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Review Article

Liver transplantation for colorectal cancer with liver metastases

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Abstract

Over the last decade, multiple clinical trials have demonstrated a survival benefit for liver transplantation in colorectal cancer with liver metastases. Additionally, advances in donor organ preservation have expanded organ availability affording the opportunity to expand indications for liver transplantation, such as colorectal cancer with unresectable liver metastases. Current data support comparable overall survival (OS) for liver transplantation for colorectal cancer with liver metastases compared with general liver transplantation recipients. Supported by this data, in the United States, allocation policy is changing to include deceased donor livers for patients with unresectable colorectal cancer liver metastases. Available studies to date demonstrate improved outcomes with primary tumor R0 resection, 6-12 months of pretransplantation chemotherapy, and careful radiologic restaging (including positron emission tomography/computed tomography) to confirm lack of extrahepatic disease. A response to pretransplantation chemotherapy is a key predictor of long-term outcomes and progression during chemotherapy appears to be a contraindication to proceeding to transplant. A carcinoembryonic antigen level ≤80 μg/L and largest liver tumor dimension <5.5 cm are both associated with improved progression-free and OS in the available literature. Liver transplantation for colorectal cancer with unresectable liver metastases is associated with longer progression-free and OS compared with chemotherapy alone. Patient selection based on imaging, laboratory, and clinical findings is critical to identify patients most likely to benefit. Liver transplantation should be considered at all centers with an active transplant program to improve outcomes for patients with advanced colorectal cancer.

Key words: colon cancer; rectal cancer; liver transplantation; metastasis; chemotherapy.

Implications for Practice

Liver transplantation significantly improves overall survival compared with chemotherapy alone for patients with colorectal cancer with unresectable liver metastases who meet specific clinical criteria. As the donor-liver pool increases, widespread implementation of transplantation for liver metastases is more achievable than ever before. Clinical data are available to aid in optimal patient selection to identify patients who will derive long-term benefit from transplantation, and ongoing optimization of these clinical factors and allocation guidance are likely to improve outcomes further. Centers with existing liver transplantation programs can implement transplantation for unresectable liver metastases to improve the survival of advanced colorectal cancer patients.

Introduction

Colorectal cancer (CRC) encompasses epithelial malignancies of the large intestine. In 2023, there were an estimated 152 810 new cases of CRC in the United States (USA) with 53 010 CRC-related deaths, accounting for 7.6% of all new cancer diagnoses and 8.7% of cancer-related deaths, respectively.[1] The most recent data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program report a 5-year relative survival of 65.0% across all stages of CRC.[1] At diagnosis, nearly a quarter of patients (23%) have disease spread beyond the primary site and regional lymph nodes. While 5-year survival rates for localized and regional disease are both upward of 70%, the 5-year survival rate for distant metastases remains poor with just 15.7% of patients alive at 5 years.[1]

An estimated 60% of patients with metastatic CRC have metastatic deposit(s) in the liver.[2] Current guidelines state that hepatic resection is the treatment of choice for resectable CRLM based on improvements in survival outcomes compared with chemotherapy alone.[3-7] Recent study has shown similar survival outcomes with thermal ablation of small liver metastases compared with metastasectomy.[8] Staged liver resection, portal vein embolization, radiofrequency ablation (RFA), chemo-embolization, and yttrium-90 radioembolization are other liver-directed therapies that can be considered alone or in conjunction with limited liver metastasectomy for CRLM

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that cannot safely be resected.[9] Of note, when tumor debulking was added to palliative chemotherapy for metastatic CRC, there was no survival benefit.[10] Hepatic arterial infusion (HAI) pumps are another liver-directed option that utilizes a surgically implanted pump to administer chemotherapy, most commonly fluoropyrimidines, directly into the hepatic circulation. In the limited studies to date, HAI has shown better control of liver metastases without a clear OS benefit compared with systemic chemotherapy.[11-14] Comparison with other liver-directed therapies and long-term outcomes is lacking, and deployment of HAI generally requires surgical and medical expertise not available outside of expert centers.

Unfortunately, in many cases, liver-directed therapies are contraindicated and/or tumors unresectable, most commonly due to large tumor burden in the liver, leading to the consideration of liver transplantation for CRLM. The first reports of transplant for CRLM came from Europe during the late 1970s through the early 1990s.[15] Results were initially disappointing, with a 3-year overall survival (OS) rate of 36% and a 5-year OS of 18%. Since then, significant advances have been made in CRC staging, prognostication, and treatment, immunosuppression, complication management, and, perhaps most importantly, rigid selection protocols for transplant candidacy. Current data demonstrate a 5-year OS of >80% in highly selected patients, a large increase compared with 5-year OS rates for metastatic CRLM (<20%), and comparable to 5-year outcomes for transplant recipients (80.2%).[16,17] Other malignancies such as hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma have shown the benefits of transplant for malignant indications.[18] A limited study of highly selected CRLM patients suggested similar survival outcomes to those undergoing transplant for HCC.[19] The success of transplant in hepatic malignancies, along with improvements in the transplant process in general, have rekindled interest for transplant in CRLM. This article reviews the salient clinical trials, highlighting areas of active study and further need.

Methods

PubMed and Google Scholar databases were queried using combinations of the following terms: "colon cancer," "rectal cancer," "colorectal cancer," "liver metastasis," "liver metastases," and "liver transplantation." All potential articles relevant to the topic at hand were reviewed by all authors for relevance. Articles were limited to those written in English. Reference lists within articles identified via database search were further reviewed to ensure a comprehensive list of all potentially relevant articles. Other articles deemed relevant to related topics (including but not limited to chemotherapy, metastasectomy, and liver-directed therapies) were included with agreement from all authors. Given the limited randomized controlled trials of transplant in CRLM, relevant studies with retrospective and observational designs were also included as agreed upon by all authors.

Results

Ten articles were identified which included primary study for CRLM patients undergoing transplant. Eight of these studies were distinct cohorts of patients.[20-27] A subsequent study of the SECA trial cohort involved a cross-trial comparison with a matched chemotherapy cohort (from the NORDIC-VII trial).[28] One study reported long-term outcomes of the SECA trial cohort.[29]

Discussion

Outcomes of LT in CRLM

Multiple recent studies have evaluated transplant for CRLM, primarily led by a group in Oslo, Norway, which generally has shorter transplant wait times compared with many other countries. Smaller, retrospective studies are available from a few US cohorts. The published data on these trials are summarized below, as well as in Table 1.

TRANSMET

Recently, Adam et al. provided results on the TRANSMET trial comparing chemotherapy alone to chemotherapy followed by transplant for patients with unresectable liver metastases ($n = 94$).[20] All patients received at least 3 months of chemotherapy, and stable disease (SD) or a partial response (PR) per Response Evaluation Criteria in Solid Tumors (RECIST) was required to proceed to randomization. This is an important inclusion criterion, as it is distinct from the SECA study described below that allowed patients to proceed with transplant, so long as progression was confined to the liver and may partially explain the worse outcomes seen in that study. Other key inclusion criteria included *BRAF* wild-type; previous resection with "safe" margin of resection (definition of "safe" was not clearly delineated); no extrahepatic disease by fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT), contrast-enhanced CT (ceCT), colonoscopy, and a carcinoembryonic antigen (CEA) level of <80 µg/L or a decrease of ≥50% from the highest level on record. The latter is an interesting, novel addition to prior CEA cutoffs that could provide a unique CEA assessment beyond the existing static number of 80 µg/L used elsewhere. Median time from primary tumor resection to transplant was 14.6 months. Nine patients experienced progressive disease (PD) after randomization but before transplant. Three of 38 transplanted patients required retransplantation, and 1 of these patients died. This represents a 97.4% patient survival rate and 92.2% graft survival rate, both better than expected compared with 1-year United Network for Organ Sharing (UNOS) outcomes.[17,30] The majority (68%) of patients received posttransplant chemotherapy, left to provider discretion. There was an unintentional crossover with 9 patients in the chemotherapy-alone arm undergoing metastasectomy or transplant.

Intention-to-treat analysis yielded a 5-year OS rate of 57% in the transplant arm and 13% in the chemotherapy-alone arm ($P = .0003$; HR 0.37, 95%CI, 0.21-0.65). In the perprotocol analysis, the 5-year OS rate was 73% and 9%, respectively (HR 0.16, 95% CI, 0.07-0.33). Median progression-free survival (PFS) was 17.4 versus 6.4 months (HR 0.34, 95% CI, 0.20-0.58), respectively. By comparison, UNOS data in the United States for patient survival at 5 years after transplant across all indications are 80.2%; with the 73% 5-year OS in this trial, equity of organ utilization is acceptable compared with the general transplant population.[17,30]

In the transplant group, 28 patients (74%) experienced recurrence, with the dominant minority being recurrence to lung (39%). With the option to treat recurrence included in study design (surgery or ablation), 15 of 38 transplanted patients were disease-free at publication. The strengths of this

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

Authors, year, name	Location	Time period	Sample size	Design	Inclusion criteria	Exclusion criteria	Summary of findings
Adam et al. 2024 TRANSMET trial	France Italy Belgium	2016–2021	*n* = 94	- Prospective, randomized to CTX (n = 47) vs CTX + LT (*n* = 47)	- Response to CTX for 3 + mos. pre-LT (SD or PR by RECIST) - Pre-LT colonoscopy - CEA < 80 µg/L or ≥50% decrease in highest CEA	- SD or PD during pre-LT CTX - *BRAF*-mutated primary tumor - Extrahepatic disease - Other malignancy	- OS at 5 years: 73% for LT + CTX vs 9% for CTX (HR 0.16; 95%CI, 0.07-0.33). - mPFS: 17.4 vs 6.4 months (HR 0.34; 95% CI, 0.20-0.58) - Including pts with post-LT treatment, 15/38 were disease-free at study completion
Sasaki et al. 2023	United States	2017–2022	*n* = 64 (listed) *n* = 46 (transplant)	- Retrospective report of LT for CRLM from UNOS database	- No specific criteria mentioned - No report of pre-LT CTX	- NOS due to retrospective, observational design	- DFS at 1 and 3 years: 75.1%, 53.7% - OS at 1 and 3 years: 89.0%, 60.4% - mMELD-Na of 8
Hernandez-Alejandro et al. 2022	United States Canada	2017–2021	*n* = 10	- Retrospective report across 3 N. American LT centers	- International Hepato-Pancreato-Biliary Association Consensus Guidelines	- PD during pre-LT CTX	- DFS at 1.5 years: 62% - OS at 1.5 years: 100% - Recurrences (*n* = 3) at 99, 121, and 199 days post-LT
Kaltenmeier et al. 2023	United States	2019–2022	*n* = 10	- Retrospective report of LT for CRLM at single center (University of Pittsburgh)	- Resected primary - 6-12 weeks pre-LT CTX with SD or PR - Pre-LT colonoscopy - No extrahepatic mets - CEA < 100 ng/dL	- Other malignancy per institutional guidelines - *BRAF*-mutated tumors	- Mean RFS: 2.2 years - Mean OS: 3.0 years - mMELD-Na of 10.5 - Lung recurrence (*n* = 2) treated with segmentectomy and liver recurrence (*n* = 1) treated with RFA
Hagness et al. 2013 SECA-I trial	Norway	2006–2011	*n* = 21	- Single-arm, prospective - Pts followed with CT CAP every 3-6 months for 5 years	- Resected primary - Minimum 6 weeks of CTX preceding LT - Lack of extrahepatic mets confirmed by CT and ex lap	- Extrahepatic metastases - Other malignancy - Weight loss > 10%	- OS rate at 1, 3, 5 years: 95%, 68%, 60% - DFS rate at 1 year: 35% - CEA > 80 µg/L and largest tumor > 5.5 cm associated with shorter OS
Dueland et al. 2015	Norway	2006–2012	*n* = 21 (each cohort)	- Compared SECA-I cohort to 21 patients from NORDIC-VII CTX trial (cross-trial) - Subgroup of 21 longest OS CTX compared with LT pts	Same as above: - Resected primary - Minimum 6 weeks of CTX preceding LT	Same as above: - Extrahepatic metastases - Other malignancy - Weight loss > 10%	- mPFS 10 vs 8 months (LT vs CTX) - OS at 5 years for LT vs CTX cohorts: 56% vs 9% (*P* <.001) - OS at 5 years for LT vs longest-surviving CTX cohorts: 56% vs 19% (*P* =.012) - OS at 5 years after relapse for LT vs CTX: 53% vs 6% (*P* <.001)
Solheim et al. 2023	Norway	2006–2012	*n* = 23	- Reported long-term (10 years or more) follow-up of patients from SECA-I enrollment period through 2022	Same as above: - Resected primary - Minimum 6 weeks of CTX preceding LT	Same as above: - Extrahepatic metastases - Other malignancy - Weight loss > 10%	- mDFS: 10 months - OS rate at 5 years: 43.5% - OS rate at 10 years: 26.1% (4 pts alive with NED at last follow-up) - All 4 living pts underwent metastasectomy for lung-only PD - Associated with shorter OS: --- Largest tumor > 5.5cm (*P* =.003) --- CEA > 80 µg/L (*P* =.008) --- SD or PR at time of LT (*P* =.045)

Table 1. Continued

Authors, year, name	Location	Time period	Sample size	Design	Inclusion criteria	Exclusion criteria	Summary of findings
Dueland et al. 2020 SECA-II	Norway	2012–2016	*n* = 15	- Prospective design without CTX or other control group	- Primary resected - Pre-LT PET/CT and CT CAP NED beyond liver metastases - PR to 6 weeks (or more) of pre-LT CTX - Negative pre-LT colonoscopy - No tumor > 10 cm	- Weight loss > 10% - BMI > 30 kg/m^2 - Other malignancy - Extrahepatic metastatic disease - Investigator discretion	- mDFS: 13.7 months - OS at 1, 3, and 5 years: 100%, 83%, 83% - DFS at 1, 2, and 3 years: 53%, 44%, 35% - SAR at 1, 2, and 4 years: 100%, 73%, 73% - Longer DFS for FCRS 1-2 vs 3-4 (11.8 months vs NR, *P* =.044)
Smedman et al. 2020 SECA-II Arm D	Norway	2014–2018	*n* = 10	- Single-arm, observational report of "arm D" of SECA-II trial (not eligible for other arms) - Intentional use of ECD organs (*n* = 9) - Cross-trial comparison with SECA-I and SECA-II Arm C	- Same as SECA-II above, but allowed for pts with resectable lung metastases - ECD organ details: HBsAg + (*n* = 4), DCD (*n* = 2), both HBsAg+ & DCD (*n* = 1), ependymoma (*n* = 1), older age (*n* = 1), > 80% steatosis (*n* = 1), remote lymphogranulomatosis (*n* = 1)	Reasons for SECA-II exclusion: - <10% CTX response (*n* = 5) - PD on third line CTX - Extrahepatic metastases - Papillary thyroid carcinoma	- mDFS: 4 months. - mOS: 18 months. - mOS of Arm D pts significantly shorter than Arm C (*P* =.002) - mOS from CTX for PD after LT was 17.4 months for SECA-II arm C vs 8.6 months for arm D (*P* =.003) - OS rates at 2 years for SECA-II vs SECA-I vs SECA-II arm D: 100% vs 91% vs 43%
Toso et al. 2017	Portugal France Switzerland	1995–2015	*n* = 12	- Retrospective, observational report - Patients not a candidate for metastasectomy offered LT	- Resected primary - All 11 pts with pre-LT CTX had PR	- NOS due to retrospective, observational design	- OS rates at 1, 3, and 5 years: 83%, 62%, 50% - DFS rates at 1, 3, and 5 years: 56%, 38%, 38% - Pre-LT CEA ≥ 80 μg/L and TTLT ≥ 24 months. associated with shorter DFS

Abbreviations: μg/L, Micrograms per liter; 95% CI, 95% confidence interval; CAP, chest/abdomen/pelvis; CEA, carcinoembryonic antigen; cm, centimeter(s); CRLM, colorectal cancer with liver metastases; CT, computed tomography; CTX, chemotherapy; DCD, donation after circulatory death; DFS, disease-free survival; ECD, expanded criteria donor; Ex lap, Exploratory laparotomy; FCRS, Fong Clinical Risk Score; HBsAg+, Hepatitis B surface antigen positive; HR, Hazard ratio; kg/m^2, Kilograms per meter squared; LT, Liver transplantation; mDFS, Median disease-free survival; Mets, Metastases; mMELD-Na, Median model for end-stage liver disease score; mPFS, Median progression-free survival; MRI, Magnetic resonance imaging; N. American, North American; NED, No evidence of disease; ng/dL, Nanograms per deciliter; NOS, Not otherwise specified; NR, Not reached; OS, Overall survival; PD, Progressive disease; PET, Positron emission tomography; PR, Partial response; Pts, Patients; RECIST, Response evaluation criteria in solid tumors; RFA, Radiofrequency ablation; RFS, Recurrence-free survival; SAR, Survival after relapse; SD, Stable disease; TTLT, Time to liver transplantation; UNOS, United Network for Organ Sharing; Vs, Versus.

study include the first-of-its-kind randomized design, regimented pretransplant chemotherapy and response criteria, incorporation of CEA, PET/CT, and ceCT into pretransplant evaluation, and comparatively large sample size. These data are by far the strongest to date, showing that transplant significantly improves both OS and PFS compared with chemotherapy alone for a modern cohort of CRLM patients.

North American studies

In regards to the USA and North America, although outside of a formal clinical trial setting, Sasaki et al. provided a useful review of transplant for CRLM in the USA, identifying patients through the UNOS database.[25] Of the 64 CRLM patients listed for transplant between 2017 and 2022, 46 (71.9%) ultimately underwent transplantation. Important qualitative observations include the majority of transplant listings being from high-volume centers (84.2%), a broad geographic distribution (listings in all but one of the UNOS regions), and a steady increase in listings from 2017-18 through 2020-21, indicating increased interest in transplant for CRLM during this period. Importantly, patient travel was a significant component with 53.1% of listed patients traveling from a different state to transplant center and 32.8% of listed patients being from nonadjacent states.

During a median follow-up of 360 days, 10 transplant patients (21.7%) experienced disease recurrence, with 6 of the 10 deaths (13.0%) during the follow-up period attributed to recurrent malignancy. They report 1- and 3-year DFS rates of 75.1% and 53.7%, respectively, and 1- and 3-year OS rates of 89.0% and 60.4%, respectively. There were significantly shorter 1- and 3-year OS rates for deceased versus living-donor liver transplant (LDLT; 77.1% and 51.4% vs 100% and 71.4%, P =.049). Compared with high-risk HCC and cholangiocarcinoma during the same period, there was no significant difference in OS rates. Selection criteria were not specified. Nonetheless, this article provides an important update on the already active CRLM transplant programs at some high-volume centers, as well as strong OS rates comparable to the TRANSMET above, specifically within the USA.

In another North American cohort (2 US centers, 1 Canadian center), Hernandez-Alejandro et al. retrospectively reported outcomes for 10 CRLM patients who underwent LDLT following Hepato-Pancreato-Biliary Association Consensus guidelines.[23,31] Of note, this cohort included 4 patients with T4b primary tumor, 7 patients with node-positive disease, and 3 patients with poorly differentiated histology. Two patients had right-sided primary tumors, and 1 patient had a *BRAF* D594G mutation.

An aggregate of selection criteria, the Oslo score affords one point each for CEA above 80 µg/L, largest tumor diameter greater than 5.5 cm, PD during pretransplant chemotherapy, and an interval between primary tumor resection and transplant of less than 2 years. In a post hoc analysis of combined SECA-I and SECA-II, higher Oslo scores (3-4 vs 0-2) were associated with shorter time to recurrence and OS, leading to its inclusion in multiple transplant trials, including this one.[32]

In this study, the median Oslo score was 1.5, consistent with a highly selected patient population. All 10 patients had a documented response to 5-fluorouracil-based chemotherapy. With a median follow-up of 1.5 years, recurrence was seen in 3 patients (30%). One death occurred in follow-up, leading to 1.5-year DFS and OS rates of 62% and 100%, respectively. Although limited by small sample size, this report provides an important perspective on effectively implementing transplant for CRLM in the USA, with specific adherence to available patient selection criteria and related outcomes.

In a single-center report from the University of Pittsburgh Medical Center, Kaltenmeier et al. retrospectively reviewed outcomes for 10 patients who underwent LDLT for CRLM.[24] Inclusion criteria were highlighted by primary tumor resection at least 6 months before proceeding to transplant, 6-12 weeks of chemotherapy with SD or response, pretransplant imaging for extrahepatic metastases, CEA < 100 ng/dL, and an available living donor. Somewhat unique in modern trials, there was no limit for number or size of liver lesions to proceed, and half of patients did have a liver tumor > 5cm. Median Oslo Score was 1.5. Two patients had T4b primary tumors, 2 primaries were right-sided, and half of patients had lymph node involvement.

With a median follow-up period of 1.6 years, 3 patients experienced recurrence, leading to a mean recurrence-free survival (RFS) of 2.2 years. Two recurrences occurred in lung, and both were treated with lung segmentectomy; the other occurrence was in the liver, and this patient underwent RFA. Mean OS was 3.0 years. A mean OS of 3.0 years is longer than recently reported OS for metastatic CRC, which was 32.4 months between 2016 and 2019.[33] Furthermore, it is important to consider the possibly significant deviation from most other studies in allowing half of patients with maximal tumor >5cm to proceed to transplant. Additionally, 6-12 weeks of pretransplant chemotherapy is one of the shortest intervals, and most centers consider at least 3-6 months chemotherapy before proceeding. These deviations are likely significant contributors to the outcomes of this study. Nonetheless, carefully selected patients clearly benefit from transplant.

European studies

The first studies on transplant for CRLM and multiple seminal studies since have come from Oslo, Norway. The robust donor program in Norway allowed for transplant for malignant indications earlier than many other countries such as the USA with longer waitlist times. Hagness et al. provided the first study named SECA-I, a cohort of 21 patients between 2006 and 2011.[22] With a median follow-up of 27 months, the authors reported a 60% 5-year OS rate and a 1-year DFS of 35%. The same cohort was compared across trials to the NORDIC-VII trial in which patients with CRLM were treated with chemotherapy in the same timeframe.[28] Noting the cross-trial limitations, transplanted patients had a significantly higher 5-year OS rate (56% vs 9%, P <.001), which held true when the authors intentionally selected the 21 chemotherapy patients with the longest OS for comparison to the transplanted group (56% vs 19%, P =.012). Finally, a long-term follow-up of this cohort in 2023 showed 5- and 10-year OS rates of 43.5% and 26.1%, respectively.[29] In the initial and 10-year follow-up studies, the following parameters were associated with significantly longer OS: Tumor diameter < 5.5 cm (P =.003), CEA < 80 µg/L (P =.008), and SD or PR at the time of transplant (P =.045), underscoring the importance of these parameters and their related aggregation as part of the Oslo Score.

In a distinct cohort of 15 patients between 2006 and 2012, the same group used more rigid selection criteria (regimented chemotherapy between primary resection and transplant with PR, pretransplant comprehensive imaging) to select patients.[21] Pretransplant chemotherapy led to significant reductions in

CEA (P =.001), largest tumor dimension (P =.003), and number of liver lesions (P =.001), highlighting the importance of pretransplant chemotherapy. With a median follow-up of 60 months, 1-, 3-, and 5-year OS rates were 100%, 83%, and 83%, respectively. Median DFS was 13.7 months with 1-, 2-, and 3-year DFS rates of 53%, 44%, and 35%, Significantly Oslo Score, CEA, and median tumor size were noted as possible contributors to improved outcomes in SECA-II compared with SECA-I.

Finally, SECA-II "arm D" evaluated a separate cohort of 10 patients enrolled in the same time frame but who were otherwise excluded from the primary SECA-II cohort (<10% response to chemotherapy, extrahepatic metastases), using expanded criteria donor organs.[26] Median DFS was 4 months and median OS was 18 months. Median DFS between SECA-II arms C (synchronous metastases) and D was similar (P =.202), but median OS was significantly longer in arm C compared with arm D (2-year OS 100% vs 43%, P =.002), again highlighting the importance of selection criteria, especially a response to pretransplant chemotherapy. In addition to the extensive work from the Norwegian group, a group of centers from southwestern Europe, predominantly Portugal, provided a narrative report of 12 transplants for CRLM performed between 1995 and 2015.[27] Most patients (11/12) received pretransplant chemotherapy. Importantly, all patients had a PR before transplant. Like SECA-I, all patients had been deemed not candidates for liver-directed therapies when the decision to proceed with transplant was made. With a median follow-up of 26 months, the authors reported 1-, 3-, and 5-year OS rates of 83%, 62%, and 50%, respectively. For DFS, 1-, 3-, and 5-year rates were 56%, 38%, and 38%. Four patients with 3.5 or more years of follow-up were without evidence of disease.

Active studies of transplant for CRLM

Multiple active clinical trials aim to answer many of the knowledge gaps with transplant for CRLM. Commonalities for eligibility include pretransplant PET/CT, ECOG PS 0-1, and measurable disease by RECIST criteria. PD at the time of randomization or transplant is also a uniform exclusion criterion based on the results discussed above.

Most pertinent to the expanding donor organ pool, the Swedish SOULMATE trial (NCT04161092) is a randomized, multicenter study specifically comparing expanded criteria donor organs.[34] Patients will be randomized to undergo transplant or best alternative care at the discretion of the treating physician.

The Oslo team is actively recruiting patients for SECA-III which will importantly utilize a randomized design for transplant versus other treatments at the discretion of the treatment team.[35] Similar to the above study, the nontransplant arm allows for any other standard-of-care treatment. Patients eligible for liver metastasectomy will not be included. The randomized design is a significant strength to add to the recent TRANSMET data. Interestingly, this study allows for resectable lung metastases, suggesting that they may report outcomes for patients undergoing transplant and lung metastasectomy. Although data are limited, the 4 patients alive in the long-term follow-up of the SECA-I trial had experienced lung-only recurrence, undergone lung metastasectomy, and were alive at 10 years with no evidence of disease.[29] This will be a key component of this study, and dedicated studies of posttransplant lung metastasectomy for lung-only recurrence are necessary.

COLT is an observational study based in Italy examining patients undergoing transplant who are concurrently enrolled in a clinical trial of triplet chemotherapy and an anti-EGFR agent for CRLM.[36] Those undergoing transplant will be compared against a matched cohort in the chemotherapy arm of the trial, a slight limitation compared with randomized design as is the case in SECA-III and TRANSMET. Finally, a Spanish group is performing an observational study of transplant with similar eligibility criteria to the studies mentioned above.[37] These studies are generally expected to report results in 2026 or later.

Patient selection and disease behavior

The International Hepato-Pancreato-Biliary Association has offered a starting point for potential transplant patient selection in CRLM.[31] With rapidly evolving data, UNOS criteria and single-center criteria are likely to continue evolving. These guidelines recommend considering transplant only if the metastatic lesions are unresectable by standard, complex, or combinatorial liver-directed approaches, generally in line with the available published literature. The performance of these parameters is discussed below and outlined in Table 2.

Molecular and histologic criteria

Furthermore, these guidelines recommend an important group of "molecular criteria." To meet these criteria, the tumor must be negative for *BRAF* V600E mutation, and microsatellite stable with proficient mismatch repair genes. *BRAF*-mutant CRC is associated with shorter DFS and OS, including after liver metastasectomy.[38,39] Furthermore, *BRAF*-directed therapies have a clear benefit throughout the systemic treatment of CRC with *BRAF* mutation, and the role of these various treatments in the context of transplant in *BRAF*-mutated tumors merits further study.[40,41] Data are currently lacking to draw conclusions on *BRAF*-mutated tumors in the transplant context. The concerns with microsatellite instability and/or deficient MMR are clearer. Multiple studies of immunotherapy in these populations with metastatic CRC have consistently demonstrated OS on the order of years, highlighted by recent CheckMate-142 results showing a median OS of 44.2 months in metastatic dMMR CRC treated with nivolumab.[42-45] Furthermore, immune checkpoint inhibitor (ICI) therapy would carry significant risks of allograft rejection if used at the time of recurrence after transplant, meaning transplantation in these patients would create a contraindication to potentially beneficial downstream ICI therapy.

Other potentially important factors in patient selection include histology (eg, poorly differentiated), right- versus left-sided (vs rectal) primary tumors, and TNM staging. Further study of these factors is necessary.

Practical considerations for transplant in CRLM

Transplant for unresectable CRLM in select patients offers superior survival compared with the current standard of care. However, there is a scarcity of available donor livers for patients awaiting solid organ transplant, and therefore, one must consider the concepts of equity and beneficence in how transplantation for CRLM is approached. Deaths from end-stage liver disease (ESLD) exceed that for CRC-related deaths, with 54 803 in 2022.[16] Only 54.5% of patients added to the transplant waitlist are transplanted at 1 year and 15.6% are removed due to death or becoming too sick.[17] In patients with ESLD that undergo transplant, 1-, 3-, and 5-year OS rates based on national data are 93.2%, 87.3%, and 80.2%, respectively.[17] It is imperative that transplant centers maintain

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

Established parameters		
Parameter	*Cutoff*	*Details*
CEA	Less than 80 μg/L	- SECA-I showed CEA > 80 μg/L was associated with shorter OS (*P* =.003) - 10-year SECA-I follow-up study confirmed CEA > 80 μg/L was associated with shorter OS (*P* =.008) - TRANSMET study allowed for higher baseline CEA so long as ≥50% reduction was seen before LT
Largest tumor diameter	Less than 5.5 cm	- SECA-I showed diameter > 5.5 cm was associated with shorter OS (*P* =.026) - 10-year SECA-I follow-up data confirmed the same (*P* =.003) - SECA-II inclusion criteria required no lesion >10 cm - Notably, not an exclusion criteria for TRANSMET trial
SD or PR to pre-LT CTX	SD or PR (vs PD)	- SECA-I included patients with SD, PR, and PD; showed that PD was negatively associated with OS (*P* =.04) - Confirmed in 10-year SECA-I follow-up (*P* =.045) - TRANSMET and SECA-II excluded patients with PD during pre-LT CTX
mTTLT *TTLT guidelines were not compared prospectively but were either listed as inclusion criteria and/or evaluated in post hoc analysis	1-2 years *Exact TTLT varies from study to study	- Derived from FCRS showing that remaining disease-free for > 1 year between primary resection and liver metastasectomy was associated with improved OS - In SECA-1, mTTLT > 2 years was associated with poorer OS (*P* =.045), but not in the 10-year follow-up (*P* =.227) - Subsequent studies have included various periods of ≥1 year before proceeding to LT: --- TRANSMET: Median 14.6 months --- SECA-II: Minimum 12 months, median 22.6 months --- Toso et al.: Median 41 months
Oslo Score (1pt each):- CEA > 80 μg/L - Largest tumor > 5.5 cm - PD on pre-LT CTX - TTLT < 2 years	Low (0-2) vs high (3-4)	- In post hoc, pooled analysis of SECA-I and SECA-II patients (*n* = 19), patients with low Oslo Scores had improved outcomes compared with those with high scores: --- mDFS: 19 vs 3 months, *P* =.004 --- 5-year OS rate: 67% vs 17%, *P* =.004 --- 5-year OS rate after relapse: 45% vs 17%, *P* =.019
Pre-LT PET/CT & ceCT	Lack of extrahepatic metastatic disease	- All active trials require pre-LT PET/CT - ceCT can detect important pre-LT extraheptic metastases missed by PET/CT, particularly small lung metastases
	MTV less than 70 cm^3	- Post hoc SECA-II analysis showed that MTV above cutoff was associated with shorter 5-year OS rates (*P* =.027)
Parameters requiring further study		
Parameter	*Cutoff*	*Details*
Histology	Well-differentiated vs poorly differentiated, undifferentiated, or signet ring cell carcinoma	- Concern that these histologic subtypes have overall poorer survival outcomes with existing treatments - SECA-II arm D study (*n* = 10) included 60% of these histologies with overall poor OS compared with other studies - SECA-II arm D 2-year OS rate significantly lower than arm C 2-year OS rate (*P* =.002) - Limited by cross-trial comparison, lack of control for other variables, and overall low sample size
Side of primary	Right vs left	- Concern that right-sided primary tumors is generally more aggressive than left-sided - Trend toward shorter DFS and OS for right-sided tumors in SECA-II arm D study did not reach significance - No clear indication to withhold LT for right-sided primary tumors alone
BRAF mutational status	Wild-type vs mutated	- Some studies include small amounts of *BRAF*-mutated tumors, but analysis is limited by small sample size - No clear impact of *BRAF* status on LT outcomes
Primary tumor stage	T4 vs lower stage	- Most studies include a minority of T4 patients, but statistical analysis is limited by small sample size - Subgroup analysis by T stage indicated in future trials
Primary tumor nodal status	Node-negative vs node-positive	- Most studies include various nodal stages, but statistical analysis is limited by small sample size - Subgroup analysis by *N* stage indicated in future trials

Table 2. Continued

Established parameters		
Parameter	*Cutoff*	*Details*
FCRS *Validated in liver metastasectomy pts only	Scored 0-4, with 4 being "worst"	- SECA-II (DFS longer for FCRS 1-2 vs 3-4, P =.044) - Largely replaced by Oslo Score, more specific to LT
Pre-LT FDG PET/CT	TLG less than 257 g	- TLG below cutoff associated with improved 5-year OS rates in post hoc analysis of SECA-II cohort (P =.026) - Largely replaced by MTV as main PET/CT parameter
Intraoperative frozen pathology exam of concerning lymph nodes	Negative intraoperative frozen pathology sectioning	- Multiple studies mention intraoperative frozen section of concerning lymph nodes prior to proceeding with LT - Limited by lack of standardization and no dedicated study

Abbreviations: µg/L, Micrograms per liter; CEA, carcinoembryonic antigen; ceCT, contrast-enhanced computed tomography; cm, centimeter; cm^3, cubic centimeters; CTX, chemotherapy; DFS, disease-free survival; FCRS, Fong Clinical Risk Score; g, grams; LT, liver transplantation; mDFS, median disease-free survival; mTTLT, median time to liver transplantation (from resection of primary tumor); MTV, metabolic tumor volume; OS, overall survival; PD, progressive disease; PET/CT, fluorodeoxyglucose positron emission tomography/computed tomography; PR, partial response; Pt, point; SD, stable disease; TLG, total lesion glycolysis.

outcomes comparable to national averages based on center-specific, risk-adjusted expected outcomes.

Organ allocation

The implementation of transplant as a treatment for select patients with CRLM must operate within the current allocation and distribution system. This system is implemented by the Organ Procurement and Transplant Network (OPTN), an entity operated by the non-profit UNOS.[46] This system bases allocation on medical urgency with additional distribution based on nautical miles from donor hospitals. Medical urgency is defined by the MELD score, a predictor of 90-day mortality in patients with ESLD.[47] Policies exist to afford patients with certain conditions exception points for allocation purposes (ie, a waitlist MELD that exceeds their biologic MELD) that approximate their risk of death on the waitlist to a comparable MELD score.[48] In June 2024, OPTN and UNOS approved updates to transplant oncology allocation policy guidance to include a MELD exception for CRLM to be formally implemented in January 2025.[49] All exceptions will be reviewed by the National Liver Review Board, comprised of transplant physicians and surgeons, and must meet specific selection criteria to be granted the exception (Table 3). The exception will be the median MELD at transplant minus 20 or 15, whichever is higher.[49]

Importantly, the above allocation and distribution policies apply to deceased donor organ recipients only. Allocation of living donor organs to recipients is dependent on each individual center's criteria without restrictions based on indication or MELD score. Therefore, LDLT remains an ideal option in these patients as it affords predictability regarding timing of transplant and graft quality, and based on limited data, may lead to superior outcomes.[23-25] In patients without living liver donors, waitlisting for deceased donor organs remains an option understanding proposed MELD exception guidance will give patients adequate priority to compete for deceased donor organs but not be atop the waitlist at most centers. In this case, the timing of transplant can be unpredictable, in part dependent on center practices, and deceased donor organs are likely to be limited to donation after circulatory death (DCD) donors. Recent advances in normothermic perfusion techniques have led to continued expansion of DCD donors. Importantly, these techniques allow for improved prognostication of organ viability and demonstrate outcomes comparable to donation after brain death donors.[50,51] These techniques are quickly becoming the standard of care in the USA and largely negating any reduction in graft or patient survival previously associated with DCD donor organs.

Limitations and opportunities for further study

Multiple active studies are evaluating the survival outcomes for transplant in CRLM and will add significantly to the literature. Larger sample sizes of patients randomized to chemotherapy alone versus chemotherapy followed by transplant are the most important as this design most directly answers the question of what to do with unresectable CRLM. The role of HAI in the era of transplant for CRLM, including conversion of unresectable liver metastases to resectable to potentially avoid or delay transplant, merits further, dedicated study. The largest HAI study to date showed a median RFS of 25 months for patients who received HAI after resection of liver metastases. While this is longer than the PFS seen in most trials of transplant for CRLM, further comparative and integrative studies of HAI and transplant are needed, given the disparity in OS outcomes between these modalities in particular.[12] Little is known about the potential impact of HAI pumps on the surgical complexity of a subsequent transplant.

Pre- and posttransplant chemotherapy

Chemotherapy duration, sequencing, and specific agents also merit further study in a randomized setting. Pretransplant chemotherapy varies from 3 to 6 months, depending on the study. The observation and treatment period preceding transplant is also ambiguous, recommended for 1 year in the available guidelines but varying from 3 months to over 2 years in the available literature,[20,31,52] and 5-Fluorouracil, irinotecan, oxaliplatin, cetuximab, and bevacizumab are all used in varying combinations in the available studies. Whether one drug or combination of drugs is superior to others is unclear. Furthermore, while pretransplant chemotherapy is the standard, posttransplant chemotherapy has been generally left to the treating team in all available studies. Dedicated study and standardization may very well improve outcomes further. The

Table 3. National liver review board guidance for LT for CRLM patient selection and MELD exception points.

Candidates can be considered for MELD exception points for CRLM if all of the following criteria are met:	
Component	**Criteria**
Primary diagnosis	Histological diagnosis of colon/rectal adenocarcinoma
	BRAF wild-type
	Microsatellite stable
	At least 12 months from time of CRLM diagnosis to time of initial MELD exception request
Treatment of primary tumor	Standard resection of primary tumor with negative resection margins
	No evidence of local recurrence by colonoscopy within 12 months prior to time of initial MELD exception request
Evaluation of extrahepatic metastatic disease	No signs of extrahepatic metastatic disease or local recurrence based on CT/MRI (chest, abdomen, and pelvis) and PET scan within 1mo of initial exception request
Evaluation of hepatic disease and prior systemic/liver-directed treatment	Received or receiving first-line chemotherapy/immunotherapy
	Relapse of liver metastases after liver resection or liver metastases not eligible for curative resection
	No hepatic lesion greater than 10 cm before start of treatment
	Stable or regressing disease with systemic and/or locoregional therapy for at least 6 months
Exclusion criteria	
Extrahepatic disease after primary tumor resection (including lymphadenopathy outside of the primary lymph node dissection)	
Local relapse of primary disease	
CEA > 80 μg/L (with or without radiographic evidence of disease progression or new lesion)	
MELD exception extension criteria	
***Assessed every 3 months**, candidates with CRLM should be considered for an MELD exception extension if they continue to meet all of the following criteria:*	
CT or MRI (chest, abdomen, and pelvis) without progression of hepatic disease or development of extrahepatic disease	
CEA < 80 μg/L	

Abbreviations: μg/L, Micrograms per liter; 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.

intersection with ctDNA may be particularly interesting here; a model such as the CIRCULATE trials could be considered, administering posttransplant chemotherapy to patients with detectable ctDNA and observation for patients with clearance of ctDNA after transplant.[53]

Quality of life and cost effectiveness

As the clinical science evolves, related topics should be addressed concurrently. Quality of life should be assessed with validated surveys in all ongoing and future studies of CRLM. Cost-effectiveness data are also lacking for transplant in CRLM, as well as comparison with standard-of-care chemotherapy. The available, limited data underscore the need for rigid selection processes to avoid significant cost concerns with mass implementation.[54,55] With more cost-effectiveness data could come workforce-related data such as differences in time in the workforce with transplant compared with other treatment modalities. Another important consideration is the rising rate of CRC in young adult populations compared with largely stagnant or even decreasing incidence in older populations.[56,57] With younger patients comes a unique cost/benefit profile for a cost-intensive treatment such as transplant, since longer OS for younger patients translates to longer time in the workforce and potentially even cost savings on that basis. Inevitably, potential cost ramifications will vary significantly from center to center, country to country, given the nuanced interactions with the transplant wait list, insurance reimbursement, and social concerns.

Donor organ source

Finally, graft source merits further study as does the specific study of the machine perfusion options for transplant in CRLM. The SOULMATE study is evaluating DCD donor organs. A specific study of moderately and severely steatotic livers and hepatitis C-positive livers with subsequent antiviral treatment would be novel in CRLM. Comparison of NMP versus HOPE for organ perfusion specifically for CRLM indications has yet to be studied, and perhaps an upcoming study could randomize donor organs to NMP versus HOPE. Methods to salvage discarded organs with NMP, such as the administration of defatting cocktails or medications, merit consideration to expand the donor pool even further. All of these efforts will require collaboration between medical oncology, transplant hepatology, and transplant surgery to optimize studies and subsequent workflows within a given expert center.

Conclusion

Liver transplantation holds significant promise to improve outcomes compared with chemotherapy and other liver-directed therapies for patients with CRLM. While DFS rates vary from study to study, it is clear that patients with unresectable liver metastases from CRC live significantly longer with transplant compared with chemotherapy alone. Transplantation for CRLM should be implemented at centers with existing transplant programs. Patient selection remains an important

area of active study, with multiple well-established parameters available to guide current patient selection for maximal benefit.

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Benjamin E. Ueberroth (Conceptualization, Investigation, Methodology, Writing—original draft, Writing—review & editing), Michael Kriss (Investigation, Methodology, Writing—original draft, Writing—review & editing), James R. Burton (Investigation, Methodology, Writing—review & editing), and Wells A. Messersmith (Conceptualization, Investigation, Methodology, Resources, Supervision, Project administration, Writing—review & editing)

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No new data were generated or analyzed in support of this research.

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