

# Contemporary Management of Colorectal Liver Metastases

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## Abstract

Colorectal liver metastases (CRLM) require treatment selection that integrates technical resectability, oncologic suitability, molecular profile, tumor behavior, and functional liver reserve. Options range from upfront local treatment for readily resectable disease to systemic conversion therapy, parenchymal-sparing surgery, thermal ablation, staged procedures, and, in highly selected patients with permanently unresectable liver-only disease, transplantation. This narrative review critically summarizes diagnostic staging, peri-operative chemotherapy, conversion strategies, local treatment, synchronous disease, recurrence, and transplantation. Evidence from pivotal trials illustrates the importance of interpreting results in context as follows: long-term follow-up of European Organisation for Research and Treatment of Cancer (EORTC) 40983 did not show a statistically significant overall survival benefit from peri-operative FOLFOX4; CAIRO5 found regimen-specific differences in progression-free survival and toxicity in initially unresectable liver-only disease; COLLISION supports ablation for selected small metastases but does not establish universal equivalence to resection; and TransMet demonstrated improved survival with transplantation plus chemotherapy in a strictly selected population. These studies address different clinical questions and should not be compared as if they enrolled interchangeable populations. Management should be reassessed by a multidisciplinary team as tumor biology, response, and feasibility of complete local clearance evolve. The review is intended for clinicians involved in colorectal and hepatobiliary oncology and emphasizes clinical applicability, quantitative outcomes, and limitations of pivotal studies rather than a systematic evidence synthesis.

**Categories:** General Surgery, Gastroenterology

**Keywords:** colorectal cancer, colorectal cancer liver metastases, conversion therapy, hepatectomy, liver resection, multidisciplinary management, systemic chemotherapy, thermal ablation

## Introduction And Background

Colorectal cancer (CRC) is a major cause of cancer-related morbidity and mortality worldwide, and the liver is its most common site of distant spread because of portal venous drainage [1,2]. Synchronous colorectal liver metastases (CRLM) are detected at or around the diagnosis of the primary tumor, whereas metachronous metastases develop later during follow-up [3-5]. The presence of hepatic metastases does not automatically preclude treatment with curative intent, but outcomes depend on disease distribution, tumor biology, extrahepatic spread, functional liver reserve, and the feasibility of complete local treatment [3,4,6].

Complete resection or complete local eradication of CRLM can offer durable disease control and long-term survival in selected patients, although recurrence remains common [7,8]. Technical resectability describes whether all known disease can be removed or ablated while preserving adequate functioning liver and essential inflow, outflow, and biliary drainage. Oncologic suitability is a related but distinct judgment that considers tumor behavior, extrahepatic disease, response to systemic therapy, molecular features, comorbidities, and patient goals [3-6].

Contemporary practice has moved beyond rigid numerical thresholds based only on the number or size of metastases. The central questions are whether all clinically relevant disease can be cleared, whether an adequate functional future liver remnant (FLR) will remain, and whether the expected benefit justifies treatment-related risk. This approach has expanded the use of parenchymal-sparing surgery, portal vein embolization, staged hepatectomy, systemic conversion therapy, and image-guided ablation [5,6,9-11].

Management requires coordination among colorectal and hepatobiliary surgeons, medical and radiation oncologists, diagnostic and interventional radiologists, pathologists, and specialist nursing teams. Existing guidelines provide broad recommendations, but practical uncertainty remains when patients move between resectable, potentially convertible, and permanently unresectable states, and when trial endpoints do not directly measure complete local clearance or overall survival [3-6,12]. This review is intended for clinicians involved in colorectal and hepatobiliary oncology. It offers a clinically oriented synthesis of treatment

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selection and sequencing across the disease course, emphasizing how eligibility criteria, endpoints, and limitations of pivotal studies should influence decisions rather than treating all treatment strategies as interchangeable.

## Review

### Literature approach

This narrative review synthesizes contemporary evidence on the diagnosis and management of colorectal liver metastases (CRLM). The source manuscript did not contain a documented, reproducible database search with search strings, dates, language restrictions, or a formal study-selection log. Those details cannot be reconstructed retrospectively and are not represented here as procedures that were performed. The review prioritizes identifiable international guidelines and consensus statements, randomized clinical trials, relevant systematic reviews, and influential observational studies addressing resectability, peri-operative therapy, conversion treatment, surgery, ablation, synchronous disease, recurrence, and transplantation. The literature discussed was current at the time of the revision undertaken in October 2026; authors should verify the latest publication records and guideline versions immediately before resubmission.

This review is not a systematic review or meta-analysis. No pooled effect estimates were calculated, and no formal study-level risk-of-bias instrument was applied. PRISMA reporting is therefore not claimed. Evidence was prioritized by study design, clinical relevance, recency, and directness to CRLM management. Randomized trials were used to inform comparative treatment effects, consensus statements and guidelines to contextualize practice, and observational studies to discuss feasibility and less frequently studied approaches. When trials differed in eligibility, treatment intent, or endpoints, their results were not directly compared as if they represented the same population. We address these limitations, including possible selection bias in the identified literature, below.

The evidence was interpreted in relation to the enrolled population, treatment intent, comparator, endpoint definitions, follow-up, and uncertainty around effect estimates. Overall survival (OS), progression-free survival (PFS), disease-free survival (DFS), objective response, conversion to resection, and complete local clearance are distinct outcomes. A higher response or conversion rate does not necessarily establish an OS benefit; non-inferiority does not mean universal equivalence. This distinction is particularly important when interpreting European Organisation for Research and Treatment of Cancer (EORTC) 40983, CAIRO5, COLLISION, and TransMet [13–17].

### Diagnostic assessment and initial staging

Accurate staging is essential before selecting treatment. The initial assessment should establish the extent of hepatic disease, identify extrahepatic metastases, characterize the primary colorectal tumor, and evaluate the patient's functional status and comorbidities. Contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis is commonly used for initial staging. Liver magnetic resonance imaging (MRI), particularly with diffusion-weighted sequences and hepatobiliary contrast agents when appropriate, improves lesion detection and characterization, especially when small metastases or complex surgical planning are involved [3–5,12].

Positron emission tomography combined with CT may be useful in selected cases when occult extrahepatic disease is suspected or when conventional imaging leaves clinically important uncertainty. It should not routinely replace high-quality CT and liver MRI. Imaging findings must be interpreted alongside the clinical history, previous treatment, and anticipated surgical plan [3,4,6].

Baseline laboratory evaluation generally includes a complete blood count, liver and renal function tests, a coagulation profile, and carcinoembryonic antigen (CEA). CEA can assist with prognostic assessment and longitudinal surveillance, but it should not be used alone to determine resectability or exclude metastatic disease [3,4].

Molecular characterization of the primary tumor or metastatic tissue is important in patients with metastatic colorectal cancer (CRC). Testing commonly includes KRAS and NRAS mutations, BRAF V600E, and mismatch repair status or microsatellite instability (MSI). Additional biomarkers, such as HER2 amplification and actionable gene fusions, may be relevant in selected clinical settings. These results influence systemic treatment selection and may provide prognostic information [3,4].

All patients with potentially resectable CRLM should be discussed by a multidisciplinary team before definitive treatment. This discussion should occur early, rather than only after systemic treatment has failed, because the sequence of chemotherapy, surgery, and local treatment may influence the likelihood of complete disease clearance.

Staging should be reviewed alongside the proposed treatment pathway rather than treated as a one-time diagnostic step. High-quality liver MRI is particularly valuable when CT identifies indeterminate lesions, when metastases are small, or when a parenchymal-sparing operation is planned. Imaging should be

reviewed jointly by radiologists and liver surgeons to map lesion number and segmental distribution, proximity to major vessels and bile ducts, and the relationship between disease and the anticipated future liver remnant. Restaging is also necessary after systemic therapy because radiological response can alter operative planning, while apparent disappearance of a lesion does not reliably establish complete pathological response [4,6,18].

## Defining resectability

Resectability is a dynamic concept that depends on both technical feasibility and oncologic appropriateness. Technical resectability generally requires the possibility of removing or locally eradicating all visible disease while preserving adequate functional liver remnant, portal and arterial inflow, venous outflow, and biliary drainage. The anticipated remnant must be sufficient to avoid post-hepatectomy liver failure [5,10].

The number, size, and bilobar distribution of metastases are not, by themselves, absolute contraindications to surgery. Selected patients with multiple bilobar lesions may undergo parenchymal-sparing resection, combined resection and ablation, or staged procedures. Conversely, a single metastasis may be unresectable if its relationship to major vascular or biliary structures prevents safe clearance while preserving sufficient functioning liver [5,6,9,19].

Future liver remnant (FLR) assessment is particularly important when major hepatectomy is planned. Volumetric CT or MRI is used to estimate the volume of liver that will remain. The adequacy of the remnant depends not only on volume but also on liver quality, including injury from chemotherapy, steatosis, fibrosis, cholestasis, or underlying chronic liver disease. Functional assessment may be necessary when volumetry alone is insufficient [10,20].

Portal vein embolization can induce hypertrophy of the intended remnant before major hepatectomy. In selected patients, liver venous deprivation or staged surgical strategies may also be considered. These procedures can expand the population eligible for resection, but they introduce additional treatment intervals during which disease progression may occur [6,10,20].

Oncologic resectability additionally considers extrahepatic disease, tumor growth kinetics, response to systemic treatment, molecular features, and the likelihood of achieving durable disease control. Limited extrahepatic disease does not automatically exclude curative-intent treatment in every patient, but uncontrolled extrahepatic disease generally reduces the rationale for major hepatic surgery.

Technical resectability and oncologic suitability should be documented separately during multidisciplinary review. Technical resectability asks whether all known disease can be removed or ablated while preserving adequate inflow, outflow, biliary drainage, and functional liver. Oncologic suitability considers the likely value of that intervention in the context of disease tempo, response or progression during systemic treatment, extrahepatic disease, molecular profile, comorbidities, and patient goals. These dimensions overlap but are not interchangeable: a technically feasible operation may not be appropriate when disease is rapidly progressing systemically, whereas extensive bilobar disease may remain amenable to curative-intent treatment if complete clearance can be achieved safely [5-7,21].

The future liver remnant should be evaluated as a functional reserve, not simply as a volume measurement. A remnant that may be adequate in a healthy liver can be insufficient after prolonged chemotherapy or in the presence of steatosis, fibrosis, cholestasis, or other chronic liver disease. Volumetry therefore needs to be interpreted with the quality of the parenchyma, baseline liver function, planned extent of resection, and the anticipated risk of post-hepatectomy liver failure. Portal vein embolization is an established option when the predicted remnant is inadequate; liver venous deprivation and staged approaches may be considered in selected centers, although comparative evidence and local expertise vary [6,10,20].

## Surgery for initially resectable CRLM

Complete hepatic resection remains a central curative-intent treatment for patients with resectable CRLM. Outcomes depend on patient selection, tumor biology, surgical expertise, the ability to achieve complete clearance, and the availability of effective treatment for recurrent disease. Long-term survival has been documented after hepatectomy, including a subset of patients with durable disease-free survival [7,8].

The surgical objective is complete eradication of visible metastases with an adequate functional liver remnant. A negative microscopic margin is desirable, but the feasibility of a wide margin must be balanced against preservation of liver parenchyma. A narrow negative margin may be acceptable when a wider resection would compromise liver function or prevent future treatment of recurrence. The decision should account for tumor location, vascular relationships, and the anticipated need for repeat local treatment [22].

Anatomic hepatectomy removes a defined portal territory, whereas parenchymal-sparing hepatectomy removes metastases with limited sacrifice of normal liver. For patients with multiple lesions or bilobar disease, parenchymal-sparing strategies may preserve more functional liver and facilitate repeat

hepatectomy if recurrence develops. A systematic review and meta-analysis found broadly comparable oncologic outcomes between parenchymal-sparing and more extensive resections, while supporting the potential value of parenchymal preservation [9,19].

The choice between open, laparoscopic, and robotic approaches depends on lesion location, tumor burden, prior surgery, surgeon expertise, and available resources. Minimally invasive hepatectomy may reduce post-operative recovery time in appropriately selected patients, but technical complexity and oncologic principles must remain the primary considerations. The surgical approach should not compromise complete disease clearance or vascular and biliary safety [6,9,19].

The operative plan should also anticipate the possibility of future recurrence. In patients with multiple or bilobar metastases, preserving uninvolved parenchyma can maintain options for repeat resection or ablation and may reduce the functional cost of subsequent treatment. The choice between anatomic and non-anatomic resection should therefore be driven by lesion location, the ability to achieve complete local clearance, vascular relationships, and the amount of liver that must be sacrificed, not by an assumption that a larger resection is intrinsically more oncologic. Parenchymal preservation is particularly relevant when it permits treatment of all disease without compromising margins or vascular safety [6,9,21,22].

### Peri-operative chemotherapy in resectable disease

The role of systemic chemotherapy around hepatectomy is individualized. Peri-operative chemotherapy may be considered for patients with higher-risk disease, borderline resectability, multiple lesions, or concern for occult systemic spread. EORTC 40983 randomized 364 patients with up to four resectable liver metastases to peri-operative FOLFOX4 plus surgery or surgery alone. Although progression-free survival improved in the trial, long-term follow-up did not demonstrate a statistically significant overall-survival advantage as follows: median OS was 61.3 versus 54.3 months (HR: 0.88, 95% CI: 0.68-1.14;  $p=0.34$ ), and five-year OS was 51.2% versus 47.8% [13,16]. The results support considering peri-operative treatment in selected patients, but not a universal requirement for chemotherapy before or after resection. Decisions should balance recurrence risk against toxicity, chemotherapy-associated liver injury, and the risk of delaying definitive local treatment [23].

The decision to administer chemotherapy before or after surgery should consider disease burden, the risk of progression during treatment, the potential for tumor shrinkage, and chemotherapy-associated liver injury. Pre-operative treatment may reveal aggressive tumor biology or improve the feasibility of resection, but prolonged treatment can cause sinusoidal injury, steatohepatitis, or other liver toxicity. These complications may increase the risk of post-operative morbidity [23].

The timing of systemic treatment should be planned jointly by medical and hepatobiliary oncology teams. Pre-operative therapy can provide an early test of tumor biology and may facilitate resection, but it can also delay surgery in patients whose disease is already resectable and expose the liver to sinusoidal injury or steatohepatitis. Conversely, surgery first may be reasonable for selected patients with favorable biology and technically straightforward disease, followed by a shared decision about post-operative treatment. The New EPOC results caution against adding cetuximab to peri-operative chemotherapy for operable metastases solely because the tumor is RAS wild-type; evidence from unresectable metastatic disease should not automatically be extrapolated to the peri-operative setting [6,23,24].

The evidence does not support a universal requirement for peri-operative chemotherapy in every patient whose metastases are readily resectable. EORTC 40983 demonstrated a progression-free survival advantage in relevant analyses with peri-operative FOLFOX4, but a clear overall survival benefit was not established. Japan Clinical Oncology Group (JCOG)0603 similarly showed improved disease-free survival with post-operative mFOLFOX6, while overall-survival interpretation remained uncertain. These findings support discussing chemotherapy according to recurrence risk, disease burden, patient fitness, and treatment-related toxicity rather than treating it as an automatic substitute for surgery or as an obligatory component for every patient [13,25].

The New EPOC trial showed that adding cetuximab to peri-operative chemotherapy in patients with operable CRLM and KRAS wild-type tumors did not improve outcomes and produced unfavorable results. This finding underscores that targeted therapies with established roles in unresectable metastatic disease should not automatically be transferred into the peri-operative setting for operable metastases [24].

Post-operative chemotherapy may be discussed according to previous treatment, recurrence risk, pathological findings, and patient fitness. In the JCOG0603 trial, adjuvant mFOLFOX6 after hepatectomy improved disease-free survival but raised important questions about overall survival and the balance between recurrence reduction and treatment toxicity [25]. Consequently, peri-operative or post-operative systemic therapy should not be regarded as mandatory for every patient with completely resected CRLM.

### Conversion therapy for initially unresectable disease

Conversion therapy aims to reduce tumor burden sufficiently to permit complete resection or another

definitive local treatment in patients whose CRLM are initially unresectable. The treatment plan should be developed jointly by medical and surgical oncology teams before systemic therapy begins, with periodic reassessment of resectability [3,4].

The choice of regimen depends on molecular profile, primary tumor location, disease burden, comorbidities, prior treatment, and the need for rapid tumor shrinkage. Doublet chemotherapy, commonly FOLFOX or FOLFIRI, combined with an appropriate biologic agent is frequently used. Selected fit patients may receive triplet chemotherapy, although increased response rates must be balanced against greater toxicity [3,4].

The goal of conversion treatment is not simply radiographic shrinkage; it is to create a safe and durable route to complete local treatment. Regimen selection should therefore be made after defining why the disease is unresectable, such as insufficient future liver remnant, bilobar distribution, or involvement of critical vascular structures, and identifying what change would make resection feasible. RAS and BRAF status, primary-tumor sidedness, mismatch-repair status, prior treatment, comorbidities, and the need for a high response rate all influence systemic choices. A biologic agent should be selected according to molecular and clinical context, not added uniformly to every regimen [3,4,6,14,26].

For patients with left-sided, RAS wild-type metastatic CRC, anti-epidermal growth factor receptor (EGFR) therapy combined with chemotherapy may provide substantial tumor response. The PARADIGM randomized trial reported improved overall survival with panitumumab compared with bevacizumab when each was added to chemotherapy in patients with RAS wild-type disease, particularly in the left-sided subgroup [26]. However, PARADIGM studied first-line treatment of metastatic CRC generally and was not designed to establish a CRLM-specific conversion-to-resection benefit. Its findings may inform regimen selection but should not be presented as direct evidence that panitumumab increases curative liver resection. Treatment selection differs for right-sided tumors and for patients with RAS mutations, in whom anti-EGFR therapy is generally not appropriate in the first-line setting.

For tumors with deficient mismatch repair or high microsatellite instability, immune checkpoint inhibition is an important treatment option in metastatic disease [3]. The presence of a targetable molecular alteration may therefore substantially alter the conversion strategy. Molecular testing should be completed early enough to inform first-line treatment.

CAIRO5 directly evaluated first-line strategies in patients with initially unresectable, liver-only CRLM, with resectability reassessed by expert panels. Among patients with right-sided tumors and/or RAS/BRAF V600E-mutated disease, FOLFOXIRI plus bevacizumab improved median PFS compared with doublet chemotherapy plus bevacizumab (10.6 versus 9.0 months; HR: 0.76, 95% CI: 0.60-0.98), but treatment intensification increased toxicity. In patients with left-sided, RAS/BRAF wild-type tumors, panitumumab plus doublet chemotherapy did not improve PFS over bevacizumab plus doublet chemotherapy in the primary comparison (10.4 versus 10.8 months; HR: 1.11, 95% CI: 0.84-1.48) [14]. These findings support molecularly and clinically tailored treatment, but PFS, response, and conversion-to-resection outcomes should not be conflated with OS. Applicability is limited to the study's liver-only, initially unresectable population and expert resectability process.

Resectability should be reassessed at regular intervals, often after approximately two to three months of systemic treatment, depending on the regimen and clinical circumstances. Imaging should evaluate both tumor response and the relationship of residual lesions to vascular and biliary structures. Surgery should be considered as soon as complete clearance becomes feasible; continuing chemotherapy until maximal radiographic response may expose patients to unnecessary toxicity and liver injury.

Reassessment should be scheduled prospectively, with the hepatobiliary surgeon involved before treatment begins and at subsequent response reviews. A practical multidisciplinary review often occurs after approximately two to three months, or earlier if symptoms, toxicity, or imaging suggest a change in disease status. The team should determine whether the original barriers to resection have been overcome, whether new lesions have emerged, and whether the proposed operation can still clear all known disease with an adequate remnant. Once complete clearance becomes feasible, continuing chemotherapy solely to achieve maximal radiographic response may add toxicity without improving the surgical opportunity [6,14,21].

A radiographic complete response does not necessarily mean that viable tumor has been eradicated. Previously documented metastases should remain part of the surgical planning process even when they are no longer visible. The location of disappearing lesions should be documented before treatment, and MRI or intra-operative ultrasonography may help guide management [18].

## Strategies to increase the possibility of complete liver clearance

For patients with bilobar or extensive disease, the treatment plan may require more than one technique. Parenchymal-sparing resection, thermal ablation, portal vein embolization, and staged hepatectomy can be combined according to tumor distribution and the functional reserve of the liver [10,19,20].

The two-stage hepatectomy strategy is an option for selected patients with bilobar disease that cannot be cleared safely in a single operation. During the first stage, lesions are removed or ablated in the future liver remnant, and portal vein embolization may be performed to stimulate hypertrophy. The second stage consists of major hepatectomy after adequate growth and functional assessment of the remnant. Disease progression or insufficient hypertrophy may prevent completion, so careful selection and interval reassessment are essential.

Two-stage hepatectomy is most useful when disease can be cleared from the intended remnant during the first stage, but the remaining involved liver cannot be safely removed at the same operation. The sequence must be tailored to the distribution of lesions and the remnant's portal and venous anatomy. Portal vein embolization may be performed between stages when hypertrophy is required. Progression between stages, inadequate hypertrophy, or deterioration in liver function may prevent completion; these risks should be discussed before initiating the strategy. The purpose is complete treatment of all disease while maintaining adequate liver function, not merely completion of two operations [6,10,11].

Parenchymal-sparing surgery is particularly relevant when multiple lesions are present or when repeat hepatectomy may be necessary. Preserving healthy liver tissue can reduce the risk of post-operative liver failure and maintain options for future treatment. Available comparative evidence suggests that this approach can achieve oncologic outcomes comparable to more extensive resections in appropriately selected patients [9,19].

The decision to use a major hepatectomy should be based on the anatomical distribution of disease and the ability to achieve clearance, rather than on a preference for a larger resection. In some patients, a combination of limited resection and ablation may preserve more functional liver than an anatomic resection.

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) and other accelerated hypertrophy strategies may be considered in highly selected patients when conventional approaches are unlikely to provide timely adequate remnant growth. However, the potential benefit of faster hypertrophy must be weighed against morbidity, mortality, and the possibility that volumetric growth may not correspond fully to functional recovery. These techniques require experienced multidisciplinary teams and should not be presented as routine solutions for all patients with extensive bilobar metastases [6,10,20].

## Thermal ablation and other local treatments

Thermal ablation, including radiofrequency and microwave ablation, can eradicate selected liver metastases while preserving surrounding parenchyma. It may be used for small lesions, for tumors in patients who are poor surgical candidates, or as part of a combined strategy with resection. Lesion size, proximity to major bile ducts and vessels, achievable ablation margins, and operator experience influence treatment suitability [27].

Ablation can be performed percutaneously or intra-operatively. Image-guided percutaneous ablation may avoid a major operation, while intra-operative ablation can be combined with resection during the same procedure. The goal is complete tumor destruction with an adequate margin of treated tissue. Incomplete ablation margins increase the risk of local tumor progression [6,15,27].

Ablation planning should specify the intended circumferential margin and account for lesion visibility, proximity to central bile ducts, adjacent bowel, and major vessels that may reduce thermal efficacy through heat-sink effects. Microwave ablation may be less susceptible to heat-sink effects than radiofrequency ablation in some settings, but no device removes the need for careful patient and lesion selection. When resection and ablation are combined, the strategy should be designed to treat all sites while preserving enough parenchyma for current function and possible future interventions [6,15,27].

The COLLISION randomized trial compared thermal ablation with surgical resection for selected small-size CRLM. Its findings support the consideration of thermal ablation as a potential alternative to resection in appropriately selected patients, rather than assuming that all technically treatable small metastases require surgical removal [15]. These findings should be applied within the eligibility criteria and clinical context of the trial, and they do not establish equivalence for all lesion sizes or anatomical locations.

The phase III COLLISION trial compared thermal ablation with resection for carefully selected small CRLM. At the reported interim analysis, 300 patients had been randomized; four were subsequently excluded after randomization because of other pathology. Median OS was not reached in either group (HR: 1.05, 95% CI: 0.69-1.58). Adverse events occurred in 19% of patients assigned to ablation versus 46% assigned to resection, and serious adverse events in 7% versus 20%. The trial stopped early after meeting predefined interim criteria for non-inferiority and safety [15]. Early stopping and limited interim follow-up constrain certainty about long-term outcomes. These findings support ablation as an alternative for appropriately selected small lesions treated by experienced teams; they do not establish equivalence for all lesion sizes, locations, or disease burdens.

Stereotactic body radiotherapy and other local therapies may be considered in selected patients when surgery and thermal ablation are not feasible. However, the evidence base and indications differ from those for hepatic resection. These modalities should be evaluated by a multidisciplinary team, with consideration of previous treatment, lesion location, normal liver constraints, and the presence of disease elsewhere [3,4].

## Management of synchronous colorectal and liver metastases

Synchronous CRLM are detected at or around the time of diagnosis of the primary colorectal tumor. Treatment sequencing should consider the symptoms and location of the primary tumor, the extent and resectability of hepatic disease, the patient's condition, and the likelihood that one component of treatment may delay another [5].

The following three broad approaches are commonly considered: simultaneous resection of the primary tumor and liver metastases, a primary-first strategy, or a liver-first strategy. Simultaneous surgery may be appropriate when both procedures can be performed safely in a selected patient. The risks of combining major colorectal surgery with major hepatectomy must be carefully assessed, particularly when post-operative complications could delay systemic treatment.

Simultaneous surgery may reduce the number of hospital admissions and avoid an interval during which one disease site progresses, but the combined operative burden can be substantial, particularly when major hepatectomy is paired with complex rectal surgery or a high-risk colorectal anastomosis. A staged strategy may be safer when either operation is extensive, when the patient requires neoadjuvant treatment, or when post-operative complications could compromise delivery of systemic therapy. The liver-first approach is most relevant when hepatic disease is the principal determinant of prognosis, and the primary tumor can be safely observed or controlled during initial treatment. Decisions should be individualized rather than based on a universal hierarchy of sequences [5,6].

A primary-first approach is often considered when the colorectal tumor is symptomatic, obstructing, bleeding, or otherwise requires prompt treatment. In contrast, a liver-first strategy may be appropriate when hepatic disease represents the main threat to prognosis, and the primary tumor is asymptomatic or can be managed without immediate resection. Systemic therapy may be used before surgery to assess disease behavior and address occult systemic disease [5,6].

The European multi-societal consensus emphasizes standardized terminology, multidisciplinary planning, and individualized sequencing for synchronous colorectal cancer and liver metastases [5]. No single sequence is appropriate for every patient. Treatment should be organized to minimize the risk of progression at either disease site while preserving the opportunity for complete treatment.

## Recurrence after hepatectomy

Recurrence after curative-intent treatment of CRLM is common, and surveillance is necessary to identify potentially treatable disease. Follow-up generally includes clinical assessment, CEA measurement, and cross-sectional imaging according to institutional protocols and the patient's risk profile [3,4].

When recurrence is confined to the liver, repeat hepatectomy, thermal ablation, or a combination of local treatments may be considered. A previous hepatectomy is not an absolute contraindication to further surgery. The decision depends on the distribution of recurrent lesions, the volume and function of the remaining liver, the disease-free interval, response to previous treatment, and the presence of extrahepatic disease.

The assessment of recurrence should repeat the principles used at initial presentation as follows: confirm the distribution of disease, evaluate extrahepatic involvement, review prior systemic therapy and liver-directed procedures, and estimate the remaining functional parenchyma. A disease-free interval and response to prior treatment may inform prognosis, but neither should be used in isolation to deny local treatment. Selected patients may benefit from repeat hepatectomy, ablation, or combined treatment, while systemic therapy may be appropriate when disease is multifocal, rapidly progressive, or not amenable to complete local control [6-8,21].

Repeat local treatment can offer meaningful disease control in carefully selected patients. Parenchymal-sparing strategies are particularly valuable because they preserve liver tissue for subsequent procedures. Systemic therapy may be used before or after local treatment depending on tumor biology, prior regimens, and the extent of recurrence.

Recurrence should also prompt reassessment of the original tumor's molecular profile when clinically indicated, particularly if previous testing was incomplete or new targeted treatment options are relevant. Treatment decisions should be made according to the current disease state rather than relying exclusively on the original staging.

## Prognostic factors and individualized treatment

Prognosis after treatment of CRLM depends on multiple factors, including the primary tumor's stage and nodal status, the number and size of hepatic lesions, CEA level, molecular characteristics, response to systemic treatment, and the feasibility of complete disease clearance. The historical clinical risk score developed by Fong et al. incorporated several clinical and pathological factors associated with recurrence after hepatic resection [7]. Such scores may assist discussion but should not be used as the sole basis for excluding patients from surgery.

The behavior of the disease during systemic therapy can provide additional prognostic information. Rapid progression despite appropriate treatment may indicate unfavorable biology and reduce the likelihood of durable benefit from major surgery. Conversely, a sustained response or disease stability may support a local treatment strategy when complete clearance is feasible [6,14,21].

Prognostic assessment should not be confused with technical resectability. A patient may have a technically resectable lesion but limited expected benefit because of uncontrolled extrahepatic disease. Conversely, patients with extensive hepatic disease may still be candidates for curative-intent treatment if a complete local strategy becomes feasible and disease biology is favorable.

Shared decision-making is important because curative-intent treatment can involve multiple procedures, systemic therapy, and substantial recovery time. The potential benefit should be weighed against operative risk, treatment toxicity, quality of life, and the patient's preferences [3-6].

## Emerging strategies and future directions

Liver transplantation is not a routine substitute for resection and should be considered only for carefully selected patients with permanently unresectable liver-only CRLM in specialist transplant-oncology programs. The 2024 TransMet randomized trial enrolled selected patients aged 18-65 years with resected, BRAF non-mutated colorectal cancer, liver-only metastases deemed permanently unresectable, good performance status, and disease controlled or responsive to systemic chemotherapy. In the intention-to-treat analysis, five-year OS was 56.6% with transplantation plus chemotherapy versus 12.6% with chemotherapy alone (HR: 0.37, 95% CI: 0.21-0.65;  $p=0.0003$ ) [28]. These results are important but cannot be generalized to patients with uncontrolled extrahepatic disease, BRAF-mutated tumors, poor performance status, or progression on treatment. Transplantation entails strict selection, donor-resource considerations, lifelong immunosuppression, and recurrence risk; it should be discussed only against current program criteria and expert multidisciplinary assessment.

Transplantation must be distinguished from routine treatment of resectable metastases. It is a resource-intensive option for a narrowly selected group with liver-only disease that cannot be removed by conventional surgery, and it requires careful evaluation of tumor biology, response to systemic treatment, exclusion of uncontrolled extrahepatic disease, and the ability to comply with long-term surveillance and immunosuppression. Prospective evidence supports the possibility of prolonged survival in selected patients, but recurrence remains a major concern and donor availability is a limiting factor. Referral should occur through specialized transplant-oncology programs and in accordance with their protocols [6,29].

Advances in molecular profiling may further refine treatment selection. Biomarkers can guide systemic therapy, identify patients who may benefit from targeted treatment or immunotherapy, and improve the understanding of tumor behavior. However, molecular findings must be integrated with radiological and clinical assessment rather than interpreted in isolation [3,4,6].

Improved imaging, intra-operative ultrasonography, minimally invasive liver surgery, and image-guided local treatments continue to expand the options available to patients. Future clinical research should focus on identifying which patients derive the greatest benefit from surgery, ablation, peri-operative chemotherapy, or combined approaches. Comparative trials and prospective registries are needed to improve treatment selection and standardize outcomes across centers [5,6].

## Limitations of the available evidence

The evidence supporting CRLM management includes randomized trials, observational cohorts, consensus statements, and systematic reviews, but important limitations remain. Studies differ in their definitions of resectability, patient selection, systemic regimens, local-treatment techniques, endpoints, and follow-up duration, complicating direct comparisons. In addition, this narrative review did not use a documented systematic search or formal study-level risk-of-bias assessment; selection of influential studies may therefore have introduced review-level selection bias, and relevant literature may have been missed.

A further limitation is that some trials were designed for metastatic colorectal cancer generally rather than specifically for conversion to liver resection, complete local clearance, or cure. Consequently, response rate, progression-free survival, overall survival, and conversion-to-resection rate should not be treated as interchangeable endpoints. Surgical series are also vulnerable to referral and selection effects, and results

from high-volume hepatobiliary centers may not be reproducible where interventional radiology, liver volumetry, specialist anesthesia, and multidisciplinary review are less accessible. These limitations support cautious interpretation and transparent reporting of patient selection and treatment intent [3,4,6,14,15].

Surgical series are vulnerable to referral and selection bias because patients selected for local treatment often have more favorable disease characteristics or better general health. Evidence for conversion therapy and complex staged procedures frequently comes from specialist centers, and outcomes may not generalize to all institutions. These limitations support cautious interpretation and transparent reporting of eligibility, treatment intent, and endpoints [3,4,6,14,15].

Evidence supporting conversion therapy and complex staged procedures often comes from specialized centers. Outcomes may not be generalizable to all institutions. Furthermore, improvements in systemic therapy and imaging mean that results from older trials may not fully represent contemporary practice. For these reasons, management decisions should be guided by current evidence and multidisciplinary expertise, while acknowledging uncertainty and avoiding the assumption that a single treatment sequence is universally superior.

### Comparative interpretation of the evidence

Across the major studies, treatment effects depend on the clinical question and population studied. EORTC 40983 addressed peri-operative chemotherapy in initially resectable disease and did not demonstrate a significant long-term OS advantage, whereas CAIRO5 addressed systemic strategies for initially unresectable liver-only disease and found regimen-specific differences in PFS and toxicity. COLLISION informs the choice between ablation and resection for selected small lesions, not all CRLM. TransMet addresses transplantation in a highly selected group with permanently unresectable liver-only disease, not routine management of resectable metastases [13-16,28]. These studies should therefore be interpreted as complementary rather than ranked against one another. The practical implication is to identify the patient's current treatment state, define the relevant endpoint, and reassess the plan as disease biology and technical feasibility evolve.

### Practical multidisciplinary decision algorithm

At multidisciplinary review, the team should (1) complete staging with CT of the chest, abdomen, and pelvis and liver MRI when indicated, obtain CEA and relevant molecular testing, and assess patient fitness; (2) classify disease as readily resectable, potentially convertible, or permanently unresectable by conventional local treatment; (3) for readily resectable disease, compare surgery-first with peri-operative systemic therapy according to disease burden, biology, and patient preference; (4) for potentially convertible disease, define the technical barrier to clearance, select systemic treatment according to molecular status and the need for response, and schedule early reassessment with a hepatobiliary surgeon; (5) once feasible, pursue complete local clearance with resection, ablation, or a combined or staged approach while preserving functional liver; (6) for permanently unresectable liver-only disease, continue appropriate systemic treatment and consider transplant-oncology referral only if strict eligibility criteria are met; and (7) reassess extrahepatic disease, toxicity, liver function, and patient goals at every transition. This framework is a practical synthesis of the evidence, not a separately validated clinical prediction rule (Table 1).

| Studies             | Population/comparison                                                                                    | Key quantitative finding                                                                                                                | Main limitation                                                                 | Clinical implication                                                                 |
|---------------------|----------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| EORTC 40983 [13,16] | 364 patients; up to four resectable CRLM; peri-operative FOLFOX4 versus surgery alone                    | Long-term median OS: 61.3 versus 54.3 months; HR: 0.88 (95% CI: 0.68-1.14), p=0.34                                                      | Selected population; no statistically significant OS difference                 | Consider peri-operative therapy selectively; universal OS benefit is not established |
| CAIRO5 [14]         | Initially unresectable liver-only CRLM; molecular/sidedness-stratified regimens                          | FOLFOXIRI-bevacizumab improved PFS in right-sided and/or RAS/BRAF-mutant disease (10.6 versus 9.0 months; HR: 0.76); increased toxicity | Specialist panel reassessment; population-specific findings                     | Choose intensity based on biology, need for response, fitness, and toxicity          |
| COLLISION [15]      | Selected small CRLM; thermal ablation versus resection                                                   | Interim OS HR: 1.05 (95% CI: 0.69-1.58); adverse events 19% versus 46%; serious events 7% versus 20%                                    | Early stopping and interim follow-up; strict selection and expertise            | Ablation is an option for selected small lesions, not all CRLM                       |
| TransMet [28]       | Selected permanently unresectable liver-only CRLM; transplantation plus chemotherapy versus chemotherapy | Five-year OS 56.6% versus 12.6% in intention-to-treat; HR: 0.37 (95% CI: 0.21-0.65)                                                     | Strict eligibility; transplant-center setting; donor and recurrence constraints | Consider transplant-oncology referral only for eligible patients                     |
| Ng et al. [17]      | Systematic review of thermal ablation techniques                                                         | Identified heterogeneity in patient selection, technique, device settings, and outcome reporting                                        | Predominantly heterogeneous non-randomized evidence                             | Standardized reporting and prospective comparisons remain important                  |

TABLE 1: Pivotal studies informing contemporary CRLM management.
OS: overall survival; CRLM: colorectal liver metastases; PFS: progression-free survival

Conclusions

Contemporary management of CRLM depends on repeated multidisciplinary assessment of technical resectability, oncologic suitability, molecular characteristics, tumor behavior, and functional liver reserve. Complete local clearance remains the objective when it can be achieved safely, using resection, ablation, or combined and staged approaches as appropriate. Systemic therapy is selected according to disease state, molecular profile, need for conversion, and patient fitness; transplantation is an option only for a highly selected population with permanently unresectable liver-only disease.

Pivotal trials should be interpreted according to their eligibility criteria, endpoints, follow-up, and limitations. A higher response rate or conversion rate does not automatically establish an OS benefit, and non-inferiority in selected patients does not mean universal equivalence. Individualized treatment should balance the probability of complete disease clearance against toxicity, preservation of liver function, patient goals, and access to specialist expertise.

Additional Information

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All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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