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SURGERY AND SURGICAL INNOVATIONS IN COLORECTAL CANCER (M AL-KASSPOOLES, SECTION EDITOR)

# Surgical Management of Metastatic Colorectal Cancer

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## Abstract

**Purpose of Review** The surgical management of metastatic colorectal cancer (CRC) has evolved over time. Most often, the management of asymptomatic primary CRC with simultaneous liver metastases (LM) proceeds with neoadjuvant chemotherapy followed by surgical resection. Although the timing of surgical resection has remained controversial, the ability to achieve R0 resection and the importance of patient selection remain widely accepted.

**Recent Findings** Preoperative novel modalities such as portal vein ligation (PVL) or portal vein embolization (PVE) have allowed for improved surgical outcomes and decreased post-surgical morbidity. Combination or hybrid management has also seen increased utility by associating ablation therapies with surgical resection. Finally, patients with significant comorbidities and surgically unresectable disease have benefited greatly from locoregional salvage therapies such as percutaneous ablation and radioembolization.

**Summary** Here we will review pertinent literature associated with surgical management for resectable disease and explore newly developed locoregional salvage therapies for unresectable disease.

**Keywords** Metastatic colorectal cancer · Simultaneous liver metastases · Locoregional salvage therapy · Trans-arterial chemoembolization

## Abbreviations

| | |
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| CRC | Colorectal cancer |
| SLM | Simultaneous liver metastasis |
| PVL | Portal vein ligation |
| PVE | Portal vein embolization |
| FLR | Future liver remnant |
| ALPPS | Associating liver partition and portal vein ligation for staged hepatectomy |
| HAI | Hepatic-arterial infusion |
| MWA | Microwave ablation |
| RFA | Radiofrequency ablation |
| DEBIRI | Irinotecan drug-eluting beads |
| TACE | Trans-arterial chemoembolization |

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## Introduction

Colorectal cancer remains the third most diagnosed cancer and the second cause of cancer-related death in the USA. The average age at time of diagnosis is sixty-eight for men and seventy-two for women (age range 35–85); with rectal cancers being diagnosed much sooner at an average age of sixty-three across both men and women [1, 3]. Among the new cases of cancer diagnosed in 2021, the incidence of colorectal cancers was 7.9% with notable risk factors being age, gender (with male being higher), smoking status, and obesity. Among cancer-related deaths, colorectal cancers were recorded at 8.7% with 5-year survival between 2011 and 2017 recorded at 64.7%.

Among patients diagnosed with colorectal cancer, 15–20% of patients present with synchronous liver metastasis [24••]. The majority of cases (80–90%) are unresectable. Five-year survival in patients with metastatic liver lesions

ranges from 27 to 73% [10••]. Detection of colorectal cancer liver metastasis is vital considering its negative impact on survival [18]. Patterns among colorectal cancers and nature of metastatic spread are directly linked to the biology of the disease. From the colon and proximal rectum, blood is drained through the portal system to the liver. However, the distal regions of the rectum bypass the liver and the first encountered organ is the lung. Expectedly, proximal rectal cancers have a higher rate of metastasis to the liver compared with distal rectal cancers which often metastasize to the lungs. Rectal cancer has a higher incidence of metastasis to the nervous system and bone; these patients have a worse prognosis when compared to patients with solitary liver or lung metastases.

When considering CRC and liver metastases, the prognosis changes when comparing synchronous to metachronous metastases. In general, synchronous lesions have a worse prognosis compared to those that are metachronous with a 5-year survival difference of 17.6% versus 7.2%, respectively [5•]. Nevertheless, surgical resection portends the best chance of long-term survival in patients with resectable disease. Unfortunately, 50–75% of patients who undergo liver resection will develop disease recurrence within 2 years of resection [26]. The optimal surgical strategy when considering simultaneous versus staged resection remains debated and controversial [22].

The scope of surgery in the management of colorectal cancer liver metastases has evolved to include surgical resection with or without chemotherapy as well as viable locoregional salvage therapies such as percutaneous ablation, radioembolization, or combinations of the various forms of locoregional therapies. We hope to provide a comprehensive review of the surgical management of colorectal cancer liver metastases and provide an introduction to locoregional therapies that have increased in utility.

## Diagnosis

Patients with CRC typically present with rectal bleeding, microcytic anemia, abdominal pain, and altered bowel patterns. The median age of diagnosis is 67. The age of detection prior to the age of 50 in the USA has increased 2% every year since 1990 [1]. Although the reasoning for such an increase is poorly understood, several contributing factors, such as obesity and Western diet, may contribute [3].

Approximately half of colorectal cancers arise from the right side or proximal colon (derived from midgut) and present with fatigue, anemia, and abdominal pain. Left-sided tumors (distal colon and rectum) present much earlier and are embryologically derived from the hindgut. These tumors usually present with narrow caliber stool, constipation, or rectal bleeding. Left-sided colon and rectal cancers have a higher incidence of liver metastasis, but right-sided colon cancers with liver metastases are associated with worse survival [4••]. One explanation for the difference in survival with respect to tumor location is that right-sided colon cancers are associated with delayed diagnosis. Alternative hypotheses include molecular differences among the tumors. Namely, right-sided tumors are more often found to have KRAS and BRAF mutations, which are associated with poorer survival outcomes, when compared to those on the left.

In addition to basic laboratory work such as complete blood count and comprehensive metabolic panel, a serum level of the carcinoembryonic antigen (CEA) protein is a critical baseline measurement and, when initially elevated at the time of primary tumor diagnosis, helps detect future cancer recurrence. Typically, colonoscopy-guided biopsy confirms the primary cancer. To complete initial clinical staging, contrast-enhanced computed tomography (CT) imaging of the chest, abdomen, and pelvis is obtained. In the setting of metastasis(es), individual biopsies of liver, lung, and/or distant lymph nodes may be necessary for pathological confirmation prior to chemotherapy and to appropriately stage the cancer (TNM Staging) [14]. Magnetic resonance imaging (MRI) and positron emission tomography (PET) scans can be helpful when CT findings are equivocal for metastatic disease.

High-quality cross-sectional imaging is essential and should be obtained prior to chemotherapy to provide information on curability and future surgical planning. In the setting of CRC with LM, CT is preferred for the initial staging [1]. MRI is more sensitive for sub-centimeter liver lesions and after neoadjuvant chemotherapy to distinguish metastases from benign lesions. For patients undergoing neoadjuvant or conversion chemotherapy, a pretreatment MRI is highly recommended [21]. The role of preoperative PET scans has shown to be associated with improved prognosis, although not required as part of the clinical staging workup, except for equivocal CT or MRI findings [6]. Radiologic imaging provides additional information for operative planning; segmental localization; relationship to surrounding structures; response after neoadjuvant chemotherapy; and assessment of the remnant liver volume following surgical resection.

Molecular profiling of tumors allows for analysis that may suggest a genetic predisposition; assessment of microsatellite instability (MSI)/mismatch repair (MMR) genes; and the utility of immunotherapy. Five percent of metastatic CRCs have MSI or MMR tumors, for which immunotherapy extends survival significant more than traditional chemotherapy [3]. Metastatic CRC requires a multidisciplinary approach with chemotherapy, surgical resection, IR-directed therapy, and immunotherapy; a 5-year disease-free survival can be achieved in approximately 10–20% of all patients with metastatic disease.

## Surgical Resection of Hepatic Metastases

The liver remains the most common site of metastasis from colorectal cancers at 70–80%. Five-year survival rates of 35–58% are reported with complete R0 resection associated with < 30% major morbidity and < 3% mortality [24••]. Synchronous liver metastases (SLM) are confined to the liver 50–80% of the time [4••].

Modification strategies to allow for resection of liver metastases while leaving a sufficient liver remnant are crucial. Future liver remnant (FLR) is the percentage of the total preoperative liver volume that is predicted to remain following an R0 resection. Although there is no definitive consensus, guidelines suggest a minimum of 20% FLR in the absence of cirrhosis or underlying liver disease. The limits of the FLR must be modified in the presence of steatosis, chemotherapeutic changes, and cirrhosis. If FLR is expected to be marginal, there are opportunities for optimization, including portal vein embolization (PVE) [25]. PVE allows for liver modeling and involves complete embolization of the portal vein branches within the segment planned for resection, inducing hypertrophy with increased portal venous flow to the FLR. Resection usually occurs 4–6 weeks after PVE.

Although preoperative PVE is the standard approach to optimize FLR, two-stage hepatectomy can also be considered for bilateral multinodular CRC LM patients, allowing the liver to remodel in the interval between resections, thus minimizing postoperative liver failure. Unfortunately, approximately one-third of patients do not proceed to the second stage due to tumor progression or inadequate FLR hypertrophy [3]. A more recent novel technique for accelerated regeneration of liver parenchyma is associating liver partition and portal vein ligation for staged hepatectomy (ALPPS). ALPPS induces FLR hypertrophy up to 80% in a short time interval; however, controversy exists due to significant morbidity (up to 40% experience postoperative liver failure and bile leak) and mortality (up to 15%).

Simultaneous versus delayed liver resection among patients with resectable CRC-SLM remains controversial. Conventional surgical strategy has been a staged operation. Resection of the primary lesion is followed by adjuvant chemotherapy; if there is a response or at least no progression of the liver metastases, a subsequent hepatic resection is undertaken. This strategy not only limits the surgical stress of large operations, but it also allows time to time to study the biology of the metastases while on chemotherapy, thereby avoiding unnecessary surgical risks if the disease progresses [2] and/or determining which systemic therapy can potentially be used if there is a subsequent recurrence after surgery. Another adaptation of the staged approach is the reverse or hepatic approach, proposing to perform the liver resection first followed by the staged resection of the primary tumor [22, 24••]. Although limited data exists, this strategy would not delay the delivery of systemic treatment of colorectal liver metastases. This approach is more commonly utilized for rectal cancers which often rely on neoadjuvant chemoradiation regimens.

Alternatively, simultaneous resection may provide potential advantages. A single operation reduces surgical risk in select patients and allows for earlier initiation of chemotherapy. In addition, hepatotoxic neoadjuvant chemotherapy may lead to postoperative liver failure and prevent interval resection [24••]. Tanaka et al. [22] performed a retrospective analysis comparing rates of postoperative complications between simultaneous versus delayed resection. They found that the decision to proceed with simultaneous resection should be made selectively. Observed complications included fistulas, liver stump abscesses, anastomotic leak, wound infection, and death. Patients who underwent simultaneous resection sustained no mortality; however, the morbidity rate was 28% (compared to 16% in the delayed resection group). Since the volume of resected liver had the greatest impact on morbidity rates, the authors concluded that simultaneous resection should be performed when all metastatic nodules can be removed by a limited resection of one segment or less.

Previously, 1-cm resection margins were advocated; however, it has been shown that resection margin width does not impact survival when microscopically negative. Patients greater than the age of 70, with poor performance status, and/or specific primary cancer subtypes (poorly differentiated or mucinous adenocarcinoma) were factors that had statistical significance in decreasing overall survival with simultaneous liver resection [22]. Assessment of the performance and functional status of the patient and his/her ability to tolerate the oncologic plan are extremely important to consider.

In 2006, a prospective multicenter randomized study (METASYNC) compared several outcomes between delayed versus simultaneous resection. The impact of major complication categories (digestive, hepatic, or general) in disease progression was compared between the two groups. There were no statistical differences found between the complication categories and disease progression when comparing simultaneous versus delayed liver resection [4••]. Furthermore, in patients undergoing delayed resection, the percentage of R1 resections was higher compared to patients undergoing simultaneous resection. Nonetheless, the difference did not achieve statistical significance.

Along with expanding surgical resection criteria and preoperative downstaging, patient selection is a major determinant in the planning process. Although the initial treatment for metastatic CRC is systemic chemotherapy, surgical resection has shown long-term survival benefits [3]. Patients with

asymptomatic CRC and resectable SLM usually receive neoadjuvant chemotherapy (with or without radiotherapy for rectal cancers) followed by surgery [24••]. Simultaneous resection of the primary should be considered for select patients. Simultaneous resection is discouraged when patients require complex rectal surgery (extensive dissection with potentially higher complication rates) and/or major hepatic resection (more than three segments) due to greater postoperative mortality and morbidity [1]. Patients with symptomatic CRC and resectable SLM most often proceeds with surgical resection of the primary mass, followed by adjuvant chemotherapy and, finally, surgical resection of LM. At times, in a patients with symptomatic bowel obstructions who would require an extensive and/or complex operation to remove the primary tumor, a diverting ostomy is needed to avoid delays in receiving systemic therapy when preferred prior to addressing surgery for the primary tumor or liver metastases.

## Chemotherapy and Targeted Therapy for Unresectable Disease

Patients with unresectable disease commonly proceed with systemic therapy with the intention to achieve conversion to ultimately undergo a surgical resection [10••]. Conversion to resection of hepatic-only metastasis is associated with prolonged 5-year survival of up to 50% [8]. Preoperative conversion chemotherapy may be offered to reduce the bulk of metastatic disease and increase the possibility of secondary SLM resectability or combinations of local liver-directed therapy to eliminate the metastatic disease.

After chemotherapy, metastases may disappear on cross-sectional imaging, despite the persistence of residual disease [21]. The disappearance of liver metastases (DLM) occurs in up to 25% of patients undergoing systemic chemotherapy. This does not necessarily equate to a complete pathological response since metastatic liver disease can often be found during surgical exploration using intra-operative ultrasound (IOUS) in those with DLM. Intra-operative detection rate is highly variable and estimated between 25 and 60% in those who achieve a complete clinical response. Sturesson et al. found that 20% of patients had the presence of calcification within tumors after chemotherapy when using IOUS, considerably more sensitive for DLM compared to contrast-enhanced (CE) IOUS [21].

Modern combination chemotherapy with hepatic-arterial infusion (HAI) has become an option in patients with unresectable CRCLM [8]. Chemotherapy is offered in unresectable cases in the form of conventional regimens or targeted therapy agents. Conventional chemotherapy includes irinotecan (FOLFIRI regimen) or oxaliplatin (FOLFOX regimen). Targeted agents use antibodies or specific protein inhibitors such as bevacizumab (vascular endothelial growth factor receptor inhibitor) or cetuximab (anti-epidermal growth factor inhibitor). The analysis of preoperative genomic alterations (such as RAS/RAF) and next-generation sequencing (NGS) has allowed for targeted biomarker therapy. Specifically, mutations in DDR and MMR signaling have been associated with worse post-operative survival in patients [26].

## Locoregional Therapies for Unresectable Metastatic Disease

Improvements in preoperative imaging modalities have led to increased utility of locoregional therapies in conjunction with systemic chemotherapy. In patients where curative intervention is not possible (unresectable disease or those who are unable to tolerate hepatic resection), several treatment options are now available to achieve the aims of improvements in progressive-free survival; improved quality of life; and palliation of symptoms. Namely, methods such as cryoablation, radiofrequency ablation (RFA), and microwave ablation (MWA) have surfaced. Cryoablation causes cell death via freezing and was used previously for liver metastases. Although cryoablation originally gained some acceptance, the method was limited due to complications from cryoshock (cytokine-mediated storm secondary to the free radical formation that resulted in multi-organ failure) [5•]. Several other strategies have further developed, including thermal ablation via RFA and MWA; non-thermal ablation via irreversible electroporation (IRE); and embolization techniques such as Y-90 radioembolization.

RFA historically was the most common thermal ablative technique used. The outcome is determined by heat conduction (convection and conduction) and attaining a tumor-free margin (360° 1-cm margin). RFA use has transitioned primarily towards MWA techniques as MWA is less affected by surrounding vessels serving as heat sinks. MWA uses a higher frequency form of electromagnetic radiation. As anticipated, the higher energy component allows for higher tumor temperatures, larger ablation volumes, and faster ablation times. However, it increases the risk of heating non-targeted surrounding tissue and possible coagulative necrosis. Finally, IRE is an emerging non-thermal ablative technique that deploys electrical impulses across the cell membrane triggering apoptosis.

Ablative strategies can be synergistic with surgical resection in combination or hybrid procedures. However, more commonly, ablation strategies are offered in the setting of unresectable disease and patients that are unable to tolerate surgical resection in conjunction with systemic chemotherapy. This poses an inherent selection bias. Prospective cohort studies have focused on analyzing the local recurrence rate following RFA versus surgical resection. The recurrence rate was higher in the RFA cohort than surgical resection, reinforcing surgical resection as the standard of care. Although there are currently no randomized controlled trials to compare RFA to surgical resection at this time, the CLOCC trial investigated the overall

survival of RFA with and without systemic chemotherapy [7, 19]. This trial investigated patients with unresectable colorectal liver metastases and noted improved progression-free survival among patients who received both RFA and systemic chemotherapy. Although further research is required, RFA and MWA technology offers utility in the setting of ablative strategies to target metastatic disease.

Radioembolization strategies with trans-arterial chemoembolization (TACE) or trans-arterial radioembolization (TARE) are the most comprehensive studied techniques in the setting of colorectal liver metastases with progression of disease despite systemic chemotherapy and well established in the salvage setting. Most commonly, radiolabeled Y90 (yttrium 90) microspheres (TheraSpheres) are used [5•]. The high-energy radioisotope has a short half-life with limited tissue penetration that is ideal for liver-directed therapy. The isotope is delivered via beads or TheraSpheres either directly into the hepatic artery or branches via microcatheters and lodges in the liver tumor capillary network. The beta radiation allows for short-range spread while sparing the surrounding healthy hepatic parenchyma. To limit potential respiratory or gastrointestinal complications due to significant collateral vessels, pre-treatment mapping of the hepatic vasculature prior to therapy is critical. The EPOCH study has shown promise for refractory metastatic CRC and hopes to establish the role of combination therapy with TARE and oxaliplatin- or irinotecan-based chemotherapy as second-line treatment [5•].

Finally, a locoregional modality that shows considerable potential is irinotecan drug-eluting beads (DEBIRI) with TACE. DEBIRI involves intra-arterial administration of the chemotherapeutic drug to the tumor arterial network. There is currently no consensus on treatment dose and timing; however, studies are ongoing to investigate DEBIRI with or without systemic chemotherapy in the setting of unresectable colorectal liver metastases. Thus far, randomized control trials have shown no statistical difference for progression-free survival [12, 16]. That said, DEBIRI represents a promising locoregional therapy with opportunity in the salvage setting that remains to be explored.

## Transplantation in the Setting of Unresectable Metastatic Disease

Although outcomes of metastatic CRCs have improved with advancements in diagnostic modalities, imaging and surgical intervention, for most patients, the treatment is palliative rather than curative. The standard of care for metastatic colorectal cancer is surgical resection with the goal of R0 resection, but only a third of patients are candidates for surgery [13]. To provide patients new treatment avenues, some have implemented a protocol with the goal to incorporate liver transplantation into the treatment plan for unresectable disease. This endeavor was undertaken after a Norwegian pilot study in 2011 was performed on twenty-one patients and revealed that liver transplantation helped achieve a 5-year survival of 60% [23]. Ongoing European trials (TRANSMET) will further provide insight into overall survival when comparing liver transplantation with conventional treatment methods for unresectable metastatic disease with systemic chemotherapy [13, 17].

## Conclusion

The surgical management of metastatic colorectal cancer is complex. The goal of surgery is to obtain an R0 resection for optimum surgical success while maintaining viable liver remnant and decreased mortality. Overall, the rate of surgical resectability at the time of laparotomy is high and long-term survival with surgical resection is increasingly promising. The intricate interplay between preoperative workup, diagnosis, the timing of chemotherapy, and surgical resection with patient selection in mind makes multidisciplinary involvement that much more critical.

## Declarations

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

**Conflict of Interest** The authors declare no competing interests.

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