Colorectal Cancer Liver Metastases: Multimodal Therapy

Berk Aykut, MD, Michael E. Lidsky, MD*

KEYWORDS

• Colorectal cancer • Liver metastasis • Chemotherapy • Randomized controlled trial • Perioperative chemotherapy • Surgery

KEY POINTS

- Colorectal liver metastases (CRLM) are the primary driver of disease-specific mortality for patients with colorectal cancer.
- Surgical metastasectomy with the aim of R0 resection remains the backbone of CRLM therapy and is the only opportunity to achieve a cure. Oncological outcomes of parenchymal-sparing hepatectomy are comparable to more aggressive anatomic resections.
- The role of neoadjuvant chemotherapy for resectable CRLM remains controversial because it may delay surgery and cause hepatotoxicity but without any proven improvement in survival.
- The associating liver partition and portal vein ligation for staged hepatectomy technique may increase resection rates for CRLM, although it remains controversial due to high morbidity and mortality rates.
- Systemic chemotherapy and locoregional therapy such as hepatic artery infusion are promising strategies and have been shown to provide durable disease control and increase resection rates in initially unresectable CRLM.

INTRODUCTION

Public initiatives to reduce the exposure to known risk factors, including smoking, and the uptake of colorectal cancer (CRC) screening programs have led to a steady decline in CRC incidence and mortality rates.[1] However, CRC remains the second most common cancer diagnosis in women and the third most common in men worldwide.[2] Moreover, the incidence of early-onset CRC in patients aged younger than 50 years has been increasing, a population more likely to be diagnosed at later stages.[3–5] Similarly, pooled analyses from clinical trials of metastatic colorectal cancer

Department of Surgery, Division of Surgical Oncology, Duke University Medical Center, Box 3966, 10 Bryan Searle Drive, 466G Seeley G. Mudd Building, Durham, NC 27710, USA
* Corresponding author.
E-mail address: Michael.Lidsky@duke.edu
Twitter: @BerkAykutMD (B.A.); @michael_lidsky (M.E.L.)

Surg Oncol Clin N Am ■ (2023) ■–■
https://doi.org/10.1016/j.soc.2022.07.009
surgonc.theclinics.com

(mCRC) patients show that younger patients have worse progression-free (PFS) and overall survival (OS).[6] Emerging data also suggest that the different embryologic origins of midgut and hindgut colon segments result in distinct molecular profiles of right-sided and left-sided colon cancers, respectively.[7,8] Right-sided tumors tend to be poorly differentiated and more frequently harbor *KRAS* mutations, and patients with liver metastases from right-sided cancers have a worse OS rate because they often present at later stages and are older at diagnosis.[9,10] Contrarily, left-sided colon cancers tend to have higher rates of distant metastases but are more commonly well-differentiated and *KRAS* wild-type, which is associated with improved response to cytotoxic and targeted therapy and a better prognosis.[11,12] Although 20% of CRC patients present with synchronous liver metastases, half of all patients with initially non-metastatic disease progress and develop liver and lung metastases.[13,14] Notably, the liver is recognized as the most common site of CRC metastasis due to the portal venous drainage, and metastases to the liver remain the most common cause of disease-specific mortality. Left untreated, 5-year OS approaches 0% for patients with colorectal liver metastases (CRLM).[15] Hence, the management of CRLM has evolved into a complex field. Today, patients with mCRC are evaluated by multidisciplinary teams, inclusive of surgeons, medical oncologists, and radiation oncologists. Optimal management of CRLM consists of an individualized treatment strategy based on patient and tumor factors, including age, comorbidities, sidedness, the location and extent of disease, as well as molecular profile. Although hepatic resection is the backbone of curative-intent treatment, management of CRLM has become increasingly multimodal during the last decade and includes the use of downstaging chemotherapy, ablation techniques, and locoregional therapy, each of which are reviewed herein.

Imaging of Colorectal Liver Metastases

During the past 2 decades, hepatic metastasectomy has emerged as a safe and promising therapy to improve outcomes in patients with CRLM.[16] The current guidelines for resection of CRLM recommend removal of all macroscopic disease with negative margins while leaving sufficient functioning liver.[17] Therefore, preoperative imaging plays a vital role in adequately identifying and characterizing the extent of disease within the liver, defining relevant anatomy, estimating the remnant liver volume, and importantly identifying extrahepatic disease that may often preclude hepatectomy. Historically, ultrasonography was the method of choice to identify CRLM; however, technological advances in computed tomography (CT), MRI, and PET have led to improved detection of occult lesions and better delineation of hepatic anatomy. Although multiphase (triphasic) CT has emerged as the modality of choice for detecting liver metastases for CRC, it is limited in detecting CRLM in obese patients, CRLM less than 10 mm, or CRLM in patients with significant chemotherapy-associated steatosis.[18,19] While liver metastases typically seem as hypoattenuating lesions, the addition of arterial and portal venous phase imaging can be helpful to define liver vascular anatomy. Compared with CT, MRI with diffusion-weighted imaging and hepatocyte-specific contrast agents facilitates improved detection of subcentimeter lesions with a sensitivity of up to 95% despite generating typically lower resolution images.[20] With no randomized data comparing CT and MRI, the choice of imaging modality is often institution-dependent, although comparative analyses are underway to determine if MRI adds value to clinical decision-making beyond CT alone.[21] Besides CT and MRI, selective use of PET imaging using the glucose analog ^{18}F-fluorodeoxyglucose may be of value in detecting occult extrahepatic disease.

Resectable Colorectal Liver Metastases

Surgical management of resectable colorectal liver metastases

Surgical resection remains the backbone of CRLM therapy and is the only potentially curative treatment. In a recent study including 1211 patients undergoing resection for CRLM, Creasy and colleagues reported a median disease-specific survival of 4.9 years and an observed cure rate of 20%.[22] As technical advancements in liver surgery have propelled the evolution of hepatic resection for CRLM, many attempts have been made to stratify patients with liver disease to determine their prognosis after surgery. Risk scores such as the Fong score (Clinical Risk Score) have been proposed to define oncologic resectability.[23] In their seminal study, which incorporated data from 1001 patients, Fong and colleagues proposed a clinical risk score that proved to be highly predictive of the outcome. This score is calculated from 5 prognostic criteria, including (1) nodal status of the primary lesion, (2) disease-free interval from diagnosis of the primary lesion to the discovery of liver metastases less than 12 months, (3) greater than 1 hepatic metastases, (4) size of largest metastasis greater than 5 cm, and (5) preoperative carcinoembryonic antigen (CEA) level greater than 200 ng/mL. Based on these criteria, patients can be stratified as either low or high risk. Patients with a low clinical risk score of 0 to 2 have a more favorable outcome with a 5-year survival rate of 52.3%. In contrast, patients with a high clinical risk score of 3 to 5 have a much more guarded prognosis with a 5-year survival rate of 20.2%.[24] Other scores that are commonly calculated for patients with CLRM are the Nagashima, Nordlinger, and Konopke scores.[16,25,26] Although most studies investigating the value of stratification schema are limited by small sample size and institutional variation in practice and referral patterns, such clinical risk scores are valuable tools to predict long-term survival of patients with CRLM and reinforce the importance of oncologic and biologic considerations in the management of this disease.

Technical resectability is also debated, and while definitions may vary, a commonly used description of unresectable disease includes that in which margin negative resection would require the removal of all 3 hepatic veins, both portal veins, or the retrohepatic vena cava, and/or leave fewer than 2 adequately perfused and drained segments of the liver.[24] Today, the combination of parenchymal preserving resection and ablation techniques, neoadjuvant therapy to downsize tumors, and strategies to increase hepatic reserve have expanded the criteria of resectability to include any patient in whom all disease can be removed with a negative margin and sufficient future liver remnant (FLR). As such, the determination of resectability is a highly nuanced and individualized approach and is optimally assessed by an experienced hepatic surgeon. A lack of input from a liver surgeon may have devastating impact on patient outcomes, as demonstrated by Vega and colleagues, who reported that more than 44% of patients destined for palliative chemotherapy by a multidisciplinary tumor board without a liver surgeon present were considered potentially resectable after retrospective review by independent liver surgeons.[27]

With the shift of focus away from the diseased liver to the FLR, several tools have been developed to predict postoperative liver function and avoid posthepatectomy liver failure (PHLF). One such tool is indocyanine green (ICG) clearance testing, although its ability to accurately predict mortality is still under debate. ICG is a water-soluble dye that binds to albumin and is exclusively cleared from the bloodstream by the liver. As such, it allows for a real-time assessment of postoperative residual liver function in addition to preoperative volumetric analyses, which remains the most widely used tool.[28] In addition to patient-specific factors, surgical factors influence the risk of PHLF. These include intraoperative blood loss greater than

1200 mL, need for vascular resection, skeletonization of the hepatoduodenal ligament, resection of greater than 50% liver volume, and major hepatectomy.[29]

In contrast to fixed factors that are predictive of prognosis, resection margin status has been investigated as a predictor of outcome. Although historically an R0 margin width of 1 cm has been considered optimal in the resection of CRLM, Pawlik and colleagues reported a similar outcome in patients with negative resection margins, regardless of margin width.[30,31] Rather, it is thought that tumor biology (eg, molecular profile) is a more important predictor than margin width for local recurrence and long-term survival. Accordingly, anatomic resection (AR) has been observed to increase disease-free survival (DFS) to 33.8 months compared with 10.5 months in the non-AR group for *KRAS* mutant CRLM.[32] These findings provide further evidence that individual tumor biology dictates local recurrence in CRLM.

To achieve the goal of metastasectomy with a successful R0 resection, many patients undergo an AR, defined by the resection of one or more anatomic liver segments. However, there is no difference in the proportion of R0 resections in patients undergoing parenchymal-sparing hepatectomy (PSH) versus AR.[33] Moreover, PSH has recently been shown to have oncological outcomes comparable with AR.[34] Although some studies report similar perioperative morbidity and mortality rates for AR and PSH, others have shown improved morbidity and mortality in patients undergoing PSH due to the reduced magnitude of resection and what is typically an increased FLR.[35–37] Additionally, the reduced volume of resected liver with PSH can expand the number of patients with CRLM eligible for repeat hepatic resection at the time of recurrence, which occurs in 70% to 80% of patients.[38] As such, AR was identified as an independent factor associated with the inability to undergo repeat resection for recurrent CRLM.[39]

In concert with continued efforts to pursue parenchymal-sparing resections, there has been a steady decline in major hepatic resections during the past 20 years. One factor that has facilitated parenchymal preservation for advanced disease is the use of ablative therapies. The trend in decreased major hepatectomies accompanied by an increase in ablation is associated with a decrease in overall complications from 53.2% to 19.9% and an improvement in perioperative mortality from 5.2% to 1.6%.[35] Ablative therapies include radiofrequency ablation (RFA), which can improve OS rates compared with chemotherapy alone for lesions that are otherwise not amenable to resection.[40,41] RFA is safe and effective, although it has only limited effectiveness adjacent to vascular structures due to the heat sink phenomenon. Similarly, microwave ablation (MWA) has been shown to be equally effective as hepatic resection in a small randomized controlled trial (RCT) consisting of 30 patients.[42] Compared with RFA, MWA can produce much faster heating and larger volume ablation zones that are less susceptible to near heat sink. Although MWA has limited use in the treatment of subcapsular or high-risk location (adjacent to central biliary tree) metastases, it is becoming more popular due to its effectiveness in metastases measuring more than 3 cm. Other percutaneous ablative techniques that have gained acceptance as treatment modalities for CRLM include cryoablation and irreversible electroporation. Today, local ablative techniques are commonly used to complement hepatic resection when complete resection of all metastases is not possible, as well as to facilitate parenchymal preservation.

Efforts to reduce surgical stress are paralleled by a trend toward increased use of minimally invasive techniques in liver surgery. Laparoscopic liver surgery for CRLM is associated with reduced blood loss (median difference 147 mL), shorter hospital stays (median difference 2.4 days), and reduced morbidity (odds ratio [OR] 0.64, 95% CI 0.55–0.75; $P < .00001$) compared with open resection techniques.[43]

Importantly, the OSLO COMET trial and other studies report similar rates of resection free margins for both laparoscopic and open surgery without differences in disease recurrence, 3-year or 5-year survival, suggesting noninferiority for these oncologic endpoints.[44,45]

Chemotherapy for Resectable Colorectal Liver Metastases

Theoretic benefits of chemotherapy for resectable CRLM include treating micrometastatic disease in the liver and systemically to decrease the risk of recurrence, downstaging disease to lessen the extent of liver resection required, as well as to test biology and improve selection of patients most likely to benefit from hepatectomy. Adjuvant chemotherapy for resected CRLM, however, has not been shown to improve OS for this patient population. A 2006 RCT suggested adjuvant fluorouracil may improve DFS; however, no improvement was observed in OS.[46] Similar findings were observed by Mitry and colleagues, where 2 European RCTs were combined to improve statistical power to detect a difference in survival.[47] Despite this analysis, adjuvant fluorouracil, although associated with a potential improvement of PFS (hazard ratio [HR] 1.32; 95% CI 1.00–1.76; $P = .058$), did not result in an improvement in OS (HR 1.32; 95% CI 0.95 - 1.82; $P = .095$). To address critiques of early studies that included the use of antiquated single-agent regimens, Ychou and colleagues conducted an RCT comparing adjuvant 5-fluorouracil/leucovorin and irinotecan (FOLFIRI) versus fluorouracil but neither PFS or OS were improved with this modern regimen.[48] Most recently, the Japan Clinical Oncology Group reported JCOG0603, which randomized patients with resected CRLM to adjuvant modified 5-fluorouracil/leucovorin and oxaliplatin (mFOLFOX6) versus surveillance. In this study, which included treatment-naïve patients, adjuvant mFOLFOX6 did improve DFS (HR 0.67; 95% CI, 0.50–0.92; $P = .006$) but not OS.[49] In fact, OS was worse in patients receiving mFOLFOX6 (71.2% for hepatectomy followed by chemotherapy vs 83.1% for hepatectomy alone), which was theorized to be due to chemotherapy-induced liver damage, imbalanced posttrial therapies, poor adherence to adjuvant chemotherapy, and/or induction of chemoresistance following elimination of chemosensitive tumor cells.

Despite lack of data supporting adjuvant chemotherapy for patients with resectable CRLM, some advocate for neoadjuvant chemotherapy. The rationale for neoadjuvant chemotherapy in this population includes optimizing the chances of an R0 resection, downstaging disease to facilitate parenchymal preserving hepatectomy, and improving patient selection for liver resection. In the landmark European Organization For Research And Treatment Of Cancer (EORTC) 40983 trial, 364 patients with 4 or fewer resectable CRLM across 78 hospitals in Europe were randomized to perioperative FOLFOX4 or surgery alone.[50] Notably, perioperative chemotherapy led to an 8.1% increase in PFS at 3 years (from 28.1%, 95.66% CI 21.2–36.6 to 36.2%, 95.66% CI 28.7–43.8; HR 0.77, 0.60–1.00; $P = .041$; **Fig. 1**A). Subgroup analysis of patients undergoing resection revealed an even more pronounced benefit of 9.2% (from 33.2%, 25.3–41.2 to 42.4%, 34.0–50.5; HR 0.73, 0.55–0.97; $P = .025$). However, with long-term follow-up, EORTC 40983 did not reveal an improvement in median OS (61.3 months for the perioperative cohort vs 54.3 months for the surgery alone cohort; $P = .34$; **Fig. 1**B).[51] Not only did perioperative chemotherapy fail to improve OS for this patient population, additional findings in EORTC 40983 include increased postoperative morbidity in the perioperative chemotherapy arm (25% vs 16%; $P = .04$). The excess morbidity was primarily related to biliary fistula (8% vs 4%), prolonged hepatic failure (6% vs 3%), and intra-abdominal infection (7% vs 2%). Of note, only 7% of patients progressed during the course of preoperative chemotherapy, with the number of patients resected in each arm being identical. These data indicate that short-course

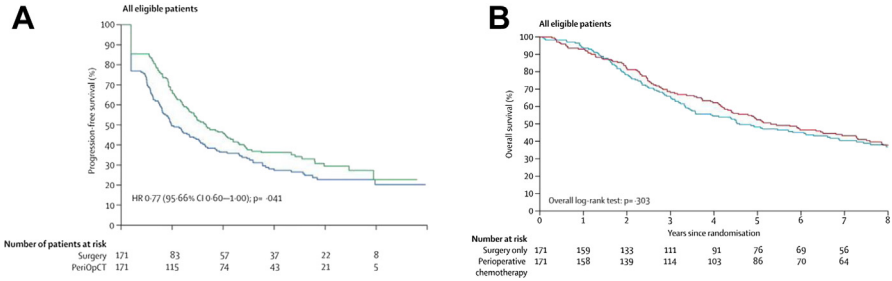

Fig. 1. Perioperative chemotherapy for resectable CRLM improves Progression-free survival but not Overall Survival. (*A*) Perioperative chemotherapy led to an 8.1% increase in PFS at 3 years in all eligible patients. (*B*) 5-year overall survival was 51.2% in the perioperative chemotherapy group versus 47.8% in the surgery-only group. PeriOpCT, perioperative chemotherapy consisting of 5-FU, leucovorin and oxaliplatin. (Reprinted with permission from Elsevier. The Lancet Oncol, Vol 14, Issue 12, 2021, p.1208-15, Nordlinger 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"", https://doi.org/10.1016/S1470-2045(13)70447-9.)

FOLFOX in patients with oligometastatic disease is an inadequate strategy to identify patients who would least likely benefit from exploration or resection. As such, the role of neoadjuvant chemotherapy for resectable CRLM remains controversial because it may delay surgery and cause hepatotoxicity. Ongoing trials such as the CHARISMA trial may answer whether subgroups of patients with primary resectable CRLM characterized as high-risk by the Fong Clinical Risk Score could benefit from neoadjuvant chemotherapy.[52]

Targeted therapies have also been studied in the neoadjuvant setting. The New EPOC study was a randomized controlled trial aimed to assess the benefit of cetuximab added to perioperative chemotherapy (FOLFOX, XELOX, or FOLFIRI) in patients with resectable *KRAS* wild-type CRLM. With an overall median follow-up of 20.7 months, PFS was noted to be significantly shorter in the chemotherapy plus cetuximab group compared with the chemotherapy alone group (14.1 months, 95% CI 11.8–15.9 vs 20.5 months, 95% CI 16.8–26.7; HR 1.48, 95% CI 1.04–2.12; $P = .030$).[53] Moreover, OS was shorter in the cetuximab group on long-term follow-up (55.4 vs 81.0 months, HR 1.45, 95% CI 1.02–2.05; $P = .036$), suggesting that cetuximab in combination with chemotherapy cannot be recommended for patients with resectable CRLM.[54]

Hepatic Artery Infusion Therapy for Resectable Colorectal Liver Metastases

Although standard systemic regimens have not been shown to improve survival for resectable CRLM, adjuvant hepatic artery infusion (HAI) was reported to improve outcomes in this population. Although normal liver parenchyma receives dual blood supply from the portal venous and arterial circulation, hepatic metastases derive their blood supply from the hepatic artery.[55] Based on this finding, Clarkson and colleagues first introduced hepatic arterial chemotherapy in 1961.[56] Their method entailed catheterization of the common hepatic artery via the brachial artery, allowing for continuous antimetabolite infusion. To further minimize systemic chemotoxic effects, Sullivan and colleagues from the Lahey Hospital described a modified technique that included ligation of all nonhepatic branches of the hepatic artery.[57] With the advent of intraoperative dye studies that ensure exclusively hepatic perfusion before

initiating therapy, HAI has gained increased enthusiasm during the past decades, although it still remains a therapy that is restricted to few select centers. Despite limitations in availability of this therapy, Kemeny and colleagues demonstrated that liver-directed therapy with HAI may improve outcomes when combined with systemic therapy in the adjuvant setting after complete resection of CRLM.[58] In the 1999 RCT, adjuvant HAI not only resulted in an improvement in hepatic-recurrence free survival from 60% to 90% at 2 years but also yielded an improvement in 2-year OS from 72% to 86% ($P = .03$). Recent studies suggest that hepatic resection followed by adjuvant HAI combined with systemic chemotherapy can achieve 5-year and 10-year survival rates as high as 78% and 61%, respectively.[59] Similarly, Koerkamp and colleagues recently reported that perioperative HAI was associated with increased OS (67 months with HAI vs 44 months without HAI, $P < .001$).[60] The largest association between HAI and improved outcomes was also found for patients with a low clinical risk score and no extrahepatic disease. Regarding somatic mutations in patients with resected CRLM, adjuvant HAI is also associated with improved OS (HR 0.53, $P < .002$) independent of *KRAS* mutational status in a retrospective analysis of 674 patients.[61] Based on these data, adjuvant HAI is the only therapy that has been shown to improve OS in a randomized trial, and contemporary retrospective analyses continue to suggest encouraging outcomes in the adjuvant setting.

Potentially Resectable and Unresectable Colorectal Liver Metastases

Chemotherapy for potentially resectable and unresectable colorectal liver metastases

Upfront surgery is feasible in only 15% to 25% of patients with CRLM.[62] As such, studies have investigated the role of chemotherapeutic strategies for potentially resectable and unresectable CRLM with the goal of downstaging to resectable status (**Table 1**). In their landmark study, Adam and colleagues reported that chemotherapy with FOLFOX, FOLFIRI, or FOLFIRINOX, allowed 12.5% of patients with initially unresectable CRLM to undergo hepatic resection.[63] In a smaller series consisting of 40 patients, the addition of irinotecan to 5-FU and folinic acid increased the resection rate in patients with initially unresectable liver metastases to 32.5%.[64] Importantly, cumulative 3-year and 5-year survival rates are comparable among patients undergoing curative-intent hepatectomy after conversion to resectable status compared with patients with resectable CRLM at diagnosis.[65] More recently, the randomized phase II METHEP trial investigated whether intensified chemotherapy can further increase resection rates and improve outcomes in patients with CRLM.[66] A total of 125 patients were randomly assigned to standard FOLFOX or FOLFIRI, or intensified chemotherapy with high-dose irinotecan (FOLFIRI-HD), high-dose oxaliplatin (FOLFOX7) or triplet therapy with FOLFIRINOX. Although the rate of toxicity was higher in patients receiving intensified chemotherapy, patients in the FOLFIRINOX arm had the best conversion to resection rate, with 67% of patients ultimately undergoing liver resection, compared with only 40% to 59% in the remaining arms.

Identification of biomarkers and development of monoclonal antibodies targeting epidermal growth factor receptor (EGFR) and vascular endothelial growth factors (VEGF) have further expanded the therapeutic arsenal for the treatment of CRC and CRLM. In the phase II CELIM trial, 114 patients with unresectable CRLM were randomly assigned to receive anti-EGFR therapy (cetuximab) with either FOLFOX or FOLFIRI.[67,68] The primary endpoint was defined as tumor response assessed by the response evaluation criteria in solid tumors criteria. Notably, although there was no significant difference in the response rate, retrospective analysis of the *KRAS* mutation status revealed a response rate of 70% (95% CI 58–81) in patients with wild-type *KRAS* compared with only 41% (95% CI 22–61) in patients with *KRAS*-mutated

Table 1
Key clinical trials of perioperative chemotherapy for potentially resectable and unresectable colorectal liver metastases

Study Name	Author	Year	Number of patients	KRAS status	Treatment	Control	DFS or PFS	OS	Resection Rate (including all R status)	R0 Resection Rate
	Adam et al.[63]	2004	1439	Not reported	FOLFOX/FOLFIRI/ FOLFIRINOX and secondary resection	Primary resection	22% and 17% at 5 and 10 y (secondary resection) Not reported (primary resection)	33% and 23% at 5 and 10 y (secondary resection) 48% and 30% at 5 and 10 y (primary resection)	12.5% after neoadjuvant chemotherapy	Not reported
	Pozzo et al.[64]	2004	40	Not reported	FOLFIRI	n/a	14.3 mo	Not reached	40% after neoadjuvant chemotherapy	32.5% after neoadjuvant chemotherapy
CRYSTAL	Van Cutsem et al.[69]	2009	599	wt/mut	Cetuximab-FOLFIRI	FOLFIRI	9.9 mo (Cetuximab-FOLFIRI; wt-KRAS) 8.7 mo (FOLFIRI; wt-KRAS) 7.6 mo (Cetuximab-FOLFIRI; mut-KRAS) 8.1 mo (FOLFIRI; mut-KRAS)	24.9 mo (Cetuximab-FOLFIRI; wt-KRAS) 21.0 mo (FOLFIRI; wt-KRAS) 17.5 mo (Cetuximab-FOLFIRI; mut-KRAS) 17.7 mo (FOLFIRI; mut-KRAS)	7% (Cetuximab-FOLFIRI) 3.7% (FOLFIRI)	4.8% (Cetuximab-FOLFIRI) 1.7% (FOLFIRI)
OPUS	Bokemeyer et al.[70,71]	2009	337	wt/mut	Cetuximab-FOLFOX-4	FOLFOX-4	7.7 mo (Cetuximab-FOLFOX-4; wt-KRAS) 7.2 mo (FOLFOX-4; wt-KRAS) 5.5 mo (Cetuximab-FOLFOX-4; mut-KRAS) 8.6 mo (FOLFOX-4; mut-KRAS)	22.8 mo (Cetuximab-FOLFOX-4; wt-KRAS) 18.5 mo (FOLFOX-4; wt-KRAS) 13.4 mo (Cetuximab-FOLFOX-4; mut-KRAS) 17.5 mo (FOLFOX-4; mut-KRAS)	Not reported	9.8% (Cetuximab-FOLFOX-4; wt-KRAS) 4.1% (FOLFOX-4; wt-KRAS) 1.9% (Cetuximab-FOLFOX-4; mut-KRAS) 2.1% (FOLFOX-4; mut-KRAS)

CELIM	Folprecht et al.[67,68]	2010	114	wt/mut	Cetuximab-FOLFOX-6	Cetuximab-FOLFIRI	11.2 mo (Cetuximab-FOLFOX-6) 10.5 mo (Cetuximab-FOLFIRI)	35.8 mo (Cetuximab-FOLFOX-6) 29 mo (Cetuximab-FOLFIRI)	42% (Cetuximab-FOLFOX-6) 44% (Cetuximab-FOLFIRI)	38% (Cetuximab-FOLFOX-6) 30% (Cetuximab-FOLFIRI)
METHEP	Ychou et al.[66]	2013	125	wt/mut	FOLFIRI-HD/ FOLFOX7/ FOLFIRINOX	FOLFIRI/ FOLFOX4	12.1 mo (FOLFIRI-HD) 8.5 mo (FOLFOX-7) 14.1 mo (FOLFIRINOX) 9.2 mo (Controls)	29.4 mo (FOLFIRI-HD) 26.9 mo (FOLFOX-7) 48.8 mo (FOLFIRINOX) 17.7 mo (Controls)	59.4% (FOLFIRI-HD) 43.3% (FOLFOX-7) 66.7% (FOLFIRINOX) 40% (Controls)	25% (FOLFIRI-HD) 23.3% (FOLFOX-7) 30% (FOLFIRINOX) 23.3% (Controls)
FIRE-3	Heinemann et al.[74]	2014	592	Wt	Cetuximab-FOLFIRI	Bevacizumab-FOLFIRI	10 mo (Cetuximab-FOLFIRI) 10.3 mo (Bevacizumab-FOLFIRI)	28.7 mo (Cetuximab-FOLFIRI) 25 mo (Bevacizumab-FOLFIRI)	12% (Cetuximab-FOLFIRI) 14% (Bevacizumab-FOLFIRI)	Not reported
OLIVIA	Gruenberger et al.[72]	2015	80	Wt	Bevacizumab-FOLFOXIRI	Bevacizumab-mFOLFOX-6	18.6 mo (Bevacizumab-FOLFOXIRI) 12.5 mo (Bevacizumab-mFOLFOX-6)	Not reached (Bevacizumab-FOLFOXIRI) 32.2 mo (Bevacizumab-mFOLFOX-6)	61% (Bevacizumab-FOLFOXIRI) 49% (Bevacizumab-mFOLFOX-6)	49% (Bevacizumab-FOLFOXIRI) 23% (Bevacizumab-mFOLFOX-6)
ATOM	Oki et al.[76]	2019	122	Wt	Bevacizumab-mFOLFOX-6	Cetuximab-mFOLFOX-6	11.5 mo (Bevacizumab-mFOLFOX-6) 14.8 mo (Cetuximab-mFOLFOX-6)	Not reported	56.1% (Bevacizumab-mFOLFOX-6) 49.2% (Cetuximab-mFOLFOX-6)	43.9% (Bevacizumab-mFOLFOX-6) 37.3% (Cetuximab-mFOLFOX-6)
BECOME	Tang et al.[73]	2020	241	Mut	Bevacizumab-mFOLFOX-6	mFOLFOX-6	9.5 mo (Bevacizumab-mFOLFOX-6) 5.6 mo (mFOLFOX-6)	25.7 mo (Bevacizumab-mFOLFOX-6) 20.5 mo (mFOLFOX-6)	Not reported	22.3 (Bevacizumab-mFOLFOX-6) 5.8% (mFOLFOX-6)

tumors ($P = .008$). Moreover, in a retrospective but blinded evaluation of resectability, 41 (60%) of 68 patients were judged to be resectable after neoadjuvant chemotherapy, compared with 22 (32%) of 68 patients at baseline. Despite this difference of 19 (28%) patients perceived to have converted to resectable status ($P < .0001$), only 34% of patients actually underwent R0 resection. The CRYSTAL trial also evaluated the impact of cetuximab, which showed a HR of 0.85 (95% CI 0.72–0.99; $P = .048$) for PFS with FOLFIRI-cetuximab as compared with the FOLFIRI alone.[69] Similarly, the OPUS study showed that the addition of cetuximab to FOLFOX-4 significantly improved PFS (HR 0.567; $P = .0064$) and response (OR 2.551; $P = .0027$) in patients with *KRAS* wild-type mCRC.[70,71]

In the phase II OLIVIA trial, patients with initially unresectable CRLM were randomized to anti-VEGF therapy (bevacizumab) plus modified FOLFOX or FOLFOXIRI.[72] In patients assigned to bevacizumab-FOLFOXIRI, the resection rate was 61% (95% CI 45–76) compared with 49% (95% CI 32–65) in the bevacizumab-mFOLFOX group; however, R0 resection rates were 49% and 23%, respectively. The observed increase in resection rate with bevacizumab-FOLFOXIRI also translated into prolonged PFS (18.6 months vs 11.5 months). Importantly, these multiagent regimens came at the cost of morbidity: 38 bevacizumab–FOLFOXIRI patients (95%) and 31 bevacizumab–mFOLFOX-6 patients (84%) experienced a grade 3 or greater toxicity event such as neutropenia, diarrhea, or febrile neutropenia. More recently, the BECOME trial tested whether adding bevacizumab to chemotherapy can improve resection rates in initially unresectable *RAS* mutant CRLM.[73] Although it is unclear which subsets of patients were converted, the R0 resection rate was 22.3% in the mFOLFOX plus bevacizumab group compared with 5.8% in the mFOLFOX group, suggesting bevacizumab can increase resection rates in *RAS*-mutant CRLM ($P < .01$).

To compare the effectiveness of cetuximab and bevacizumab, the multicenter FIRE-3 trial randomized patients with *KRAS* wild-type CRLM to either FOLFIRI plus cetuximab or bevacizumab as first-line treatment.[74] Interestingly, although no differences were observed in median PFS, patients in the cetuximab arm had a longer median OS than patients in the bevacizumab arm (28.7 vs 25.0 months, HR 0.77, 95% CI 0.62–0.96; $P = .017$). In a follow-up study of FIRE-3, the advantage of cetuximab over bevacizumab could only be observed in patients with CRLM and left-sided primary tumors.[75] As such, patients with *KRAS* wild-type CRLM from left-sided primary tumors may be considered for cytotoxic therapy in combination with anti-EGFR therapy, whereas those with right-sided primary tumors should be considered for bevacizumab, if addition of a biologic agent is deemed important. These results are congruent with the more recent ATOM trial from Japan, which demonstrated a median tumor shrinkage rate of 38% at 8 weeks in the cetuximab arm versus 25% in the bevacizumab arm. However, no differences were identified in the resection rate or PFS in that study.[76] As such, the choice of a neoadjuvant chemotherapy regimen for unresectable CRLM remains a complex and highly individualized decision.

Future Liver Remnant Augmentation Strategies: Two-Stage Hepatectomy with Portal Vein Embolization and Associating Liver Partition and Portal Vein Ligation for Staged hepatectomy

Although an FLR of approximately 25% to 30% is generally considered to be sufficient to maintain liver function in patients without liver disease, a larger future remnant liver is recommended for patients with chemotherapy-associated steatohepatitis and hepatic dysfunction to avoid PHLF.[77] To this end, several methods have been proposed to induce compensatory hypertrophy of the FLR and increase resectability in patients with extensive bilobar liver metastases. The concept of a two-stage hepatectomy

(TSH) was first introduced by Adam and colleagues as an approach involving an initial limited resection of the less affected side of the liver, followed by contralateral liver resection after a period of liver hypertrophy.[78] However, a high postoperative death rate of 15% after the second-stage procedure in this series prompted the development of an alternate 2-stage strategy involving portal vein embolization (PVE) to accelerate the liver hypertrophy process.[79] The hypertrophic potential of the liver was first demonstrated in a rabbit model by Rous and Larimore in the 1920s and is based on previous observations by James Cantlie from 1897.[80,81] However, it was not until 1975 that Honjo and colleagues introduced portal vein ligation (PVL) as part of a 2-stage extended hepatectomy approach, marking the first clinical implementation of compensatory liver hypertrophy triggered by portal vein occlusion.[82–84] Soon after, Kinoshita and Makuuchi described the strategy to induce liver hypertrophy by injection of embolizing agents in one of the portal branches in 1990. Although PVE results in ipsilateral atrophy with compensatory hypertrophy of the FLR, the absolute FLR volume seems to be less important than the kinetic growth rate (KGR). In a study by Shindoh and colleagues from MD Anderson Cancer Center, a KGR, defined as the volume of liver hypertrophy per week, exceeding 2%, was associated with decreased rates of PHLF.[85] Further, when the KGR exceeded 2% and the standardized FLR volume surpassed 30%, liver-related mortality was not observed. In a similar analysis from Memorial Sloan Kettering Cancer Center, Leung and colleagues reported a growth rate greater than 2.66% per week was necessary to mitigate the risk of PHLF.[86] As such, common practice today includes determination of the FLR volume, the degree of hypertrophy (final FLR volume − initial FLR volume), and KGR, all of which are considered before hepatectomy is performed. With these considerations now known, a contemporary series evaluated the safety and success rate of TSH with PVE. This series demonstrated a 5-year survival rate of 51% in the TSH group compared with 15% in nonsurgically treated patients ($P = .005$).[87] Importantly, the median number and size of CRLM did not differ between both groups, indicating that complete TSH is associated with excellent oncologic outcomes: 90-day mortality rate was 6% with a 49% morbidity rate after the second stage of hepatectomy, consistent with previously reported mortality and morbidity rates after TSR. In patients who do not respond to PVE, hepatic vein embolization (HVE) has been proposed as an additional strategy to increase FLR volume and achieve resectability.[88]

Beyond PVE and total venous deprivation strategies (PVE + HVE) with TSH, the associating liver partition with PVL for staged hepatectomy (ALPPS) technique, described by Schnitzbauer and colleagues, triggers a spectacularly rapid regeneration of the FLR and reduces the interval between the stage 1 and 2 hepatectomies from 4 to 6 weeks to only 7 to 14 days.[89] Despite an up to 80% reduction in the time needed to allow for sufficient FLR hypertrophy compared with PVE or PVL alone, ALPPS has gained fervent criticism due to concerns over mortality rates of up to 25%.[90] The multicenter randomized LIGRO trial was designed to assess these concerns and systematically compare ALPPS to TSH with PVL or PVE.[91] Although 87% of the patients in the ALPPS arm reached an FLR of more than 30% within just 7 days, only 30% of patients in the TSH group reached this milestone. Even after 4 weeks, only 47% of patients in the TSH group reached a 30% FLR, highlighting the extent of regeneration that can be achieved with ALPPS. Notably, the LIGRO study demonstrated a significant increase in the primary outcome of resection rate from 57% (95% CI 43–72) in the TSH arm to 92% (95% CI 84–100) in the ALPPS arm. Similarly, the estimated median survival in the ALPPS group was 46 months compared with 26 months in the TSH group in a follow-up study (95% CI 34–59 and 16–36, respectively; $P = .028$; **Fig. 2**).[92] Importantly, the LIGRO trial reported morbidity to be similar with 43% of the patients in

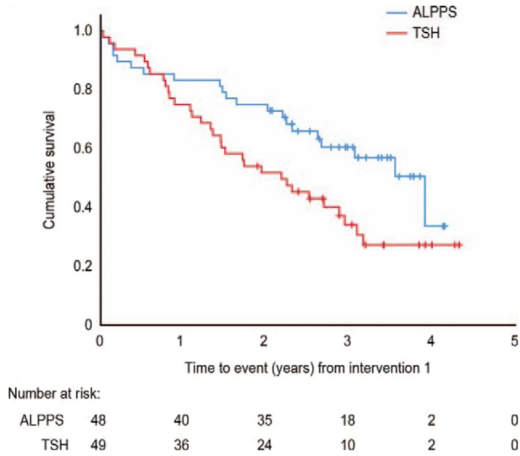

Fig. 2. ALPPS improves Overall Survival in patients with CRLM and an insufficient FLR compared with TSH. Overall survival curves for all included patients are shown. Estimated median survival in the ALPPS group was 46 months compared with 26 months in the TSH group. (*From* Hasselgren et al. ALPPS Improves Survival Compared With TSH in Patients Affected of CRLM: Survival Analysis From the Randomized Controlled Trial LIGRO. Ann Surg 2021 Mar 1;273(3):442-448.)

the ALPPS group and TSH group experiencing a grade IIIa or greater complication by Clavien–Dindo classification. Similarly, the 90-day mortality from the final intervention was 8.3% in the ALPPS group and 6.1% in the TSH group ($P = .68$), indicating similar rates of severe complications and mortality in this trial. In light of the LIGRO trial being conducted at high-volume ALPPS centers with tremendous experience, a meta-analysis inclusive of 90 studies and 4352 patients suggested ALPPS may be associated with higher morbidity and mortality rates.[93] Compared with TSH, ALPPS was associated with a trend toward increased morbidity (73% vs 59%; $P = .16$) and mortality (14% vs 7%; $P = .19$) after completion of second stage of either approach. As such, ALPPS remains controversial among hepatobiliary surgeons.

Hepatic Artery Infusion for Unresectable Colorectal Liver Metastases

Notably, although only 50% to 70% of patients with CRLM respond to first-line systemic chemotherapy, patients who fail to convert to resection ultimately reach dose-limiting toxicity and transition to second-line chemotherapy or maintenance chemotherapy. Unfortunately, response to second-line chemotherapy is typically only 5% to 20%.[94] In an RCT comparing second-line FOLFIRI with and without bevacizumab, the response rate in the combined arm was only 5% and median OS was only 11 months from the time of initiation of this regimen.[95] For patients whose therapy is de-escalated to maintenance capecitabine, PFS is improved by 2 months (3.9 vs 1.9 months, HR 0.44, 95% CI 0.33–0.57; $P < .0001$) but there is no difference in OS (15.2 vs 14.8 months; $P = .98$) compared with active monitoring (surveillance).[96] Given the limitations of systemic therapy in this population, HAI has been shown to improve survival and convert patients to resection in prospective studies. In the most recent randomized trial, the CALGB 9481 study compared HAI with FUDR alone to systemic 5-fluorouracil alone. Although these treatment arms are now both considered to be outdated regimens, Kemeny and colleagues reported an improvement in median survival (24.4 vs 20 months; $P = .0034$), longer time to hepatic progression

(9.8 vs 7.3 months; $P = .034$), and improved quality of life for patients with unresectable CRLM receiving HAI versus systemic therapy.[97] In a more recent phase II single-arm study, D'Angelica and colleagues evaluated the role of HAI combined with modern chemotherapy as a conversion strategy for patients with unresectable CRLM.[98] In this study of heavily pretreated patients (67% had already received 2–3 lines of chemotherapy) with a high disease burden (median 13 tumors), the response rate for the cohort was 73%.[98,99] Chemotherapy-naïve patients had a response rate of 86%, whereas the response rate was 67% even in previously treated patients.[98,99] Moreover, HAI combined with modern chemotherapy yielded a median OS and PFS of 38 months and 13 months, respectively. Notably, there was a significant difference in OS between chemotherapy-naive patients and those who had previously received chemotherapy (76.6 vs 29.7 months $P = .022$; **Fig. 3**A). Importantly, 52% of patients with extensive CRLM converted to resection. In the long-term follow-up landmark analysis of patients who converted to resection within 12 months of initiating HAI, 5-year survival was 63%, similar to survival endpoints in patients who are resectable at diagnosis (**Fig. 3**B).[98,99]

Although results with HAI for unresectable CRLM are encouraging, there remains ongoing skepticism regarding the safety, feasibility, and efficacy of this therapy outside of Memorial Sloan Kettering Cancer Center where this therapy has been pioneered and optimized since the 1980s. Beyond the approximately 20% of patients who experience a pump-specific complication related to the pocket, device, catheter, or artery, the major safety consideration is biliary sclerosis (defined as requiring an invasive biliary procedure); however, in the modern era, this serious complication from FUDR toxicity occurs in 2% to 8% of patients, with the risk being highest in the adjuvant setting.[59,98–100] In part due to awareness of these outcomes as well as

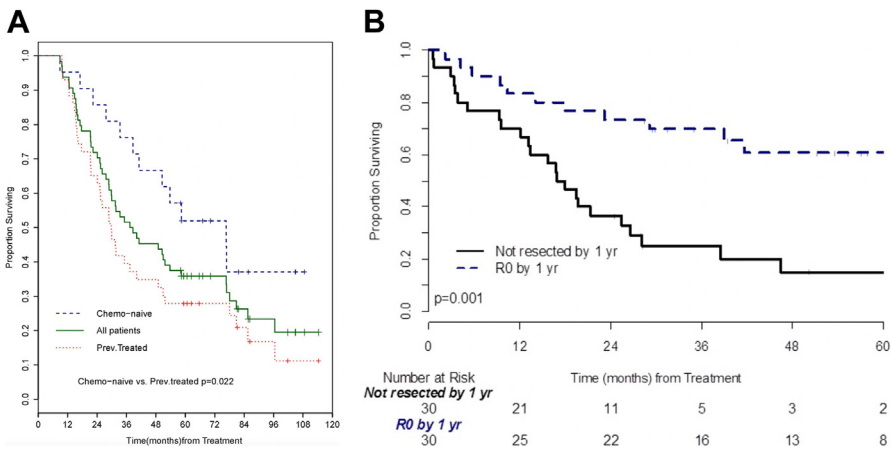

Fig. 3. Outcomes of patients with unresectable CRLM treated with HAI and systemic therapy in a nonrandomized, single-arm phase II study. (*A*) Landmark analysis demonstrated a median 3-year OS of 80% in patients who converted to and underwent resection within 12 months of initiating HAI versus 26% for those who did not convert. Time 0 to 12 months from start of treatment. (*B*) Overall survival stratified by prior chemotherapy exposure. Median survival was 38 months for all patients, 76.6 months for chemo-naïve patients and 29.7 months for previously treated patients. (*From* Pak et al. Prospective phase II trial of combination hepatic artery infusion and systemic chemotherapy for unresectable colorectal liver metastases: Long term results and curative potential. J Surg Oncol 2018 Mar;117(4):634-643. https://doi.org/10.1002/jso.24898.)

unacceptable outcomes with available systemic chemotherapy, there is renewed enthusiasm for HAI with rapid expansion of new HAI programs nationwide and worldwide.[101–104] Although it is anticipated that HAI will continue to expand, thereby improving access to many more patients, modern-day multicenter randomized trials are desperately needed to determine the exact role of HAI in standardized algorithms for patients.

Transplantation for Unresectable Colorectal Liver Metastases

Although liver transplantation is considered the standard of care for eligible patients with hepatocellular carcinoma, there are only limited data on the role of liver transplantation for CRLM. In their prospective SECA-II study, Dueland and colleagues reported OS at 1, 3, and 5 years of 100%, 83%, and 83%, respectively.[105] The median DFS was 13.7 months, with 1, 2, and 3 years DFS rates of 53%, 44%, and 35%, respectively. More recently, the group from Oslo, Norway published their results comparing highly selected patients who underwent hepatectomy after PVE versus liver transplant. The results of this study indicate that liver transplantation was associated with a 5-year OS of 33.4% compared with 6.7% for patients treated with PVE and liver resection.[106] In a subgroup analysis, 5-year OS was 45.3% for patients with liver transplantation for primary left-sided tumors compared with 0% for patients with an ascending colon primary tumor ($P<.01$). Patients receiving PVE only had a median OS of only 10.9 months, and 8 patients receiving liver resection after PVE had a median OS of 29.8 months. Consistent with these outcomes, a multicenter analysis for living-donor liver transplant from North America and the Netherlands reported acceptable donor morbidity with estimated 1.5-year recipient PFS and OS rates of 62% and 100%, respectively.[107] Because it becomes clear that transplant likely has a role in the management of patients with unresectable CRLM, recurrence seems inevitable, suggesting the importance of ongoing investigation to optimize patient selection for transplantation.

Immunotherapy

Immunotherapy has opened a new era in the management of numerous cancer types that are presumed to be immunogenic and characterized by a high tumor mutation burden. Although most CRLM do not represent disease entities with a high tumor neoantigen density, multiple strategies have been explored to enhance their immunogenicity. The REGONIVO trial evaluated the role of regorafenib and nivolumab in microsatellite stable or mismatch repair-proficient mCRC. Surprisingly, patients with liver metastases had a significantly lower response rate (8.3%) than those with lung metastases without any liver involvement (63.6%).[108] Recently, Mettu and colleagues reported that patients with refractory microsatellite/mismatch repair stable mCRC benefitted from cotargeting VEGF and programmed cell death 1 or programmed cell death ligand 1 (HR for PFS was 0.66; 95% CI 0.44–0.99).[109] Similar to the findings of the REGONIVO trial, the response rate was higher among patients without liver metastases (23.1%) compared with patients with liver metastasis (5.8%). One possible explanation for this finding comes from a recent study by Yu and colleagues investigating antitumor immunity in patients with liver metastases.[110] In a syngeneic murine model of CRC, tumor-antigen restricted cytotoxic T lymphocytes were found to undergo apoptosis on interaction with macrophages within liver metastases. As such, liver metastases might corrupt antitumor immunity and mediate resistance to immunotherapy.

DISCUSSION

During the course of their illness, nearly half of all patients diagnosed with CRC will develop metastatic disease in the liver. With CRC being one of the most common cancer diagnoses in men and women, CRLM represents the final stage of a complex multistep biological process and is a significant cause of morbidity and mortality worldwide. Although studies on the natural history of CRLM show few or no patients surviving beyond 3 years, the last few decades have seen enormous strides in the surgical and medical management of CRLM. Currently, resection of CRLM with the goal to achieve an R0 margin remains the only opportunity for cure. The extent of hepatic resection needed to achieve this goal is mainly dictated by the size, location, and the number of liver metastases. Resectability is best determined by an experienced liver surgeon who can then deploy parenchymal preserving approaches to eradicate all hepatic disease while minimizing morbidity. The decisions to use chemotherapy for resectable CRLM, and in what sequence with resection if at all, remain complex, and without clear evidence for a survival advantage with these therapies, such decisions should be tailored to each individual patient and their disease. Management strategies for patients who are not clearly resectable at diagnosis or are technically unresectable seem to be more straightforward at the outset; however, with modern systemic therapy regimens combined with aggressive surgical approaches including TSH with PVE, ALPPS, and/or liver-directed therapy with HAI, efforts may be focused on maximizing response to downstage CRLM and convert the patient to a resectable situation.

For patients with CRLM, it remains important to establish goals of therapy early on, such that treatment decisions can be formulated accordingly. As is evident from the literature included herein, evaluation of resectability, sequencing of surgery with chemotherapy, selection of the optimal chemotherapy regimen, and/or consideration of other modalities of treatment including liver-directed therapy with HAI, remains nuanced and best determined by a multidisciplinary team.

CLINICS CARE POINTS

- Higher-level evidence is needed for assessment of safety and patient outcomes in regard to the role of neoadjuvant chemotherapy for resectable CRLM.
- Determination of the optimal modality of treatment for each patient requires a multidisciplinary team.

DISCLOSURE

The authors have nothing to disclose.

REFERENCES

1. Siegel RL, Miller KD, Goding Sauer A, et al. Colorectal cancer statistics, 2020. CA Cancer J Clin 2020;70(3):145–64. https://doi.org/10.3322/caac.21601.
2. Dekker E, Tanis PJ, Vleugels JLA, et al. Colorectal cancer. Lancet 2019; 394(10207):1467–80. https://doi.org/10.1016/S0140-6736(19)32319-0.
3. Kneuertz PJ, Chang GJ, Hu CY, et al. Overtreatment of young adults with colon cancer: more intense treatments with unmatched survival gains. JAMA Surg 2015;150(5):402–9. https://doi.org/10.1001/jamasurg.2014.3572.

4. Liang JT, Huang KC, Cheng AL, et al. Clinicopathological and molecular biological features of colorectal cancer in patients less than 40 years of age. Br J Surg 2003;90(2):205–14. https://doi.org/10.1002/bjs.4015.
5. Siegel RL, Torre LA, Soerjomataram I, et al. Global patterns and trends in colorectal cancer incidence in young adults. Gut 2019;68(12):2179–85. https://doi.org/10.1136/gutjnl-2019-319511.
6. Lieu CH, Renfro LA, de Gramont A, et al. Association of age with survival in patients with metastatic colorectal cancer: analysis from the ARCAD Clinical Trials Program. J Clin Oncol 2014;32(27):2975–84. https://doi.org/10.1200/JCO.2013.54.9329.
7. Nitsche U, Stogbauer F, Spath C, et al. Right Sided Colon Cancer as a Distinct Histopathological Subtype with Reduced Prognosis. Dig Surg 2016;33(2):157–63. https://doi.org/10.1159/000443644.
8. Gervaz P, Bucher P, Morel P. Two colons-two cancers: paradigm shift and clinical implications. J Surg Oncol 2004;88(4):261–6. https://doi.org/10.1002/jso.20156.
9. Yahagi M, Okabayashi K, Hasegawa H, et al. The Worse Prognosis of Right-Sided Compared with Left-Sided Colon Cancers: a Systematic Review and Meta-analysis. J Gastrointest Surg 2016;20(3):648–55. https://doi.org/10.1007/s11605-015-3026-6.
10. Brule SY, Jonker DJ, Karapetis CS, et al. Location of colon cancer (right-sided versus left-sided) as a prognostic factor and a predictor of benefit from cetuximab in NCIC CO.17. Eur J Cancer 2015;51(11):1405–14. https://doi.org/10.1016/j.ejca.2015.03.015.
11. Engstrand J, Nilsson H, Stromberg C, et al. Colorectal cancer liver metastases - a population-based study on incidence, management and survival. BMC Cancer 2018;18(1):78. https://doi.org/10.1186/s12885-017-3925-x.
12. Petrelli F, Tomasello G, Borgonovo K, et al. Prognostic Survival Associated With Left-Sided vs Right-Sided Colon Cancer: A Systematic Review and Meta-analysis. JAMA Oncol 2017;3(2):211–9. https://doi.org/10.1001/jamaoncol.2016.4227.
13. Vayrynen V, Wirta EV, Seppala T, et al. Incidence and management of patients with colorectal cancer and synchronous and metachronous colorectal metastases: a population-based study. BJS Open 2020;4(4):685–92. https://doi.org/10.1002/bjs5.50299.
14. Andres A, Mentha G, Adam R, et al. Surgical management of patients with colorectal cancer and simultaneous liver and lung metastases. Br J Surg 2015;102(6):691–9. https://doi.org/10.1002/bjs.9783.
15. Wagner JS, Adson MA, Van Heerden JA, et al. The natural history of hepatic metastases from colorectal cancer. A comparison with resective treatment. Ann Surg 1984;199(5):502–8. https://doi.org/10.1097/00000658-198405000-00002.
16. Nordlinger B, Guiguet M, Vaillant JC, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Assoc Francaise de Chirurgie. Cancer 1996;77(7):1254–62.
17. Garden OJ, Rees M, Poston GJ, et al. Guidelines for resection of colorectal cancer liver metastases. Gut 2006;55(Suppl 3:iii):1–8. https://doi.org/10.1136/gut.2006.098053.
18. Hekimoglu K, Ustundag Y, Dusak A, et al. Small colorectal liver metastases: detection with SPIO-enhanced MRI in comparison with gadobenate

dimeglumine-enhanced MRI and CT imaging. Eur J Radiol 2011;77(3):468–72. https://doi.org/10.1016/j.ejrad.2009.09.002.
19. Sahani DV, Bajwa MA, Andrabi Y, et al. Current status of imaging and emerging techniques to evaluate liver metastases from colorectal carcinoma. Ann Surg 2014;259(5):861–72. https://doi.org/10.1097/SLA.0000000000000525.
20. Muhi A, Ichikawa T, Motosugi U, et al. Diagnosis of colorectal hepatic metastases: comparison of contrast-enhanced CT, contrast-enhanced US, superparamagnetic iron oxide-enhanced MRI, and gadoxetic acid-enhanced MRI. J Magn Reson Imaging 2011;34(2):326–35. https://doi.org/10.1002/jmri.22613.
21. Gorgec B, Hansen I, Kemmerich G, et al. Clinical added value of MRI to CT in patients scheduled for local therapy of colorectal liver metastases (CAMINO): study protocol for an international multicentre prospective diagnostic accuracy study. BMC Cancer 2021;21(1):1116. https://doi.org/10.1186/s12885-021-08833-1.
22. Creasy JM, Sadot E, Koerkamp BG, et al. Actual 10-year survival after hepatic resection of colorectal liver metastases: what factors preclude cure? Surgery 2018;163(6):1238–44. https://doi.org/10.1016/j.surg.2018.01.004.
23. 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(3):309–18. https://doi.org/10.1097/00000658-199909000-00004 ; discussion 318-21.
24. Mann CD, Metcalfe MS, Leopardi LN, et al. The clinical risk score: emerging as a reliable preoperative prognostic index in hepatectomy for colorectal metastases. Arch Surg 2004;139(11):1168–72. https://doi.org/10.1001/archsurg.139.11.1168.
25. Nagashima I, Takada T, Adachi M, et al. Proposal of criteria to select candidates with colorectal liver metastases for hepatic resection: comparison of our scoring system to the positive number of risk factors. World J Gastroenterol 2006;12(39):6305–9. https://doi.org/10.3748/wjg.v12.i39.6305.
26. Konopke R, Kersting S, Distler M, et al. Prognostic factors and evaluation of a clinical score for predicting survival after resection of colorectal liver metastases. Liver Int 2009;29(1):89–102. https://doi.org/10.1111/j.1478-3231.2008.01845.x.
27. Vega EA, Salehi O, Nicolaescu D, et al. Correction to: Failure to Cure Patients with Colorectal Liver Metastases: The Impact of the Liver Surgeon. Ann Surg Oncol 2021;28(Suppl 3):879. https://doi.org/10.1245/s10434-021-10185-w.
28. Akita H, Sasaki Y, Yamada T, et al. Real-time intraoperative assessment of residual liver functional reserve using pulse dye densitometry. World J Surg 2008;32(12):2668–74. https://doi.org/10.1007/s00268-008-9752-0.
29. Kauffmann R, Fong Y. Post-hepatectomy liver failure. Hepatobiliary Surg Nutr 2014;3(5):238–46. https://doi.org/10.3978/j.issn.2304-3881.2014.09.01.
30. Margonis GA, Sergentanis TN, Ntanasis-Stathopoulos I, et al. Impact of Surgical Margin Width on Recurrence and Overall Survival Following R0 Hepatic Resection of Colorectal Metastases: A Systematic Review and Meta-analysis. Ann Surg 2018;267(6):1047–55. https://doi.org/10.1097/SLA.0000000000002552.
31. Pawlik TM, Scoggins CR, Zorzi D, et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. Ann Surg 2005;241(5):715–22. https://doi.org/10.1097/01.sla.0000160703.75808.7d, discussion 722-4.
32. Margonis GA, Buettner S, Andreatos N, et al. Anatomical Resections Improve Disease-free Survival in Patients With KRAS-mutated Colorectal Liver

Metastases. Ann Surg 2017;266(4):641–9. https://doi.org/10.1097/SLA.0000000000002367.
33. Muratore A, Ribero D, Zimmitti G, et al. Resection margin and recurrence-free survival after liver resection of colorectal metastases. Ann Surg Oncol 2010; 17(5):1324–9. https://doi.org/10.1245/s10434-009-0770-4.
34. Matsumura M, Mise Y, Saiura A, et al. Parenchymal-Sparing Hepatectomy Does Not Increase Intrahepatic Recurrence in Patients with Advanced Colorectal Liver Metastases. Ann Surg Oncol 2016;23(11):3718–26. https://doi.org/10.1245/s10434-016-5278-0.
35. Kingham TP, Correa-Gallego C, D'Angelica MI, et al. Hepatic parenchymal preservation surgery: decreasing morbidity and mortality rates in 4,152 resections for malignancy. J Am Coll Surg 2015;220(4):471–9. https://doi.org/10.1016/j.jamcollsurg.2014.12.026.
36. Deng G, Li H, Jia GQ, et al. Parenchymal-sparing versus extended hepatectomy for colorectal liver metastases: A systematic review and meta-analysis. Cancer Med 2019;8(14):6165–75. https://doi.org/10.1002/cam4.2515.
37. Moris D, Ronnekleiv-Kelly S, Rahnemai-Azar AA, et al. Parenchymal-Sparing Versus Anatomic Liver Resection for Colorectal Liver Metastases: a Systematic Review. J Gastrointest Surg 2017;21(6):1076–85. https://doi.org/10.1007/s11605-017-3397-y.
38. Matsuki R, Mise Y, Saiura A, et al. Parenchymal-sparing hepatectomy for deep-placed colorectal liver metastases. Surgery 2016;160(5):1256–63. https://doi.org/10.1016/j.surg.2016.06.041.
39. Mise Y, Aloia TA, Brudvik KW, et al. Parenchymal-sparing Hepatectomy in Colorectal Liver Metastasis Improves Salvageability and Survival. Ann Surg 2016; 263(1):146–52. https://doi.org/10.1097/SLA.0000000000001194.
40. 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(10):2619–26. https://doi.org/10.1093/annonc/mds053.
41. Siperstein AE, Berber E, Ballem N, et al. Survival after radiofrequency ablation of colorectal liver metastases: 10-year experience. Ann Surg 2007;246(4):559–65. https://doi.org/10.1097/SLA.0b013e318155a7b6 ; discussion 565-7.
42. Shibata T, Niinobu T, Ogata N, et al. Microwave coagulation therapy for multiple hepatic metastases from colorectal carcinoma. Cancer 2000;89(2):276–84.
43. Cheng Y, Zhang L, Li H, et al. Laparoscopic versus open liver resection for colorectal liver metastases: a systematic review. J Surg Res 2017;220:234–46. https://doi.org/10.1016/j.jss.2017.05.110.
44. Syn NL, Kabir T, Koh YX, et al. Survival Advantage of Laparoscopic Versus Open Resection For Colorectal Liver Metastases: A Meta-analysis of Individual Patient Data From Randomized Trials and Propensity-score Matched Studies. Ann Surg 2020;272(2):253–65. https://doi.org/10.1097/SLA.0000000000003672.
45. Fretland AA, Dagenborg VJ, Bjornelv GMW, et al. Laparoscopic Versus Open Resection for Colorectal Liver Metastases: The OSLO-COMET Randomized Controlled Trial. Ann Surg 2018;267(2):199–207. https://doi.org/10.1097/SLA.0000000000002353.
46. Portier G, Elias D, Bouche O, et al. Multicenter randomized trial of adjuvant fluorouracil and folinic acid compared with surgery alone after resection of colorectal liver metastases: FFCD ACHBTH AURC 9002 trial. J Clin Oncol 2006; 24(31):4976–82. https://doi.org/10.1200/JCO.2006.06.8353.

47. Mitry E, Fields AL, Bleiberg H, et al. Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials. J Clin Oncol 2008;26(30):4906–11. https://doi.org/10.1200/JCO.2008.17.3781.
48. Ychou M, Raoul JL, Douillard JY, et al. A phase III randomised trial of LV5FU2 + irinotecan versus LV5FU2 alone in adjuvant high-risk colon cancer (FNCLCC Accord02/FFCD9802). Ann Oncol 2009;20(4):674–80. https://doi.org/10.1093/annonc/mdn680.
49. 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(34):3789–99. https://doi.org/10.1200/JCO.21.01032.
50. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet 2008;371(9617):1007–16. https://doi.org/10.1016/S0140-6736(08)60455-9.
51. 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(12):1208–15. https://doi.org/10.1016/S1470-2045(13)70447-9.
52. Ayez N, van der Stok EP, de Wilt H, et al. Neo-adjuvant chemotherapy followed by surgery versus surgery alone in high-risk patients with resectable colorectal liver metastases: the CHARISMA randomized multicenter clinical trial. BMC Cancer 2015;15:180. https://doi.org/10.1186/s12885-015-1199-8.
53. Primrose J, Falk S, Finch-Jones M, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial. Lancet Oncol 2014;15(6):601–11. https://doi.org/10.1016/S1470-2045(14)70105-6.
54. Bridgewater JA, Pugh SA, Maishman T, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis (New EPOC): long-term results of a multicentre, randomised, controlled, phase 3 trial. Lancet Oncol 2020;21(3):398–411. https://doi.org/10.1016/S1470-2045(19)30798-3.
55. Breedis C, Young G. The blood supply of neoplasms in the liver. Am J Pathol 1954;30(5):969–77.
56. Clarkson B, Young C, Dierick W, et al. Effects of continuous hepatic artery infusion of antimetabolites on primary and metastatic cancer of the liver. Cancer 1962;15:472–88.
57. Sullivan RD, Norcross JW, Watkins E Jr. Chemotherapy of Metastatic Liver Cancer by Prolonged Hepatic-Artery Infusion. N Engl J Med 1964;270:321–7. https://doi.org/10.1056/NEJM196402132700701.
58. Kemeny N, Huang Y, Cohen AM, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. N Engl J Med 1999;341(27):2039–48. https://doi.org/10.1056/NEJM199912303412702.
59. Kemeny NE, Chou JF, Boucher TM, et al. Updated long-term survival for patients with metastatic colorectal cancer treated with liver resection followed by hepatic arterial infusion and systemic chemotherapy. J Surg Oncol 2016;113(5):477–84. https://doi.org/10.1002/jso.24189.

60. Groot Koerkamp B, Sadot E, Kemeny NE, et al. Perioperative Hepatic Arterial Infusion Pump Chemotherapy Is Associated With Longer Survival After Resection of Colorectal Liver Metastases: A Propensity Score Analysis. J Clin Oncol 2017;35(17):1938–44. https://doi.org/10.1200/JCO.2016.71.8346.
61. Gholami S, Kemeny NE, Boucher TM, et al. Adjuvant Hepatic Artery Infusion Chemotherapy is Associated With Improved Survival Regardless of KRAS Mutation Status in Patients With Resected Colorectal Liver Metastases: A Retrospective Analysis of 674 Patients. Ann Surg 2020;272(2):352–6. https://doi.org/10.1097/SLA.0000000000003248.
62. Altendorf-Hofmann A, Scheele J. A critical review of the major indicators of prognosis after resection of hepatic metastases from colorectal carcinoma. Surg Oncol Clin N Am 2003;12(1):165–92. https://doi.org/10.1016/s1055-3207(02)00091-1, xi.
63. Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg 2004;240(4):644–57. https://doi.org/10.1097/01.sla.0000141198.92114.f6 [discussion: 657-8].
64. Pozzo C, Basso M, Cassano A, et al. Neoadjuvant treatment of unresectable liver disease with irinotecan and 5-fluorouracil plus folinic acid in colorectal cancer patients. Ann Oncol 2004;15(6):933–9. https://doi.org/10.1093/annonc/mdh217.
65. Bismuth H, Adam R, Levi F, et al. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. Ann Surg 1996;224(4):509–20. https://doi.org/10.1097/00000658-199610000-00009 [discussion 520-2].
66. Ychou M, Rivoire M, Thezenas S, et al. A randomized phase II trial of three intensified chemotherapy regimens in first-line treatment of colorectal cancer patients with initially unresectable or not optimally resectable liver metastases. The METHEP trial. Ann Surg Oncol 2013;20(13):4289–97. https://doi.org/10.1245/s10434-013-3217-x.
67. Folprecht G, Gruenberger T, Bechstein WO, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. Lancet Oncol 2010;11(1):38–47. https://doi.org/10.1016/S1470-2045(09)70330-4.
68. Folprecht G, Gruenberger T, Bechstein W, et al. Survival of patients with initially unresectable colorectal liver metastases treated with FOLFOX/cetuximab or FOLFIRI/cetuximab in a multidisciplinary concept (CELIM study). Ann Oncol 2014;25(5):1018–25. https://doi.org/10.1093/annonc/mdu088.
69. Van Cutsem E, Kohne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 2009;360(14):1408–17. https://doi.org/10.1056/NEJMoa0805019.
70. Bokemeyer C, Bondarenko I, Hartmann JT, et al. Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study. Ann Oncol 2011;22(7):1535–46. https://doi.org/10.1093/annonc/mdq632.
71. Bokemeyer C, Bondarenko I, Makhson A, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol 2009;27(5):663–71. https://doi.org/10.1200/JCO.2008.20.8397.
72. 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(4):702–8. https://doi.org/10.1093/annonc/mdu580.
73. Tang W, Ren L, Liu T, et al. Bevacizumab Plus mFOLFOX6 Versus mFOLFOX6 Alone as First-Line Treatment for RAS Mutant Unresectable Colorectal Liver-Limited Metastases: The BECOME Randomized Controlled Trial. J Clin Oncol 2020;38(27):3175–84. https://doi.org/10.1200/JCO.20.00174.
74. 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(10):1065–75. https://doi.org/10.1016/S1470-2045(14)70330-4.
75. Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab or bevacizumab for advanced colorectal cancer: final survival and per-protocol analysis of FIRE-3, a randomised clinical trial. Br J Cancer 2021;124(3): 587–94. https://doi.org/10.1038/s41416-020-01140-9.
76. Oki E, Emi Y, Yamanaka T, et al. Randomised phase II trial of mFOLFOX6 plus bevacizumab versus mFOLFOX6 plus cetuximab as first-line treatment for colorectal liver metastasis (ATOM trial). Br J Cancer 2019;121(3):222–9. https://doi.org/10.1038/s41416-019-0518-2.
77. Tucker ON, Heaton N. The 'small for size' liver syndrome. Curr Opin Crit Care 2005;11(2):150–5. https://doi.org/10.1097/01.ccx.0000157080.11117.45.
78. Adam R, Laurent A, Azoulay D, et al. Two-stage hepatectomy: A planned strategy to treat irresectable liver tumors. Ann Surg 2000;232(6):777–85. https://doi.org/10.1097/00000658-200012000-00006.
79. Jaeck D, Oussoultzoglou E, Rosso E, et al. A two-stage hepatectomy procedure combined with portal vein embolization to achieve curative resection for initially unresectable multiple and bilobar colorectal liver metastases. Ann Surg 2004; 240(6):1037–49. https://doi.org/10.1097/01.sla.0000145965.86383.89 [discussion: 1049-51].
80. Rous P, Larimore LD. Relation of the Portal Blood to Liver Maintenance : A Demonstration of Liver Atrophy Conditional on Compensation. J Exp Med 1920;31(5):609–32. https://doi.org/10.1084/jem.31.5.609.
81. van Gulik TM, van den Esschert JW. James Cantlie's early messages for hepatic surgeons: how the concept of pre-operative portal vein occlusion was defined. HPB (Oxford) 2010;12(2):81–3.
82. Kinoshita H, Sakai K, Hirohashi K, et al. Preoperative portal vein embolization for hepatocellular carcinoma. World J Surg 1986;10(5):803–8. https://doi.org/10.1007/BF01655244.
83. Makuuchi M, Thai BL, Takayasu K, et al. Preoperative portal embolization to increase safety of major hepatectomy for hilar bile duct carcinoma: a preliminary report. Surgery 1990;107(5):521–7.
84. Honjo I, Suzuki T, Ozawa K, et al. Ligation of a branch of the portal vein for carcinoma of the liver. Am J Surg 1975;130(3):296–302. https://doi.org/10.1016/0002-9610(75)90389-x.
85. Shindoh J, Truty MJ, Aloia TA, et al. Kinetic growth rate after portal vein embolization predicts posthepatectomy outcomes: toward zero liver-related mortality in patients with colorectal liver metastases and small future liver remnant. J Am Coll Surg 2013;216(2):201–9. https://doi.org/10.1016/j.jamcollsurg.2012.10.018.
86. Leung U, Simpson AL, Araujo RL, et al. Remnant growth rate after portal vein embolization is a good early predictor of post-hepatectomy liver failure. J Am

Coll Surg 2014;219(4):620–30. https://doi.org/10.1016/j.jamcollsurg.2014.04.022.
87. Brouquet A, Abdalla EK, Kopetz S, et al. High survival rate after two-stage resection of advanced colorectal liver metastases: response-based selection and complete resection define outcome. J Clin Oncol 2011;29(8):1083–90. https://doi.org/10.1200/JCO.2010.32.6132.
88. Hwang S, Lee SG, Ko GY, et al. Sequential preoperative ipsilateral hepatic vein embolization after portal vein embolization to induce further liver regeneration in patients with hepatobiliary malignancy. Ann Surg 2009;249(4):608–16. https://doi.org/10.1097/SLA.0b013e31819ecc5c.
89. Schnitzbauer AA, Lang SA, Goessmann H, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. Ann Surg 2012;255(3):405–14. https://doi.org/10.1097/SLA.0b013e31824856f5.
90. Kang D, Schadde E. Hypertrophy and Liver Function in ALPPS: Correlation with Morbidity and Mortality. Visc Med 2017;33(6):426–33. https://doi.org/10.1159/000479477.
91. Sandstrom P, Rosok BI, Sparrelid E, et al. ALPPS Improves Resectability Compared With Conventional Two-stage Hepatectomy in Patients With Advanced Colorectal Liver Metastasis: Results From a Scandinavian Multicenter Randomized Controlled Trial (LIGRO Trial). Ann Surg 2018;267(5):833–40. https://doi.org/10.1097/SLA.0000000000002511.
92. Hasselgren K, Rosok BI, Larsen PN, et al. ALPPS Improves Survival Compared With TSH in Patients Affected of CRLM: Survival Analysis From the Randomized Controlled Trial LIGRO. Ann Surg 2021;273(3):442–8. https://doi.org/10.1097/SLA.0000000000003701.
93. Eshmuminov D, Raptis DA, Linecker M, et al. Meta-analysis of associating liver partition with portal vein ligation and portal vein occlusion for two-stage hepatectomy. Br J Surg 2016;103(13):1768–82. https://doi.org/10.1002/bjs.10290.
94. Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004;22(2):229–37. https://doi.org/10.1200/JCO.2004.05.113.
95. Bennouna J, Sastre J, Arnold D, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. Lancet Oncol 2013;14(1):29–37. https://doi.org/10.1016/S1470-2045(12)70477-1.
96. Adams RA, Fisher DJ, Graham J, et al. Capecitabine Versus Active Monitoring in Stable or Responding Metastatic Colorectal Cancer After 16 Weeks of First-Line Therapy: Results of the Randomized FOCUS4-N Trial. J Clin Oncol 2021;39(33):3693–704. https://doi.org/10.1200/JCO.21.01436.
97. 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(9):1395–403. https://doi.org/10.1200/JCO.2005.03.8166.
98. D'Angelica MI, Correa-Gallego C, Paty PB, et al. Phase II trial of hepatic artery infusional and systemic chemotherapy for patients with unresectable hepatic metastases from colorectal cancer: conversion to resection and long-term outcomes. Ann Surg 2015;261(2):353–60. https://doi.org/10.1097/SLA.0000000000000614.

99. Pak LM, Kemeny NE, Capanu M, et al. Prospective phase II trial of combination hepatic artery infusion and systemic chemotherapy for unresectable colorectal liver metastases: Long term results and curative potential. J Surg Oncol 2018; 117(4):634–43. https://doi.org/10.1002/jso.24898.
100. Allen PJ, Nissan A, Picon AI, et al. Technical complications and durability of hepatic artery infusion pumps for unresectable colorectal liver metastases: an institutional experience of 544 consecutive cases. J Am Coll Surg 2005; 201(1):57–65. https://doi.org/10.1016/j.jamcollsurg.2005.03.019.
101. Chakedis J, Beal EW, Sun S, et al. Implementation and early outcomes for a surgeon-directed hepatic arterial infusion pump program for colorectal liver metastases. J Surg Oncol 2018;118(7):1065–73. https://doi.org/10.1002/jso.25249.
102. Creasy JM, Napier KJ, Reed SA, et al. Implementation of a Hepatic Artery Infusion Program: Initial Patient Selection and Perioperative Outcomes of Concurrent Hepatic Artery Infusion and Systemic Chemotherapy for Colorectal Liver Metastases. Ann Surg Oncol 2020. https://doi.org/10.1245/s10434-020-08972-y.
103. Dhir M, Jones HL, Shuai Y, et al. Hepatic Arterial Infusion in Combination with Modern Systemic Chemotherapy is Associated with Improved Survival Compared with Modern Systemic Chemotherapy Alone in Patients with Isolated Unresectable Colorectal Liver Metastases: A Case-Control Study. Ann Surg Oncol 2017;24(1):150–8. https://doi.org/10.1245/s10434-016-5418-6.
104. Muaddi H, D'Angelica M, Wiseman JT, et al. Safety and feasibility of initiating a hepatic artery infusion pump chemotherapy program for unresectable colorectal liver metastases: A multicenter, retrospective cohort study. J Surg Oncol 2021;123(1):252–60. https://doi.org/10.1002/jso.26270.
105. Dueland S, Syversveen T, Solheim JM, et al. Survival Following Liver Transplantation for Patients With Nonresectable Liver-only Colorectal Metastases. Ann Surg 2020;271(2):212–8. https://doi.org/10.1097/SLA.0000000000003404.
106. Dueland S, Yaqub S, Syversveen T, et al. Survival Outcomes After Portal Vein Embolization and Liver Resection Compared With Liver Transplant for Patients With Extensive Colorectal Cancer Liver Metastases. JAMA Surg 2021;156(6): 550–7. https://doi.org/10.1001/jamasurg.2021.0267.
107. Hernandez-Alejandro R, Ruffolo LI, Sasaki K, et al. Recipient and Donor Outcomes After Living-Donor Liver Transplant for Unresectable Colorectal Liver Metastases. JAMA Surg 2022. https://doi.org/10.1001/jamasurg.2022.0300.
108. Fukuoka S, Hara H, Takahashi N, et al. Regorafenib Plus Nivolumab in Patients With Advanced Gastric or Colorectal Cancer: An Open-Label, Dose-Escalation, and Dose-Expansion Phase Ib Trial (REGONIVO, EPOC1603). J Clin Oncol 2020;38(18):2053–61. https://doi.org/10.1200/JCO.19.03296.
109. Mettu NB, Ou FS, Zemla TJ, et al. Assessment of Capecitabine and Bevacizumab With or Without Atezolizumab for the Treatment of Refractory Metastatic Colorectal Cancer: A Randomized Clinical Trial. JAMA Netw Open 2022;5(2): e2149040. https://doi.org/10.1001/jamanetworkopen.2021.49040.
110. Yu J, Green MD, Li S, et al. Liver metastasis restrains immunotherapy efficacy via macrophage-mediated T cell elimination. Nat Med 2021;27(1):152–64. https://doi.org/10.1038/s41591-020-1131-x.