cmgh
CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

REVIEW

# Updated Management of Colorectal Cancer Liver Metastases: Scientific Advances Driving Modern Therapeutic Innovations

Ranish K. Patel,[1] Shahrose Rahman,[1] Issac R. Schwantes,[1] Alexandra Bartlett,[2] Robert Eil,[2,3] Khashayar Farsad,[4] Kathryn Fowler,[1] Shaun M. Goodyear,[3,5] Lissi Hansen,[3,6] Adel Kardosh,[3,5] Nima Nabavizadeh,[3,7] Flavio G. Rocha,[2,3] V. Liana Tsikitis,[3,8] Melissa H. Wong,[3,9] and Skye C. Mayo[2,3]

[1]*Department of Surgery, Oregon Health & Science University (OHSU), Portland, Oregon;* [2]*Division of Surgical Oncology, Department of Surgery, OHSU, Portland, Oregon;* [3]*The Knight Cancer Institute, OHSU, Portland, Oregon;* [4]*Charles T. Dotter Department of Interventional Radiology, OHSU, Portland, Oregon;* [5]*Division of Hematology and Oncology, School of Medicine, OHSU, Portland, Oregon;* [6]*School of Nursing, OHSU, Portland, Oregon;* [7]*Department of Radiation Medicine, OHSU, Portland, Oregon;* [8]*Division of Gastrointestinal Surgery, Department of Surgery, OHSU, Portland, Oregon; and* [9]*Department of Cell, Developmental and Cancer Biology, OHSU, Portland, Oregon*

**SUMMARY**

Metastatic disease to the liver from colorectal cancer remains a significant treatment challenge. Herein, we provide an update to our group's previous review regarding the innovative scientific and clinical advances in the management of this disease.

***Gastroenterol Hepatol 2023;16:881–894; https://doi.org/10.1016/j.jcmgh.2023.08.012)***

*Keywords:* Colorectal Liver Metastases; Adoptive T-Cell Therapy; Tumor Microbiome; Circulating Hybrid Cells; Surgical Resection; Hepatic Arterial Infusion; Molecular Profiling; Quality of Life.

**Colorectal cancer is the second leading cause of cancer-related deaths in the United States and accounts for an estimated 1 million deaths annually worldwide. The liver is the most common site of metastatic spread from colorectal cancer, significantly driving both morbidity and mortality. Although remarkable advances have been made in recent years in the management for patients with colorectal cancer liver metastases, significant challenges remain in early detection, prevention of progression and recurrence, and in the development of more effective therapeutics. In 2017, our group held a multidisciplinary state-of-the-science symposium to discuss the rapidly evolving clinical and scientific advances in the field of colorectal liver metastases, including novel early detection and prognostic liquid biomarkers, identification of high-risk cohorts, advances in tumor-immune therapy, and different regional and systemic therapeutic strategies. Since that time, there have been scientific discoveries translating into therapeutic innovations addressing the current management challenges. These innovations are currently reshaping the treatment paradigms and spurring further scientific discovery. Herein, we present an updated discussion of both the scientific and clinical advances and future directions in the management of colorectal liver metastases, including adoptive T-cell therapies, novel blood-based biomarkers, and the role of the tumor microbiome. In addition, we provide a comprehensive overview detailing the role of modern multidisciplinary clinical approaches used in the management of patients with colorectal liver metastases, including considerations toward specific molecular tumor profiles identified on next generation sequencing, as well as quality of life implications for these innovative treatments. *(Cell Mol***

Colorectal cancer (CRC) is the third most common malignancy worldwide.[1] Although CRC incidence and mortality have decreased in many Western countries, there is a rising global incidence of CRC in young adults, contributing to nearly 1 million deaths annually worldwide, and it is the second leading cause of cancer-related death in the United States.[1] Importantly, more than 50% of patients will ultimately develop metastatic disease, with the liver being the common site of metastases in approximately 70% of cases. Colorectal liver metastases (CRLM) are a major contributor toward mortality and morbidity for patients with CRC, because preservation of liver function in the face of liver metastases influences survival and quality of life.

***Abbreviations used in this paper:*** **CAR, chimeric antigen receptor; CEA, carcinoembryonic antigen; cfDNA, cell-free tumor DNA; CHC, circulating hybrid cell; CRC, colorectal cancer; CRLM, colorectal liver metastases; CTC, circulating tumor cell; EGFR, epidermal growth factor receptor; EORTC, European Organization for Research and Treatment of Cancer; EV, extracellular vesicles; FACT-G, Functional Assessment of Cancer Therapy-General; FU, fluorouracil; GVB, gut-vascular barrier; HAI, hepatic arterial infusion; ICI, immune checkpoint inhibitors; IRE, irreversible electroporation; mCRC, metastatic colorectal cancer; mPFS, median progression free survival; MSI-H, high microsatellite instability; MSS, microsatellite stable; MWA, microwave ablation; ORR, overall response rates; OS, overall survival; PFS, progression free survival; pMMR, mismatch repair proficient; PRO, patient-reported outcome; QOL, quality of life; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; SOC, standard of care; TACE, transarterial chemoembolization; TCR, T-cell receptor; Y-90, yttrium-90.**

**Most current article**



2352-345X
https://doi.org/10.1016/j.jcmgh.2023.08.012

Surgical resection of CRLM remains the only potentially curative therapeutic strategy, with modern series and randomized clinical trials reporting a 5-year overall survival (OS) upward of 50%–70% in the era of modern systemic therapies.[2] However, it is estimated that as many as 80% of patients with CRLM are not candidates for surgical resection at the outset,[3,4] and up to 50%–60% of patients develop disease recurrence after a curative-intent hepatic resection.[5] Therefore, there is great need for continued discovery and clinical translation of novel and improved strategies for early identification, prevention, and treatment of patients with CRLM.

In 2017, our group summarized the evolving paradigms in CRLM.[6] Since our review was published, there have been numerous scientific discoveries that have been translated into novel therapeutic strategies that have reshaped modern treatment approaches for this disease. In this review, we provide a contemporary overview of both the scientific and clinical advances related to CRLM with attention to how these discoveries will impact the future treatment and ultimately survival outcomes for patients with this disease (Figure 1).

## Scientific Progress in CRLM

### *Blood-based Biomarkers*

Monitoring of the disease burden and treatment response in patients with CRLM represents an essential component of disease management. Radiographic imaging and biopsy-based approaches to measure disease response carry practical and diagnostic limitations, highlighting the considerable interest in the development of noninvasive clinical biomarkers. The circulating protein, carcinoembryonic antigen (CEA), remains a standard blood-based biomarker for patients with CRC who have an elevation of this protein. However, when using CEA to assess treatment response and as part of surveillance after resection of both primary CRC and CRLM, CEA is limited by variable sensitivity and specificity, because the protein is produced in a number of benign conditions and not expressed in every patient with CRC. Given this, a new generation of promising blood-based biomarkers have emerged, which have the potential to inform prognostic and staging information in CRLM, allowing insights into the patient's unique tumor biology.

Cell-free tumor DNA or nucleic acids (cfDNA), or naked DNA arising from tumor cell death, is one such marker detectable in peripheral blood. A study of 14 patients with CRC demonstrated that serum cfDNA harbored identical KRAS point mutations found in the associated primary tumor, indicating potential utility of cfDNA to provide as a snapshot of tumor microenvironment and genetics.[7] Recent reports have prospectively demonstrated that peripheral cfDNA levels are associated with disease recurrence in patients with CRLM after hepatic resection.[8,9] However, cfDNA is limited by its rarity in the peripheral blood and the dissemination of cfDNA from non-tumor cells. An alternative blood-based biomarker under development are extracellular vesicles (EVs) or exosomes. These membrane-bound vesicles carry tumor cargo such as miRNA, protein, and DNA. Exosomes show potential to provide information on tumor state and mutational evolution. Discrete profiles of functional miRNAs contained within serum-isolated EVs from patients with CRLM may relate to aggressive disease states and have superior test characteristics when compared with using CEA for surveillance of disease recurrence.[10,11] However, EVs are generated from both normal healthy cells as well as tumor cells; thus challenges with their specificity exist.

Circulating, disseminated neoplastic cells have great promise as a biomarker to provide information on disease burden, revealing a spectrum of tumor information including mutational status, tissue origin, RNA, as well as protein and cell signaling pathway activation. Conventionally defined circulating tumor cells (CTC) are neoplastic cells found in circulation that express tumor epitopes/protein but do not express immune identity.[12] In CRC, CTCs correlate with poorer disease-free survival and may predict metastatic potential when detected in higher numbers with specific molecular profiles.[13,14] However, the predominant limitation of CTCs remains their relative paucity in circulation; as few as 1–5 CTCs in 7.5 mL of peripheral blood are found in patients with a high tumor burden, exemplifying a significant limitation to their utility for robust genomic or phenotypic assessment.[15,16]

Recent investigations have identified novel populations of circulating neoplastic cells expressing both tumor and immune identity and are referred to as circulating hybrid cells (CHCs).[17–21] CHCs are defined by co-expression of epithelial markers (such as EPCAM and/or CK) and the pan-leukocyte antigen CD45. These cells express phenotypic and genotypic attributes of both neoplastic and immune cells and have increased tumorigenic and metastatic potential when compared with CTCs.[18] Importantly, CHCs are reliably found in peripheral blood at levels that are an order of magnitude greater than CTCs, across a wide number of malignancies, and are associated with disease progression and burden in CRC.[19,21–23] In a recent study, CHCs were longitudinally assessed in patients with rectal adenocarcinoma during treatment and were found to correlate with disease response to neoadjuvant therapy, whereas CEA levels remained unchanged.[21] Furthermore, in 2 patients with advanced, initially unresectable CRLM who were longitudinally analyzed for their CHC levels during hepatic arterial infusion (HAI) pump therapy, CHC levels decreased during periods of treatment response and subsequently increased before radiographic evidence of progression, whereas CEA remained low until late in the disease process.[21] Taken together, these data provide exciting evidence toward an important role for CHCs as a transformative blood-based biomarker for both surveillance of disease recurrence and an assessment of treatment response for patients with CRLM.

### *Adoptive T-Cell Therapies*

A diverse accumulation of infiltrating immune cells is a prominent feature of all cancers.[24,25] The immune system has the ability to recognize cancer cells and destroy established tumors by directing effector functions of cancer-killing T cells.[26,27] However, constraint of tumor T-cell

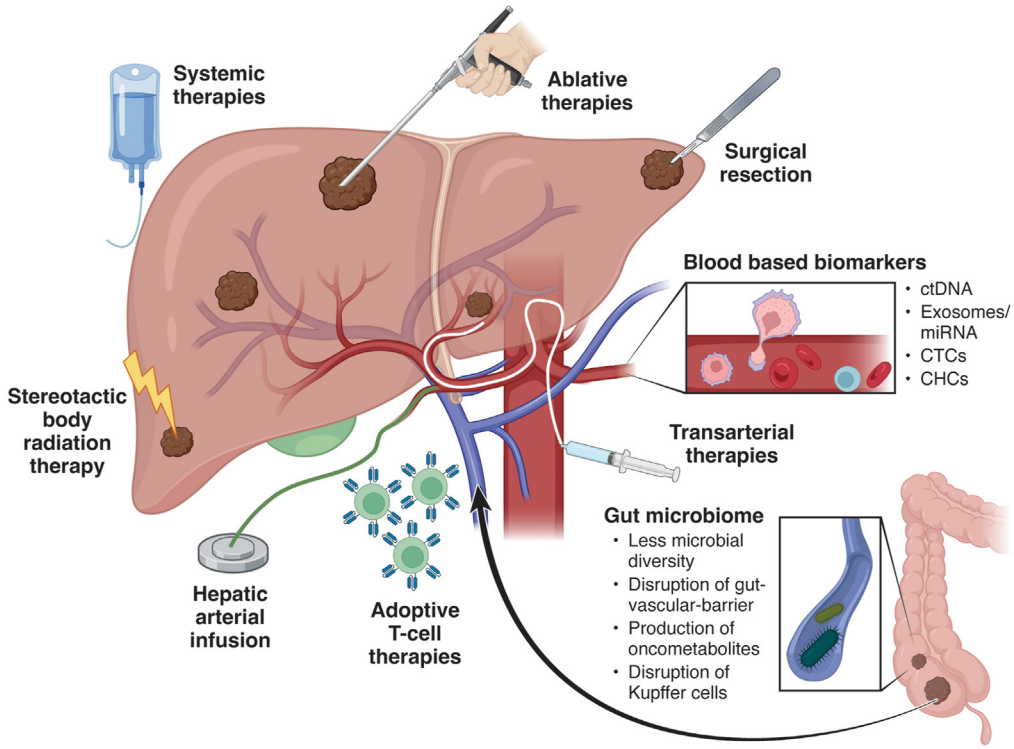


**Figure 1. Modern scientific and clinical paradigms in management and treatment options for patients with colorectal cancer liver metastases (CRLM).**

effector function underlies disease progression and contributes to therapeutic resistance to immune checkpoint blockade (ie, αPD-1, αCTLA4) and the T-cell transfer therapies (ie, chimeric antigen receptor [CAR], T-cell receptor [TCR], TIL).[27] In select solid cancers, such as melanoma, non-small cell lung cancer, and mismatch repair deficient CRC, immune checkpoint blockade has achieved significant overall response rates (ORR) of up to 50%, even in advanced disease.[28,29] However, in mismatch repair proficient (pMMR) CRCs, with a low tumor mutation burden and therefore neoantigen burden, response rates have been disappointing (reliably <10% ORR).[30,31]

An additional challenge to the application of immunotherapies in CRLM includes the phenomenon of immunodominant suppression observed in other settings of metastatic cancers to the liver. Liver metastases have been identified as a negative indicator for response to immune checkpoint inhibitors (ICI) in multiple trials involving various primary cancers.[32,33] In a cohort limited to metastatic CRC (mCRC), the presence of liver metastases was again associated with resistance to immune checkpoint therapy.[34] Approaches to improve checkpoint inhibitor efficacy in mCRC include combination with anti-angiogenic drugs, as reviewed by Maiorano et al.[35]

These data raise the possibility of a unique biology associated with liver metastases that prevents efficacy of therapies that rely on invigorating an endogenous immune response. One proposed mechanism suggests that tumor-specific cytotoxic T cells accumulate and undergo apoptosis in the liver, thereby hampering the anti-tumor immune response ICI aim to boost.[36] Another proposed mechanism includes T regulatory cells driving tolerance to tumor antigens, specifically when those antigens are present in the liver.[37] An additional, not mutually exclusive, explanation is that the unique immunologic hallmarks of the liver, including resident macrophages and significant numbers of natural killer and natural killer T cells,[38] constrain T-cell responses. Resolution of these hurdles will require novel combinations or approaches.

Adoptive T-cell transfer therapies represent a programmable and flexible alternative. T cells used in transfer for the treatment of solid cancer include those that target antigens unique to tumor cells and those that share expression with healthy tissues. In one scenario, a patient's own tumor-reactive T cells are isolated from their tumor, exponentially expanded ex vivo, and infused back into the patient. This approach is referred to as tumor infiltrating lymphocyte adoptive therapy and has been successful in patients with melanoma.[39,40] Another strategy relies on genetic engineering of autologous T cells to imbue the recognition of a cancer antigen (unique or shared). This strategy includes T cells that express an engineered TCR or CAR. The most clinically successful case is CD19 CAR-T cells (76% ORR), of which there are 6 Food and Drug Administration–approved treatments for treatment-resistant hematologic malignancies.[41]

The potential of adoptive T-cell therapy in the setting of mCRC is nicely illustrated by 2 examples. In one case, a patient with CRC metastatic to the lung had their own tumor reactive T cells expanded ex vivo and reinfused, resulting in shrinkage of all lung lesions.[42] In the second example, patient cells were engineered to express a TCR against CEA,

which is overexpressed in mCRC.[43] In both patients, serum CEA decreased after engineered cell infusion, and one patient had measurable decrease in liver lesion size.

The current limitation to the widespread adoption of CAR-T cell therapy in solid cancers, including patients with CRLM, is treatment-induced toxicity. For example, all of the patients who received cells engineered with a CEA-targeting TCR developed severe, dose-limiting colitis. This was a result of on-target, off-tumor toxicity: the engineered T cells attacked any cells expressing CEA, which include the healthy colonic epithelium. This example is emblematic of the larger problem; most engineered T cells target a shared antigen, which is overexpressed in cancer and also may be found on healthy cells in the body. As a result, on-target off-tumor toxicity is a major barrier to implementation; efforts are underway to limit this toxicity.[44] If successful, strategies to limit on-target, off-tumor toxicity will unleash the potential of adoptive cell therapy for treating patients with CRLM.

*Tumor Microbiome.* The gut microbiome refers to the collective group of microorganisms (ie, bacteria, virus, and fungi) inhabiting the gastrointestinal tract and producing metabolites vital to human health. Whereas gut dysbiosis has been implicated in the development of CRC, recent evidence supports an association between the gut microbiome and the development of CRLM, postulated to be influenced by enterohepatic circulation directly linking the gastrointestinal tract to the liver. Sun et al[45] found that patients with mCRC had significantly decreased microbial diversity, and in the subset of patients with CRLM, there was an enrichment of select species of bacteria including *Fusobacterium* specifically. Perhaps even more compelling, Bullman et al[46] demonstrated that patients who have a primary CRC with synchronous liver metastases exhibit concordant intratumoral microbial genera in the primary and metastatic sites, with a similar enrichment of *Fusobacterium* species. In addition, Chen et al[47] reported that the abundance of fecal *Fusobacterium* is significantly increased in patients with intact primary CRC with synchronous CRLM compared with patients without metastatic disease. Taken together, these studies suggest that decreased intestinal microbial diversity and potentially a predominance of *Fusobacterium* species are associated with the development of CRLM development.

A number of groups have investigated underlying mechanisms for how the microbiome influences the development of CRLM. The gut-vascular barrier (GVB), presence of microbiome-produced oncometabolites, and microbiome-induced Kupffer cell reduction are identified as potential drivers of metastasis.[48–55] The GVB regulates the exposure of metabolites and microorganisms between the intestinal epithelial layer and the systemic circulation. Damage to the GVB leads to systemic inflammation and may promote CRLM development.[48,49] Bertoochi et al[48] identified a specific strain of *Escherichia coli* (C17) that directly disrupts the GVB, promoting bacterial translocation to the liver, to form a premetastatic niche. The authors hypothesize this creates a pro-tumorigenic inflammatory milieu potentially favoring the development of liver metastases.

Specific gut-derived oncometabolites have been implicated in the development of CRLM. Formate is a metabolite derived from a variety of bacteria, including *Fusobacterium*, and has been shown to increase the invasive potential of CRC cells in experimental models by inducing stem cell traits that propagate metastasis.[52] D-2-hydroxyglutarate, a by-product of cancer-cell glutamine metabolism, was shown to directly induce epithelial-mesenchymal transition in colorectal cancer cells.[50] Kynurenine, a metabolite of tryptophan, was found to regulate the growth-promoting genes in colon cancer cells.[53] Taken together, these 3 oncometabolites may drive the development of CRLM within the microbial milieu.

Kupffer cells are resident liver macrophages hypothesized to play a role in cancer progression. These cells are able to undergo M1 (pro-inflammatory) and M2 (anti-inflammatory) repolarization.[51] Although the gut-liver-Kupffer cell interaction is complex and incompletely understood, there is evidence to suggest that Kupffer cells have inhibitory and stimulatory roles in tumor development. Murine Kupffer cell-depletion models demonstrate this bimodal effect, with Kupffer cells exhibiting an early inhibitory function and a later stimulatory effect on tumor growth.[54] Furthermore, inoculation with *Proteus mirabilis* inhibited Kupffer cell proliferation, promoting an increased risk of developing liver metastases in murine models, whereas inoculation of *Bacteroides vulgatus* significantly increased Kupffer cell proliferation, leading to a decrease in liver metastases development.[55]

## Clinical Progress in CRLM

### Hepatic Resection

Despite only a minority of patients being candidates, hepatic resection of liver metastases remains the only curative treatment modality in the management of patients with CRLM. For a patient to be considered resectable, the liver remaining after resection must have intact hepatic arterial and portal venous inflow along with intact biliary and hepatic venous outflow in a liver volume sufficient to support physiological function. In a series of more than 1000 patients Scheele et al[56] reported a median OS of 7 months and 15 months in patients with unresected and resected CRLM, respectively. For patients who had resections with negative liver parenchymal margins, the median survival increased to 30 months with 5-year OS of 38%. In a follow-up study by the same group, 5 years later, for patients resected with negative margins, the authors reported 5- and 10-year OS of 40% and 24%, respectively, with a recurrence-free survival of 34% at 5 years.[57] These data were reported in the 1990s and have since been validated by several high-volume institutions with modern chemotherapy regimens.[58–60] In the current era, treatment with cytotoxic chemotherapy alone without hepatic resection has reached 10%–12% OS at 5 years as compared with 5-year OS of 40%–60% when patients with CRLM have their metastatic disease resected as part of their management.[61–63]

Recurrence of metastatic disease after the initial hepatic resection of CRLM occurs in upward of 50%–60% of patients, with intrahepatic recurrence being the predominant site in 20%–47% of patients.[5,64,65] The phenomenon of

disease recurrence after a curative intent resection of all radiographically and intraoperative disease is reflective of the undoubted occult micrometastatic disease burden that is not visualized and addressed during an operation. For patients with recurrent CRLM, when limited to the liver and technically feasible, repeat resection is safe and is associated with an improvement in OS compared with treatment with chemotherapy alone.[65] Although no randomized controlled trials have investigated this, several retrospective studies have demonstrated 5-year OS from 30% to 50% after repeat resection.[61,65–67] In a retrospective review of 488 patients, Neal et al[68] demonstrated 3- and 5-year OS of 82% and 48%, respectively, in those undergoing repeat resections for CRLM liver recurrence, compared with 46% and 32% for those who did not; median survival was 59 months compared with 33 months, favoring those who underwent repeat resection. Furthermore, de Jong et al[61] demonstrated 5-year OS of 33% and 24% for first and second repeat hepatic resections, respectively. It is important to note that patient selection and disease biology are important factors in predicting long-term outcomes, because patients with good clinical performance status, longer disease-free intervals, and solitary lesions tend to have improved survival outcomes with hepatic resection.[69] These considerations are essential for a disease where there are now 2 phase III trials randomizing patients with resectable CRLM to hepatic resection alone compared with perioperative treatment with modern chemotherapy regimens that do not show an OS benefit with the addition of chemotherapy.[70,71]

*Systemic Therapies and Molecular Profiling.* Current treatment guidelines for patients with CRLM recommend first-line chemotherapy with fluoropyrimidines (5-fluorouracil [FU], capecitabine), oxaliplatin, and/or irinotecan delivered as either doublet (FOLFOX, CAPOX, FOLFIRI) or triplet (FOLFOXFIRI) regimens. In the last 15 years, these cytotoxic chemotherapy regimens have often included the addition of monoclonal antibodies targeting epidermal growth factor receptor (EGFR) (ie, cetuximab, panitumumab) or angiogenesis (ie, anti-vascular endothelial growth factor receptor [ie, bevacizumab]).[72,73] However, the specific regimen, timing, and duration of therapy are nuanced because treatment management must account for several patient-specific factors (ie, surgical resectability, performance status, hepatotoxicity risk, right-sided versus left-sided primary CRC disease, and mutational profile from next generation sequencing). All of these factors are weighed together along with the patient's overall clinical goals including prolonging survival, disease down-staging to facilitate a potential hepatic resection, or for palliative intent.

For patients with upfront technically resectable CRLM, perioperative chemotherapy is associated with improved progression free survival (PFS) of upward of 10% at 5 years but no difference in OS as demonstrated in the European Organization for Research and Treatment of Cancer (EORTC) 40983 and JCOG0603 randomized phase III clinical trials.[70,71] However, for patients with resectable CRLM, preoperative chemotherapy is used in many centers throughout the world to "test the disease biology" and often helps facilitate liver resection with maximal parenchymal perseveration to minimize postoperative morbidity. Combining chemotherapy with EGFR or vascular endothelial growth factor receptor blockade is a well-documented approach for disease downsizing in patients with CRLM initially considered unresectable.[74,75] For patients with initially unresectable disease that is microsatellite stable (MSS)/pMMR, doublet regimens (FOLFOX or FOLFIRI) are recommended as a first-line strategy. The choice of targeting EGFR or angiogenesis is largely influenced by mutational status and primary CRC disease sidedness.[76] For example, constitutive downstream signaling in RAS or BRAF mutant tumors renders tumors insensitive to EGFR-based therapy and should be avoided.[72,77] Likewise, first-line anti-EGFR containing chemotherapy regimens are not recommended for patients with mCRC originating from right-sided primary tumors, which are characterized by wild-type KRAS/NRAS or BRAF mutations.[78,79] In contrast, for patients with RAS wild-type, primarily non-resectable mCRC, combined treatment with FOLFOXIRI and panitumumab converted 75% of patients to resectable, as compared with 36% of patients who received FOLFOXIRI alone.[75] However, the toxicity of the triplet chemotherapy regimen warrants careful patient selection.[79]

For patients with unresectable CRLM, treatment is largely with doublet or triplet chemotherapy regimens, often combined with an agent targeting EGFR or angiogenesis. A meta-analysis of 5 phase II or III randomized controlled trials shows a strong association with improved clinical outcomes among patients with mCRC who receive FOLFOXIRI and bevacizumab as compared with doublet regimens with bevacizumab, with a doubling of the estimated 5-year OS (22% vs 11%) for patients treated with FOLFOXIRI with bevacizumab.[80–82] Patient selection and support of side effects during this chemotherapy regimen are paramount because there can be a frequent occurrence of diarrhea, neurotoxicity, and neutropenia with younger and more fit patients with right-sided and/or RAS-mutated CRC thought best able to tolerate and derive the most benefit from this more intensive first-line regimen.[80] Treatment options for patients who are not candidates for intensive doublet or triplet chemotherapy include 5-FU or capecitabine with or without bevacizumab or irinotecan alone.[73,83] Findings from the recent PANDA trial suggest that 5-FU with panitumumab may provide yet another alternative for elderly patients with RAS/BRAF wild-type mCRC and CRLM.[84]

Current guidelines recommend completion of next generation sequencing from the primary CRC or CRLM biopsy at the outset of metastatic disease diagnosis. This facilitates consideration of possible targeted treatment options relating to KRAS, NRAS, BRAF, TP53, PIK3CA, APC, HER2 amplification (ERBB2), neurotrophic tyrosine receptor kinase, rearranged during transfection (RET) fusions, as well as high microsatellite instability (MSI-H) and deficient MMR.[73] The continued improvements in the identification of biomarkers and altered molecular pathways have enabled optimization of existing treatment strategies, as well as development of novel targets that can be therapeutically exploited, including those previously thought to be undruggable. Recently, there has been significant work in the development of inhibitors targeting tumors harboring

KRAS mutations, such as adagrasib and sotorasib, that selectively inhibit KRAS G12C.[85–89] As a monotherapy, targeting KRAS G12C alone may not be an ideal strategy because adaptive feedback within the RAS-MAPK signaling pathway may provide a mechanism of resistance.[90] Rather, several ongoing trials are examining targeting of KRAS G12C in combination with EGFR inhibition. In the phase II CodeBreak-101 trial, the combination of sotorasib and panitumumab in 26 patients with KRAS G12C mCRC achieved ORR of 30% and median PFS (mPFS) of 6 months.[89] Comparably, the phase I/II KRYSTAL trial combining adagrasib and cetuximab was associated with ORR of 46% and mPFS of 7 months.[88] Although KRAS G12C mutations comprise only 7% of all colorectal cancer, the ability to effectively target this mutation marks an important milestone for treating this small subset of patients. These advancements have aided the development of newer agents targeting other KRAS mutations, including the more common KRAS G12D.[90,91]

Patients with BRAF mutations represent another small subset that may benefit from targeted therapy.[92] Found in approximately 10% of CRC cases, BRAF V600E mutations occur more commonly in RAS wild-type and right-sided tumors. On the basis of findings from the BEACON trial, targeting BRAF mutant CRC with the oral tyrosine kinase inhibitor, encorafenib, in combination with cetuximab is a Food and Drug Administration–approved second-line therapy.[92] Building on this, the BREAKWATER trial is currently examining this combination in previously untreated mCRC with or with chemotherapy.[93] Encouraging preliminary findings from 12 mCRC patients with BRAF V600E mutations receiving treatment in the first-line setting showed that encorafenib in combination with cetuximab and mFOLFOX6 achieved ORR of 75%.[93] Additional correlative analyses also suggest there is an increase in T-cell infiltration after BRAF inhibition; subsequent trials are exploring the combination of BRAF inhibition with immunotherapy.[94,95]

The current use of immunotherapy for CRC is largely limited to a small subset (~5%) of patients with MSI-H/dMMR cancers. The addition of immune checkpoint blockade to upfront chemotherapy (with or without anti-EGFR or anti-angiogenic agents) confers significant clinical benefit for this subset of patients.[96–99] Findings from the KEYNOTE-177 trial show that anti-PD-1 antibody, pembrolizumab, in combination with chemotherapy (with or without bevacizumab or cetuximab) achieves a nearly doubled mPFS (17 months) compared with chemotherapy alone (8 months). Importantly, the median OS was not reached for patients receiving pembrolizumab, whereas the mOS was 37 months among those given traditional systemic therapy.[96,97] Likewise, in the CheckMate-142 trial, first-line treatment with the combination of anti-PD-1, nivolumab, and anti-CTLA4, ipilimumab, yielded 2-year PFS and OS rates of 51% and 72%, respectively.[98,99] This combination of nivolumab and ipilimumab provides a treatment option for when potential toxicity from chemotherapy is concerning in patients with poor functional status. Unfortunately, for the majority of patients with MSS/pMMR tumors, attaining robust and durable responses using current immunotherapy strategies has not been successful.[100–103] Ongoing efforts to improve immunotherapy options for patients with mCRC having MSS/pMMR include combinatorial approaches leveraging chemotherapy, angiogenesis blockers, and other targeted therapies.[102,104,105]

## Ablative Therapies

A growing body of evidence has supported the integration of thermal ablation into the treatment paradigm of patients with CRLM. A number of ablative techniques exist and are offered through percutaneous, laparoscopic, or open surgical techniques. The 2 most common modalities are radiofrequency ablation (RFA) and microwave ablation (MWA), which both induce coagulative tissue necrosis through inducing locally directed hyperthermia. In addition, irreversible electroporation (IRE) has emerged as a nonthermal ablative modality that can safely ablate small tumors adjacent to sensitive ductal and vascular structures, such as central tumors near the biliary tree, without damage to these structures, allowing for preserved hepatic function of the involved liver.[106] The experience with the newer technologies of MWA and IRE is more limited with few direct head-to-head prospective comparisons.[107] Similar outcomes to RFA have generally been reported, and outcomes from RFA are thought to extrapolate to MWA as a closely related thermal ablation modality.[108] Although IRE has proportionally most limited data regarding treatment outcomes, it is a modality that has a niche application, with outcomes to date suggesting similar outcomes to standard thermal ablative techniques.[109] Regardless of the modality used, careful patient selection and application of technique are crucial to effective outcomes. Achieving a suitable ablation margin of at least 5–10 mm has also been shown to correlate with more effective tumor control and recurrence-free intervals.[108,110]

Tumor ablation most conventionally is a treatment option for nonsurgical candidates, such as those who are unable to proceed with hepatic resection because of tumor location, medical comorbidities, and insufficient future liver remnant. In a randomized phase II clinical trial comparing systemic therapy alone versus systemic therapy combined with RFA for those with unresectable CRLM, Ruers et al[111] demonstrated improved 3-year PFS in patients receiving combined treatment when compared with systemic therapy only (28% vs 11%). A follow-up analysis in the same cohort demonstrated 3-, 5-, and 8-year OS of 57%, 43%, and 36% in the combined arm, as compared with 55%, 30%, and 9%, respectively.[112] Similarly, Solbati et al[113] evaluated long-term survival outcomes with systemic therapy plus RFA in a cohort of patients not eligible for surgical resection and demonstrated 5- and 10-year survival of 48% and 18%, respectively. It is important to note that regardless of modality, ablative therapies are typically most effective with solitary or few lesions that are relatively small (<3 cm), are not located near large blood vessels (heat sink effect), and with complete ablation of the entire lesion with sufficient ablation margins, because these factors are associated with decreased local recurrence.[110,112]

There is growing evidence to suggest a role for tumor ablation for lesions that are technically resectable, in conjunction with surgical resection or possibly alone. Percutaneous thermal ablation offers several benefits as compared with hepatic resection; it is typically an outpatient procedure, associated with less post-procedural morbidity, can preserve more healthy hepatic parenchyma, and may have similar long-term survival outcomes in carefully selected patients. In a multicenter retrospective review, Evrard et al[114] reported on the safety and efficacy of combined intraoperative ablation and hepatic resection, with reported 5-year OS of 45%. Data comparing hepatic resection head-to-head against thermal ablation are difficult to interpret because of their retrospective and inherently biased nature. One systematic review of the literature suggested similar survival in those undergoing surgical resection as compared with RFA with systemic chemotherapy or MWA alone.[115] However, a separate meta-analysis suggested a lower complication rate associated with RFA when compared with surgical resection, although also an associated lower OS.[116] Although it is clear that ablative therapies play an integral role in the management of CRLM, more data are needed to define the scope of these therapies. Randomized prospective clinical trials are ongoing to accurately assess hepatic resection vs thermal ablation in those with CRLM (eg, COLLISION trial; NCT03088150).

## Hepatic Arterial Infusion

For patients with multifocal, unresectable CRLM, treatment with systemic chemotherapy remains an essential cornerstone of disease management. However, treatment with chemotherapy can be associated with intolerable side effects and toxicities. HAI offers liver-directed regional therapy with the potential to provide maximal disease control while minimizing systemic toxicity. The delivery of HAI chemotherapy is facilitated by surgical implantation of a chemotherapy pump into the abdominal wall with a connected intra-abdominal catheter sutured into the hepatic arterial system. The HAI pump reservoir is subsequently filled with chemotherapy, which is then delivered as fixed daily dose.[117] Treatment with HAI exploits tumor biology to provide maximal treatment to cancer cells in the liver, because normal hepatocytes derive a majority of their blood supply from the portal venous system, whereas cancer cells derive their blood supply predominantly from the hepatic arterial system.[118] In addition, chemotherapeutic agents with optimal pharmacokinetic profiles are favored as HAI agents. For example, floxuridine is the most commonly used agent because of its pharmacokinetic characteristics including a high first-pass extraction and short plasma half-life that result in a 400-fold greater hepatic drug exposure compared with systemic delivery, with minimal systemic toxicity.[119,120]

In patients with unresectable CRLM, treatment with HAI floxuridine alone compared with systemic 5-FU has demonstrated an increased median OS (24 vs 20 months, $P = .0034$).[121] However, current therapeutic strategies involve using HAI in conjunction with systemic therapy to maximize hepatic disease response for both disease control and conversion to resectability, although randomized prospective data evaluating this strategy are lacking at present. This will be investigated in the upcoming EA222 PUMP trial (NCT05863195), which will randomize patients with unresectable CRLM in a 2:1 fashion to combined treatment with HAI floxuridine and systemic therapy or to treatment with continued systemic therapy alone. In addition, for patients with unresectable CRLM, HAI is emerging as an effective therapeutic strategy to facilitate downstaging of the liver disease to allow for complete hepatic clearance of the metastases.[122] Kemeny et al[123] reported on their experience of 49 patients with unresectable CRLM treated with HAI floxuridine in combination with modern systemic chemotherapy. Liver-directed therapy allowed conversion to resection in 23 patients (47% overall conversion to resection) and 45 patients having either partial or complete radiologic responses. Both patients who were chemotherapy-naive and previously treated patients had significant response rates to therapy (100% and 85% response rates, respectively). Patients who were chemotherapy-naive also had longer median overall survival of 51 months vs 35 months ($P = .02$). Ultimately, by providing maximal treatment to patients with unresectable disease, the integration of HAI therapies can offer superior response rates and facilitate the ultimate goal of hepatic resection to offer the best chance at long-term survival.

## Transarterial Therapies

Percutaneous transarterial therapies for liver cancers grew as an extension of HAI therapy, with the earliest experiences in the 1970s and 1980s.[124,125] The recognition that transarterial therapy in the liver was well-tolerated and potentially more efficacious than intravenous drug delivery, along with the developing technology of embolization to concomitantly disrupt tumor blood supply, spurred the growth of transarterial chemoembolization (TACE). Despite the conceptual benefit of transarterial therapy, the primary indication remains palliation for disease refractory to systemic chemotherapy. Various chemotherapeutic drugs have been used in the setting of TACE for CRLM with variable outcomes.[126] Treatment with irinotecan-loaded polymer microspheres has been one of the more modern iterations of TACE for colorectal liver metastases, with favorable safety and efficacy relative to historical standards.[127] However, the role of TACE in the palliative setting and the heterogeneity of clinical protocols limit the granularity of data with which to compare this strategy with others.

Transarterial radioembolization, most commonly using the beta-emitter, yttrium-90 (Y90), has rapidly grown in use for primary liver cancers such as hepatocellular carcinoma and intrahepatic cholangiocarcinoma but has been used in patients with CRLM since the early 2000s. As a form of very high-dose brachytherapy leveraging delivery via the primary arterial blood supply of hepatic tumors, radioembolization has been shown to be safe and well-tolerated in select patients.[128] The first Food and Drug Administration-–approved indication for Y90 radioembolization was for the treatment of

CRLM. This indication was based on a phase III randomized controlled trial that demonstrated improved radiographic objective response rates, biochemical response rates, and PFS comparing transarterial delivery of Y90 to the liver with concomitant hepatic arterial chemoinfusion therapy with hepatic arterial chemoinfusion therapy alone.[129] Use of Y90 radioembolization for CRLM has subsequently been studied in first-line, second-line, and salvage settings.[128,130–132] For chemorefractory disease, radioembolization has been shown to be safe and well-tolerated and results in improved OS compared with supportive care by historical controls in observational retrospective studies.[128] Recent prospective randomized controlled trials have assessed the role of radioembolization with concomitant systemic therapy in both first- and second-line treatment of mCRC with liver-only or liver-dominant disease.[130–132] Outcomes using radioembolization as part of first-line treatment have thus far shown no benefit over systemic therapy alone for OS, with the possible exception of metastatic disease from a right-sided colonic primary.[130,132] In the second-line, a recent trial reached its intended endpoint with improved PFS with radioembolization and systemic therapy compared with systemic therapy alone, with a similar safety profile.[131] However, overall survival remained similar between the 2 strategies. Thus, despite prolonged recurrence-free survival in the liver, at present there is not enough evidence to suggest that use of Y90 will impact OS compared with other therapeutic options. Ongoing strategies regarding delivery technique, sequencing of treatments, and potential synergy with immunotherapy remain areas of active investigation.[133]

## Stereotactic Body Radiation Therapy

Stereotactic body radiation therapy (SBRT) is a highly focused outpatient delivery of noninvasive but potent radiation therapy doses to the tumor while minimizing radiation dose to surrounding organs at risk. Although SBRT has not been directly compared with other liver-directed therapy modalities for the treatment of CRLM, there are a multitude of prospective clinical trials reporting on its safety and local control capabilities.[134–136] A pooled analysis of multiple studies assessing SBRT local control for a total of 290 liver metastases revealed that higher vs lower biological effective doses yielded higher 1- (96% vs 84%), 2- (93% vs 70%), and 3-year (93% vs 65%) local control,[137] suggesting a relative radio-resistance of CRLM as compared with primary liver cancers.

There are limited reported randomized clinical trials for patients with oligometastatic colorectal cancer comparing chemotherapy alone with chemotherapy plus local therapy for metastases for any modality, surgical or nonsurgical. The SABR-COMET trial was an international randomized phase II clinical trial of 99 patients with primary cancers controlled with systemic therapy and 1–5 metastatic lesions amenable to SBRT. Patients were randomized in 1:2 ratio between palliative standard of care (SOC) treatments and SOC plus SBRT to all metastatic lesions. All cancer histologies were included (CRC in 27% in SOC arm and 14% in SOC plus SBRT arm) with an over-representation of breast and prostate cancers. Most common sites of metastases were bone and lung, with nearly 20% of patients harboring liver metastases. The addition of SBRT to SOC treatments (chemotherapy) improved 5-year OS from 18% to 42% ($P = .006$), with a limited sample size preventing any conclusions to be drawn from the CRLM only disease cohort.[138] Larger and confirmatory phase III trials of SBRT in the oligometastatic setting are ongoing and will include patients with CRLM.[139]

Liver SBRT in patients without cirrhosis is well-tolerated, with a minimal risk of radiation-induced liver disease for properly selected patients with sufficient liver volumes. Proximity of metastatic lesions (<5 mm) to radiosensitive endoluminal organs poses the greatest challenge to safely delivering SBRT. However, respiratory motion management and image-guided techniques with or without fiducial markers may allow for smaller treatment margins and resultant minimization of ablative doses to surrounding organs. More recently, development of on-treatment magnetic resonance image guidance with MR-Linac technologies has allowed for more superior and real-time soft tissue visualization that may in turn allow for even smaller and safer setup margins. Similar to percutaneous thermal ablative techniques and transcatheter arterial treatments, SBRT can be used in conjunction with resection in patients with short-interval radiographic recurrence after hepatic resection as part of a multidisciplinary approach to eradicate liver metastases.

## Quality of Life and Survivorship Considerations

Having cancer has an unquestionable negative impact on the quality of life (QOL) of patients, which is related to the disease process itself, symptoms, treatment used, and sociodemographic factors.[140,141] The concept of QOL is multidimensional and defined as “an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns”.[142] Importantly, QOL embodies the wholeness of a person’s experience and includes physical (ie, pain, sleep), psychological (ie, anxiety, depression), social (ie, roles, finances), and spiritual domains (ie, meaning of illness).[143,144]

As a patient-reported outcome (PRO), QOL assessments are being integrated into clinical trials but in a limited capacity at present. For patients with mCRC, QOL is not adequately captured and is absent in a high portion of seminal publications including recent randomized trials.[145] In a recent published literature review on QOL assessment and reporting in phase III trials for patients with CRC, QOL was not listed among endpoints in 41 of 67 publications.[145] In 12 of 18 mCRC trials with OS as the primary endpoint and in 20 of 29 trials with other endpoints (PFS, treatment response), no QOL data were available.[145] Because of the modest benefit in OS with repeat hepatic resection compared with chemotherapy alone and the larger impact on PFS, there are important QOL and survivorship considerations. PRO measures reflecting the “time toxicity” of amount of time patients spend in the infusion unit and the cumulative side effects associated with systemic treatment

deserve attention. These considerations are essential for a disease where there are now 2 randomized trials that do not show an overall survival benefit with the addition of perioperative chemotherapy for patients with resectable CRLM, although they do suggest a 15% incidence of permanent neuropathy as related to oxaliplatin-based therapy.[146] The only potential benefit is a modest improvement in recurrence-free survival that may come at the expense of significant treatment toxicity and an impact on the QOL for patients and their families.

The most commonly used measures to assess QOL for patients with cancer include the EORTC QOL Questionnaire (EORTC QLQ-C30),[147] the Functional Assessment of Cancer Therapy-General (FACT-G),[148] the EuroQOL-5D,[147] and the Medical Outcome Study Short Form.[149] The EORTC QLQ-C30 and the FACT-G are cancer specific, whereas the EuroQOL-5D and Medical Outcome Study Short Form can be used with different diseases. To capture symptoms specific to patients with CRC and CRLM the EORTC QLQ-CR29 or the EORTC QLQ-LMC21 are also used, which cover CRC-specific questions and symptoms related to liver metastases including activity and nutritional experiences, respectively. Importantly, these measures assess physical, psychological, and social QOL domains, with a lack of attention to spirituality. Although data have been mixed, studies have reported positive correlations between spirituality and mental and physical health.[150] These findings speak to the importance of including spirituality as a specific domain in QOL assessments. In a qualitative study of patients with mCRC receiving non-curative chemotherapy, the authors report that patients used cognitive, affective, and behavioral strategies to increase spiritual well-being as changes occurred in their life. Most patients focused on achievable positive goals and adjusted long-term goals.[143]

Future research should include the development of well-designed and validated QOL measures addressing the needs of patients with mCRC and specifically CRLM. Furthermore, incorporating the collection of qualitative data (ie, interviews) as essential endpoints in clinical trials will provide in-depth patient perspectives on how they define QOL, how the domains of QOL play into the most relevant considerations and goals of their choice of treatment, and how each domain may change over time. Combining results from quantitative and qualitative patient QOL assessments allows the treatment team to consider the impacts of treatment benefits, safety, feasibility, and tolerability to provide a more granular insight to guide treatment selection and decisions that are patient centered.

## Conclusions and Future Directions

Patients with CRLM have an unquestionably unique disease biology among those with stage IV cancers. Compared with other patients with stage IV gastrointestinal cancers, treatment of the metastatic disease in the liver can confer upward of 20% cure with no evidence of disease at 10 years in carefully selected patients. The efforts to understand these exceptional responders have led to numerous novel scientific discoveries and to the evolution of clinical paradigms all directed to improve the outcome of patients diagnosed with CRLM. In the era of molecular profiling, it remains clear that a one-size-fits-all approach is ineffective for the spectrum of cancer biology contained within the broad category of CRLM. We believe a multidisciplinary treatment strategy should be tailored to the individual patient and their unique cancer biology. Ultimately, we need to support ongoing basic scientific investigations having the potential to translate discovery from the bench to patients to improve the clinical outcomes for patients with CRLM.

## References


1. Xi Y, Xu P. Global colorectal cancer burden in 2020 and projections to 2040. Transl Oncol 2021;14:101174.
2. Calderon Novoa F, Ardiles V, de Santibañes E, et al. Pushing the limits of surgical resection in colorectal liver metastasis: how far can we go? Cancers (Basel) 2023:15.
3. Dawood O, Mahadevan A, Goodman KA. Stereotactic body radiation therapy for liver metastases. Eur J Cancer 2009;45:2947–2959.
4. Muratore A, Zorzi D, Bouzari H, et al. Asymptomatic colorectal cancer with un-resectable liver metastases: immediate colorectal resection or up-front systemic chemotherapy? Ann Surg Oncol 2007;14:766–770.
5. de Jong MC, Pulitano C, Ribero D, et al. Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1669 patients. Ann Surg 2009; 250:440–448.
6. Zarour LR, Anand S, Billingsley KG, et al. Colorectal cancer liver metastasis: evolving paradigms and future directions. Cell Mol Gastroenterol Hepatol 2017;3:163–173.
7. Ito S, Hibi K, Nakayama H, et al. Detection of tumor DNA in serum of colorectal cancer patients. Jpn J Cancer Res 2002;93:1266–1269.
8. Liu W, Jin KM, Zhang MH, et al. Recurrence prediction by circulating tumor DNA in the patient with colorectal liver metastases after hepatectomy: a prospective biomarker study. Ann Surg Oncol 2023.
9. Newhook TE, Overman MJ, Chun YS, et al. Prospective study of perioperative circulating tumor DNA dynamics in patients undergoing hepatectomy for colorectal liver metastases. Ann Surg 2022.
10. Matsumura T, Sugimachi K, Iinuma H, et al. Exosomal microRNA in serum is a novel biomarker of recurrence in human colorectal cancer. Br J Cancer 2015;113:275–281.
11. Ogata-Kawata H, Izumiya M, Kurioka D, et al. Circulating exosomal microRNAs as biomarkers of colon cancer. PLoS One 2014;9:e92921.
12. Strati A, Markou A, Kyriakopoulou E, et al. Detection and molecular characterization of circulating tumour cells: challenges for the clinical setting. Cancers (Basel) 2023:15.
13. Messaritakis I, Sfakianaki M, Papadaki C, et al. Prognostic significance of CEACAM5mRNA-positive circulating tumor cells in patients with metastatic colorectal cancer. Cancer Chemother Pharmacol 2018;82:767–775.
14. Tsai WS, Chen JS, Shao HJ, et al. Circulating tumor cell count correlates with colorectal neoplasm progression and is a prognostic marker for distant metastasis in non-metastatic patients. Sci Rep 2016;6:24517.

15. Hardingham JE, Grover P, Winter M, et al. Detection and clinical significance of circulating tumor cells in colorectal cancer: 20 years of progress. Mol Med 2015;21-(Suppl 1):S25–S31.
16. Miller MC, Doyle GV, Terstappen LW. Significance of circulating tumor cells detected by the cellsearch system in patients with metastatic breast colorectal and prostate cancer. J Oncol 2010;2010:617421.
17. Clawson GA. Cancer: fusion for moving. Science 2013; 342:699–700.
18. Gast CE, Silk AD, Zarour L, et al. Cell fusion potentiates tumor heterogeneity and reveals circulating hybrid cells that correlate with stage and survival. Sci Adv 2018;4: eaat7828.
19. Parappilly MS, Chin Y, Whalen RM, et al. Circulating neoplastic-immune hybrid cells predict metastatic progression in uveal melanoma. Cancers (Basel) 2022;14.
20. Pawelek JM, Chakraborty AK. The cancer cell: leukocyte fusion theory of metastasis. Adv Cancer Res 2008; 101:397–444.
21. Walker BS, Sutton TL, Zarour L, et al. Circulating hybrid cells: a novel liquid biomarker of treatment response in gastrointestinal cancers. Ann Surg Oncol 2021; 28:8567–8578.
22. Dietz MS, Sutton TL, Walker BS, et al. Relevance of circulating hybrid cells as a non-invasive biomarker for myriad solid tumors. Sci Rep 2021;11:13630.
23. Henn TE, Anderson AN, Hollett YR, et al. Circulating hybrid cells predict presence of occult nodal metastases in oral cavity carcinoma. Head Neck 2021; 43:2193–2201.
24. Palucka AK, Coussens LM. The basis of oncoimmunology. Cell 2016;164:1233–1247.
25. Tsujikawa T, Kumar S, Borkar RN, et al. Quantitative multiplex immunohistochemistry reveals myeloid-inflamed tumor-immune complexity associated with poor prognosis. Cell Rep 2017;19:203–217.
26. Rosenberg SA, Restifo NP. Adoptive cell transfer as personalized immunotherapy for human cancer. Science 2015;348:62–68.
27. Waldman AD, Fritz JM, Lenardo MJ. A guide to cancer immunotherapy: from T cell basic science to clinical practice. Nat Rev Immunol 2020;20:651–668.
28. Cercek A, Lumish M, Sinopoli J, et al. PD-1 blockade in mismatch repair-deficient, locally advanced rectal cancer. N Engl J Med 2022;386:2363–2376.
29. Tumeh PC, Hellmann MD, Hamid O, et al. Liver metastasis and treatment outcome with anti-PD-1 monoclonal antibody in patients with melanoma and NSCLC. Cancer Immunol Res 2017;5:417–424.
30. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015; 372:2509–2520.
31. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. Lancet Oncol 2017;18:1182–1191.
32. Bilen MA, Shabto JM, Martini DJ, et al. Sites of metastasis and association with clinical outcome in advanced stage cancer patients treated with immunotherapy. BMC Cancer 2019;19:857.
33. Topalian SL, Hodi FS, Brahmer JR, et al. Five-year survival and correlates among patients with advanced melanoma, renal cell carcinoma, or non-small cell lung cancer treated with nivolumab. JAMA Oncol 2019; 5:1411–1420.
34. Wang C, Sandhu J, Ouyang C, et al. Clinical response to immunotherapy targeting programmed cell death receptor 1/programmed cell death ligand 1 in patients with treatment-resistant microsatellite stable colorectal cancer with and without liver metastases. JAMA Netw Open 2021;4:e2118416.
35. Maiorano BA, Parisi A, Maiello E, et al. The interplay between anti-angiogenics and immunotherapy in colorectal cancer. Life (Basel) 2022;12.
36. Yu J, Green MD, Li S, et al. Liver metastasis restrains immunotherapy efficacy via macrophage-mediated T cell elimination. Nat Med 2021;27:152–164.
37. Lee JC, Mehdizadeh S, Smith J, et al. Regulatory T cell control of systemic immunity and immunotherapy response in liver metastasis. Sci Immunol 2020;5.
38. Gao B. Basic liver immunology. Cell Mol Immunol 2016; 13:265–266.
39. Rohaan MW, Borch TH, van den Berg JH, et al. Tumor-infiltrating lymphocyte therapy or ipilimumab in advanced melanoma. N Engl J Med 2022; 387:2113–2125.
40. Rosenberg SA, Yang JC, Sherry RM, et al. Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy. Clin Cancer Res 2011;17:4550–4557.
41. Elsallab M, Ellithi M, Hempel S, et al. Long-term response to autologous anti-CD19 chimeric antigen receptor T cells in relapsed or refractory B cell acute lymphoblastic leukemia: a systematic review and meta-analysis. Cancer Gene Ther, 2023.
42. Tran E, Robbins PF, Lu YC, et al. T-cell transfer therapy targeting mutant KRAS in cancer. N Engl J Med 2016; 375:2255–2262.
43. Parkhurst MR, Yang JC, Langan RC, et al. T cells targeting carcinoembryonic antigen can mediate regression of metastatic colorectal cancer but induce severe transient colitis. Mol Ther 2011;19:620–626.
44. Flugel CL, Majzner RG, Krenciute G, et al. Overcoming on-target, off-tumour toxicity of CAR T cell therapy for solid tumours. Nat Rev Clin Oncol 2023;20:49–62.
45. Sun L, Zhu Z, Jia X, et al. The difference of human gut microbiome in colorectal cancer with and without metastases. Front Oncol 2022;12:982744.
46. Bullman S, Pedamallu CS, Sicinska E, et al. Analysis of Fusobacterium persistence and antibiotic response in colorectal cancer. Science 2017;358:1443–1448.
47. Chen S, Su T, Zhang Y, et al. Fusobacterium nucleatum promotes colorectal cancer metastasis by modulating KRT7-AS/KRT7. Gut Microbes 2020;11:511–525.
48. Bertocchi A, Carloni S, Ravenda PS, et al. Gut vascular barrier impairment leads to intestinal bacteria dissemination and colorectal cancer metastasis to liver. Cancer Cell 2021;39:708–724.e11.

49. Brescia P, Rescigno M. The gut vascular barrier: a new player in the gut-liver-brain axis. Trends Mol Med 2021; 27:844–855.
50. Colvin H, Nishida N, Konno M, et al. Oncometabolite D-2-hydroxyglurate directly induces epithelial-mesenchymal transition and is associated with distant metastasis in colorectal cancer. Sci Rep 2016;6:36289.
51. Hao NB, Lü MH, Fan YH, et al. Macrophages in tumor microenvironments and the progression of tumors. Clin Dev Immunol 2012;2012:948098.
52. Ternes D, Tsenkova M, Pozdeev VI, et al. The gut microbial metabolite formate exacerbates colorectal cancer progression. Nat Metab 2022;4:458–475.
53. Venkateswaran N, Conacci-Sorrell M. Kynurenine: an oncometabolite in colon cancer. Cell Stress 2020; 4:24–26.
54. Wen SW, Ager EI, Christophi C. Bimodal role of Kupffer cells during colorectal cancer liver metastasis. Cancer Biol Ther 2013;14:606–613.
55. Yuan N, Li X, Wang M, et al. Gut microbiota alteration influences colorectal cancer metastasis to the liver by remodeling the liver immune microenvironment. Gut Liver 2022;16:575–588.
56. Scheele J, Stangl R, Altendorf-Hofmann A. Hepatic metastases from colorectal carcinoma: impact of surgical resection on the natural history. Br J Surg 1990; 77:1241–1246.
57. Scheele J, Stang R, Altendorf-Hofmann A, et al. Resection of colorectal liver metastases. World J Surg 1995;19:59–71.
58. House MG, Ito H, Gönen M, et al. Survival after hepatic resection for metastatic colorectal cancer: trends in outcomes for 1,600 patients during two decades at a single institution. J Am Coll Surg 2010; 210(744–752):752–755.
59. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 1999;230:309–318; discussion 318–321.
60. Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg 2002;235:759–766.
61. de Jong MC, Mayo SC, Pulitano C, et al. Repeat curative intent liver surgery is safe and effective for recurrent colorectal liver metastasis: results from an international multi-institutional analysis. J Gastrointest Surg 2009; 13:2141–2151.
62. Morris EJ, Forman D, Thomas JD, et al. Surgical management and outcomes of colorectal cancer liver metastases. Br J Surg 2010;97:1110–1118.
63. Ferrarotto R, Pathak P, Maru D, et al. Durable complete responses in metastatic colorectal cancer treated with chemotherapy alone. Clin Colorectal Cancer 2011; 10:178–182.
64. Sorbye H. Recurrence patterns after resection of liver metastases from colorectal cancer. Recent Results Cancer Res 2014;203:243–252.
65. Sutton TL, Wong LH, Walker BS, et al. Hepatectomy is associated with improved oncologic outcomes in recurrent colorectal liver metastases: a propensity-matched analysis. Surgery 2023;173:1314–1321.
66. Luo LX, Yu ZY, Huang JW, et al. Selecting patients for a second hepatectomy for colorectal metastases: an systemic review and meta-analysis. Eur J Surg Oncol 2014;40:1036–1048.
67. Andreou A, Brouquet A, Abdalla EK, et al. Repeat hepatectomy for recurrent colorectal liver metastases is associated with a high survival rate. HPB (Oxford) 2011; 13:774–782.
68. Neal CP, Nana GR, Jones M, et al. Repeat hepatectomy is independently associated with favorable long-term outcome in patients with colorectal liver metastases. Cancer Med 2017;6:331–338.
69. Ishiguro S, Akasu T, Fujimoto Y, et al. Second hepatectomy for recurrent colorectal liver metastasis: analysis of preoperative prognostic factors. Ann Surg Oncol 2006;13:1579–1587.
70. Kanemitsu Y, Shimizu Y, Mizusawa J, et al. Hepatectomy followed by mFOLFOX6 versus hepatectomy alone for liver-only metastatic colorectal cancer (JCOG0603): a phase II or III randomized controlled trial. J Clin Oncol 2021;39:3789–3799.
71. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol 2013; 14:1208–1215.
72. Van Cutsem E, Köhne CH, Láng I, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol 2011;29:2011–2019.
73. Benson AB, Venook AP, Al-Hawary MM, et al. Colon cancer, version 2.2023, NCCN clinical practice guidelines in oncology. National Comprehensive Cancer Network, 2023.
74. Gruenberger T, Bridgewater J, Chau I, et al. Bevacizumab plus mFOLFOX-6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: the OLIVIA multinational randomised phase II trial. Ann Oncol 2015;26:702–708.
75. Modest DP, Martens UM, Riera-Knorrenschild J, et al. FOLFOXIRI plus panitumumab as first-line treatment of RAS wild-type metastatic colorectal cancer: the randomized, open-label, phase II VOLFI study (AIO KRK0109). J Clin Oncol 2019;37:3401–3411.
76. Loupakis F, Yang D, Yau L, et al. Primary tumor location as a prognostic factor in metastatic colorectal cancer. J Natl Cancer Inst 2015;107:dju427.
77. Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol 2014;15:1065–1075.
78. Schwartzberg LS, Rivera F, Karthaus M, et al. PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in

patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. J Clin Oncol 2014;32:2240–2247.
79. Morris VK, Kennedy EB, Baxter NN, et al. Treatment of metastatic colorectal cancer: ASCO guideline. J Clin Oncol 2022;41:678–700.
80. Cremolini C, Antoniotti C, Stein A, et al. Individual patient data meta-analysis of FOLFOXIRI plus bevacizumab versus doublets plus bevacizumab as initial therapy of unresectable metastatic colorectal cancer. J Clin Oncol 2020;38:3314–3324.
81. Cremolini C, Antoniotti C, Rossini D, et al. Upfront FOLFOXIRI plus bevacizumab and reintroduction after progression versus mFOLFOX6 plus bevacizumab followed by FOLFIRI plus bevacizumab in the treatment of patients with metastatic colorectal cancer (TRIBE2): a multicentre, open-label, phase 3, randomised, controlled trial. Lancet Oncol 2020;21:497–507.
82. Schmoll H, Garlipp B, Junghanß C, et al. FOLFOX/bevacizumab +/- irinotecan in advanced colorectal cancer (CHARTA): long term outcome. Ann Oncol 2018;29:v108.
83. Cunningham D, Lang I, Marcuello E, et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. Lancet Oncol 2013;14:1077–1085.
84. Verschoor YL, Kodach L, van den Berg J, et al. Neoadjuvant atezolizumab plus docetaxel/oxaliplatin/capecitabine in non-metastatic gastric and gastroesophageal junction adenocarcinoma: the PANDA trial. J Clin Oncol 2022;40(suppl):4059, 4059.
85. Hong DS, Fakih MG, Strickler JH, et al. KRAS(G12C) inhibition with sotorasib in advanced solid tumors. N Engl J Med 2020;383:1207–1217.
86. Fakih MG, Kopetz S, Kuboki Y, et al. Sotorasib for previously treated colorectal cancers with KRAS(G12C) mutation (CodeBreaK100): a prespecified analysis of a single-arm, phase 2 trial. Lancet Oncol 2022;23:115–124.
87. Ou S-HI, Jänne PA, Leal TA, et al. First-in-human phase I/IB dose-finding study of adagrasib (MRTX849) in patients with advanced KRASG12C solid tumors (KRYSTAL-1). J Clin Oncol 2022;40:2530–2538.
88. Yaeger R, Weiss J, Pelster MS, et al. Adagrasib with or without cetuximab in colorectal cancer with mutated KRAS G12C. N Engl J Med 2022;388:44–54.
89. Kuboki Y, Yaeger R, Fakih MG, et al. Sotorasib in combination with panitumumab in refractory KRAS G12C-mutated colorectal cancer: safety and efficacy for phase Ib full expansion cohort. Ann Oncol 2022;33:S680–S681.
90. Parikh K, Banna G, Liu SV, et al. Drugging KRAS: current perspectives and state-of-art review. Journal of Hematology & Oncology 2022;15:152.
91. Tolcher AW, Park W, Wang JS, et al. Trial in progress: a phase 1, first-in-human, open-label, multicenter, dose-escalation and dose-expansion study of ASP3082 in patients with previously treated advanced solid tumors and KRAS G12D mutations. J Clin Oncol 2023;41-(suppl):TPS764, TPS764.
92. Kopetz S, Grothey A, Yaeger R, et al. Encorafenib, binimetinib, and cetuximab in BRAF V600E–mutated colorectal cancer. N Engl J Med 2019;381:1632–1643.
93. Kopetz S, Yoshino T, Kim TW, et al. BREAKWATER safety lead-in (SLI): encorafenib + cetuximab (EC) ± chemotherapy for first-line (1L) treatment (tx) of BRAF V600E-mutant (BRAFV600E) metastatic colorectal cancer (mCRC). J Clin Oncol 2022;40(suppl):134, 134.
94. Corcoran R, Giannakis M, Allen J, et al. Clinical efficacy of combined BRAF, MEK, and PD-1 inhibition in BRAFV600E colorectal cancer patients. Ann Oncol 2020;31:S226–S227.
95. Morris VK, Parseghian CM, Escano M, et al. Phase I/II trial of encorafenib, cetuximab, and nivolumab in patients with microsatellite stable, BRAFV600E metastatic colorectal cancer. J Clin Oncol 2022;40(suppl):12, 12.
96. Diaz LA Jr, Shiu KK, Kim TW, et al. Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study. Lancet Oncol 2022;23:659–670.
97. Andre T, Amonkar M, Norquist JM, et al. Health-related quality of life in patients with microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer treated with first-line pembrolizumab versus chemotherapy (KEYNOTE-177): an open-label, randomised, phase 3 trial. Lancet Oncol 2021;22:665–677.
98. Lenz HJ, Van Cutsem E, Luisa Limon M, et al. First-line nivolumab plus low-dose ipilimumab for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: the phase II CheckMate 142 study. J Clin Oncol 2022;40:161–170.
99. Overman MJ, Lenz H-J, Andre T, et al. Nivolumab (NIVO) ± ipilimumab (IPI) in patients (pts) with microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): five-year follow-up from CheckMate 142. J Clin Oncol 2022;40(suppl):3510–3510.
100. Eng C, Kim TW, Bendell J, et al. Atezolizumab with or without cobimetinib versus regorafenib in previously treated metastatic colorectal cancer (IMblaze370): a multicentre, open-label, phase 3, randomised, controlled trial. Lancet Oncol 2019;20:849–861.
101. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti–PD-1 antibody in cancer. N Engl J Med 2012;366:2443–2454.
102. Cremolini C, Rossini D, Antoniotti C, et al. LBA20 FOLFOXIRI plus bevacizumab (bev) plus atezolizumab (atezo) versus FOLFOXIRI plus bev as first-line treatment of unresectable metastatic colorectal cancer (mCRC) patients: results of the phase II randomized AtezoTRIBE study by GONO. Ann Oncol 2021;32:S1294–S1295.
103. Stein A, Binder M, Goekkurt E, et al. Avelumab and cetuximab in combination with FOLFOX in patients with previously untreated metastatic colorectal cancer (MCRC): final results of the phase II AVETUX trial (AIO-KRK-0216). J Clin Oncol 2020;38(suppl):96–96.

104. Lenz H-J, Parikh AR, Spigel DR, et al. Nivolumab (NIVO) + 5-fluorouracil/leucovorin/oxaliplatin (mFOLFOX6)/bevacizumab (BEV) versus mFOLFOX6/BEV for first-line (1L) treatment of metastatic colorectal cancer (mCRC): phase 2 results from CheckMate 9X8. J Clin Oncol 2022;40(suppl):8, 8.
105. Ros J, Balconi F, Baraibar I, et al. Advances in immune checkpoint inhibitor combination strategies for microsatellite stable colorectal cancer. Front Oncol 2023;13:1112276.
106. Deipolyi AR, Golberg A, Yarmush ML, et al. Irreversible electroporation: evolution of a laboratory technique in interventional oncology. Diagn Interv Radiol 2014;20:147–154.
107. Radosevic A, Quesada R, Serlavos C, et al. Microwave versus radiofrequency ablation for the treatment of liver malignancies: a randomized controlled phase 2 trial. Sci Rep 2022;12:316.
108. Kaye EA, Cornelis FH, Petre EN, et al. Volumetric 3D assessment of ablation zones after thermal ablation of colorectal liver metastases to improve prediction of local tumor progression. Eur Radiol 2019;29:2698–2705.
109. Koethe Y, Wilson N, Narayanan G. Irreversible electroporation for colorectal cancer liver metastasis: a review. Int J Hyperthermia 2022;39:682–687.
110. Shady W, Petre EN, Gonen M, et al. Percutaneous radiofrequency ablation of colorectal cancer liver metastases: factors affecting outcomes—a 10-year experience at a single center. Radiology 2016;278:601–611.
111. Ruers T, Punt C, Van Coevorden F, et al. Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004). Ann Oncol 2012;23:2619–2626.
112. Ruers T, Van Coevorden F, Punt CJ, et al. Local treatment of unresectable colorectal liver metastases: results of a randomized phase II trial. J Natl Cancer Inst 2017;109:djx015.
113. Solbiati L, Ahmed M, Cova L, et al. Small liver colorectal metastases treated with percutaneous radiofrequency ablation: local response rate and long-term survival with up to 10-year follow-up. Radiology 2012;265:958–968.
114. Evrard S, Poston G, Kissmeyer-Nielsen P, et al. Combined ablation and resection (CARe) as an effective parenchymal sparing treatment for extensive colorectal liver metastases. PLoS One 2014;9:e114404.
115. Meijerink MR, Puijk RS, van Tilborg A, et al. Radiofrequency and microwave ablation compared to systemic chemotherapy and to partial hepatectomy in the treatment of colorectal liver metastases: a systematic review and meta-analysis. Cardiovasc Intervent Radiol 2018;41:1189–1204.
116. van Amerongen MJ, Jenniskens SFM, van den Boezem PB, et al. Radiofrequency ablation compared to surgical resection for curative treatment of patients with colorectal liver metastases: a meta-analysis. HPB (Oxford) 2017;19:749–756.
117. Qadan M, Kemeny NE. Chapter 99: regional chemotherapy for liver tumors. In: Jarnagin WR, ed. Blumgart's surgery of the liver, biliary tract and pancreas. 6th ed. Amsterdam, the Netherlands: Elsevier, 2017:1470–1487.e3.
118. Breedis C, Young G. The blood supply of neoplasms in the liver. Am J Pathol 1954;30:969–977.
119. Ensminger WD. Intrahepatic arterial infusion of chemotherapy: pharmacologic principles. Semin Oncol 2002;29:119–125.
120. Ensminger WD, Gyves JW. Clinical pharmacology of hepatic arterial chemotherapy. Semin Oncol 1983;10:176–182.
121. Kemeny NE, Niedzwiecki D, Hollis DR, et al. Hepatic arterial infusion versus systemic therapy for hepatic metastases from colorectal cancer: a randomized trial of efficacy, quality of life, and molecular markers (CALGB 9481). J Clin Oncol 2006;24:1395–1403.
122. Ammori JB, Kemeny NE, Fong Y, et al. Conversion to complete resection and/or ablation using hepatic artery infusional chemotherapy in patients with unresectable liver metastases from colorectal cancer: a decade of experience at a single institution. Ann Surg Oncol 2013;20:2901–2907.
123. Kemeny NE, Melendez FD, Capanu M, et al. Conversion to resectability using hepatic artery infusion plus systemic chemotherapy for the treatment of unresectable liver metastases from colorectal carcinoma. J Clin Oncol 2009;27:3465–3471.
124. Doyon D, Mouzon A, Jourde AM, et al. [Hepatic, arterial embolization in patients with malignant liver tumours (author's transl)]. Ann Radiol (Paris) 1974;17:593–603.
125. Yamada R, Nakatsuka H, Nakamura K, et al. Hepatic artery embolization in 32 patients with unresectable hepatoma. Osaka City Med J 1980;26:81–96.
126. Vogl TJ, Lahrsow M. The role of conventional TACE (cTACE) and DEBIRI-TACE in colorectal cancer liver metastases. Cancers (Basel) 2022;14.
127. Jones RP, Malik HZ, Fenwick SW, et al. PARAGON II: a single arm multicentre phase II study of neoadjuvant therapy using irinotecan bead in patients with resectable liver metastases from colorectal cancer. Eur J Surg Oncol 2016;42:1866–1872.
128. Emmons EC, Bishay S, Du L, et al. Survival and toxicities after (90)Y transarterial radioembolization of metastatic colorectal cancer in the RESIN registry. Radiology 2022;305:228–236.
129. Gray B, Van Hazel G, Hope M, et al. Randomised trial of SIR-Spheres plus chemotherapy vs chemotherapy alone for treating patients with liver metastases from primary large bowel cancer. Ann Oncol 2001;12:1711–1720.
130. Dutton SJ, Kenealy N, Love SB, et al. FOXFIRE protocol: an open-label, randomised, phase III trial of 5-fluorouracil, oxaliplatin and folinic acid (OxMdG) with or without interventional Selective Internal Radiation Therapy (SIRT) as first-line treatment for patients with unresectable liver-only or liver-dominant metastatic colorectal cancer. BMC Cancer 2014;14:497.
131. Mulcahy MF, Mahvash A, Pracht M, et al. Radioembolization with chemotherapy for colorectal liver metastases: a randomized, open-label, international, multicenter, phase III trial. J Clin Oncol 2021;39:3897–3907.

132. van Hazel GA, Heinemann V, Sharma NK, et al. SIR-FLOX: randomized phase III trial comparing first-line mFOLFOX6 (plus or minus bevacizumab) versus mFOLFOX6 (plus or minus bevacizumab) plus selective internal radiation therapy in patients with metastatic colorectal cancer. J Clin Oncol 2016;34:1723–1731.
133. Fabritius MP, Ricke J. Overview of ongoing clinical trials on radioembolization. Cardiovasc Intervent Radiol 2022; 45:1659–1662.
134. Lee MT, Kim JJ, Dinniwell R, et al. Phase I study of individualized stereotactic body radiotherapy of liver metastases. J Clin Oncol 2009;27:1585–1591.
135. Rusthoven KE, Kavanagh BD, Cardenes H, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. J Clin Oncol 2009; 27:1572–1578.
136. Scorsetti M, Arcangeli S, Tozzi A, et al. Is stereotactic body radiation therapy an attractive option for unresectable liver metastases? a preliminary report from a phase 2 trial. Int J Radiat Oncol Biol Phys 2013;86:336–342.
137. Ohri N, Tomé WA, Méndez Romero A, et al. Local control after stereotactic body radiation therapy for liver tumors. Int J Radiat Oncol Biol Phys 2021;110:188–195.
138. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the SABR-COMET phase II randomized trial. J Clin Oncol 2020; 38:2830–2838.
139. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of 4-10 oligometastatic tumors (SABR-COMET-10): study protocol for a randomized phase III trial. BMC Cancer 2019;19:816.
140. Flyum IR, Mahic S, Grov EK, et al. Health-related quality of life in patients with colorectal cancer in the palliative phase: a systematic review and meta-analysis. BMC Palliat Care 2021;20:144.
141. Sodergren SC, Vassilios V. Colorectal cancer and quality of life. In: Kassianos AP, ed. Handbook of quality of life in cancer. Berlin/Heidelberg, Germany: Springer International Publishing, 2022:409–424.
142. WHOQOL. measuring quality of life. Geneva, Switzerland: World Health Organization; 1997. Available at: https://www.who.int/tools/whoqol. Accessed June 23, 2023.
143. Rohde G, Kersten C, Vistad I, et al. Spiritual well-being in patients with metastatic colorectal cancer receiving noncurative chemotherapy: a qualitative study. Cancer Nurs 2017;40:209–216.
144. Ferrell BR, Dow KH, Grant M. Measurement of the quality of life in cancer survivors. Qual Life Res 1995; 4:523–531.
145. Lombardi P, Marandino L, De Luca E, et al. Quality of life assessment and reporting in colorectal cancer: a systematic review of phase III trials published between 2012 and 2018. Crit Rev Oncol Hematol 2020;146:102877.
146. André T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol 2009;27:3109–3116.
147. European Organisation for Research and Treatment of Cancer. Available at: https://www.eortc.org/. Accessed June 23, 2023.
148. Functional Assessment of Cancer Therapy. FACIT.org Available at: https://www.facit.org/measures/FACT-G. Accessed June 23, 2023.
149. RAND Healthcare. RAND Corporation Available at: https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form.html. Accessed June 23, 2023.
150. Palmer Kelly E, Paredes AZ, Tsilimigras DI, et al. The role of religion and spirituality in cancer care: an umbrella review of the literature. Surg Oncol 2022;42: 101389.

**Received July 1, 2023. Accepted August 30, 2023.**

**Correspondence**
Address correspondence to: Skye C. Mayo, MD, MPH, FACS, FSSO, Division of Surgical Oncology, Oregon Health & Science University, Knight Cancer Institute, Portland, Oregon 97239. e-mail: mayos@ohsu.edu.

**CRediT Authorship Contributions**
Ranish K. Patel Conceptualization; Writing - Original Draft; Writing - Review & Editing; Visualization)
Shahrose Rahman (Conceptualization; Writing - Original Draft; Visualization)
Issac R. Schwantes (Conceptualization; Writing - Original Draft)
Alexandra Bartlett (Conceptualization; Writing - Original Draft)
Robert Eil (Conceptualization; Writing - Original Draft)
Khashayar Farsad (Conceptualization; Writing - Original Draft)
Kathryn Fowler (Conceptualization; Writing - Original Draft)
Shaun M. Goodyear (Conceptualization; Writing - Original Draft)
Lissi Hansen (Conceptualization; Writing - Original Draft)
Adel Kardosh (Conceptualization; Writing - Original Draft)
Nima Nabavizadeh (Conceptualization; Writing - Original Draft)
Flavio G. Rocha (Conceptualization; Writing - Original Draft)
V. Liana Tsikitis (Conceptualization; Writing - Original Draft)
Melissa H. Wong (Conceptualization; Writing - Original Draft; Writing - Review & Editing; Supervision)
Skye C. Mayo (Conceptualization; Writing - Original Draft; Writing - Review & Editing; Supervision)

**Conflicts of interest**
The authors disclose no conflicts.