8 weeks; thus, 1/3 of patients unfortunately experience disease progression during this waiting time and the survival of patients who drop out is lower than that of patients treated only with chemotherapy (*102*). This is the historical reason for development of the ALPPS: by associating portal vein ligation with in situ transection of the parenchyma during the first stage, a more rapid hypertrophy is induced with a lower risk of tumour progression (*103*). ALPPS was, however, in early studies on the subject, correlated with high morbidity and mortality rates (*5*).

Despite historical evidence indicating that ALPPS is associated with elevated postoperative mortality and complication rates, several modifications have been introduced over time (T-ALPPS (*104*), RALPPS (*105*), p-ALPPS (*106*), *etc.*), resulting in a reduction in perioperative mortality to 3.8% (*107*). More recently, the LIGRO trial found that compared with traditional TSH, ALPPS can improve resection rate (92% *vs.* 57%) without changing the surgical margins, complication rates, or short-term mortality (*108*). In 2019, the ALPPS registry group published benchmark values for ALPPS (*109*) as well as a preoperative ALPPS risk score to evaluate possible candidates (*110*). Nevertheless, a prospective study on the subject indicates that the strategy remains relatively uncommon in Europe (nine countries included in the study (*111*)) on the other hand, TSH with PVE is described as safe and effective in the treatment of extensive bilobar metastases with both laparoscopic and open techniques (*112*), also remembering that an ALPPS technique can be a rescue in case of TSH/PVE with insufficient hypertrophy, with adequate oncological results (*113*). Finally, according to a systematic review and meta-analysis in 2022 (*114*), the superiority of one technique over the other cannot be determined.

In 2016 (*115*), the Montpellier group described a new interventional radiology technique with the aim of rapid hypertrophy of the FLR: the LVD technique, which consisted of adding suprahepatic venous deprivation to the classic portal vein embolisation in a single interventional radiology procedure. Although in recent retrospective cohorts the technique can induce hypertrophy rates similar to ALPPS with reduced hospital stay (*116*), randomised multicentre studies are needed to define what will be the gold standard for hypertrophy in the near future.

5.2. Parenchymal-sparing *vs.* major hepatectomy and the concept of repeated hepatectomy

The treatment of multiple and small CRLM has recently evolved from predominantly anatomic resections, such as major hepatectomy or extended hemihepatectomy, to parenchymal-sparing approaches for both unilateral and bilateral lesions.

A meta-analysis regarding anatomical versus non-anatomical resections showed that surgical margins, OS, and DFS did not differ significantly between the two groups (*117*).

Torzilli *et al.* validated use of intraoperative

ultrasonography (IOUS) and subsequently demonstrated that this technique (IOUS-guided parenchymal-sparing hepatectomy [PSH]) could also be employed for lesions near the hepatocaval confluence, a location that would otherwise necessitate a significant hepatectomy with the potential for vascular reconstruction (*118*). PSH for solitary lesions with a diameter of less than 3 cm does not result in an increased recurrence rate and has been linked to improved survival outcomes. This is due to the fact that it enhances the possibility of successful salvage in cases of liver recurrence (*119*). In fact, this technique could reduce the number of major hepatectomies by up to 80%, and subsequent recurrences can be re-resected with excellent 5-year OS (*120*). This concept of repeated hepatectomy, repeated LR of CRLM, can achieve comparable perioperative mortality and long-term survival rates with primary LR (*121*). It is true that PSH may result in a certain risk of intrahepatic recurrence, however it has comparable results to anatomical resection in terms of hepatic recurrence free survival at 3 and 5 years, as analysed in a recent meta-analysis. The most recent data therefore strengthen its application in this category of patients (*122*).

5.3. Role of minimally invasive surgery

Laparoscopic liver resection (LLR) has been the accepted standard of care for peripheral lesions in the so-called "laparoscopic segments" II, III, V, and VI for over a decade (*123*). However, the utilization of minimally invasive surgery (MIS) for hepatic lobectomy remains more constrained and has been considerably slower in achieving widespread acceptance. A recent consensus statement recommends the use of minimally invasive techniques as appropriate options for both primary tumor and liver metastases (*12*). Indeed, two randomized clinical trials, OSLO-COMET (*124*) and LapOpHuva (*125*), compared laparoscopic and laparotomic resections in two heterogeneous cohorts of patients. The results demonstrated the efficacy of laparoscopy for CRLM with equivalent oncologic outcomes, a faster return to work, and reduced periprocedural morbidity, length of stay (LOS) and perioperative pain.

The advent of robotic liver surgery has led to an increase in the utilization of MIS for all LR. The robotic surgical system has been shown to be particularly beneficial in facilitating the completion of complex procedures such as major lobectomies, which have a higher conversion rate to open surgery when attempted laparoscopically (*126*). A recent multicenter retrospective analysis comparing robotic liver resection (RLR) with LLR revealed that RLR was associated with lower rates of R1 resection (16.9 *vs.* 28.8%, $p = 0.025$). Furthermore, the benefit of RLR over LLR was observed to be greater for more challenging operations or for lesions located in posterosuperior segments (*127*).

It is important to note that, in contrast to the comparison between open liver resection (OLR) and LLR, there are currently no randomized trials that specifically examine RLR. Nonetheless, the first international recommendations are beginning to emerge (*128*).

Furthermore, it is important to note that MIS facilitates a more expeditious resumption of postoperative chemotherapy, which has a beneficial impact on natural history of the disease (*129*).

Notwithstanding the aforementioned data, it is imperative to acknowledge that although MIS has been regarded as a viable option for a long time, recently published quality benchmarks, based on over 11,000 patients worldwide, have been established with the objective of offering patients the most efficacious oncological outcomes and the fewest possible postoperative complications (*130*).

6. Locoregional therapy

Local treatments for CRLM include hepatic arterial infusion chemotherapy (HAIC), radiofrequency ablation (RFA) or microwave ablation (MWA), stereotactic body radiotherapy (SBRT) and selective internal radiotherapy (SIRT).

The combination of HAIC and systemic chemotherapy has been demonstrated to enhance the response rate of patients undergoing first-line chemotherapy to a level exceeding 90% and to elevate the response rate of previously treated patients with unresectable CRLM to 85% (*131,132*). As demonstrated in the phase II/III PACHA trial, adjuvant HAIC with oxaliplatin has been shown to increase OS in patients at high risk of recurrence (*133*). Additionally, data from four prospective trials on HAIC combined with systemic chemotherapy after LR have demonstrated excellent long-term survival, with modern-era patients demonstrating 5-year survival rates of up to 78% and 10-year survival rates of 61% (*134*).

In patients with unresectable CRLM, the long-term results of the recent EORTC-CLOCC trial demonstrated that the combination of RFA (± surgical resection) and chemotherapy yielded an 8-year survival rate of 35.9%, in comparison with 8.9% observed in patients treated with chemotherapy alone (*135*).

In a recent publication reporting 465 ablations, microwave cancer destruction was shown to be an effective and durable therapeutic modality. In cases where the tumor was 1 cm or less, complete death of the cancer cells was achieved in 99% of cases (*136*). Karagkounis *et al.* demonstrated that factors associated with local recurrence on multivariate analysis included increasing size as a continuous variable (HR: 1.04, 95% CI: 1.01-1.08; $p = 0.006$) and subcapsular location (HR: 2, 95% CI: 1.09-3.65; $p = 0.02$). In addition, they observed that the cumulative rate of local recurrence at two years was 6.8% for tumors ≤ 10 mm, 12.4% for tumors of 11-

20 mm, and 30.2% for tumors > 20 mm (*137*). It thus emerges that as the size of the lesions (CRLM < 1 cm in diameter) decreases, the effectiveness of the method increases. A recent multi-centre prospective trial has therefore confirmed that local destruction is effective in small CRLM (*138*), especially in patients who are more fragile and exposed to the possible complications of surgical treatment.

Given the minimal periprocedural complications associated with local ablative therapies and their demonstrated efficacy in treating small tumors, there has been growing interest in comparing ablative therapy with hepatectomy for resectable CRLM. Consequently, a randomized phase III clinical trial, the COLLISION trial, is currently in progress with the target of demonstrating the non-inferiority of ablative therapy (RFA or MWA) to hepatectomy for resectable disease (*139*). The results are awaited, and although the gold standard is currently considered to be liver resection in cases where the disease is resectable, local destruction must be considered in several cases: patients with poor functional reserve with small metastases who cannot undergo surgery (*140*) or associated with resection to avoid major hepatectomy (with better surgical outcomes) (*141*).

SBRT has been shown to be an effective and safe local therapy in patients with unresectable CRLM, with the potential to achieve a high local control rate (*142*). The SIRFLOX trial was designed to compare the efficacy of SIRT in combination with systemic chemotherapy versus systemic chemotherapy alone in treatment of unresectable CRLM. The findings demonstrated that SIRT can extend progression-free survival and enhance response rates in the liver (*143*).

Subgroup analyses in relevant studies have demonstrated that SBRT provides superior local control compared to RFA for tumours measuring over 2 cm. However, for tumours measuring 2 cm or smaller, RFA has been shown to be superior (*144*).

7. Combined liver resection and tumor ablation

In the context of parenchymal preservation, a significant number of surgeons will utilize ablation in cases of deeper parenchymal lesions, where attempted resection would result in an unacceptably small FLR, or when the aim is to achieve limited resections. The prevailing view is that this approach, when combined with appropriately timed systemic therapy, can result in a cure or, at the very least, a significant disease-free interval. To illustrate, the recent CLOCC trial was a randomized phase II trial that was terminated prematurely following evidence that combined surgery with RFA of otherwise unresectable tumors in conjunction with systemic therapy was associated with a significant improvement in OS (*145*). In the context of a parenchymal-sparing strategy, the combination of RFA and LR is safe with regard to oncological outcomes when the appropriate criteria are adhered to (small-size lesions, oligometastatic disease *etc.*) (*146*). A recent nationwide population-based propensity score-matched study from the Netherlands (*147*) has revealed that combined resection and ablation should be available and considered as an alternative to resection alone in any patient with multiple metastases.

8. Disappearing liver metastasis

In the context of modern chemotherapeutics, treatment effects may result in the disappearance of CRLM on standard preoperative imaging. The prevailing view in the past has been that all areas of known disease, whether quiescent or otherwise, should be resected. This implies that if the disease was initially identified on a scan, it should be included in the resection field. In patients with unidentified and untreated disappearing liver metastases (DLMs), local recurrence at the site of the original tumor has been observed in up to 59% of cases (*148*). The idea of the past has been gradually confirmed by more recent studies. A systematic review on the subject published in 2025 (*149*) confirms the increased risk of local recurrence in the case of unresected DLMs, suggesting that all primary sites should be removed.

In a study comprising 40 patients with 126 DLMs, van Vledder *et al.* identified that the occurrence of > 3 metastases prior to chemotherapy (OR 13.1; $p < 0.001$) and the number of preoperative chemotherapy cycles (OR 1.18; $p = 0.03$) were independently associated with the development of DLMs. These findings contribute to the growing body of evidence from studies of this nature, which facilitate the identification of preoperative risk factors for the development of DLMs (*148*).

Furthermore, a recent series of studies has demonstrated that utilization of Eovist-based magnetic resonance imaging or contrast-enhanced ultrasound techniques can effectively identify up to 55% of disappearing lesions, with 69% of these cases exhibiting residual disease (*150*). Thus, in the case of DLMs, it would be appropriate to perform preoperative staging with CT and MRI and perform an aggressive surgical strategy (*151*). In addition, intraoperative ultrasound with contrast enhancement (CEIOUS) should be routinely adopted for the intraoperative detection of DLMs (*152*). In light of increased pre- and intra-operative diagnostic accuracy of DLMs, it could follow that, should these investigations prove negative, a decision could be made to postpone resection and opt for close surveillance. Some works in the literature support this possibility, which did not describe a statistically significant difference in overall survival between patients with resected DLMs and patients with DLMs left in place (*153*). Moreover, in the absence of recommendations on the management of DLMs, the attitude of surgeons varies greatly depending on the clinical case, with obvious reticence to perform surgery when *e.g.* they are only localisations that are no longer visible on preoperative

imaging (*154*), instead of suggesting close surveillance (*155*).

So, despite the enhanced understanding of this clinical situation, surgeons' dispositions remain markedly disparate, as evidenced by another recent review examining the attitudes of 67 surgeons from 25 disparate countries (*154*).

There is a clear need for quality prospective studies and consensus building to define the best management on a case-by-case basis.

9. Liver transplantation

Liver transplantation (LT) for unresectable CRLM was initially investigated in the SECA trials, which demonstrated a 5-year OS rate of up to 83% (*156*). The results of TransMet, a prospective randomized trial on the subject, have recently been published (*157*): a total of 94 patients were randomly assigned and included in the intention-to-treat population, with 47 patients receiving LT plus chemotherapy and 47 receiving chemotherapy alone. The 5-year OS rate for the intention-to-treat population was 56.6% (95% CI: 43.2-74.1) for LT plus chemotherapy and 12.6% (5.2-30.1) for chemotherapy alone. The HR was 0.37 (95% CI: 0.21-0.65), with a *p*-value of 0.0003. The 5-year OS rates were 73.3% (95% CI: 59.6-90.0) and 9.3% (3.2-26.8) for the LT plus chemotherapy and chemotherapy alone groups, respectively.

It can be postulated that there may be a threshold tumor load for which LR yields an acceptable survival rate. Consequently, it might be hypothesized that LT could provide a survival benefit over LR in a subset of patients with a high tumor load. However, the situation in Norway with regard to the availability of grafts for liver transplantation is much rosier than in the rest of the world, which is constantly faced with the problem of organ shortage. This is the reason why this therapeutic option can only be offered to a highly selected group of patients: patients under 70 years of age with excellent performance status, no extrahepatic disease or lymph node metastases and a primary left colon operated at least one year previously (with a T stage < 4), after an excellent response to chemotherapy (*158,159*). In all other cases, only palliative strategies can be proposed (such as cytoreductive surgery for patients with good performance status). The strict selection criteria are justified not only by the shortage of organs but also by the realisation that adherence to these criteria is essential to achieve post-transplant survival rates in line with conventional indications (*160*). When considering liver transplantation for CRLM as a treatment option, it is more important to discuss biological resectability than technical resectability, in the interest of providing the best treatment to those with the best prognostic predictive factors. In fact, as a recent review points out, an Oslo score of 1 or less, metabolic tumour volume on PET/CT less than 70 cm3, metachronous disease or tumour burden score (TBS) less than 9 are predictive of better post-transplant outcomes (*160*).

The experience accrued over the course of these years provides clear evidence that the prognosis following LT for colorectal liver metastases is dependent on the morphological and biological characteristics of the tumor, including tumor burden, metabolic tumor volume, genetic phenotype and response to chemotherapy (*161,162*).

On the one hand, the use of small segmental grafts from deceased or living donors could be a way to expand the donor pool with less impact on the waiting list for deceased donor transplantation and minimal risk to the donor in the case of living donor liver transplantation (*163*). On the other hand, in addition to increasing the pool of available organs, we need to know more about the biological aspects of the tumour in order to define increasingly targeted indications (*164*).

10. Cytoreductive surgery

As we move forward in the era of highly efficacious chemotherapy, it becomes pertinent to consider the role of resection in patients with multifocal bilateral disease, where the initial tumor load could not be fully excised through R0 or R1 resection. In such patients, LT is becoming an appealing treatment with promising results, as discussed. However, it seems that the feasibility of this approach may be limited by the organ shortage and the rigorous selection criteria. This is particularly the case for young patients with "liver-only" disease, in the absence of obvious comorbidities, who represent a small fraction of patients. For patients who are unable to be transplanted (*e.g.*, due to age ≥ 70 years, limited EHD, or LT not available) but who are responding very well to chemotherapy and has an excellent performance status to tolerate an aggressive surgical strategy, it may be worthwhile exploring the possibility of cytoreductive surgery (*165-167*). There is currently little literature available on debulking surgery in this patient category, and prospective studies on the subject are awaited.

The currently available data do not allow us to propose clear recommendations regarding patient selection and appropriate threshold for tumor cytoreduction or on optimal duration of chemotherapy before debulking surgery. Nevertheless, a number of findings appear to indicate that a cytoreductive approach may be a valuable option for patients with unresectable multinodular CRLM who are responding to systemic treatment, similar to the benefits typically observed in patients who achieve a partial or complete response to chemotherapy. It may be beneficial to consider this approach on a case-by-case basis, with input from a multidisciplinary team with expertise in liver surgery, to identify suitable candidates and ensure use of an effective systemic perioperative chemotherapy (*168*).

11. Artificial intelligence

It seems that the use of AI may offer a potential advantage in the early diagnosis and management of CRLM (*169,170*). As previously mentioned, there are a number of factors to consider when providing clinical and surgical care for a patient with liver metastases from the colon-rectum. It is often the case that the decision-making process is complex and varies from one center to another, depending on the clinical judgment of the local multidisciplinary team (*11*). Given the numerous variables involved, it is becoming increasingly clear that AI-related technologies can offer valuable assistance. As outlined in a recent review by Rompianesi *et al.* (*169*), which provides a comprehensive overview of potential applications of AI in this field, the Radiomics Intelligent Analysis Toolkit-based analysis platform developed by Li *et al.* (*171*) is a promising approach. Construction of individualized nomograms was made possible by the use of maximum-level enhanced computed tomography images in the portal venous phase and patients' clinical information (age, sex, CEA and carbohydrate antigen 19-9) to predict development of CRLM in patients with colorectal cancer. A recent systematic meta-analysis (*172*) describes that in 11 of the 14 included studies, radiomics is able to predict prognosis and better select patients for treatment strategy candidating itself as a useful future diagnostic-predictive tool. It might be of interest to consider, for instance, the development of other AI-based predictive models, such as those designed to predict response to chemotherapy treatment (*173*) or local ablative treatment (*174*), or AI-based techniques to determine the correct surgical margin depending on the clinical case (*175*). The utilisation of machine learning algorithms for development of prognostic indicators, such as those capable of predicting early recurrence, has already been extensively explored in experimental settings (*176*). Translation of these algorithms into clinical practice holds significant potential for enhancing patient care. It is evident that the progressive implementation of AI in clinical practice appears to be an inevitable phenomenon. Recent studies have demonstrated a promising experimental basis for this development. However, it is important to acknowledge limitations that currently exist, which are not insignificant. The training of AI systems necessitates substantial datasets, which, in clinical contexts, would demand the establishment of extensive, multi-centre data databases, accompanied by all the concomitant privacy concerns that this would entail. Moreover, it is imperative to consider the ethical implications, as the machine can merely suggest but cannot supplant the clinical sensibilities of medical professionals. Finally, It is evident that the technical capabilities of disparate medical institutions, contingent on their respective economic capacities, could act as a hindrance to the extensive implementation of AI in clinical practice.

12. Prognostic scores

Predicting prognosis can help identify patients who may benefit from different treatments. For many years, a clinical outcome established by Fong *et al.* is widely used to predict the prognosis of patients with CRLM. They identified seven significant independent predictors of poor long-term outcomes, which they believe may be useful to consider in future studies: positive margins, EHD, positive primary nodal disease, disease-free interval between primary disease and metastases less than 12 months, more than one liver tumor, the largest liver tumor > 5 cm, and CEA levels > 200 ng/mL. The last five of these criteria were used to create a preoperative scoring system that has been shown to accurately predict prognosis (*15*). Today, it has become increasingly common to make prognostic predictions based on other technologies, such as radiomics, genomics, and proteomics (*177-179*).

It would seem that RAS mutation status may also have an impact on outcomes independent of the chosen local therapy (*180,181*). For patients with RAS-mutant tumors, there is an earlier onset of local tumor progression regardless of the size of the tumor (*182*); they also tend to have positive and narrower margins after LR (*183*). Indeed, the rate of margin positivity was higher in patients with a RAS mutation than in patients with wild-type RAS (11.4% *vs.* 5.4%, $p = 0.007$) in the aforementioned study. In patients who later presented with liver-first recurrence, the width of the resection margin was significantly smaller in patients with a RAS mutation than in patients with wild-type RAS (4 mm *vs.* 7 mm, $p = 0.031$).

A recent study indicated that a "triple mutation" in TP53, RAS, and SMAD4 was associated with inferior overall and recurrence-free survival in CRLM patients compared with double mutations in any two of the three genes (*184*).

A recent retrospective analysis of the randomized phase III study, NEW EPOC, has classified metastases into three molecular subtypes from a biological perspective. The analysis demonstrates that the biologically derived molecular subtypes of CRLM and integrated clinical-molecular risk groups are highly prognostic. This novel molecular classification requires further investigation as a potential predictive biomarker for the development of personalized systemic treatments for colorectal liver metastases (*185*). The field of molecular mechanisms of CRLM remains relatively unexplored, and it is likely to yield new insights into the development of personalized treatments for these patients.

13. Conclusions

Over the past decade, there have been notable advancements in the diagnosis and treatment of

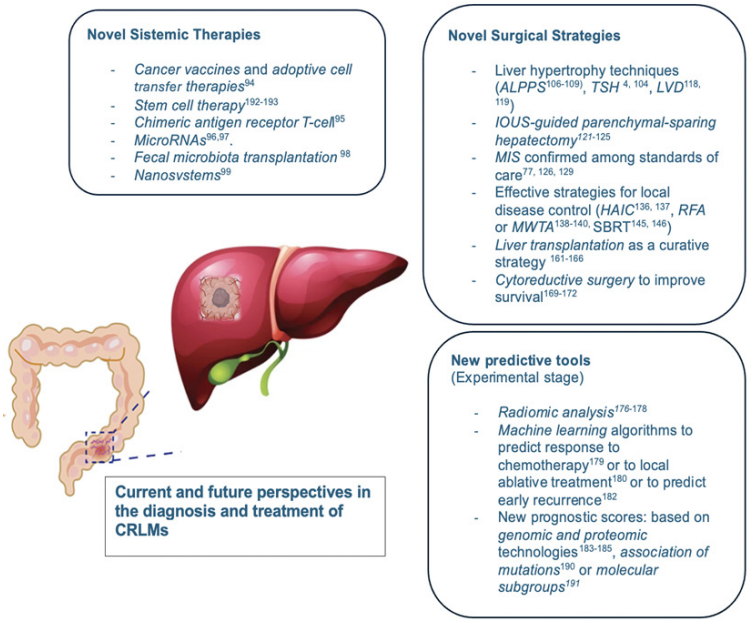

Figure 1. Current and future perspectives in the diagnosis and treatment of CRLMs. ALPPS: Associating Liver Partition and Portal vein ligation for Staged hepatectomy; TSH: Two-Stage Hepatectomy; LVD: Liver Venous Deprivation; IOUS: Intra-Operative UltraSound; MIS: Minimally Invasive Surgery; HAIC: Hepatic Arterial Infusion chemotherapy; RFA: RadioFrequency Ablation; MWTA: Micro-Wawe ThermoAblation; SBRT: Stereotactic Body Radiation Therapy.

CRLM, as outlined in this review and summarized in Figure 1. The multiplicity of proposed treatments and the divergence of opinion regarding the definition of resectability and the treatment of these patients in different centers necessitates further efforts to standardize treatment protocols, which must, nevertheless, be tailored to each case. Individualized treatment remains a key research topic in the future. The goal is to perform surgical resection or LT in selected cases; however, the introduction of new treatments and new technologies permits the advancement of the boundaries of knowledge and an increase in survival rates in these patients, as it is being attempted with a better understanding of tumour biology and personalized medicine (*186,187*). Probably, AI will suggest the appropriate treatment pathway in terms of oncological outcome and patient safety based on individual patient variables, with a targeted but standard pathway in different centers.

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