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Liver Transplantation in the Management of Colorectal Cancer with Liver Metastases

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Abstract

Over the past ten years, accumulating evidence from several clinical investigations has shown that liver transplantation offers a meaningful survival advantage for selected patients with colorectal cancer and liver metastases. In parallel, progress in donor organ preservation techniques has increased the available donor pool, thereby enabling consideration of broader indications for liver transplantation, including patients with unresectable colorectal cancer liver metastases. Current evidence indicates that overall survival (OS) following liver transplantation in this population is comparable to outcomes observed in standard liver transplant recipients. On the basis of these findings, organ allocation policies in the United States are evolving to permit the use of deceased donor livers for carefully selected patients with unresectable colorectal cancer liver metastases. Published studies consistently highlight improved outcomes among patients who undergo complete (R0) resection of the primary tumor, receive 6–12 months of systemic chemotherapy before transplantation, and undergo meticulous radiologic reassessment—often incorporating positron emission tomography/computed tomography—to exclude extrahepatic disease. Tumor responsiveness to pretransplant chemotherapy is a critical determinant of long-term benefit, whereas disease progression during chemotherapy is generally regarded as a contraindication to transplantation. Favorable prognostic indicators reported in the literature include a carcinoembryonic antigen level ≤80 µg/L and a maximum liver lesion diameter <5.5 cm, both of which correlate with superior progression-free survival and OS. Compared with chemotherapy alone, liver transplantation for unresectable colorectal cancer liver metastases is associated with prolonged progression-free and overall survival. Rigorous patient selection using imaging, laboratory parameters, and clinical assessment is essential to identify individuals most likely to benefit. Accordingly, liver transplantation should be considered at centers with active transplant programs as a strategy to improve outcomes in patients with advanced colorectal cancer.

Keywords: Colon cancer, Rectal cancer, Liver transplantation, Metastasis, Chemotherapy

Introduction

Colorectal cancer (CRC) comprises malignant epithelial tumors arising in the large intestine. In 2023, approximately 152,810 new CRC cases and 53,010 CRC-related deaths were reported in the United States, representing 7.6% of new cancer diagnoses and 8.7% of cancer-related mortality, respectively [1]. Data from the Surveillance, Epidemiology, and End Results (SEER) program indicate an overall 5-year relative survival rate of 65.0% across all CRC stages [1]. At initial diagnosis, about 23% of patients present with disease extending beyond the primary tumor and regional lymph nodes. Although 5-year survival exceeds 70% for localized and regional disease, outcomes remain poor for patients with distant metastases, with only 15.7% surviving at 5 years [1].

Liver involvement is common in metastatic CRC, with approximately 60% of patients developing hepatic metastases [2]. For patients with resectable colorectal cancer liver metastases (CRLM), hepatic resection remains the preferred treatment, as it offers superior survival compared with systemic chemotherapy alone [3–7]. Recent evidence suggests that thermal ablation for small hepatic lesions may yield survival outcomes

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comparable to surgical metastasectomy [8]. Additional liver-directed strategies—including staged hepatectomy, portal vein embolization, radiofrequency ablation, chemoembolization, and yttrium-90 radioembolization—may be employed alone or alongside limited surgical resection in selected cases where complete resection is not feasible [9]. Importantly, adding tumor debulking to palliative chemotherapy has not demonstrated a survival benefit in metastatic CRC [10].

Hepatic arterial infusion (HAI) chemotherapy represents another liver-focused approach, delivering agents—most often fluoropyrimidines—directly into the hepatic circulation via an implanted pump. Although early studies suggest improved local disease control compared with systemic therapy, a clear overall survival benefit has not been established, and comparative data with other liver-directed modalities and long-term outcomes remain limited [11–14]. Moreover, HAI therapy requires specialized surgical and oncologic expertise typically confined to high-volume centers.

In many patients, liver-directed treatments are either unsuitable or contraindicated, most often because of extensive intrahepatic tumor burden, prompting consideration of liver transplantation for CRLM. Early European experiences with transplantation for CRLM in the late 1970s through early 1990s yielded modest results, with reported 3-year and 5-year OS rates of 36% and 18%, respectively [15]. Since that time, major advances in CRC staging, prognostic assessment, systemic therapy, immunosuppressive management, and perioperative care—together with the implementation of stringent selection criteria—have transformed outcomes. Contemporary studies now report 5-year OS rates exceeding 80% in highly selected patients, a striking improvement compared with historical outcomes for metastatic CRLM (<20%) and comparable to survival after liver transplantation for nonmalignant indications (approximately 80.2%) [16, 17].

The success of transplantation for other hepatic malignancies, including hepatocellular carcinoma and intrahepatic cholangiocarcinoma, further supports its oncologic potential [18]. In a small, carefully selected cohort, survival after transplantation for CRLM was reported to be similar to outcomes observed in patients transplanted for hepatocellular carcinoma [19]. These advances, combined with overall improvements in transplant practice, have renewed interest in liver transplantation as a therapeutic option for CRLM. This review summarizes key clinical studies, emphasizing current evidence, ongoing areas of investigation, and remaining knowledge gaps.

Materials and Methods

A comprehensive literature search was conducted using PubMed and Google Scholar with combinations of the following keywords: “colon cancer,” “rectal cancer,” “colorectal cancer,” “liver metastasis,” “liver metastases,” and “liver transplantation.” All articles deemed relevant were independently reviewed by all authors. Only English-language publications were included. Reference lists of selected articles were examined to identify additional pertinent studies. Related literature addressing chemotherapy, metastasectomy, and liver-directed therapies was incorporated when agreed upon by all authors. Given the scarcity of randomized controlled trials in this field, retrospective and observational studies were also included by consensus.

Results and Discussion

Ten publications reporting primary data on patients with CRLM undergoing liver transplantation were identified. Eight of these represented distinct patient cohorts [20–27]. One subsequent analysis compared outcomes from the SECA trial cohort with a matched chemotherapy-treated population from the NORDIC-VII trial [28]. An additional study provided extended follow-up data for the SECA trial cohort, reporting long-term outcomes [29].

Outcomes of liver transplantation in CRLM

Recent investigations of liver transplantation for CRLM have been driven largely by centers in Oslo, Norway, where comparatively shorter waiting times for donor organs facilitate timely transplantation. Smaller retrospective series from the United States have also contributed to the growing body of evidence. The available results from these studies are summarized below and presented in **Table 1**.

Table 1. Summary of existing studies of liver transplantation for colorectal cancer with liver metastases

Authors (Year), Study Name	Location	Time Period	Sample Size	Study Design	Inclusion Criteria	Exclusion Criteria	Key Findings
Hernandez-Alejandro *et al*. (2022)	United States, Canada	2017–2021	n = 10	Retrospective review from three North American transplant centers	Adherence to International Hepato-Pancreato-Biliary Association Consensus Guidelines	Disease progression during pre-transplant chemotherapy	• 1.5-year disease-free survival: 62% • 1.5-year overall survival: 100% • Recurrences in 3 patients at 99, 121, and 199 days after transplantation
Sasaki *et al*. (2023)	United States	2017–2022	n = 64 listed n = 46 transplanted	Retrospective analysis of liver transplantation for colorectal liver metastases using UNOS database	No specific criteria reported No mention of pre-transplant chemotherapy	Not reported	• 1- and 3-year disease-free survival: 75.1% and 53.7% • 1- and 3-year overall survival: 89.0% and 60.4% • Median MELD-Na score: 8
Adam *et al*. (2024), TRANSMET trial	France, Italy, Belgium	2016–2021	n = 94	Prospective, randomized trial comparing chemotherapy alone (n = 47) versus chemotherapy plus liver transplantation (n = 47)	• Stable disease or partial response to chemotherapy for at least 3 months before transplantation (per RECIST criteria) • Colonoscopy performed prior to transplantation • CEA level < 80 µg/L or at least 50% reduction from peak value	• Stable disease or disease progression during chemotherapy before transplantation • Primary tumor with BRAF mutation • Presence of extrahepatic disease • History of other malignancy	• 5-year overall survival: 73% in transplantation + chemotherapy group vs. 9% in chemotherapy alone group (HR 0.16; 95% CI 0.07–0.33) • Median progression-free survival: 17.4 months vs. 6.4 months (HR 0.34; 95% CI 0.20–0.58) • Among patients with post-transplant therapy, 15 of 38 were disease-free at the end of the study

Solheim *et al*. (2023)	Dueland *et al*. (2015)	Hagness *et al*. (2013), SECA-I trial	Kaltenmeier *et al*. (2023)
Norway	Norway	Norway	United States
2006–2012	2006–2012	2006–2011	2019–2022
n = 23	n = 21 per group	n = 21	n = 10
Long-term (≥10 years) follow-up of patients enrolled during SECA-I period	Cross-trial comparison of SECA-I transplant cohort with 21 longest-surviving patients from NORDIC-VII chemotherapy trial	Prospective single-arm study	Retrospective single-center (University of Pittsburgh) report of liver transplantation for colorectal liver metastases
Same as SECA-I: • Primary tumor resected • At least 6 weeks of pre-transplant chemotherapy	Same as SECA-I: • Primary tumor resected • At least 6 weeks of pre-transplant chemotherapy	• Primary tumor resected • At least 6 weeks of chemotherapy prior to transplantation • No extrahepatic metastases (confirmed by CT and exploratory laparotomy)	• Primary tumor resected • 6–12 weeks of pre-transplant chemotherapy with stable disease or partial response • Pre-transplant colonoscopy • No extrahepatic metastases • CEA < 100 ng/dL
Same as SECA-I: • Extrahepatic metastases • Other malignancy • Weight loss > 10%	Same as SECA-I: • Extrahepatic metastases • Other malignancy • Weight loss > 10%	• Extrahepatic metastases • Other malignancy • Weight loss > 10%	• Other malignancies (per institutional policy) • BRAF-mutated primary tumors
• Median disease-free survival: 10 months • 5-year overall survival: 43.5% • 10-year overall survival: 26.1% (4 patients alive without evidence of disease at last follow-up) • All 4 long-term survivors had lung metastasectomy for isolated pulmonary recurrence • Factors associated with shorter overall survival: largest tumor > 5.5 cm (P = .003), CEA > 80 µg/L (P = .008), stable or partial response at transplantation (P = .045)	• Median progression-free survival: 10 months (transplant) vs. 8 months (chemotherapy) • 5-year overall survival: 56% (transplant) vs. 9% (chemotherapy cohort; P < .001) and vs. 19% (longest-surviving chemotherapy subgroup; P = .012) • 5-year overall survival after relapse: 53% (transplant) vs. 6% (chemotherapy; P < .001)	• Overall survival at 1, 3, and 5 years: 95%, 68%, 60% • 1-year disease-free survival: 35% • Factors linked to poorer overall survival: CEA > 80 µg/L and largest metastasis > 5.5 cm	• Mean recurrence-free survival: 2.2 years • Mean overall survival: 3.0 years • Median MELD-Na score: 10.5 • Recurrences: lung (n = 2, treated with segmentectomy) and liver (n = 1, treated with radiofrequency ablation)

Toso *et al.* (2017)	Smedman *et al.* (2020), SECA-II Arm D	Dueland *et al.* (2020), SECA-II
Portugal, France, Switzerland	Norway	Norway
1995–2015	2014–2018	2012–2016
n = 12	n = 10	n = 15
Retrospective observational study	Observational single-arm report of " Arm D" patients ineligible for other SECA-II arms; intentional use of expanded-criteria donor organs (n = 9)	Prospective single-arm study (no chemotherapy control)
• Primary tumor resected • Offered transplantation when not candidate for liver resection • All 11 patients with pre-transplant chemotherapy achieved partial response	Similar to main SECA-II but permitted resectable pulmonary metastases	• Primary tumor resected • Pre-transplant PET/CT and CT chest/abdomen/pelvis showing no disease outside liver • Partial response to ≥6 weeks of pre-transplant chemotherapy • Negative pre-transplant colonoscopy • No tumor > 10 cm
Not otherwise specified	Reasons for exclusion from other SECA-II arms: • <10% response to chemotherapy (n = 5) • Progression on third-line chemotherapy • Extrahepatic metastases • History of papillary thyroid cancer	• Weight loss > 10% • BMI > 30 kg/m² • Other malignancy • Extrahepatic metastatic disease • Investigator judgment
• Overall survival at 1, 3, and 5 years: 83%, 62%, 50% • Disease-free survival at 1, 3, and 5 years: 56%, 38%, 38% • Pre-transplant CEA ≥ 80 µg/L and time to liver transplantation ≥ 24 months associated with shorter disease-free survival	• Median disease-free survival: 4 months • Median overall survival: 18 months • Overall survival significantly shorter than SECA-II Arm C (P = .002) • Post-relapse overall survival after chemotherapy: 17.4 months (Arm C) vs. 8.6 months (Arm D; P = .003) • 2-year overall survival: 43% (Arm D) vs. 100% (main SECA-II) vs. 91% (SECA-I)	• Median disease-free survival: 13.7 months • Overall survival at 1, 3, and 5 years: 100%, 83%, 83% • Disease-free survival at 1, 2, and 3 years: 53%, 44%, 35% • Survival after relapse at 1, 2, and 4 years: 100%, 73%, 73% • Longer disease-free survival with Fong Clinical Risk Score 1–2 vs. 3–4 (11.8 months vs. not reached; P = .044)

Abbreviations: BMI, body mass index; CEA, carcinoembryonic antigen; CI, confidence interval; CT, computed tomography; DFS, disease-free survival; HR, hazard ratio; LT, liver transplantation; MELD-Na, model for end-stage liver disease-sodium; OS, overall survival; PET, positron emission tomography; RECIST, Response Evaluation Criteria in Solid Tumors.

TRANSMET

More recently, Adam and colleagues reported the findings of the TRANSMET randomized trial, which compared systemic chemotherapy alone with chemotherapy followed by liver transplantation in patients with unresectable colorectal cancer liver metastases (CRLM; n = 94) [20]. All enrolled patients received a minimum of 3 months of chemotherapy, and only those achieving stable disease (SD) or a partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST) were eligible for randomization. This response-based requirement is a notable distinction from the earlier SECA study, in which transplantation was permitted despite disease progression

provided it remained confined to the liver, a difference that may partly explain the inferior outcomes observed in SECA.

Additional eligibility criteria included BRAF wild-type status, prior resection of the primary tumor with a "safe" surgical margin (although this margin was not explicitly defined), absence of extrahepatic disease as confirmed by fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT), contrast-enhanced CT (ceCT), and colonoscopy, as well as a carcinoembryonic antigen (CEA) level <80 µg/L or a ≥50% reduction from the highest previously recorded value. The latter represents a novel and dynamic use of CEA, potentially offering a more informative assessment than reliance on a fixed cutoff alone. The median interval from primary tumor resection to transplantation was 14.6 months.

After randomization but prior to transplantation, nine patients developed progressive disease (PD). Among the 38 patients who ultimately underwent transplantation, three required retransplantation, with one associated death. This corresponded to a patient survival rate of 97.4% and a graft survival rate of 92.2%, both exceeding expected 1-year outcomes reported by the United Network for Organ Sharing (UNOS) [17, 30]. Posttransplant chemotherapy was administered to most patients (68%), at the discretion of treating physicians. An unintended crossover occurred, with nine patients in the chemotherapy-only arm subsequently undergoing either metastasectomy or transplantation.

In the intention-to-treat analysis, the 5-year overall survival (OS) rate was 57% in the transplant group compared with 13% in the chemotherapy-only group (P = .0003; hazard ratio [HR] 0.37, 95% CI 0.21–0.65). Per-protocol analysis demonstrated even greater separation, with 5-year OS rates of 73% versus 9%, respectively (HR 0.16, 95% CI 0.07–0.33). Median progression-free survival (PFS) was also significantly prolonged in the transplant arm (17.4 vs 6.4 months; HR 0.34, 95% CI 0.20–0.58). When contextualized against UNOS data showing a 5-year OS of 80.2% across all liver transplant indications in the United States, the 73% 5-year OS observed in TRANSMET supports acceptable equity in organ allocation [17, 30].

Disease recurrence occurred in 28 transplanted patients (74%), most commonly involving the lungs (39%). Importantly, the study design allowed for active treatment of recurrence using surgical resection or ablation. At the time of publication, 15 of the 38 transplanted patients were disease-free. Major strengths of TRANSMET include its randomized design, standardized pretransplant chemotherapy and response criteria, systematic incorporation of CEA dynamics and advanced imaging (PET/CT and ceCT), and a relatively large cohort. Collectively, these data represent the most robust evidence to date that liver transplantation confers significant improvements in both OS and PFS over chemotherapy alone in a contemporary CRLM population.

North american studies

Within the United States and broader North America, evidence has largely emerged outside of formal randomized trials. Sasaki *et al*. analyzed liver transplantation for CRLM using data from the UNOS registry, identifying patients listed between 2017 and 2022 [25]. Of 64 listed patients, 46 (71.9%) ultimately received a transplant. Several important trends were noted: most listings originated from high-volume transplant centers (84.2%), patients were distributed across nearly all UNOS regions, and listings increased steadily from 2017–2018 through 2020–2021, reflecting growing interest in transplantation for CRLM. Notably, patient travel was common, with 53.1% traveling from another state and 32.8% coming from nonadjacent states. After a median follow-up of 360 days, disease recurrence was documented in 10 transplanted patients (21.7%), and 6 deaths (13.0%) during follow-up were attributed to recurrent cancer. Reported disease-free survival (DFS) rates at 1 and 3 years were 75.1% and 53.7%, respectively, while OS rates at 1 and 3 years were 89.0% and 60.4%. Outcomes differed by donor type, with significantly lower 1- and 3-year OS following deceased-donor transplantation compared with living-donor liver transplantation (LDLT; 77.1% and 51.4% vs 100% and 71.4%, P = .049). OS did not differ significantly when compared with contemporaneous cohorts transplanted for high-risk hepatocellular carcinoma or cholangiocarcinoma. Although specific selection criteria were not detailed, this analysis provides valuable insight into the expanding practice of CRLM transplantation at high-volume U.S. centers and demonstrates OS outcomes comparable to those reported in TRANSMET.

In another North American experience involving two U.S. centers and one Canadian center, Hernandez-Alejandro *et al*. retrospectively evaluated 10 patients with CRLM who underwent LDLT in accordance with Hepato-Pancreato-Biliary Association consensus

recommendations [23, 31]. This cohort included several high-risk features: four patients had T4b primary tumors, seven had nodal involvement, three exhibited poorly differentiated histology, two had right-sided primaries, and one harbored a BRAF D594G mutation.

Patient selection was informed in part by the Oslo score, which assigns one point each for CEA >80 µg/L, maximum tumor diameter >5.5 cm, PD during pretransplant chemotherapy, and an interval of less than 2 years between primary tumor resection and transplantation. Post hoc analyses of combined SECA-I and SECA-II cohorts demonstrated that higher Oslo scores (3–4 vs 0–2) were associated with shorter OS and earlier recurrence, leading to its adoption in several transplant trials, including this one [32].

In the Hernandez-Alejandro cohort, the median Oslo score was 1.5, consistent with stringent patient selection. All patients demonstrated a response to 5-fluorouracil–based chemotherapy. With a median follow-up of 1.5 years, recurrence occurred in three patients (30%). One death was reported, yielding 1.5-year DFS and OS rates of 62% and 100%, respectively. Despite the small sample size, this study highlights the feasibility of applying established selection criteria for CRLM transplantation in North America with favorable early outcomes.

A separate single-center series from the University of Pittsburgh Medical Center was reported by Kaltenmeier *et al*., who retrospectively reviewed outcomes in 10 patients undergoing LDLT for CRLM [24]. Eligibility criteria included resection of the primary tumor at least 6 months before transplantation, 6–12 weeks of chemotherapy resulting in SD or response, comprehensive pretransplant imaging to exclude extrahepatic disease, a CEA level <100 ng/dL, and the presence of a suitable living donor. Unlike most contemporary studies, no upper limit was placed on the number or size of liver metastases; notably, half of the patients had lesions exceeding 5 cm in diameter. The median Oslo score was 1.5. Two patients had T4b primaries, two had right-sided tumors, and lymph node involvement was present in half of the cohort.

With a median follow-up of 1.6 years, three patients experienced recurrence, resulting in a mean recurrence-free survival of 2.2 years. Two recurrences involved the lungs and were managed surgically with segmentectomy, while one hepatic recurrence was treated with radiofrequency ablation. Mean OS was 3.0 years, exceeding the recently reported median OS of 32.4 months for metastatic CRC treated between 2016 and 2019 [33]. However, deviations from prevailing practice—particularly the inclusion of patients with large tumors and the relatively short duration of pretransplant chemotherapy—likely influenced outcomes. Despite these differences, the findings reinforce that carefully selected patients with CRLM can derive meaningful survival benefit from liver transplantation.

European studies

The earliest experiences with liver transplantation for colorectal cancer liver metastases (CRLM), along with many landmark investigations, originated in Oslo, Norway. Norway's relatively robust donor organ availability enabled exploration of transplantation for malignant indications earlier than in countries with longer waiting times, such as the United States. Hagness *et al*. reported the first of these studies, SECA-I, which included 21 patients transplanted between 2006 and 2011 [22]. With a median follow-up of 27 months, the investigators observed a 5-year overall survival (OS) rate of 60% and a 1-year disease-free survival (DFS) rate of 35%.

This same cohort was later compared, in a cross-trial analysis, with patients treated with chemotherapy alone in the contemporaneous NORDIC-VII trial [28]. Despite the inherent limitations of such comparisons, transplanted patients demonstrated markedly superior outcomes, with a 5-year OS of 56% versus 9% in the chemotherapy group (P < .001). This survival advantage persisted even when the comparison was restricted to the 21 chemotherapy patients with the longest survival (56 percent vs 19 percent, P = .012). Long-term follow-up published in 2023 further demonstrated sustained benefit, reporting 5- and 10-year OS rates of 43.5 percent and 26.1 percent, respectively [29]. Across both the initial and extended analyses, smaller tumor size (<5.5 cm; P = .003), lower carcinoembryonic antigen (CEA) levels (<80 µg/L; P = .008), and stable disease or partial response at the time of transplantation (P = .045) were consistently associated with prolonged survival, reinforcing the prognostic relevance of these factors and their incorporation into the Oslo Score.

A subsequent and distinct cohort study from the same group evaluated 15 patients transplanted between 2006 and 2012 using more stringent selection criteria, including standardized chemotherapy between primary tumor resection and transplantation with documented partial response and comprehensive pretransplant imaging [21]. Pretransplant chemotherapy resulted in

significant reductions in CEA levels (P = .001), maximum tumor diameter (P = .003), and the number of hepatic lesions (P = .001), emphasizing the central role of systemic therapy before transplantation. With a median follow-up of 60 months, reported 1-, 3-, and 5-year OS rates were 100%, 83%, and 83%, respectively. Median DFS was 13.7 months, with corresponding 1-, 2-, and 3-year DFS rates of 53%, 44%, and 35%. Lower Oslo scores, reduced CEA levels, and smaller tumor size were proposed as key contributors to the improved outcomes observed in SECA-II compared with SECA-I.

SECA-II also included an additional exploratory cohort, designated arm D, consisting of 10 patients transplanted during the same period but excluded from the main SECA-II cohort because of poor chemotherapy response (<10%) or the presence of extrahepatic disease; these patients received expanded-criteria donor organs [26]. In this group, median DFS was only 4 months and median OS was 18 months. While DFS did not differ significantly between SECA-II arms C (synchronous metastases) and D (P = .202), OS was substantially longer in arm C (2-year OS 100% vs 43%, P = .002), again underscoring the critical importance of strict selection criteria and, in particular, responsiveness to pretransplant chemotherapy.

Beyond Norway, a collaborative group from southwestern Europe—predominantly Portugal—reported a narrative series of 12 liver transplants performed for CRLM between 1995 and 2015 [27]. Nearly all patients (11/12) received chemotherapy before transplantation, and all achieved a partial response prior to transplant. Similar to SECA-I, all patients were considered unsuitable for liver-directed therapies at the time transplantation was pursued. With a median follow-up of 26 months, 1-, 3-, and 5-year OS rates were 83%, 62 percent, and 50 percent, respectively, while DFS rates at the same time points were 56 percent, 38 percent, and 38 percent. Notably, four patients with at least 3.5 years of follow-up remained free of disease.

Active studies of transplantation for CRLM

Several ongoing clinical trials aim to address remaining uncertainties regarding liver transplantation for CRLM. Common eligibility criteria across these studies include pretransplant PET/CT imaging, Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, and measurable disease according to RECIST. Consistent with existing evidence, disease progression at the time of randomization or transplantation is uniformly considered an exclusion criterion.

Of particular relevance to the expanding donor pool, the Swedish SOULMATE trial (NCT04161092) is a randomized, multicenter study evaluating transplantation using expanded-criteria donor organs compared with best alternative nontransplant care, as determined by the treating physician [34].

The Oslo group is also actively enrolling patients in SECA-III, a randomized trial comparing liver transplantation with alternative standard-of-care treatments selected by the multidisciplinary team [35]. Patients eligible for liver metastasectomy are excluded. The randomized design represents a major strength, complementing evidence from TRANSMET. Notably, SECA-III permits resectable lung metastases, potentially allowing evaluation of outcomes in patients undergoing transplantation combined with pulmonary metastasectomy. This is supported by long-term SECA-I follow-up, in which all four patients alive at 10 years had experienced lung-only recurrence treated with metastasectomy and remained disease-free [29]. Focused investigation of posttransplant lung metastasectomy for isolated pulmonary recurrence is therefore warranted.

In Italy, the COLT observational study is evaluating patients who undergo liver transplantation while concurrently enrolled in a clinical trial involving triplet chemotherapy plus an anti-EGFR agent for CRLM [36]. Outcomes in transplanted patients will be compared with a matched cohort receiving chemotherapy alone, a design that is inherently less robust than the randomized approaches used in SECA-III and TRANSMET. Additionally, a Spanish observational study employing similar eligibility criteria is underway [37]. Most of these trials are expected to report results in 2026 or later.

Patient selection and disease biology

The International Hepato-Pancreato-Biliary Association has proposed preliminary guidance for selecting candidates for liver transplantation in CRLM [31]. As evidence continues to evolve, both UNOS policies and center-specific criteria are expected to be refined. Current recommendations generally restrict transplantation to patients whose liver metastases are deemed unresectable despite standard, advanced, or combined liver-directed approaches, consistent with published data. The prognostic performance of individual selection parameters is discussed below and summarized in **Table 2**.

Table 2. Existing parameters to optimize patient selection for liver transplantation in colorectal cancer with liver metastases

Category	Parameter	Cutoff/Definition	Details
Established parameters	CEA	< 80 µg/L	• In SECA-I, CEA > 80 µg/L linked to reduced overall survival (P = .003) • Confirmed in 10-year SECA-I follow-up (P = .008) • TRANSMET trial permitted higher initial CEA if ≥50% decrease occurred prior to transplantation
	Largest tumor diameter	< 5.5 cm	• SECA-I demonstrated diameter > 5.5 cm associated with poorer overall survival (P = .026) • Reconfirmed in 10-year follow-up (P = .003) • SECA-II excluded lesions > 10 cm • Not used as exclusion in TRANSMET trial
	Response to pre-transplant chemotherapy	Stable disease or partial response (vs. progressive disease)	• SECA-I included patients with various responses; progressive disease negatively impacted overall survival (P = .04) • Reaffirmed in 10-year follow-up (P = .045) • Both TRANSMET and SECA-II excluded patients with progressive disease on pre-transplant chemotherapy
	Time to liver transplantation (from primary tumor resection)	Preferably 1–2 years (Exact interval varies across studies)	• Derived from Fong Clinical Risk Score, where >1 year disease-free interval after primary resection improved outcomes in metastasectomy • In SECA-I, time >2 years linked to worse overall survival (P = .045), but not significant in 10-year follow-up (P = .227) • Later studies used ≥1 year: – TRANSMET: median 14.6 months – SECA-II: minimum 12 months, median 22.6 months – Toso *et al*.: median 41 months
	Oslo Score (1 point each for: CEA > 80 µg/L, largest tumor > 5.5 cm, progressive disease on pre-transplant chemotherapy, time to transplantation < 2 years)	Low risk (0–2 points) vs. high risk (3–4 points)	• Post hoc analysis combining SECA-I and SECA-II patients (n = 19) showed low scores associated with better outcomes: – Median disease-free survival: 19 vs. 3 months (P = .004) – 5-year overall survival: 67% vs. 17% (P = .004) – 5-year survival after relapse: 45% vs. 17% (P = .019)
	Pre-transplant PET/CT and contrast-enhanced CT	No evidence of extrahepatic metastatic disease	• Required in all ongoing trials • Contrast-enhanced CT identifies extrahepatic metastases (especially small pulmonary lesions) that may be missed by PET/CT
	Metabolic tumor volume (MTV) on PET/CT	< 70 cm^3	• Post hoc SECA-II analysis: MTV ≥ cutoff associated with lower 5-year overall survival (P = .027)
Parameters requiring further study	Histology	Well/moderately differentiated vs. poorly differentiated, undifferentiated, or signet ring cell	• Poorly differentiated subtypes generally have worse prognosis with standard therapies • SECA-II Arm D (60% poor histologies) showed inferior overall survival vs. other cohorts • 2-year overall survival significantly lower than SECA-II Arm C (P = .002) • Limitations: cross-trial comparisons, confounding variables, small numbers
	Primary tumor sidedness	Left-sided vs. right-sided	• Right-sided primaries considered more aggressive overall • SECA-II Arm D showed trend toward shorter disease-free and overall survival for right-sided tumors (not statistically significant) • Insufficient evidence to exclude based on sidedness alone

	BRAF mutational status	Wild-type vs. mutated	• Limited inclusion of mutated cases in studies; analyses underpowered • No definitive impact on transplantation outcomes identified
	Primary tumor T stage	T1–T3 vs. T4	• Most trials include few T4 cases; subgroup analyses limited by sample size • Future trials recommended to perform T-stage subgroup evaluation
	Primary tumor nodal status	Node-negative vs. node-positive	• Trials include mixed nodal stages; subgroup analyses limited by sample size • Future trials recommended to perform N-stage subgroup evaluation
	Fong Clinical Risk Score (FCRS)	Lower scores (0–2) preferred (Validated only in metastasectomy)	• In SECA-II, longer disease-free survival for scores 1–2 vs. 3–4 (P = .044) • Largely superseded by Oslo Score, which is more transplantation-specific
	Pre-transplant FDG PET/CT total lesion glycolysis (TLG)	< 257 g	• Post hoc SECA-II analysis: lower TLG linked to better 5-year overall survival (P = .026) • Now largely replaced by MTV as primary PET metric
	Intraoperative frozen section of suspicious lymph nodes	Negative for malignancy	• Several studies perform frozen section analysis of concerning nodes before proceeding to transplantation • No standardized protocol or dedicated outcomes study

Abbreviations: CEA, carcinoembryonic antigen; CT, computed tomography; DFS, disease-free survival; FDG, fluorodeoxyglucose; LT, liver transplantation; MTV, metabolic tumor volume; OS, overall survival; PET/CT, positron emission tomography/computed tomography; TLG, total lesion glycolysis.

Molecular and histologic criteria

In addition, current guidance emphasizes a distinct set of "molecular criteria" for candidate selection. Specifically, eligible tumors should lack the BRAF V600E mutation and demonstrate microsatellite stability with intact mismatch repair (MMR) function. Colorectal cancers harboring BRAF mutations are consistently associated with inferior disease-free survival (DFS) and overall survival (OS), including in patients undergoing liver metastasectomy [38, 39]. Although BRAF-targeted therapies have shown clear benefit in the systemic management of BRAF-mutant CRC, their role in the setting of liver transplantation remains undefined and requires further investigation [40, 41]. At present, evidence is insufficient to support firm conclusions regarding transplantation outcomes in patients with BRAF-mutated disease.

Concerns related to microsatellite instability (MSI) or deficient MMR (dMMR) are more substantial. Multiple trials evaluating immunotherapy in metastatic CRC with MSI-high or dMMR status have demonstrated prolonged survival, often extending for several years. Notably, results from the CheckMate-142 study reported a median OS of 44.2 months in patients with metastatic dMMR CRC treated with nivolumab [42–45]. Importantly, immune checkpoint inhibitor (ICI) therapy carries a high risk of allograft rejection when administered after solid organ transplantation. Consequently, proceeding with transplantation in this subgroup could preclude the future use of highly effective ICI therapy, representing a significant therapeutic trade-off.

Other histopathologic and clinical features that may influence transplant candidacy include tumor differentiation (eg, poorly differentiated histology), tumor sidedness (right-sided versus left-sided colon or rectal primaries), and TNM stage. These variables warrant further systematic evaluation before being fully integrated into standardized selection algorithms.

Practical considerations for transplantation in CRLM

For carefully selected patients with unresectable CRLM, liver transplantation provides a clear survival advantage over current standard therapies. Nevertheless, the limited supply of donor livers necessitates careful consideration of ethical principles, particularly equity and beneficence, when expanding transplantation to oncologic indications. Mortality attributable to end-stage liver disease (ESLD) exceeds deaths related to CRC, with 54,803 ESLD-related deaths reported in 2022 [16]. Among patients placed on the transplant waitlist, only 54.5% undergo

transplantation within one year, while 15.6% are removed because of death or clinical deterioration [17]. National outcomes following transplantation for ESLD demonstrate 1-, 3-, and 5-year OS rates of 93.2%, 87.3%, and 80.2%, respectively [17]. Consequently, transplant centers offering transplantation for CRLM must achieve outcomes comparable to national benchmarks, accounting for center-specific risk adjustment, to justify appropriate utilization of scarce organs.

Organ allocation

The adoption of liver transplantation as a treatment option for selected CRLM patients must align with the existing organ allocation and distribution framework. In the United States, this system is governed by the Organ Procurement and Transplant Network (OPTN) and administered by the United Network for Organ Sharing (UNOS) [46]. Allocation is primarily driven by medical urgency, supplemented by geographic considerations based on nautical distance from the donor hospital. Medical urgency is quantified using the Model for End-Stage Liver Disease (MELD) score, which estimates 90-day mortality risk in patients with ESLD [47].

Established policies allow certain patient groups to receive MELD exception points, effectively increasing their waitlist priority to reflect mortality risk comparable to patients with higher biologic MELD scores [48]. In June 2024, OPTN and UNOS approved revisions to transplant oncology allocation policy to formally include MELD exceptions for patients with CRLM, with implementation scheduled for January 2025 [49]. These exception requests will be evaluated by the National Liver Review Board, composed of transplant physicians and surgeons, and must satisfy predefined selection criteria to be approved **(Table 3)**. The granted exception score will correspond to the median MELD at transplant minus either 20 or 15 points, whichever value is higher [49].

Table 3. National liver review board guidance for liver transplantation in colorectal cancer with liver metastases: patient selection criteria and MELD exception points

Category	Component	Criteria	Category
Eligibility for initial MELD exception points	Primary diagnosis	• Confirmed histological diagnosis of colorectal adenocarcinoma • BRAF wild-type • Microsatellite stable • Minimum of 12 months from diagnosis of colorectal liver metastases to initial MELD exception request	**Eligibility for initial MELD exception points**
	Treatment of primary tumor	• Complete resection of primary tumor with clear (negative) margins • No evidence of local recurrence on colonoscopy performed within 12 months before initial exception request	
	Evaluation of extrahepatic disease	• No evidence of extrahepatic metastatic disease or local recurrence on CT/MRI (chest, abdomen, pelvis) and PET scan within 1 month of initial request	
	Hepatic disease and prior treatment	• Ongoing or completed first-line systemic chemotherapy/immunotherapy • Liver metastases either relapsed after prior liver resection or deemed ineligible for curative-intent resection • No hepatic lesion exceeding 10 cm in diameter prior to initiation of treatment • Disease stable or responding (regressing) to systemic and/or locoregional therapy for at least 6 months	
Exclusion criteria	—	• Any extrahepatic disease following primary tumor resection (including lymphadenopathy beyond the primary drainage basin) • Local recurrence of primary tumor • CEA > 80 µg/L (regardless of radiographic progression or new lesions)	**Exclusion criteria**
MELD exception extension criteria (Reassessed every 3 months)	—	Candidates with colorectal liver metastases may qualify for continued MELD exception if they satisfy all of the following: • CT or MRI (chest, abdomen, pelvis) showing no progression of intrahepatic disease and no extrahepatic disease • CEA < 80 µg/L	**MELD exception extension criteria** (Reassessed every 3 months)

Abbreviations: CEA, carcinoembryonic antigen; cm, centimeters; CRLM, colorectal cancer with liver metastases; CT, computed tomography; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; MRI, magnetic resonance imaging; PET, positron emission tomography; µg/L, micrograms per liter.

Importantly, the allocation and distribution frameworks described above apply exclusively to recipients of deceased donor organs. In contrast, the use of living donor liver transplantation (LDLT) is governed by center-specific criteria and is not constrained by transplant indication or MELD score. Consequently, LDLT represents a particularly attractive option for patients with CRLM, as it offers greater predictability regarding transplant timing and graft quality and, based on limited available evidence, may be associated with improved outcomes [23–25]. For patients without access to a living donor, placement on the deceased donor waitlist remains feasible, with the understanding that proposed MELD exception policies are intended to provide sufficient priority to compete for organs, although such patients are unlikely to rank at the top of the waitlist at most centers. In this setting, transplant timing may be variable and influenced by institutional practices, and available grafts are more likely to derive from donation after circulatory death (DCD) donors. Recent progress in normothermic machine perfusion has substantially expanded the utilization of DCD grafts by enabling improved assessment of organ viability and achieving outcomes comparable to those of donation after brain death donors [50, 51]. These advances are rapidly becoming standard practice in the United States and have largely mitigated the historical concerns regarding inferior graft or patient survival associated with DCD organs.

Limitations and opportunities for further study

Ongoing clinical trials evaluating transplantation for CRLM are expected to substantially enrich the evidence base. Of particular importance are studies with larger cohorts randomized to chemotherapy alone versus chemotherapy followed by transplantation, as this design most directly addresses management decisions for unresectable CRLM. The role of hepatic arterial infusion (HAI) therapy in the context of transplantation also warrants focused investigation, particularly its potential to convert unresectable disease to resectable status and thereby delay or obviate the need for transplant. The largest HAI study to date reported a median recurrence-free survival (RFS) of 25 months following resection of liver metastases, exceeding the progression-free survival reported in most transplant trials; however, overall survival outcomes differ substantially, underscoring the need for comparative and integrative studies of HAI and transplantation [12]. Moreover, the impact of prior HAI pump placement on the technical complexity and outcomes of subsequent liver transplantation remains poorly characterized.

Pre- and posttransplant chemotherapy

Key aspects of systemic therapy—including optimal duration, sequencing, and drug selection—require further evaluation in randomized trials. Reported durations of pretransplant chemotherapy range from 3 to 6 months across studies, while the recommended observation interval before transplantation varies widely, from as short as 3 months to more than 2 years, despite guideline suggestions of approximately 1 year [20, 31, 52]. A variety of agents, including 5-fluorouracil, irinotecan, oxaliplatin, cetuximab, and bevacizumab, have been used in differing combinations, and no clear evidence currently supports the superiority of any specific regimen. Although pretransplant chemotherapy is uniformly applied, the use of posttransplant chemotherapy has largely been left to clinician discretion. More standardized approaches may further improve outcomes. In this context, circulating tumor DNA (ctDNA) represents a promising tool; strategies modeled after the CIRCULATE trials—such as administering posttransplant chemotherapy only to patients with detectable ctDNA while observing those with ctDNA clearance—may be particularly informative [53].

Quality of life and cost-effectiveness

As the clinical evidence continues to evolve, parallel evaluation of patient-centered and economic outcomes is essential. Quality-of-life assessments using validated instruments should be incorporated into all ongoing and future CRLM transplant studies. Similarly, robust cost-effectiveness analyses comparing transplantation with standard chemotherapy are lacking. Existing data highlight the necessity of stringent patient selection to avoid excessive costs associated with widespread implementation [54, 55]. More comprehensive cost-effectiveness analyses could also inform workforce-related outcomes, such as differences in duration of employment following transplantation versus alternative therapies. These considerations are especially relevant given the rising incidence of CRC among younger adults, in contrast to stable or declining rates in older populations [56, 57]. For younger patients, the extended survival associated with transplantation may translate into prolonged workforce participation and potential

long-term economic benefit. Nevertheless, cost implications are likely to vary substantially across centers and countries, reflecting differences in waitlist dynamics, reimbursement structures, and societal factors.

Donor organ source

Further investigation is also needed regarding graft source and the role of machine perfusion technologies in CRLM transplantation. The SOULMATE trial specifically evaluates the use of DCD grafts, but additional studies examining moderately to severely steatotic livers or hepatitis C–positive grafts followed by antiviral therapy would be novel in this context. Comparative analyses of normothermic machine perfusion versus hypothermic oxygenated perfusion (HOPE) for CRLM indications have not yet been performed and could be addressed in future randomized studies. Strategies to rehabilitate otherwise discarded organs using normothermic perfusion—such as defatting protocols or pharmacologic interventions—may further expand the donor pool. Achieving these advances will require close collaboration among medical oncologists, transplant hepatologists, and transplant surgeons to optimize study design and clinical workflows within specialized centers.

Conclusion

Liver transplantation offers substantial potential to improve outcomes for patients with colorectal cancer liver metastases compared with chemotherapy and other liver-directed therapies. Although disease-free survival varies across studies, the cumulative evidence clearly demonstrates a significant overall survival advantage for patients with unresectable CRLM who undergo transplantation relative to chemotherapy alone. Implementation of transplantation for CRLM should therefore be considered at centers with established transplant programs. Continued refinement of patient selection remains a critical area of investigation, with several well-validated clinical, radiologic, and molecular parameters currently available to guide selection and maximize therapeutic benefit.

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References

1. Cancer Stat Facts: Colorectal Cancer. National Cancer Institute. Accessed May 22, 2024. https://seer.cancer.gov/statfacts/html/colorect.html
2. Riihimaki M, Hemminki A, Sundquist J, Hemminki K.. Patterns of metastasis in colon and rectal cancer. Sci Rep. 2016;6:29765. https://doi.org/10.1038/srep29765
3. Benson AB, Venook AP, Al-Hawary MM, et al. Colon Cancer, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021;19:329-359. https://doi.org/10.6004/jnccn.2021.0012
4. Benson AB, Venook AP, Al-Hawary MM, et al. Rectal cancer, version 2.2022, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2022;20:1139-1167. https://doi.org/10.6004/jnccn.2022.0051
5. 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;163:1238-1244. https://doi.org/10.1016/j.surg.2018.01.004
6. Kanas GP, Taylor A, Primrose JN, et al. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. Clin Epidemiol. 2012;4:283-301. https://doi.org/10.2147/CLEP.S34285
7. Tomlinson JS, Jarnagin WR, DeMatteo RP, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. J Clin Oncol. 2007;25:4575-4580. https://doi.org/10.1200/JCO.2007.11.0833
8. Meijerink MR vdLS, Dijkstra M, Versteeg KS, et al. Surgery versus thermal ablation for small-size colorectal liver metastases (COLLISION): an international, multicenter, phase III randomized controlled trial. J Clin Oncol. 2024;42. https://doi.org/10.1200/JCO.2024.42.17_suppl.LBA3501
9. Martin J, Petrillo A, Smyth EC, et al. Colorectal liver metastases: Current management and future perspectives. World J Clin Oncol. 2020;11:761-808. https://doi.org/ 10.5306/wjco.v11.i10.761
10. Gootjes EC AA, Bakkerus L, Zonderhuis BM, et al. Primary outcome analysis of the ORCHESTRA trial: a randomized phase III trial of additional tumor debulking to first-line palliative systemic therapy for patients with multiorgan metastatic colorectal cancer. J Clin Oncol. 2024;42. https://doi.org/10.1200/JCO.2024.42.17_suppl.LBA3502
11. Chan DL, Alzahrani NA, Morris DL, Chua TC.. Systematic review and meta-analysis of hepatic arterial infusion chemotherapy as bridging therapy for colorectal liver metastases. Surg Oncol. 2015;24:162-171. https://doi.org/10.1016/j.suronc.2015.06.014
12. Goere D, Pignon JP, Gelli M, et al. Postoperative hepatic arterial chemotherapy in high-risk patients as adjuvant treatment after resection of colorectal liver metastases - a randomized phase II/III trial - PACHA-01 (NCT02494973). BMC Cancer. 2018;18:787. https://doi.org/ 10.1186/s12885-018-4697-7
13. 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;341:2039-2048. https://doi.org/10.1056/NEJM199912303412702
14. Kemeny NE, Gonen M.. Hepatic arterial infusion after liver resection. N Engl J Med. 2005;352:734-735. https://doi.org/10.1056/NEJM200502173520723
15. Muhlbacher F, Huk I, Steininger R, et al. Is orthotopic liver transplantation a feasible treatment for secondary cancer of the liver? Transplant Proc. 1991;23:1567-1568.
16. Kenneth D, Kochanek MA, Murphy SL, Xu J, Arias E.. Mortality in the United States, 2022. Vol. 492. 2024, United States Center for Disease Control, Atlanta, GA, USA. https://www.cdc.gov/nchs/data/databriefs/db492.pdf
17. Kwong AJ, Kim WR, Lake JR, et al. OPTN/SRTR 2022 annual data report: liver. Am J Transplant. 2024;24:S176-S265. https://doi.org/10.1016/j.ajt.2024.01.014
18. Benson AB, D'Angelica MI, Abbott DE, et al. Hepatobiliary Cancers, Version 2.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2021;19:541-565. https://doi.org/ 10.6004/jnccn.2021.0022
19. Dueland S, Foss A, Solheim JM, Hagness M, Line PD.. Survival following liver transplantation for liver-only colorectal metastases compared with hepatocellular carcinoma. Br J Surg. 2018;105:736-742. https://doi.org/ 10.1002/bjs.10769
20. Adam R, Badrudin D, Chiche L, et al. Safety and feasibility of chemotherapy followed by liver transplantation for patients with definitely unresectable colorectal liver metastases: insights from the TransMet randomised clinical trial. EClinicalMedicine. 2024;72:102608. https://doi.org/ 10.1016/j.eclinm.2024.102608
21. Dueland S, Syversveen T, Solheim JM, et al. Survival following liver transplantation for patients with nonresectable liver-only colorectal metastases. Ann Surg. 2020;271:212-218. https://doi.org/10.1097/SLA.0000000000003404
22. Hagness M, Foss A, Line PD, et al. Liver transplantation for nonresectable liver metastases from colorectal cancer. Ann Surg. 2013;257:800-806. https://doi.org/10.1097/SLA.0b013e3182823957
23. 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;157:524-530. https://doi.org/ 10.1001/jamasurg.2022.0300

24. Kaltenmeier C, Geller DA, Ganesh S, et al. Living donor liver transplantation for colorectal cancer liver metastases: Midterm outcomes at a single center in North America. Am J Transplant. 2024;24:681-687. https://doi.org/ 10.1016/j.ajt.2023.09.001
25. Sasaki K, Ruffolo LI, Kim MH, et al. The current state of liver transplantation for colorectal liver metastases in the United States: a call for standardized reporting. Ann Surg Oncol. 2023;30:2769-2777. https://doi.org/ 10.1245/s10434-023-13147-6
26. Smedman TM, Line PD, Hagness M, et al. Liver transplantation for unresectable colorectal liver metastases in patients and donors with extended criteria (SECA-II arm D study). BJS Open. 2020;4:467-477. https://doi.org/ 10.1002/bjs5.50278
27. Toso C, Pinto Marques H, Andres A, et al. ; Compagnons Hépato-Biliaires Group. Liver transplantation for colorectal liver metastasis: survival without recurrence can be achieved. Liver Transpl. 2017;23:1073-1076. https://doi.org/ 10.1002/lt.24791
28. Dueland S, Guren TK, Hagness M, et al. Chemotherapy or liver transplantation for nonresectable liver metastases from colorectal cancer? Ann Surg. 2015;261:956-960. https://doi.org/ 10.1097/SLA.0000000000000786
29. Solheim JM, Dueland S, Line PD, Hagness M.. Transplantation for nonresectable colorectal liver metastases: long-term follow-up of the first prospective pilot study. Ann Surg. 2023;278:239-245. https://doi.org/ 10.1097/SLA.0000000000005703
30. Roberts MS, Angus DC, Bryce CL, Valenta Z, Weissfeld L.. Survival after liver transplantation in the United States: a disease-specific analysis of the UNOS database. Liver Transpl. 2004;10:886-897. https://doi.org/ 10.1002/lt.20137
31. Bonney GK, Chew CA, Lodge P, et al. Liver transplantation for non-resectable colorectal liver metastases: the International Hepato-Pancreato-Biliary Association consensus guidelines. Lancet Gastroenterol Hepatol. 2021;6:933-946. https://doi.org/ 10.1016/S2468-1253(21)00219-3
32. Dueland S, Grut H, Syversveen T, Hagness M, Line PD.. Selection criteria related to long-term survival following liver transplantation for colorectal liver metastasis. Am J Transplant. 2020;20:530-537. https://doi.org/ 10.1111/ajt.15682
33. Zeineddine FA, Zeineddine MA, Yousef A, et al. Survival improvement for patients with metastatic colorectal cancer over twenty years. NPJ Precis Oncol. 2023;7:16. https://doi.org/ 10.1038/s41698-023-00353-4
34. Reivell V, Hagman H, Haux J, et al. SOULMATE: the Swedish study of liver transplantation for isolated colorectal cancer liver metastases not suitable for operation or ablation, compared to best established treatment-a randomized controlled multicenter trial. Trials. 2022;23:831. https://doi.org/ 10.1186/s13063-022-06778-9
35. Smedman TM. Liver Transplantation Compared to Chemotherapy in Patients With ColoRectal Cancer (SECAIII). Accessed May 23, 2024. https://clinicaltrials.gov/study/NCT03494946
36. Sposito C, Pietrantonio F, Maspero M, et al. Improving outcome of selected patients with non-resectable hepatic metastases from colorectal cancer with liver transplantation: a prospective parallel trial (COLT trial). Clin Colorectal Cancer. 2023;22:250-255. https://doi.org/ 10.1016/j.clcc.2023.01.003
37. Montalva EM. Liver Transplantation in Patients with Unresectable Colorectal Liver Metastases (TRASMETIR). Accessed May 23, 2024. https://classic.clinicaltrials.gov/ct2/show/NCT04616495
38. Gagniere J, Dupre A, Gholami SS, et al. Is hepatectomy justified for BRAF mutant colorectal liver metastases? A multi-institutional analysis of 1497 patients. Ann Surg. 2020;271:147-154. https://doi.org/ 10.1097/SLA.0000000000002968
39. Schirripa M, Bergamo F, Cremolini C, et al. BRAF and RAS mutations as prognostic factors in metastatic colorectal cancer patients undergoing liver resection. Br J Cancer. 2015;112:1921-1928. https://doi.org/ 10.1038/bjc.2015.142
40. Tabernero J, Grothey A, Van Cutsem E, et al. Encorafenib plus cetuximab as a new standard of care for previously treated BRAF V600E-mutant metastatic colorectal cancer: updated survival results and subgroup analyses from the BEACON study. J Clin Oncol. 2021;39:273-284. https://doi.org/ 10.1200/JCO.20.02088
41. Kopetz S, Grothey A, Yaeger R, et al. BREAKWATER: Randomized phase 3 study of

encorafenib (enco) + cetuximab (cetux) ± chemotherapy for first-line (1L) treatment (tx) of BRAF V600E-mutant (BRAFV600E) metastatic colorectal cancer (mCRC). J Clin Oncol. 2021;39:TPS3619-TPS3619. https://doi.org/10.1200/jco.2021.39.15_suppl.tps3619

42. Andre T, Lonardi S, Wong KYM, et al. Nivolumab plus low-dose ipilimumab in previously treated patients with microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: 4-year follow-up from CheckMate 142. Ann Oncol. 2022;33:1052-1060. https://doi.org/10.1016/j.annonc.2022.06.008
43. Diaz LA Jr, Shiu KK, Kim TW, et al. ; KEYNOTE-177 Investigators. 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. https://doi.org/10.1016/S1470-2045(22)00197-8
44. 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. https://doi.org/ 10.1200/JCO.21.01015
45. Overman MJ, Lenz HJ, 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. https://doi.org/10.1200/jco.2022.40.16_suppl.351035201903
46. Organ Procurment and Transplant Network Policies. 2024. United Network for Organ Sharing, Richmond, VA, USA. https://unos.org/news/policy-and-programming-changes/.
47. Kim WR, Mannalithara A, Heimbach JK, et al. MELD 3.0: the model for end-stage liver disease updated for the modern era. Gastroenterology. 2021;161:1887-1895.e4. https://doi.org/10.1053/j.gastro.2021.08.050
48. Kriss M, Biggins SW.. Evaluation and selection of the liver transplant candidate: updates on a dynamic and evolving process. Curr Opin Organ Transplant. 2021;26:52-61. https://doi.org/10.1097/MOT.0000000000000829
49. National Liver Review Board (NLRB) Updates Related to Transplant Oncology. 2024. Health Resources and Services Administration, Rockford, MD, USA. https://optn.transplant.hrsa.gov/media/byjl4tjf/lic_nlrb_transplant-oncology_pcjan24.pdf.
50. Okumura K, Dhand A, Misawa R, et al. Normothermic machine perfusion is associated with improvement in mortality and graft failure in donation after cardiac death liver transplant recipients in the United States. Transplant Direct. 2024;10:e1679. https://doi.org/10.1097/TXD.0000000000001679
51. Bluhme E, Gabel M, Martinez de la Maza L, et al. Normothermic regional perfusion in controlled DCD liver procurement: Outcomes of the Swedish national implementation protocol. Liver Transpl. 2024;30:1132-1144. https://doi.org/10.1097/lvt.0000000000000434
52. Dueland S, Syversveen T, Hagness M, Grut H, Line PD.. Liver transplantation for advanced liver-only colorectal metastases. Br J Surg. 2021;108:1402-1405. https://doi.org/ 10.1093/bjs/znab196
53. Sahin IH, Lin Y, Yothers G, et al. Minimal residual disease-directed adjuvant therapy for patients with early-stage colon cancer: CIRCULATE-US. Oncology (Williston Park). 2022;36:604-608. https://doi.org/ 10.46883/2022.25920976
54. Bjornelv GMW, Dueland S, Line PD, et al. Cost-effectiveness of liver transplantation in patients with colorectal metastases confined to the liver. Br J Surg. 2019;106:132-141. https://doi.org/10.1002/bjs.10962
55. Bjornelv GMW, Zolic-Karlsson Z, Dueland S, Line PD, Aas E.. Cost-effectiveness of liver transplantation versus last-resort systemic therapy for colorectal liver metastases. Br J Surg. 2022;109:483-485. https://doi.org/10.1093/bjs/znac022
56. O'Connell JB, Maggard MA, Liu JH, et al. Rates of colon and rectal cancers are increasing in young adults. Am Surg. 2003;69:866-872.
57. You YN, Lee LD, Deschner BW, Shibata D.. Colorectal cancer in the adolescent and young adult population. JCO Oncol Pract. 2020;16:19-27. https://doi.org/ 10.1200/JOP.19.00153