



A contemporary systematic review on liver transplantation for unresectable liver metastases of colorectal cancer

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The 5-year overall survival rate of a patient with unresectable metastatic colorectal cancer is poor at approximately 14%. Similarly, historical data on liver transplantation (LT) in those with colorectal liver metastases (CRLM) showed poor outcomes, with 5-year survival rates between 12% and 21%. More recently, limited data have shown improved outcomes in select patients with 5-year overall survival rates of approximately 60%. Despite these reported survival improvements, there is no significant improvement in disease-free survival. Given the uncertain benefit with this therapeutic approach and a renewed investigational interest, we aimed to conduct a contemporary systematic review on LT for CRLM. A systematic review of the literature was performed according to the preferred reporting items for systematic reviews and meta-analysis statement. English articles reporting on data regarding LT for CRLM were identified through the MEDLINE (via PubMed), Cochrane Library, and ClinicalTrials.gov databases (last search date: December 16th, 2021) by 2 researchers independently. A total of 58 studies (45 published and 13 ongoing) were included. Although early retrospective studies suggest the possibility that some carefully selected patients may benefit from LT, there is minimal prospective data on the topic and LT remains exploratory in the setting of CRLM. Additionally, several other challenges, such as the limited availability of deceased donor organs and defining appropriate selection criteria, remain when considering the implementation of LT for these patients. Further evidence from ongoing prospective trials is needed to determine if and to what extent there is a role for LT in patients with surgically unresectable CRLM. **Cancer 2022;128:2243-2257.** © 2022 The Authors. *Cancer* published by Wiley Periodicals LLC on behalf of American Cancer Society. This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

KEYWORDS: colorectal neoplasms, liver metastases, liver neoplasms, liver transplantation, unresectable metastatic colorectal cancer.

INTRODUCTION

It is expected that 149,500 cases of colorectal cancer (CRC) will be diagnosed in the United States in 2021, with approximately 52,980 deaths.¹ Twenty percent of newly diagnosed CRC patients will present with de novo metastatic disease. Over the past several years, treatments for metastatic CRC have significantly improved outcomes. Comparing data from 2018, the death rate from CRC is 55% lower when compared to that of the 1970s.² More recently, the 2-year relative survival rate for distant stage disease has increased from 21% in the mid-1990s, to 37% for those diagnosed between 2009 through 2015.³ Approximately 10% to 20% of these patients with metastatic CRC will have disease that is amenable to both chemotherapy and surgery, which in some cases can lead to curable outcomes.⁴ The 5-year overall survival (OS) of a patient with metastatic CRC is approximately 14%, with improvement to 30% to 50% following resection of their colorectal liver metastases (CRLM).⁵⁻⁷ However, only 20% of patients with CRLM are candidates for resection. For those who do undergo surgery, many will develop recurrent disease within the first 3 years.^{8,9}

For those not considered surgical candidates, locoregional therapies can be considered. Most commonly, these can include: chemotherapy via hepatic intraarterial infusion pumps (HAIC), selective internal radiation therapy (SIRT), microwave ablation (MWA), radiofrequency ablation (RFA), and stereotactic body radiotherapy (SBRT). Prior studies have indicated that in the adjuvant setting, HAIC can lead to improved disease-free survival (DFS) and OS.^{10,11} In the setting of unresectable CRLM, inconsistent improvement in OS is noted. A large meta-analysis revealed improved response rates, but no improvement in OS.¹² However, a randomized controlled trial comparing systemic bolus fluorouracil and HAIC did report a significant improvement in median OS with HAIC (20 vs 24.4 months).¹³ In addition, SIRT has recently been evaluated in a combined analysis of 3 randomized trials encompassing 1103 patients that revealed no improvement in OS with addition of first-line SIRT to FOLFOX.¹⁴ In the chemo-refractory setting, although SIRT did not appear

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to improve OS, a prior randomized trial did show significant improvement in time to tumor progression, as well as time to liver progression compared to chemotherapy.¹⁵ Although SIRT may have a role in later line therapies, it does not appear to have a role in the first line setting. Thermal ablative techniques such as MWA and RFA have also been evaluated, and although there may be fewer potential complications and improved post-procedural quality of life compared to resection, there are worse outcomes and higher recurrence rates.¹⁶⁻¹⁸ For tumors <3 cm, some studies have shown that RFA can obtain similar outcomes to resection.¹⁹ Last, SBRT can be considered in select patients who are not candidates for ablation or resection. A recent systematic review of 18 total studies revealed a pooled 2-year survival rate of 56.5% and a pooled 2-year local control rate of 59.3%. Median PFS and OS were 11.5 and 31.5 months, respectively.²⁰ Although each of these treatment modalities may have a role in patients with unresectable CRLM, based on the current evidence, no clearly superior treatment modality exists. In addition, further limitations exist given the lack of high-quality evidence comparing these treatments, as well as the variable expertise in performing these procedures at different medical centers.

Given the current and heterogeneous application of these locoregional approaches, in conjunction with the limited number of patients who have resectable liver disease, the role of liver transplantation (LT) is being investigated as an additional treatment option. Currently, the data for LT as a treatment for liver-only metastatic CRC is limited and exploratory; historically, LT has been studied with disappointing results. The largest data set demonstrating poor outcomes came from 58 patients in the European Liver Transplant Registry.^{21,22} They report 1- and 5-year OS rates of 62% and 18%, respectively. In this registry, 50 of 58 patients received their LT before 1995 and in 44% of cases, graft loss was not due to recurrent malignancy.²³ Further data from this period showed similar results. In a cohort of 41 patients (10 with unresectable CRLM) at the University of Cincinnati who received a LT for their metastatic disease, 5-year survival rates were 21%.²⁴ In addition, data from the University of Vienna showed 5-year survival rates of 12% in their cohort of 25 patients who underwent transplantation between 1983 through 1994.²⁵

Although the historical data regarding LT for CRLM revealed poor outcomes, there have since been significant improvements in transplant and oncologic care that could potentially lead to better outcomes. Yet, although there have been several case reports and series reporting

successful outcomes,²⁶⁻³⁶ there were no recent prospective studies to evaluate this topic until the Secondary Cancer-1 (SECA-1) study in 2013.³⁷ Thereafter, a renewed investigational interest in LT for CRLM has occurred with at least 13 ongoing studies (Table 2). Here, we detail the current literature on the topic and review the available data as they pertain to the use of LT for unresectable CRLM.

MATERIALS AND METHODS

Study Design, Search Strategy, Study Eligibility, and Selection

A systematic review of the literature was performed according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement.³⁸ No institutional review board approval or patient written consent was necessary, because the systematic review used only published data. Articles published in English reporting on demographic, clinical characteristics, and outcomes of patients undergoing LT for CRLM were searched through the MEDLINE (via PubMed), Cochrane Library, and ClinicalTrials.gov databases (last search date: December 16th, 2021) using the following algorithm: (colon OR colorectal OR rectal) AND metast* AND (liver transpl*). Two researchers (C.L.L. and I.A.Z.) performed the title/abstract and full-text screening stages of the literature search independently. The citations of the systematically reviewed studies and relevant review articles were hand-searched for potentially eligible, missed studies using the snowball methodology.³⁹ No sample size restriction or other search filters were applied. Any conflicts were resolved through quality control discussions.

Data Extraction and Tabulation

A standardized, pre-piloted form was used for data tabulation and extraction from the included studies for evidence synthesis. Two reviewers (C.L.L. and I.A.Z.) extracted the data independently and any discrepancies were identified and resolved through quality control discussions. The following data were extracted for each eligible study: first author, year of publication, transplant country, and number of patients.

RESULTS

Our initial database search yielded 2256 unique records, 80 of which were retrieved for full-text assessment. A total of 58 studies fulfilled the inclusion criteria and were ultimately included (40 published and 13 ongoing), whereas another 5 studies were identified through the snowball

methodology (Fig. 1). The characteristics of the included studies are shown in Tables 1 and 2.

The SECA-1 Study

The SECA-1 study is a prospective pilot study in Norway that evaluated LT in 21 patients with CRC who had unresectable CRLM and no signs of extrahepatic disease.³⁷ The main inclusion criteria were prior radical excision of the primary tumor, good performance status (Eastern Cooperative Oncology Group 0-1), and a minimum of 6 weeks of prior chemotherapy. Exclusion criteria included a weight loss of >10% 6 months before inclusion, other malignancies, and standard contraindications to LT. Notable baseline characteristics include: 76% of patients had progressed on first-line or later chemotherapy, 19% had metachronous metastases whereas 81% had synchronous, and the median number of hepatic tumors was 8. The results of this study revealed 1-, 3-, and 5-year OS rates of 95%, 68%, and 60%, respectively. Although the OS rates are improved compared to the 5-year historical rates of 12% to 21%, recurrent disease in this population was prevalent, with 19 of 21 patients having recurrence in a median time of 6 months. Most of these recurrences

were not in the transplanted liver, and 1-year DFS was 35%. Four factors were significantly associated with survival: diameter of the largest hepatic lesion based on CT scans before LT or by examination of the explanted liver (<5.5 cm), pretransplant carcinoembryonic antigen (CEA) levels <80 µg/L, stable or partial response to chemotherapy before transplant, and a time interval of more than 2 years between resection of the primary tumor and LT. From a surgical perspective, no patients died of surgical complications or any other nonmalignant cause. Based on Clavien-Dindo classifications,⁴⁰ 52% of patients had a grade I-II complication whereas 33% had complications requiring intervention. Two patients required repeat transplantation and 1 temporarily required dialysis due to hepatorenal syndrome.

Although DFS was limited in the SECA study, another study evaluating 12 patients undergoing LT for CRLM reported DFS rates of 56% ± 14%, 38% ± 15%, and 38% ± 15% at 1, 3, and 5 years, respectively.⁴¹ OS rates were 83% ± 11%, 62% ± 15%, and 50% ± 16% at 1, 3, and 5 years, respectively. They also noted similar findings to the SECA study regarding the importance of pretransplant CEA levels and the time interval between

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources

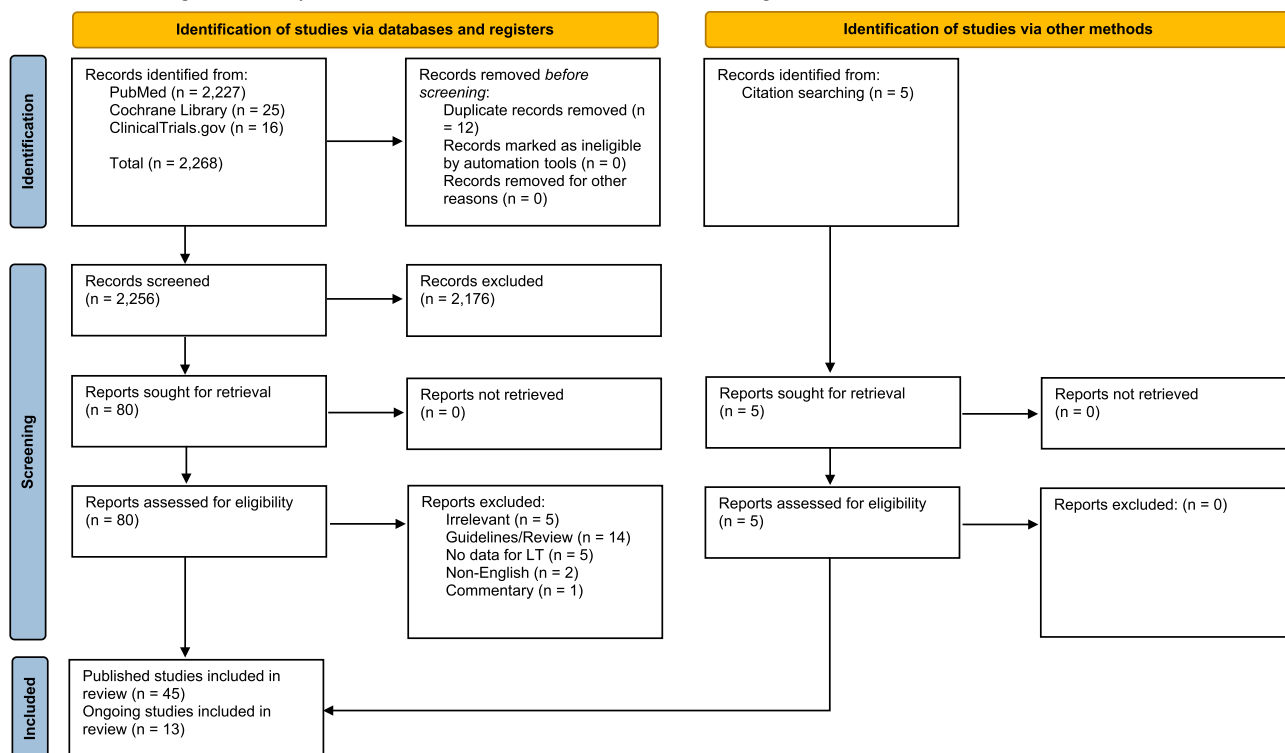


FIGURE 1. Preferred reporting items for systematic reviews and meta-analysis 2020 flow diagram for new systematic reviews that included searches of databases, registers, and other sources.

TABLE 1. Published Studies Included After Review

PMID/Study Identifier	Author	Publication Year	Country	No. of LT for CRLM
34117498	S. Dueland	2021	Norway	4
34792825	S. Dueland	2021	Norway	56
34448271	J. Lanari	2021	Norway and Italy	56
33787838	S. Dueland	2021	Norway	50
33906639	M. Tabbal	2021	Saudi Arabia	1
34924292	H. Grut	2021	Norway	12
32967602	J. Botha	2020	South Africa	5
32762027	G. Brandi	2020	Italy	3
32333527	T. Smedman	2020	Norway	10
32457265	J. Choi	2020	Korea	1
32302748	S. Nadalin	2020	Norway	11
31674105	S. Dueland	2019	Norway	19
31188200	S. Dueland	2020	Norway	15
31859921	E. Fernandez	2019	Brazil	1
31611117	Z. Yang	2019	China	1
31209941	T. Smedman	2019	Norway	23
31521538	J. Lerut	2019	Belgium	4
29916882	A. Konigsrainer	2019	Germany	1
30957065	S. Dueland	2018	Norway	23
30621712	F. Rauchfub	2019	Germany	3
30041968	M. Ravaoli	2018	Italy	1
29532908	S. Dueland	2018	Norway	21
29168565	H. Grut	2017	Norway	11
29026950	H. Grut	2017	Norway	23
28544246	C. Toso	2017	Switzerland	12
28203128	L. Caicedo	2017	Colombia	1
25692361	P. Line	2015	Norway	1
25297902	S. Dueland	2014	Norway	6
24950280	S. Dueland	2015	Norway	21
24370906	M. Hagness	2013	Norway	21
24157119	D. Hrehoret	2013	Romania	1
23360920	M. Hagness	2013	Norway	21
22452269	M. Andersen	2012	Norway	10
22172891	B. Kocman	2011	Croatia	1
21693328	O. Uskudar	2011	United States	2
20477993	A. Foss	2010	Norway	16
18713148	E. Hoti	2008	Europe	55
16421478	S. Kappel	2006	Austria	21
12802483	C. Honore	2003	Belgium	1
https://doi.org/10.1007/BF02620205	R. Steininger	1998	Austria	17
10388047	R. Pichlmayr	1997	Germany	4
1656538	I. Penn	1991	United States	10
1989293	F. Muhlbacher	1991	Austria	25
3274525	F. Muhlbacher	1987	Austria	9
4563508	S. Aune	1972	Norway	1

Abbreviations: CRLM, colorectal liver metastases; LT, liver transplant; PMID, PubMed identification number.

primary tumor resection and LT, because both were significant predictors of DFS. Although these data are of interest, certainly the small sample size and retrospective nature of the study present significant limitations when interpreting its results.

The discordance between OS and DFS is noteworthy given the opposite is often seen in studies evaluating liver-directed therapies in CRLM. For example, in the FOXFIRE, SIRFLOX, and FOXFIRE-Global studies, no significant improvement in OS was noted with the addition of SIRT to first-line chemotherapy with FOLFOX.^{14,42} Although such studies have shown a significant delay in disease progression in the liver, this

does not correlate to an increase in OS. However, in the SECA studies (Table 3), the opposite trend is seen with improving OS despite the low DFS rates. One potential reason for this may lie in the recurrence patterns noted in these early studies. For those undergoing LT, most recurrences appear to be slow growing solitary pulmonary metastases, and not recurrences in the liver or other sites.⁴³ Furthermore, most of these lesions appear to be amenable to resection. Although DFS may be limited, if a leading cause of this is pulmonary metastases that are slow growing and amenable to interventions, it could explain some of the DFS and OS discordance. Given the very limited data and small sample sizes of the studies showing these

TABLE 2. Current Studies Evaluating Liver Transplantation in Colorectal Liver Metastases

NCT No.	Trial Description	Primary End Point	Secondary End Point	Estimated Enrollment	Estimated Completion Date
02597348 (TRANSMET)	Multicenter randomized trial comparing the 5-y survival of chemotherapy followed by LT versus chemotherapy alone	OS	DFS, PFS, recurrence rates, QOL	90	February 2027
03488953 (LIVER-TWO-HEAL)	Nonrandomized trial evaluating the use of a two stage hepatectomy combined with a left lateral LDLT	OS	DFS, morbidity of donor and recipient, recurrence free survival	40	December 2023
02864485	Nonrandomized trial evaluating the use of neoadjuvant chemotherapy followed by LDLT	OS, DFS	Recurrence patterns, QOL, DFS, OS	20	December 2023
03494946 (SECA-III)	Randomized controlled trial comparing LT versus chemotherapy/TACE/SIRT or other treatment options	OS		30	January 2027
04161092 (SOULMATE)	Multicenter randomized controlled trial evaluating the use of liver grafts from ECD compared to best alternative care	OS	PFS, QOL, recurrence free survival, cost-effectiveness	45	June 2030
03803436 (COLT)	Multicenter nonrandomized trial evaluating the efficacy of LT compared to chemotherapy plus anti-EGFR therapy	OS	PFS, surgical complication rate	22	January 2024
04616495 (TRASMETTR)	Multicenter nonrandomized trial assessing the efficacy of LT	OS	DFS, QOL	30	May 2028
04874259	Nonrandomized trial evaluating the efficacy of LDLT	OS	DFS, sites and patterns of recurrence	20	May 2026
04870879 (MELODIC)	Nonrandomized trial evaluating the efficacy of LT compared to a matched cohort treated with chemotherapy	OS	PFS, complication rate 90 d after LT	18	October 2025
02215889	Nonrandomized trial evaluating the use of a two stage hepatectomy and partial segment LT	Percentage of transplanted patients receiving a second stage hepatectomy within 4 wk of segment 2/3 transplantation	OS	20	June 2028
04865471 (RAPID-Padova)	Nonrandomized trial evaluating the RAPID technique for liver transplantation	Percentage of transplanted patients receiving a second stage hepatectomy within 4 wk of segment 2/3 transplantation	PFS, survival after transplantation, mortality, complication rates	18	October 2025
04742621	Nonrandomized, single-arm, pilot registry of liver transplantation in patients with unresectable colorectal liver only metastases	Development of a registry of LT in patients with liver limited mCRC	DFS, OS	20	July 2034
04898504 (Excalibur 1+2)	Three arm parallel randomized trial between 2nd line chemotherapy + HAI-floxuridine or LT versus 2nd line chemotherapy alone; making it 3 arms, HAI, liver-Tx, and 2nd line chemotherapy alone	2-y OS	QOL, operative complications, 30- and 90-d post-op mortality and morbidity	45	May 2026

Abbreviations: DFS, disease-free survival; ECD, extended criteria donors; HAI, hepatic artery infusion; LDLT, living donor liver transplant; LDLT, liver resection; LT, liver transplantation; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival; QOL, quality of life; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolization.

TABLE 3. Summary of SECA Studies

Study Name/ Design	Total Patients	Main Inclusion Criteria	Main Exclusion Criteria	Notable Baseline Characteristics	OS	DFS	Other Notable Findings
SECA-1, prospec- tive, single-center	21	<ul style="list-style-type: none"> • Prior radical excision of primary tumor • ECOG 0-1 • No extrahepatic disease • Minimum of 6 wk of prior chemotherapy 	<ul style="list-style-type: none"> • Weight loss >10% 6 mo before inclusion • Standard LT contraindications • Other malignancies 	<ul style="list-style-type: none"> • 76% progressed on 1st line or later chemotherapy • Median of 8 liver lesions • Median diameter of largest lesion 4.5 cm • 19% metastatic synchronous and 81% synchronous • Median CEA at LT 15 µg/L • Median FCRS 3 • 70% (y) pT3 • 5/10 right-sided tumors • Median CEA at LT 4 µg/L • Median FCRS 3 • Median of 38 liver lesions • All patients received at least 2 prior lines of chemotherapy • All patients had synchronous metastases • Median time from primary tumor resection and LT 17.5 mo 	<ul style="list-style-type: none"> • 1-y 95% • 3-y 68% • 5-y 60% 	<ul style="list-style-type: none"> • 1-y 35% 	<ul style="list-style-type: none"> • 4 negative prognostic factors: CEA >80 µg/L, largest liver lesion >5.5 cm, progressive disease at time of LT, and <2 y between primary tumor resection and LT • 19/21 patients had recurrence in a median time of 6 mo; majority of recurrences were pulmonary • 33% had ≥ grade 3 postoperative complications
SECA-2 arm D, prospective single-center	10	<ul style="list-style-type: none"> • Patients who did not meet the below SECA-II inclusion criteria • Reasons for exclusion included <10% RECIST response, prior resected extrahepatic disease, <1 y from primary diagnosis, progressive disease, relapsed/new primary, other malignancy 	<ul style="list-style-type: none"> • Similar to SECA-II as below 	<ul style="list-style-type: none"> • Median CEA at LT 4 µg/L • Median FCRS 3 • Median of 38 liver lesions • All patients received at least 2 prior lines of chemotherapy • All patients had synchronous metastases • Median time from primary tumor resection and LT 17.5 mo 	<ul style="list-style-type: none"> • 18 mo (median) 	<ul style="list-style-type: none"> • 4 mo (median) 	<ul style="list-style-type: none"> • 9/10 received ECD grafts • 8/10 patients relapsed (6 pulmonary metastases, none resectable) • Median OS after recurrence 8 mo • Significantly greater FCRS and Oslo scores as well as median no./size of liver lesions compared to SECA-II patients with synchronous metastases • No deaths due to graft failure (1 graft failure noted with >80% steatosis, required retransplant)

TABLE 3. Continued

Study Name/ Design	Total Patients	Main Inclusion Criteria	Main Exclusion Criteria	Notable Baseline Characteristics	OS	DFS	Other Notable Findings
SECA-2, prospective, single-center	15	<ul style="list-style-type: none"> • Prior radical excision of primary tumor (adequate margins, CRM ≥ 2 mm) • ECOG 0-1 • No extrahepatic disease • Received 1st line chemotherapy • No lesion > 10 cm before chemotherapy • Lesions < 5 cm and at least 30% response by RECIST if > 30 lesions • 10% RECIST response to chemotherapy • 1-y time span from CRC diagnosis and date of LT listing 	<ul style="list-style-type: none"> • Weight loss $> 10\%$ in the last 6 mo • Standard LT contraindications • Other malignancies • BMI > 30 • Palliative resection of primary CRC tumor • Lack of standard pre-op, peri-op, or post-op treatment of primary tumor 	<ul style="list-style-type: none"> • 73% (V)PT3 • Median time from primary tumor resection and LT 22.6 mo • Median of 12 liver lesions (5 at time of LT) • Median diameter of largest lesion 4.5 cm (2.4 cm at time of LT) • 7% metachronous and 93% synchronous • Median CEA at LT 2 $\mu\text{g/L}$ • Median FCRS 3 (2 at LT) 	<ul style="list-style-type: none"> • 1-y 100% • 3-y 83% • 5-y 83% 	<ul style="list-style-type: none"> • 1-y 53% • 2-y 44% • 3-y 35% • 13.7 mo (median) 	<ul style="list-style-type: none"> • Survival after relapse at 1, 2, and 4 y was 100%, 73%, and 73%, respectively • Median DFS improved if < 8 liver lesions at time of LT (24.3 vs 11.6 mo) • Median DFS improved if FCRS ≤ 2 at diagnosis (not reached vs 11.8 mo) • Median DFS improved if N0 at time of primary resection (24.3 vs 11.6 mo) • 6/8 patients who relapsed after LT had pulmonary metastases as the 1st or only site. 5/6 had resectable disease • 11/15 patients had NED at end of 36-mo follow-up (7 no relapse and 4 NED after resection of pulmonary lesion)

Abbreviations: BMI, body mass index; CEA, carcinoembryonic antigen; CRC, colorectal cancer; DFS, disease-free survival; ECD, extended criteria donor; ECOG, Eastern Cooperative Oncology Group; FCRS, Fong clinical risk score; LT, liver transplant; NED, no evidence of disease; OS, overall survival; RECIST, response evaluation criteria in solid tumor; SECA, Secondary Cancer.

recurrence patterns, it is difficult to draw any definitive conclusions. For patients being considered for LT, there is an inherent and uncertain risk that pretransplant visible liver metastases may be a sign of disseminated micro-metastatic disease, thereby emphasizing the need to carefully select patients.

Selection Criteria for Liver Transplantation

The average waiting time for LT in Norway is significantly better than many parts of the world, with the average wait time for transplant being less than 1 month.³⁷ In 2020 alone, a total of 1105 patients in the United States died on the transplant list while in Norway, that number was only 4.^{44,45} Given the inadequate supply of deceased donor organs in many countries, the importance of appropriate selection criteria becomes paramount. To help investigate this, the prospective SECA-2 study was completed.⁴⁶ In this study, a total of 15 patients with CRC and unresectable CRLM underwent LT similar to SECA-1. However, more stringent inclusion criteria were required. Specifically, a response to chemotherapy of at least 10% by response evaluation criteria in solid tumors (RECIST) criteria was required. In addition, before the start of chemotherapy, no lesion could be larger than 10 cm. If there were more than 30 lesions, all were required to be <5 cm and the patients needed at least a 30% response based on RECIST criteria. Last, the time from primary diagnosis to LT was required to be more than 1 year and no patient had a CEA level >80 µg/L at the time of transplant. With more stringent criteria, DFS was noted to be 13.7 months. Additionally, DFS was improved in patients who had fewer than 8 hepatic lesions at the time of LT (DFS, 24.3 months), Fong clinical risk scores (FCRS) ≤2 at the time of diagnosis (DFS not reached), and in those who were N0 after primary tumor resection (DFS, 24.3 months). One-, 3-, and 5-year OS rates were 100%, 83%, and 83%, respectively. Survival after relapse at 1, 2, and 4 years was 100%, 73%, and 73%, respectively.

Three different clinical scoring systems have been evaluated to predict long-term OS, DFS, and survival after relapse.⁴⁷ Based on data from both SECA studies, 19 total patients were evaluated using 3 different criteria: the metabolic tumor volume (MTV) on positron emission tomographic/computed tomography scans (PET/CT) within 90 days before transplant, FCRS, and Oslo scores. Those with a low MTV (<70 cm³) had significant improvement in median DFS (23 months vs 3.5 months), 5-year OS rates (78% vs 22%), and 5-year survival after relapse (71% vs 11%) compared to the high MTV group. Those in the low MTV group also had a significantly

TABLE 4. Fong Clinical Risk Score and Oslo Score Criteria^{37,48}

Oslo Score (0-4)	Fong Clinical Risk Score (0-5)
Largest tumor >5.5 cm	Node-positive primary tumor
Less than a 2-y interval between primary tumor resection and LT	Disease-free interval from the primary to discovery of the liver metastases of <12 mo
Progressive disease at the time of LT	No. of tumors >1
Preoperative CEA >80 µg/L	Preoperative CEA >200 µg/mL
	Largest tumor >5.0 cm

Abbreviations: CEA, carcinoembryonic antigen; LT, liver transplant.

lower median number and size of liver lesions, FCRS, CEA levels, and Oslo scores compared to the high MTV group. Similar results were noted with improved DFS, OS, and survival after relapse when comparing low Oslo scores (0-2) and FCRS (0-2) to those with higher scores (Table 4). Notably, those with right sided tumors had worse DFS and OS after relapse compared to left-sided tumors. Overall, those with a low FCRS had the best OS.

Availability of Organs for Transplantation

Although clinical risk stratification is vital in the allocation of organs, there are other potential interventions that may increase access to transplantation for these patients. Newer surgical techniques, living donor transplantation, and the use of extended criteria donor (ECD) grafts are being evaluated that potentially could increase the availability of LT for CRLM. One such surgical technique deemed the “RAPID concept” describes a partial segment 1 to 3 resection, followed by transplant of a left lateral segment (2+3) allograft. Then, a delayed second stage hepatectomy is completed once the graft has hypertrophied to an appropriate volume.^{49,50} Although the initial case report indicates the potential feasibility of this technique, problems still exist given the availability of splittable organs is poor and may not offer a realistic solution. In 2019, Konigsrainer et al⁵¹ used the RAPID approach but with a living donor transplant. In this report, both the donor and recipient did well, demonstrating potential proof of concept with such a technique. Beyond these surgical techniques, ECD grafts represent another possible avenue to increase the availability of organs. As a small arm of the SECA-2 study, 10 patients were evaluated who did not meet the stricter criteria for enrollment in SECA-2.⁵² Nine of 10 patients received an ECD graft in the study. Compared to those in SECA-2, these patients had a higher median number and size of hepatic lesions, as well as higher FCRS and Oslo scores at the

time of transplant. Eight of 10 patients developed recurrent disease, 6 of which were pulmonary metastases. The median DFS was 4 months and OS was 18 months. Patients with a higher MTV ($>70 \text{ cm}^3$) and right-sided tumors had worse overall outcomes. When comparing the ECD graft population to those in SECA-2, the OS and OS after relapse was significantly worse for ECD grafts. Although there were no deaths due to graft failure, 1 case of graft failure was noted in which repeat transplantation was required. Although the use of ECD grafts may be possible, given the increased risks of these grafts, and the relatively short OS in this study, their overall use may be limited.

Other potential strategies to increase access to LT include the use of donation after circulatory death grafts (DCD) and novel perfusion strategies such as hypothermic oxygenated machine perfusion (HOPE). Historically, DCD transplants had worse long-term outcomes due to higher rates of biliary complications, primary non function and hepatic artery thrombosis.^{53,54} However, with the advent of machine perfusion and overall improvements in transplant surgery, more recent studies have shown decreased risks of biliary complication with DCD grafts. In a recent meta-analysis, there was no difference in patient survival, biliary complications, severe complications, length of stay, or acute renal failure between DCD grafts and donation after brain death grafts (DBD).⁵⁵ DCD grafts showed an increased risk of graft loss, retransplant and primary non function compared to DBD grafts; however, this effect was lessened when accounting for publication bias. In a recent randomized trial, the use of HOPE for DCD grafts has been shown to decrease the risk of nonanastomotic biliary strictures, post-reperfusion syndrome and early allograft dysfunction compared to DCD grafts where conventional static cold storage was used.⁵⁶ Additional studies have indicated that HOPE may be associated with equivalent graft survival compared to DBD grafts and improved graft survival compared to non-HOPE DCD grafts.⁵⁷ Furthermore, in some studies, postmortem normothermic regional perfusion in controlled DCD grafts has shown decreased postoperative biliary complications, ischemic type biliary lesions, and graft loss compared to conventional super rapid recovery.⁵⁸ Although these novel perfusion strategies may have the potential to increase the availability of LT, their use in the United States has been limited given no machine perfusion device received Food and Drug Administration approval until September 2021.^{59,60}

Moreover, the potential use of LT in CRLM may be dependent on not only careful patient selection, but also policy changes that may allow for access to liver grafts. Currently, MELD exception points are granted for a multitude of conditions including both neuroendocrine tumors and hilar cholangiocarcinoma. Although specific criteria must be met to be considered for transplantation in these populations, a framework of similar criteria could be considered for those with CRLM. Although the exact criteria are an open area of research, to make LT for metastatic CRC feasible in the United States, MELD exception points could potentially be considered for patients meeting a set criteria.

Transplantation Versus Resection and Patterns of Relapsed Disease

Currently, there are no prospective published data comparing LT to resection in CRLM. A recent retrospective analysis has been completed in patients who underwent LT in the SECA studies compared to a cohort of patients who underwent portal vein embolization (PVE) and subsequent liver resection (LR).⁶¹ A total of 50 patients in the LT cohort and 53 patients in the PVE cohort were evaluated. Of the 53 patients in the PVE cohort, 38 underwent subsequent LR. They were divided into 2 groups based on the authors' classification of high and low tumor burden, after chemotherapy and before the time of their respective procedure. High tumor burden was defined as 9 or more metastatic lesions or a diameter of the largest metastasis $\geq 5.5 \text{ cm}$. In the low tumor burden group, PVE and LR resulted in a 5-year OS rate of 69.3% compared to 72.4% in the LT cohort. For the high tumor burden group, PVE and LR resulted in a median OS of 29.8 months compared to 40.5 months for LT. When comparing the side of the primary tumor, those with left-sided tumors and a high tumor burden had significantly better outcomes compared to those with right-sided tumors. Those with left-sided tumors and a high tumor burden who underwent LT had a median OS of 59.9 months and a 5-year OS rate of 45.3%. In contrast, those who underwent PVE and LR had a median OS of 29.8 months and a 5-year OS rate of 12.5%. For comparison, the 5-year median OS rate with LR is approximately 38% with the median survival time being 43.2 months.⁶² An additional retrospective study compared the survival benefit of LR to LT based on tumor burden scores (TBS). This study reported that in patients with Oslo scores <2 and TBS >9 , 5-year OS was 69.1% for LT and 14.6% for LR. The 1- and 3-year DFS rates in this subset of patients undergoing LR was

TABLE 5. Eligibility Criteria of Current Prospective Studies Evaluating Liver Transplant for Unresectable Colorectal Liver Metastases

NCT No.	Main Inclusion Criteria	Main Exclusion Criteria
02597348 (TRANSMET)	<ul style="list-style-type: none"> BRAF wild-type High standard oncological surgical resection Colonoscopy 12 mo before inclusion (except in case of primary tumor resection <12 mo) excluding recurrence ≥3 mo of tumor control during the last chemotherapy line: stable or partial response by RECIST criteria ≤2 lines of chemotherapy CEA <80 µg/L or a decrease ≥50% of the highest serum levels Absence of extrahepatic disease Patients with irresectable colorectal liver metastases without extrahepatic tumor burden, except resectable pulmonary metastases Stable disease or regression after at least 8 wk of systemic chemotherapy by RECIST criteria ECOG 0-1 at all times before LDLT (excursions to ECOG 2 allowed at investigator's discretion) Primary CRC tumor stage is ≤T4a Time from primary CRC resection to LT is ≥6 mo Bilateral and nonresectable LM, no major vascular invasion by LM; metastases isolated to liver Systemic chemotherapy for ≥3 mo Stability or regression of LM over at minimum the 3 mo preceding screening CEA values are stable or decreasing at all time points before the LT No signs of extra hepatic metastatic disease or local recurrence according to PET/CT scan within 6 wk before transplant meeting, except patients may have resectable lung lesions all <15 mm No signs of extra hepatic metastatic disease on CT or MRI thorax/abdomen/pelvis within 6 wk before transplant meeting, except resectable lung lesions all <15 mm Progressive disease according to RECIST-criteria, or intolerance to 1st line chemotherapy; patients must be randomized before evaluation 8-12 wk after starting 2nd line chemotherapy 	<ul style="list-style-type: none"> General contraindication to LT (severe cardiopulmonary disease or other life-limiting co-existing medical conditions, extrahepatic malignancy, active alcohol or substance abuse, active infection or uncontrolled sepsis, lack of psychosocial support or inability to comply with medical treatment) Other malignancies either concomitant or within 5 y before LT Not having received standard treatment for the primary CRC according to recommended guidelines Prior extra hepatic metastatic disease or local relapse Comorbidities precluding liver transplantation Extrahepatic tumor spread, except resectable pulmonary metastases Progression during chemotherapy Previous or concurrent cancer (with some exceptions) Prior lung resection Progression of LM at any time point before transplant surgery Renal dysfunction with an estimated creatinine clearance of less than 50 mL/min Pulmonary insufficiency History of cardiac disease Patients with debilitating neuropathy (CTCAE >grade 2) BRAF + tumors BMI >30 Weight loss >10% in the last 6 mo Previous resection of local relapse or nonhepatic metastasis within the last 2 y or resection of pulmonary or liver hilus lymph node metastases the last year Previous diagnosed bone or CNS metastatic disease or thoracic or abdominal metastatic lymph nodes Previous diagnosed cancer mammae or malignant melanoma Non resected or palliative resection of primary CRC tumor Liver metastases affecting the diaphragm Liver lesion >10 cm Three negative prognostic factors at time of randomization (CEA >80 µg/L, <2 y from diagnosis, diameter of largest liver lesion >5.5 cm) Weight loss >10% the last 6 mo Other malignancies within the last 5 y, except CRC and low risk tumors Liver metastases larger than 10 cm Pathological lymphatic nodes in the abdomen BRAF mutations Microsatellite instability (MSI-H) in primary tumor Hereditary CRC syndromes Prior extra hepatic metastatic disease or primary tumor local relapse Extra-peritoneal cancers (rectum) Other malignancies in the previous 5 y
03488953 (LIVER-TWO-HEAL)	<ul style="list-style-type: none"> Stable disease or regression after at least 8 wk of systemic chemotherapy by RECIST criteria ECOG 0-1 at all times before LDLT (excursions to ECOG 2 allowed at investigator's discretion) Primary CRC tumor stage is ≤T4a Time from primary CRC resection to LT is ≥6 mo Bilateral and nonresectable LM, no major vascular invasion by LM; metastases isolated to liver Systemic chemotherapy for ≥3 mo Stability or regression of LM over at minimum the 3 mo preceding screening CEA values are stable or decreasing at all time points before the LT No signs of extra hepatic metastatic disease or local recurrence according to PET/CT scan within 6 wk before transplant meeting, except patients may have resectable lung lesions all <15 mm No signs of extra hepatic metastatic disease on CT or MRI thorax/abdomen/pelvis within 6 wk before transplant meeting, except resectable lung lesions all <15 mm Progressive disease according to RECIST-criteria, or intolerance to 1st line chemotherapy; patients must be randomized before evaluation 8-12 wk after starting 2nd line chemotherapy 	<ul style="list-style-type: none"> General contraindication to LT (severe cardiopulmonary disease or other life-limiting co-existing medical conditions, extrahepatic malignancy, active alcohol or substance abuse, active infection or uncontrolled sepsis, lack of psychosocial support or inability to comply with medical treatment) Other malignancies either concomitant or within 5 y before LT Not having received standard treatment for the primary CRC according to recommended guidelines Prior extra hepatic metastatic disease or local relapse Comorbidities precluding liver transplantation Extrahepatic tumor spread, except resectable pulmonary metastases Progression during chemotherapy Previous or concurrent cancer (with some exceptions) Prior lung resection Progression of LM at any time point before transplant surgery Renal dysfunction with an estimated creatinine clearance of less than 50 mL/min Pulmonary insufficiency History of cardiac disease Patients with debilitating neuropathy (CTCAE >grade 2) BRAF + tumors BMI >30 Weight loss >10% in the last 6 mo Previous resection of local relapse or nonhepatic metastasis within the last 2 y or resection of pulmonary or liver hilus lymph node metastases the last year Previous diagnosed bone or CNS metastatic disease or thoracic or abdominal metastatic lymph nodes Previous diagnosed cancer mammae or malignant melanoma Non resected or palliative resection of primary CRC tumor Liver metastases affecting the diaphragm Liver lesion >10 cm Three negative prognostic factors at time of randomization (CEA >80 µg/L, <2 y from diagnosis, diameter of largest liver lesion >5.5 cm) Weight loss >10% the last 6 mo Other malignancies within the last 5 y, except CRC and low risk tumors Liver metastases larger than 10 cm Pathological lymphatic nodes in the abdomen BRAF mutations Microsatellite instability (MSI-H) in primary tumor Hereditary CRC syndromes Prior extra hepatic metastatic disease or primary tumor local relapse Extra-peritoneal cancers (rectum) Other malignancies in the previous 5 y
04161092 (SOULMATE)	<ul style="list-style-type: none"> R0 primary tumor resection No signs of extra hepatic disease/local recurrence Colonoscopy within the last 12 mo excluding recurrence At least 2 mo of chemotherapy with no signs of progressive disease according to RECIST-criteria at the last evaluation before randomization ≥1 y from the initial CRC diagnosis to the date of inclusion Nonmucinous colon adenocarcinoma Primary tumor as pT1-3, pN0, or pN1 (metastases in <4 regional lymph nodes), confirmed R0 resection RAS and BRAF wild-type and MSS molecular status Objective response according to RECIST to 1st line treatment, with sustained response for at least 4 mo, or disease control during 2nd line treatment for at least 4 mo Maximum of 2 prior chemotherapy lines CEA <50 ng/mL 	<ul style="list-style-type: none"> General contraindication to LT (severe cardiopulmonary disease or other life-limiting co-existing medical conditions, extrahepatic malignancy, active alcohol or substance abuse, active infection or uncontrolled sepsis, lack of psychosocial support or inability to comply with medical treatment) Other malignancies either concomitant or within 5 y before LT Not having received standard treatment for the primary CRC according to recommended guidelines Prior extra hepatic metastatic disease or local relapse Comorbidities precluding liver transplantation Extrahepatic tumor spread, except resectable pulmonary metastases Progression during chemotherapy Previous or concurrent cancer (with some exceptions) Prior lung resection Progression of LM at any time point before transplant surgery Renal dysfunction with an estimated creatinine clearance of less than 50 mL/min Pulmonary insufficiency History of cardiac disease Patients with debilitating neuropathy (CTCAE >grade 2) BRAF + tumors BMI >30 Weight loss >10% in the last 6 mo Previous resection of local relapse or nonhepatic metastasis within the last 2 y or resection of pulmonary or liver hilus lymph node metastases the last year Previous diagnosed bone or CNS metastatic disease or thoracic or abdominal metastatic lymph nodes Previous diagnosed cancer mammae or malignant melanoma Non resected or palliative resection of primary CRC tumor Liver metastases affecting the diaphragm Liver lesion >10 cm Three negative prognostic factors at time of randomization (CEA >80 µg/L, <2 y from diagnosis, diameter of largest liver lesion >5.5 cm) Weight loss >10% the last 6 mo Other malignancies within the last 5 y, except CRC and low risk tumors Liver metastases larger than 10 cm Pathological lymphatic nodes in the abdomen BRAF mutations Microsatellite instability (MSI-H) in primary tumor Hereditary CRC syndromes Prior extra hepatic metastatic disease or primary tumor local relapse Extra-peritoneal cancers (rectum) Other malignancies in the previous 5 y
03803436 (COLT)	<ul style="list-style-type: none"> Objective response according to RECIST to 1st line treatment, with sustained response for at least 4 mo, or disease control during 2nd line treatment for at least 4 mo Maximum of 2 prior chemotherapy lines CEA <50 ng/mL 	<ul style="list-style-type: none"> General contraindication to LT (severe cardiopulmonary disease or other life-limiting co-existing medical conditions, extrahepatic malignancy, active alcohol or substance abuse, active infection or uncontrolled sepsis, lack of psychosocial support or inability to comply with medical treatment) Other malignancies either concomitant or within 5 y before LT Not having received standard treatment for the primary CRC according to recommended guidelines Prior extra hepatic metastatic disease or local relapse Comorbidities precluding liver transplantation Extrahepatic tumor spread, except resectable pulmonary metastases Progression during chemotherapy Previous or concurrent cancer (with some exceptions) Prior lung resection Progression of LM at any time point before transplant surgery Renal dysfunction with an estimated creatinine clearance of less than 50 mL/min Pulmonary insufficiency History of cardiac disease Patients with debilitating neuropathy (CTCAE >grade 2) BRAF + tumors BMI >30 Weight loss >10% in the last 6 mo Previous resection of local relapse or nonhepatic metastasis within the last 2 y or resection of pulmonary or liver hilus lymph node metastases the last year Previous diagnosed bone or CNS metastatic disease or thoracic or abdominal metastatic lymph nodes Previous diagnosed cancer mammae or malignant melanoma Non resected or palliative resection of primary CRC tumor Liver metastases affecting the diaphragm Liver lesion >10 cm Three negative prognostic factors at time of randomization (CEA >80 µg/L, <2 y from diagnosis, diameter of largest liver lesion >5.5 cm) Weight loss >10% the last 6 mo Other malignancies within the last 5 y, except CRC and low risk tumors Liver metastases larger than 10 cm Pathological lymphatic nodes in the abdomen BRAF mutations Microsatellite instability (MSI-H) in primary tumor Hereditary CRC syndromes Prior extra hepatic metastatic disease or primary tumor local relapse Extra-peritoneal cancers (rectum) Other malignancies in the previous 5 y

TABLE 5. Continued

NCT No.	Main Inclusion Criteria	Main Exclusion Criteria
04616495 (TRASMETIR)	<ul style="list-style-type: none"> • R0 primary tumor resection • No extra hepatic disease • Response to ≤ 2 lines of chemotherapy (RECIST criteria) • ≥ 1 y period since diagnosis of colorectal cancer to enrollment in liver transplant waiting list 	<ul style="list-style-type: none"> • BMI > 30 • BRAF mutated status • Deterioration of general condition (10% weight loss in the prior 6 mo) • Other malignancy with disease free survival < 5 y • Concomitant or prior extrahepatic metastases (histologically or radiologically proved), even if surgically resected • Palliative resection of primary colorectal adenocarcinoma • Liver metastases size > 5 cm (in the last imaging technique) • CEA > 80 ng/mL (at time of enrollment in waiting list) • No neoadjuvant chemotherapy treatment • Patients with active peptic ulcer within 2 wk of transplantation • Persistent CRC after colon resection • Progression of LM at any time point before transplant surgery (assessed in a multidisciplinary meeting) • Weight loss $> 10\%$ the last 6 mo • BMI > 30 • Previous diagnosed bone or CNS metastatic disease • Previous diagnosed cancer mammae or malignant melanoma • Palliative resection of primary CRC tumor
04874259	<ul style="list-style-type: none"> • Proven CRC liver metastases that are stable without other treatments (such as immunotherapy, chemotherapy, surgical resection, and radiofrequency ablation) • No evidence of extra hepatic disease 	<ul style="list-style-type: none"> • Progression of LM at any time point before transplant surgery (assessed in a multidisciplinary meeting) • Weight loss $> 10\%$ the last 6 mo • BMI > 30 • Previous diagnosed bone or CNS metastatic disease • Previous diagnosed cancer mammae or malignant melanoma • Palliative resection of primary CRC tumor
02216889	<ul style="list-style-type: none"> • No signs of extra hepatic metastatic disease or local recurrence according to PET/CT and CT scans within 4 wk before transplant meeting, except patients may have 1-3 resectable lung lesions all < 15 mm • No local recurrence according to MRI-pelvis scan in patients with rectal cancer within 4 wk before transplant meeting • No signs of local recurrence judged by colonoscopy/CT colography within 12 mo before transplant meeting 	<ul style="list-style-type: none"> • Weight loss $> 10\%$ the last 6 mo • BMI > 30 • General contraindications to LT • Prior extra hepatic metastatic disease or primary tumor local relapse • Other malignancies in the previous 5 y
04870879 (MELODIC)	<ul style="list-style-type: none"> • BRAF wild-type CRC • High standard oncological surgical resection of the primary tumor • At least one line (3 mo) of chemotherapy • No signs of extra hepatic metastatic disease or local recurrence on CT, MRI, and PET/CT within 4 wk before transplant meeting • Before the start of chemotherapy, no lesion should be > 10 cm • Objective response according to RECIST 1.1 or stable disease at 2 consecutive CT without CEA increase • Patient with $< 10\%$ response on chemotherapy may be included if they obtain at least 20% response after TACE (DEB-IRI) or by 90Y-spheres • At least 10-mo time span from CRC resection and date of being listed on the transplantation list 	<ul style="list-style-type: none"> • Weight loss $> 10\%$ the last 6 mo • BMI > 30 • General contraindications to LT • Prior extra hepatic metastatic disease or primary tumor local relapse • Other malignancies in the previous 5 y
04865471 (RAPID-Padova)	<ul style="list-style-type: none"> • CEA < 100 ng/mL • BRAF wild-type CRC • High standard oncological surgical resection of the primary tumor • At least 1 line (3 mo) of chemotherapy • At least a 6-mo time span from CRC resection and date of being listed on the transplantation list • At least 8 wk of tumor control: stable disease or partial response according to RECIST 1.1 criteria • No signs of extra hepatic metastatic disease or local recurrence on CT, MRI, and Pet-CT except patients may have < 3 lung lesions all < 15 mm resected or treated by radiotherapy or metastatic hilar nodes treated by resection and without recurrence at 3 mo from resection or radiotherapy • CEA stable or decreasing 	<ul style="list-style-type: none"> • BMI > 30 • Weight loss $> 10\%$ in the last 6 mo • General contraindications to LT • Other malignancies in the previous 5 y

TABLE 5. Continued

NCT No.	Main Inclusion Criteria	Main Exclusion Criteria
04742621	<ul style="list-style-type: none"> No evidence of extrahepatic metastases or local recurrence based on PET/CT and colonoscopy No signs of extrahepatic metastases or local recurrence according to PET/CT 4 wk before consideration of transplant Stability or regression of liver metastasis for at least 6 mo Minimum of 1 y between diagnosis of colon cancer and liver transplant and 6 mo from primary tumor resection and liver transplant Minimum of 6 mo chemotherapy CEA <200 µg/L 3 mo before transplant Prior adenocarcinoma radically resected with adequate margins/preoperative treatment Six or more liver metastases that have progression (or insufficient response on 1st line chemotherapy, including toxicity) Plans for 2nd line chemotherapy If patients are switched to 2nd line chemotherapy, randomization can only be allowed before first evaluation on 2nd line chemotherapy regimen 	<ul style="list-style-type: none"> Evidence of extrahepatic disease or local recurrence Previous resection of lung metastases MSI-H/dMMR or BRAF mutation Arterial anatomy not suited for HAI pump-line insertion Liver metastatic ingrowth to the diaphragm Previous bone or CNS metastatic disease Noncurable pulmonary/peritoneal metastases, nonregional lymph-nodes, or local recurrence on imaging dated within 6 wk before the trial hospital meeting Patients in a poor nutritional state, depressed bone marrow function, or potentially serious infections
04898504 (Excalibur 1+2)		

Abbreviations: BMI, body mass index; CEA, carcinoembryonic antigen; CNS, central nervous system; CRC, colorectal cancer; dMMR, deficient DNA mismatch repair; ECOG, Eastern Cooperative Oncology Group; HAI, hepatic artery infusion; LDLT, living donor liver transplant; LM, liver metastases; LT, liver transplant; MRI, magnetic resonance imaging; MSI-H, microsatellite instability-high; MSS, microsatellite stable; PET/CT, positron emission tomographic/computed tomography scans; RECIST, response evaluation criteria in solid tumor; TACE, transarterial chemoembolization.

11.5% and 0%, respectively. Whereas those undergoing LT had 1-, 3-, and 5-year DFS rates of 54.2%, 22.9%, and 22.9%, respectively.⁶³

Although DFS may be lower than expected and relapsed disease more common in these early studies, it is important to note the patterns of recurrence and recurrence site-specific survival outcomes in post-LT CRC. For the majority of patients with recurrent disease post-transplant, slow growing pulmonary lesions are most common.^{41,43,46,52} When evaluating recurrences in the SECA population,⁴³ single site recurrences occurred in the lungs (62%), lymph nodes (11%), and rectum (5%). Multiple site recurrences occurred in the liver and lung (11%) and the liver and ovaries (5%). Interestingly, no patient had the liver as the sole first site of disease recurrence. These patterns differ from those undergoing LR. For those who undergo LR, overall recurrence rates are between 57.8% to 70%, with the most common site of recurrence being the liver.⁶⁴⁻⁶⁶ For the 13 patients whom the lung was the first site of recurrence, 7 had no other metastatic site. Of those 7, 3 were able to undergo resection, and all 7 were alive at the end of the follow-up period. Those with the lung as the only site of recurrent disease had a 5-year OS rate of 72% from their time of LT. Comparing this to those with hepatic metastases, 6 of 7 patients with hepatic metastases died by the end of follow-up, with a median time from diagnosis to death being 14 months. Notably, all 12 patients who did not develop liver recurrences were alive at the end of the follow-up period.

Based on the current data, the role of LT for CRLM is exploratory and should be limited to the clinical trial setting. However, given the reported potential improvements in OS for these patients compared to current treatment options, the limited published data suggests further prospective investigation could be explored. Historical data indicating poor outcomes for this patient population may be outdated, due to ongoing improvements in oncologic care and LT practices. This is highlighted in a systematic review that evaluated 110 patients who underwent LT for CRLM from 18 studies.⁶⁷ Data showed the outcomes were improved for those who underwent LT after 2005 with 1-, 2-, 3-, and 5-year OS rates of 94.5%, 86.9%, 71.8%, and 65.8%, respectively. However, it should be noted that in these patients, 57.3% had nodal disease at the time of diagnosis of their primary tumor, 51.8% did not undergo PET/CT before LT, mean FCRS were >2, mean CEA levels were >80 µg/L, and the mean number of tumors was 14.5. Optimal patient selection criteria for LT are still to be determined.

Although limited access to liver grafts may always present a significant limitation when considering transplantation, there are several possible options being studied at this time. These include the use of DCD/ECD grafts, living donor transplantation, novel liver perfusion strategies, and the use of alternative surgical techniques (RAPID and RAPID-LD), which may help in preventing the prolongation of already long wait times on transplantation lists. However, given that most patients do not have living donors, and ECD grafts come with increased risks, policy changes such the possibility of MELD exception points become equally as important when considering the true feasibility of LT for this population. Ultimately, it is unclear if any of these interventions will increase access to LT and improve OS for our metastatic CRC patients, but several studies are ongoing in this area which may help answer this question (Table 5). NCT01479608 is an ongoing pilot trial comparing LT to chemotherapy in a 1:1 randomization and is currently enrolling. Transmet (NCT02597348) is a randomized trial that has completed enrollment and is comparing 5-year survival of chemotherapy followed by LT versus chemotherapy alone in patients with confirmed unresectable liver-only metastases; final results are pending.

Given the current available data, further evidence from ongoing prospective trials are needed to determine if and to what extent there is a role for LT in liver-limited surgically unresectable metastatic CRC.

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