

Review

Liver Transplantation for Colorectal Liver Metastasis: A Comprehensive Review of Current Practices and Future Trends

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Abstract

Colorectal cancer (CRC) remains a leading cause of cancer-related mortality worldwide, with liver metastases (CRLM) representing a common and often incurable manifestation. While surgical resection combined with chemotherapy remains the standard for resectable disease, a significant subset of patients presents with unresectable CRLM. Recent advances have positioned liver transplantation (LT) as a promising therapeutic option for select patients with unresectable CRLM. This review synthesizes current evidence from landmark studies—including the SECA and TRANSMET trials—and emerging data from North American cohorts, highlighting the evolution of patient selection criteria, prognostic indicators such as the Oslo score and metabolic tumor volume, and the role of living-donor and extended-criteria grafts. Outcomes from recent studies demonstrate that LT can achieve 5-year overall survival rates exceeding 70% in well-selected patients, rivaling those of traditional transplant indications. Ongoing trials such as SECA-III and SOULMATE aim to refine indications and address organ allocation challenges. Collectively, these findings suggest that LT can offer long-term survival benefits comparable to traditional transplant indications, marking a paradigm shift in the management of metastatic CRC.

Keywords: LT—liver transplantation; CRLM—colorectal liver metastases; CRC—colorectal cancer; PHLF—post-hepatectomy liver failure; FLR—future liver remnant; HCC—hepatocellular carcinoma; MTV—metabolic tumor volume; LDLT—living donor liver transplant; CEA—carcinoembryonic antigen



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1. Introduction

The second most common cause of cancer-related deaths globally and the third most common cancer overall is colorectal cancer (CRC) [1]. A total of 20–25% of patients have stage IV illness at diagnosis [2], with as many as 80% having liver-only involvement and 15–25% having synchronous colorectal liver metastases (CRLM) [3,4].

CRLM can be classified as unresectable, resectable, or borderline (perhaps resectable upon shrinking). In order to prevent post-hepatectomy liver failure (PHLF), complete resection should be achieved while maintaining a sufficient future liver remnant (FLR), which is what refers to resectability with curative purpose [5]. Tumor burden [6], biology (for example, response to therapy, sidedness, molecular profile) [7,8], and technical factors such as proximity to major vascular structures [9] are several factors that affect resectability.

When these requirements are not satisfied because of severe disease, insufficient FLR, significant vascular involvement, extrahepatic dissemination, or low patient fitness, CRLM are considered incurable [10].

The usual course of treatment for resectable CRLM is surgical resection combined with chemotherapy. The treatment of incurable CRLM is still debatable, though. Palliative chemotherapy, systemic therapy for possible downstaging, and, more recently, liver transplantation in certain situations are available options. The purpose of this review is to provide an overview of current approaches and future trends of CRLM management with emphasis on liver transplantation.

2. Background

Systemic chemotherapy, targeted therapy, immunotherapy, and locoregional therapies such as radioembolization and hepatic artery infusion pumps are currently the standard of care for unresectable CRLM [11]. Conversion to resectability may also be a reasonable objective for patients with solitary, incurable liver metastases. To ascertain resectability, the patient's reaction to neoadjuvant chemotherapy should be assessed as soon as therapy is started. However, systemic therapy might not be necessary for certain patients with disease that is technically treatable [12]. Although they have better results than matched patients who remain unresected, patients with originally incurable liver metastases who receive effective conversion therapy and then have surgical resection have worse outcomes than those who present with resectable disease [12,13].

After liver metastases are removed, hepatic artery infusion pump (HAIP) has been demonstrated to increase overall survival and disease-free survival. It may also make it easier to turn initially incurable lesions into disease that can be removed [14]. Regretfully, a considerable proportion of patients who receive locoregional therapy, such as resection, eventually have a recurrence of their disease [15]. For unresectable CRLM, alternative therapeutic options such as liver transplantation are becoming more popular due to the low number of patients who qualify for resection and the high likelihood of cancer recurrence following downstaging/resection.

Between the late 1970s and the early 1990s, the first attempts at liver transplantation for colorectal liver metastases (CRLM) were made in Europe. With 3-year overall survival (OS) rates of 36% and 5-year OS of only 18%, results were depressing [16]. These results were due to lack of selection strategies, operative expertise, and standard immunosuppression protocols. However, results have significantly improved as a result of later developments in colorectal cancer staging (through improvement in imaging technology), prognostic evaluation, assessment of tumor biology, response to systemic treatments, immunosuppressive techniques, perioperative care, and—most importantly—stringent patient selection criteria (Table 1). According to recent statistics, 5-year OS in carefully chosen patients who receive liver transplant for CRLM is over 80%, which is equivalent to results seen in normal liver transplant cases (about 80.2%) and a significant improvement over the <20% 5-year OS usually seen in unresectable CRLM handled without transplantation [17,18]. Transplantation has already shown survival advantages in various hepatic cancers, including hepatocellular carcinoma (HCC), hemangioendothelioma [19], and intrahepatic cholangiocarcinoma.

Table 1. Published studies on LT for colorectal liver metastases.

Study/Trial	Location/Center	Year(s)	Sample Size (n)	Inclusion Criteria Highlights	Intervention	Key Outcomes	Survival Rates (OS, DFS)	Notes/Comments
SECA I	University of Oslo, Norway	2013	21	Liver-only CRLM, resected primary, ECOG 0–1, ≥6 weeks treatment, no extrahepatic disease	LT	76% progressed on chemo, recurrences mostly in liver graft or lungs	OS: 95% (1 yr), 68% (3 yr), 60% (5 yr); recurrence in 19/21 patients	First study showing promising OS despite recurrence
SECA II	University of Oslo, Norway	2020	15	No tumor > 10 cm, ≥10–20% radiologic response, BMI < 30, ≥1 year from diagnosis to LT	LT	Majority of recurrences were small treatable lung nodules	OS: 100% (1 yr), 83% (3 yr); DFS: 35% (3 yr)	Improved selection criteria improved survival
SECA Arm D (extended criteria)	Oslo	After 2020	10	High tumor burden, signet ring histology, KRAS mutations, prior extrahepatic disease	LT with extended donor grafts	Poor outcomes: median DFS 4 months, OS 18 months	Very poor survival compared to SECA II	Highlights importance of selection criteria
SECA I—10-year follow-up	Oslo	10-year FU	21	Same as SECA I	LT	All recurred, mostly lungs; many recurrences curable and indolent	OS: 43.5% (5 yr), 26.1% (10 yr); better OS with low Oslo score (0–1)	Low metabolic tumor volume associated with better outcomes
SECA vs. Liver Resection (Padua cohort)	Oslo vs. Padua, Italy	NA	NA (184 resection pts)	NA	LT vs. Liver Resection	LT with low Oslo score had better OS than resection group	5 yr OS: 69% (LT) vs. 14.6% (resection)	Interpretation limited by differences in patient biology
SECA 15-year combined follow-up (SECA I, II + RAPID)	Oslo	2023	61	NA	LT	Oslo score ≥ 3: 5 yr OS 8.3%, 10 yr OS 0%; Oslo 0: 5 yr OS 88.9%	Shows prognostic value of Oslo score	
TRANSMET Trial	Multicenter RCT (Europe)	Recent	94	≥3 months systemic chemo with PR or SD by RECIST; no extrahepatic disease; BRAF wild type; CEA < 80 or 50% reduction	LT + chemo vs. chemo alone	74% recurred (lung most common); 3 retransplants; 1 death from transplant complications	5 yr OS: 57% (LT) vs. 13% (Chemo); per protocol: 73% vs. 9%; median PFS: 17.4 vs. 6.4 months	Strongest evidence supporting LT over chemo alone
UNOS registry retrospective study (USA)	US National registry	2017–2022	64 (46 transplanted)	No standardized criteria; increased listings; geographic mobility	LT (mostly deceased donor)	10 recurrences (21.7%) at median 360 d; 6 deaths (13.1%)	OS: 89% (1 yr), 60.4% (3 yr); DFS: 75.1% (1 yr), 53.7% (3 yr)	Living donor LT had better OS than deceased donor

Table 1. Cont.

Study/Trial	Location/ Center	Year(s)	Sample Size (n)	Inclusion Criteria Highlights	Intervention	Key Outcomes	Survival Rates (OS, DFS)	Notes/ Comments
Hernandez-Alejandro et al.	US and Canada (multi-institution)	Recent	10	HPB consensus criteria; poor prognostic markers included	LDLT	30% recurrence; 1 death at median 1.5 years	DFS: 62% at 1.5 years; OS: 100% at 1.5 years	Small cohort, promising results with rigorous selection
University of Pittsburgh LDLT cohort	Pittsburgh, USA	2017–2022	10	Primary tumor resected $\geq$ 6 months prior; 6–12 weeks chemo with response; no extrahepatic disease	LDLT	3 recurrences treated locally; mean OS 3 years; mean RFS 2.2 years	Surpassed median OS of historical controls (32.4 months)	Flexible tumor size criteria; confirms survival benefit

3. The Secondary Cancer (SECA) Trials

The SECA (Secondary Cancer) trials, conducted by the University of Oslo, have played an important role in redefining the role of liver transplantation (LT) for unresectable colorectal liver metastases (CRLM). Norway’s unique transplant infrastructure in the late 2000s—characterized by short wait times and a surplus of deceased donor livers—provided a rare opportunity to explore LT in oncologic indications beyond traditional criteria [20].

In the 2013 SECA I trial, 21 carefully chosen patients with liver-only CRLM, resected original tumors, satisfactory performance status (Eastern Cooperative Oncology Group ECOG performance status 0–1), and at least six weeks of treatment were enrolled. Extensive staging was employed to rule out extrahepatic illness, including CT and laparotomy. Overall survival (OS) rates were 95%, 68%, and 60% at 1, 3, and 5 years, respectively, in the experiment, even though 76% had progressed on chemotherapy. But in 19 out of 21 patients, recurrence occurred, usually in the liver allograft or lungs [20].

Stricter inclusion criteria were introduced in the 2020 SECA II trial, which included no single tumor larger than 10 cm, a radiologic response after chemotherapy of at least 10% (or 20% if the response was to trans arterial treatments), and a minimum of one year between diagnosis and LT. Patients who did not respond well to chemotherapy or had a BMI of more than 30 were not included. The overall survival (OS) for the 15 patients was 100% at 1 year, 83% at 3, and 83% at 5 years. The majority of recurrences were again tiny, treatable pulmonary nodules, and the disease-free survival (DFS) at three years was 35% [21].

Ten patients who did not fit SECA II criteria had transplants in a different experimental cohort known as “SECA arm D.” These included people with a high tumor burden, signet ring histology, KRAS mutations, and a history of extrahepatic illness. Extended criterion donor (ECD) grafts were given to them. This group’s median DFS and OS were 4 and 18 months, respectively, indicating far worse outcomes [22]. According to long-term data from the SECA I 10-year follow-up, all patients eventually experienced recurrence, mostly in the lungs. Many of these metastases were nevertheless curable and indolent. The 5-year OS was 43.5%, and the 10-year OS was 26.1%. The survival rate was significantly higher for patients with an Oslo score of 0 or 1 (75% and 50% at 5 and 10 years, respectively) [23]. A low metabolic tumor volume (MTV) ($<70 \text{ cm}^3$) was linked to better OS, DFS, and post-recurrence survival, according to the validation of the predictive value of MTV on PET-CT [24].

LT patients with low Oslo scores and high tumor burden ratings had better 5-year OS, according to a comparison between SECA LT recipients and a group of 184 patients who received liver resection for CRLM in Padua (69% vs. 14.6%) [25]. However, due to

inherent disparities in disease biology and selection criteria, interpretation is limited [26]. In 2023, a 15-year follow-up study that included 61 patients combined data from the RAPID trial, SECA I, and SECA II. Patients with scores ≥ 3 had 5- and 10-year OS of 8.3% and 0%, respectively, whereas those with an Oslo score of 0 had an outstanding 5- and 10-year OS of 88.9% [27,28].

4. TRANSMET Clinical Trial

Adam et al. recently published the results of the TRANSMET trial, a multicenter randomized controlled trial that compared the effects of chemotherapy prior to liver transplantation versus chemotherapy alone in patients with unresectable colorectal liver metastases (CRLM) ($n = 94$) [29]. Prior to randomization, patients were eligible if they had received systemic chemotherapy for at least three months and had shown either a partial response or stable illness according to RECIST criteria. In contrast, previous trials like SECA allowed transplants even when the disease was limited to the liver, which may have contributed to the relatively worse outcomes in SECA.

Additional inclusion criteria included FDG-PET/CT, contrast-enhanced CT and colonoscopy confirmation of the absence of extrahepatic disease, complete resection of the primary tumor with histologically negative margins (though the margin criteria were not clearly defined), BRAF wild-type status, and a carcinoembryonic antigen (CEA) level below 80 $\mu\text{g/L}$ or a reduction of at least 50% from peak levels. The latter is an innovative change to earlier CEA-based eligibility requirements that might provide a more dynamic evaluation of tumor biology.

14.6 months was the median time between primary tumor resection and transplantation. While waiting for a transplant, nine patients experienced worsening illness. Three people ($n = 38$) who received liver transplants needed re-transplants, and one person died as a result. These results show a one-year graft survival rate of 92.2% and a patient survival rate of 97.4%, which are in good agreement with current UNOS transplant statistics [17,30].

Adjuvant chemotherapy was administered postoperatively to the majority of patients (68%) in the transplant group, at the discretion of the treating physician. Notably, nine patients in the chemotherapy-only arm received either a transplant or a metastasectomy, resulting in an unintended crossover.

With a hazard ratio (HR) of 0.37 (95% CI: 0.21–0.65; $p = 0.0003$), the 5-year overall survival (OS) in the transplant arm was considerably greater (57%) than in the chemotherapy-only group (13%). With a 5-year OS of 73% in the transplant group and 9% in the chemotherapy group (HR 0.16; 95% CI: 0.07–0.33), per-protocol analysis showed even better results. The transplant cohort's median progression-free survival (PFS) was 17.4 months, while the controls' was 6.4 months (HR 0.34; 95% CI: 0.20–0.58).

The research design permitted aggressive care of recurrence through surgical resection or local ablation, despite the fact that 74% of transplant recipients experienced disease recurrence, with lung recurrence accounting for 39% of cases. Lung recurrence usually has indolent character [31] (Table 2) [20,21,32–34]. Consequently, at the time of publishing, 15 out of 38 patients were disease-free. Overall, with survival rates comparable to those observed in other transplant indications, the TRANSMET study offers the strongest evidence to date that liver transplantation is a better treatment choice than chemotherapy alone for a subset of patients with incurable CRLM.

Table 2. Recurrence and survival after LT for CRLM.

Factor	Observed Rates and Insights
Recurrence incidence	High—ranging from ~50% (meta-analysis) to ~80% (prospective cohorts)
First site of recurrence	Most commonly the lungs
Disease-free survival (DFS)	1-year: 35–62%, 3-year: ~33–53%, 5-year: ~13%
Overall survival (OS)	5-year OS: ~50–70% when treated with curative intent
Impact of recurrence on outcomes	Recurrence alone does not preclude long-term survival, especially with aggressive treatment

5. Other Studies in North America

Even though the majority of prospective trials for liver transplantation in CRLM were conducted in Europe, new data from North America offer important practical insights into the viability and results of this strategy. A retrospective analysis of liver transplantation for CRLM in the United States from 2017 to 2022 was carried out by Sasaki et al. using the UNOS registry [35]. A total of 46 (71.9%) of the 64 patients who were designated for transplants eventually received the operation. Only one UNOS region was under-represented; most transplants (84.2%) took place in high-volume centers spread out over a wide geographic area. From 2017 to 2021, listings rose gradually, indicating a rise in clinical interest in this therapeutic approach. Notably, there was significant patient mobility—nearly one-third (32.8%) traveled from nonadjacent states to receive care, and more than half (53.1%) traveled over state lines.

Ten patients (21.7%) experienced disease recurrence after a median follow-up of 360 days, and six out of ten fatalities (13.1%) were due to recurrent malignancy. Overall survival (OS) was 89.0% and 60.4% at 1 and 3 years, respectively, while the disease-free survival (DFS) rates were 75.1% and 53.7%. Recipients of deceased-donor grafts demonstrated inferior 1- and 3-year OS in comparison to those who underwent living-donor liver transplants (LDLT) (100% and 71.4% vs. 77.1% and 51.4%, respectively; $p = 0.049$). The results confirm that CRLM transplant programs are growing throughout the United States, attaining encouraging early outcomes similar to those observed in controlled settings like the TRANSMET trial, despite the lack of specified standardized selection criteria in this cohort.

Hernandez-Alejandro et al. examined 10 LDLT recipients with CRLM who were chosen based on the HPB Association Consensus criteria in a smaller multi-institutional cohort from North America (two U.S. centers and one Canadian) [36,37]. Patients with poor prognostic markers, including T4b staging ($n = 4$), nodal positivity ($n = 7$), poorly differentiated tumors ($n = 3$), and BRAF D594G mutation ($n = 1$), were included in the group. Notably, recurrence risk was stratified using the Oslo score; individuals who scored three or higher generally had worse outcomes. The median Oslo score in this group was 1.5, indicating that the patients were carefully chosen [38]. Chemotherapy based on 5-FU was effective for every patient. Three patients (30%) had a recurrence and one patient died after a median follow-up of 1.5 years; the 1.5-year DFS and OS rates were 62% and 100%, respectively. This study, despite small size, shows the promise of LDLT when rigorous selection criteria are used.

Additional information on LDLT for CRLM was provided by a third report from the University of Pittsburgh, which concentrated on 10 patients who received treatment between 2017 and 2022 [39]. Patients had to have their initial tumor removed at least six months earlier, finish 6–12 weeks of chemotherapy and show a response or stable

disease, and have no imaging evidence of extrahepatic dissemination. In contrast to prior trials, there were no particular limitations on the size or quantity of tumors; however, half of the patients had tumors larger than 5 cm. Half of the sample had nodal involvement, and the median Oslo score was 1.5 once more. Three individuals experienced recurrence over a median follow-up of 1.6 years; two of these patients had segmentectomy-treated pulmonary lesions, and the third patient had an intrahepatic recurrence that was treated with ablation. The median OS for metastatic colorectal cancer reported between 2016 and 2019 (about 32.4 months) was surpassed by the mean OS of 3.0 years and the mean recurrence-free survival (RFS) of 2.2 years [40]. Crucially, results might have been affected by the study's loose tumor definitions and comparatively brief chemotherapy duration. However, the statistics confirm that liver transplantation can provide a significant survival benefit in well-chosen individuals, even in flexible circumstances.

Byrne M et al. reported an OS of 100% and 91%, and a RFS of 100% and 40%, at 1 and 3 years with LDLT for unresectable CRLM, utilizing "The Rochester Protocol" [41].

6. International Hepato-Pancreato-Biliary Association Guidelines

An early framework for choosing liver transplant candidates in the event of colorectal liver metastases (CRLM) has been developed by the International Hepato-Pancreato-Biliary Association. Although these guidelines provide a useful foundation, they are always changing in tandem with newly available clinical data and institutional protocol revisions, including those from UNOS and individual transplant centers. Liver transplantation is often saved for situations in which metastatic lesions are thought to be incurable by the use of traditional, intricate, or multimodal liver-directed techniques. To maximize patient selection, a number of radiologic and clinical criteria have been developed [42]. Pre-transplant carcinoembryonic antigen (CEA) levels should be below 80 µg/L since higher levels have been linked to worse survival results in both SECA and TRANSMET investigations.

Another important consideration is tumor load; lesions bigger than 5.5 cm in diameter indicate a poorer prognosis, albeit inclusion criteria differ significantly between trials. With increasing disease consistently associated with worse outcomes, favorable response to pre-transplant chemotherapy—defined as stable disease or partial remission—has also emerged as a criterion. Although precise thresholds vary, most protocols advocate a disease-free period of at least one year between primary tumor resection and liver transplantation (TTLT).

The Oslo score, which considers TTLT, tumor size, response to chemotherapy, and CEA level, has demonstrated promise in patient stratification based on projected survival benefit. Metabolic tumor volume (MTV) on PET/CT has been found to be a valuable prognostic indicator, and advanced imaging, especially PET/CT and contrast-enhanced CT, is crucial for ruling out extrahepatic illness. Candidate selection is further refined by molecular profiling. Based on available data, it appears that only patients with microsatellite-stable tumors and wild-type BRAF V600E benefit significantly from transplantation, as patients with dMMR or BRAF-mutant tumors typically have worse post-transplant outcomes or may benefit more from systemic therapies such as immune checkpoint inhibitors, which may cause graft rejection after transplantation. Although they are being studied, other characteristics such as tumor histology, primary tumor site, TNM staging, and nodal involvement do not yet have enough data to be used as strict selection criteria. Future research is anticipated to further elucidate and improve these dynamic factors.

7. OPTN and UNOS Policy Updates

The OPTN and UNOS have approved updates on transplant oncology allocation policy to include MELD exception points with CRLM. The allocation policy requires candidates

to meet strict inclusion and exclusion criteria reviewed by the National Liver Transplant Oncology Review Board, as follows.

Initial MELD Exception Criteria

Candidates can be considered for MELD exception points for CRLM if all of the following criteria are met:

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 exception request.

Treatment of primary colorectal cancer:

- Standard resection of the primary tumor with negative resection margins;
- No evidence of local recurrence by colonoscopy within 12 months prior to time of initial exception request.

Evaluation of extrahepatic disease:

- No signs of extrahepatic disease or local recurrence based on CT/MRI (chest, abdomen and pelvis) and PET scan within one month 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 should be greater than 10 cm before start of treatment;
- Must have stability or regression of disease with systemic and/or locoregional therapy for at least 6 months.

In cases of synchronous colon lesions, in addition to above criteria, all of the following are required:

- Resection of the primary tumor is performed more than 6 months after initial diagnosis;
- Minimum of 6 months of chemotherapy after primary tumor resection before exception request with stability of disease for a total of at least 12 months after initial diagnosis.

Candidates meeting the criteria described should be considered for a MELD exception score equal to MMaT-20. If MMaT-20 results in an exception score below 15, the candidate's exception score will automatically be set to a MELD score of 15 per OPTN Policy 9.4.E: MELD or PELD Exception Scores Relative to Median MELD or PELD at Transplant.

Exclusion Criteria

Candidates should not be considered for an initial MELD exception for CRLM if any of the following criteria are met:

- Extra-hepatic disease after primary tumor resection (including lymphadenopathy outside of the primary lymph node resection);
- Local relapse of primary disease;
- Carcinoembryonic antigen (CEA) >80 µg/L with or without radiographic evidence of disease progression or new lesion.

MELD Exception Extension Criteria

Candidates with CRLM should be considered for a MELD exception extension if they continue to meet all of the following criteria:

- Every 3 months from initial MELD exception:
 - Perform CT or MRI (chest, abdomen and pelvis);

- Perform CEA testing;
- No progression of hepatic disease;
- No development of extrahepatic disease;
- CEA < 80 µg/L.

The University of Oslo also has updated the management algorithm for workup and evaluation of CRLM for liver transplantation, adopted from IHPBA guidelines.

8. Ongoing Clinical Trials in Liver Transplantation for Colorectal Liver Metastases

Liver transplantation (LT) for colorectal liver metastases (CRLM) is an emerging therapeutic approach under active investigation in numerous clinical trials (Table 3). These studies aim to resolve critical questions regarding patient selection, tumor biology, graft utilization, perioperative management, and long-term outcomes. Most trials share common eligibility criteria, including Eastern Cooperative Oncology Group (ECOG) performance status 0–1, pretransplant PET/CT imaging, and measurable disease by RECIST criteria. Patients with progressive disease (PD) at the time of randomization or transplantation are uniformly excluded, consistent with previous findings linking PD with poorer survival outcomes.

Table 3. Ongoing clinical trials on LT for CRLM from clinicaltrials.gov.

Trial Name	Country	Design	Focus	NCT Number
EXCALIBUR	Norway	Phase II Randomized Controlled Trial	Chemotherapy vs. FUDR + LT after 1st-line failure	NCT05398380
COLT	Italy	Matched Cohort Study	LT vs. chemotherapy + anti-EGFR in RAS/BRAF wild-type tumors	NCT03803436
RAPID-Padova	Italy	Pilot Feasibility Study	Two-stage RAPID LT using partial grafts	NCT04865471
AVG-001	Germany	Prospective Interventional Study	Phased LDLT + right portal vein ligation	NCT04616495
Toronto UHN LDLT	Canada	Single-Arm Interventional Study	LDLT for chemo-stabilized liver-limited CRLM	NCT04870879
SNUH LDLT	South Korea	Single-Arm Study	LDLT in chemo-naïve CRLM patients	NCT05175092
Northwestern Observational	USA	Prospective Observational Study	Real-world LT strategies (DDLT, LDLT, RAPID, etc.)	NCT04825470
MELODIC	Italy	Single-Arm Study	LT in liver-only CRLM post-chemotherapy	NCT04898504
LITORALE2020	Italy	Single-Arm Study	LT for CRLM	NCT06698146
METLIVER	Spain	Single-Arm Study	Translational biomarkers and tumor heterogeneity in LT	NCT06069960
LIVERMORE	Italy	Single-Arm Study	Split-liver and LDLT graft strategies for expanded access	NCT06801665
Weill Cornell Registry	USA	Registry/Observational Study	Long-term survival comparison post-LT vs. non-LT	NCT07001085
Modena Flexible Graft Study	Italy	Observational Study	LDLT, split, and RAPID graft combinations for CRLM	NCT05186116
RAPID Oslo Feasibility	Norway	Feasibility Study	Two-stage RAPID in CRLM with resectable lung metastases	NCT02215889

Table 3. Cont.

Trial Name	Country	Design	Focus	NCT Number
Jena Two-Stage LDLT	Germany	Interventional Study	Two-stage LDLT using portal vein ligation	NCT03488953
LTLR-LC	China	Interventional Study	Auxiliary liver transplant in tumors including CRLM	NCT05750329
Durvalumab + Tremelimumab Trial	USA	Phase II Study	Neoadjuvant immunotherapy before LT	NCT05027425
HOPE Study	Italy	Interventional Study	Hypothermic oxygenated perfusion in LT	NCT05876052
ImmunoXXL	Italy	Observational Study	LT after downstaging with ate-zolizumab/bevacizumab	NCT05879328

8.1. Randomized Controlled Trials

The **SOULMATE trial** in Sweden is a pivotal randomized controlled study assessing LT in patients with isolated, unresectable CRLM. Given that only 20% of patients with liver metastases are eligible for curative resection and the five-year survival rate under palliative care is <10%, this trial evaluates whether LT offers a survival benefit over best established therapy (BET). Participants are randomized to receive either BET alone or LT using extended criteria donor (ECD) grafts in conjunction with BET. By incorporating ECDs, the trial also addresses the global issue of organ shortage, potentially broadening its clinical relevance [43].

The **SECA-III trial** from the Oslo group is a randomized comparison of LT versus standard-of-care treatment selected by a multidisciplinary team. Importantly, patients with resectable liver metastases are excluded, focusing the trial on truly incurable disease. A unique feature of SECA-III is the inclusion of patients with resectable lung metastases, allowing the study to examine outcomes of combined LT and pulmonary metastasectomy. This design is supported by long-term survivors from SECA-I, where some patients achieved disease-free survival 10 years after pulmonary recurrence [44,45].

8.2. Observational and Matched Cohort Studies

In Italy, the **OLT study** is an observational analysis evaluating outcomes in CRLM patients undergoing LT in combination with triplet chemotherapy and anti-EGFR therapy. Outcomes will be compared with a matched cohort from a prior chemotherapy arm. While the lack of randomization limits definitive conclusions, the study offers practical insights into combination therapy strategies [46].

A Spanish observational study, with inclusion criteria paralleling those of SECA and TRANSMET, further reflects the growing international interest in LT as a potential treatment for well-selected patients with CRLM [47].

Currently, numerous ongoing trials have been registered in Clinical Trials Registry to support the changing landscape of liver transplantation for unresectable CRLM (Table 2) [48].

8.3. Novel Interventional Studies

Several innovative phase II trials are exploring new strategies in LT for CRLM:

- The **EXCALIBUR trial** (Norway) is a two-arm phase II study comparing floxuridine plus LT versus chemotherapy alone in patients who have progressed after first-line systemic therapy. The trial aims to determine whether aggressive locoregional therapy followed by LT can improve long-term survival in this high-risk population.

- The **COLT trial** (Italy) targets patients with RAS/BRAF wild-type tumors and compares LT to a matched cohort treated with chemotherapy and anti-EGFR therapy. The study aims to establish oncologic benefit in a molecularly favorable subset.
- Two advanced graft hypertrophy-based strategies are also under evaluation. The **RAPID-Padova study** uses a two-stage technique involving initial implantation of a left-lateral graft followed by native liver removal after hypertrophy. In Germany, the **AVG-001 trial** applies a similar approach using right portal vein ligation to promote graft growth.

These approaches aim to expand transplant eligibility by optimizing the use of partial or marginal grafts.

8.4. Living-Donor Liver Transplantation (LDLT)

LDLT is under active investigation, particularly in Asia and North America. The **Toronto UHN trial** enrolls patients with unresectable, liver-limited CRLM who have demonstrated disease stability following chemotherapy, offering LDLT as a curative alternative. The **SNUH study** in South Korea investigates LDLT in chemotherapy-naïve patients with biopsy-confirmed CRLM and no prior liver-directed therapy. These studies aim to define the role of LDLT across a range of clinical scenarios, from salvage to first-line therapy, while emphasizing donor safety and technical feasibility.

8.5. Prospective Registries and Real-World Cohorts

The **Northwestern University prospective registry** (USA) is a significant non-interventional study collecting data on LT strategies for CRLM, including deceased donor, living donor, RAPID, and two-stage procedures. Although not randomized, the registry allows for comprehensive comparisons of graft types, surgical techniques, and patient-reported outcomes, providing valuable real-world evidence.

8.6. Additional Single-Arm and Translational Studies

Several single-arm studies in Europe continue to assess LT feasibility in CRLM:

- The **MELODIC project** (Naples) and **LITORALE2020** (Bologna) evaluate LT in patients with liver-only CRLM and stable disease after chemotherapy.
- **METLIVER** (Spain) incorporates tumor profiling and liquid biopsy data to correlate molecular features with recurrence risk.
- The **LIVERMORE trial** (Italy) explores multiple graft types, including split-liver and LDLT, to expand transplant accessibility.
- The **Weill Cornell registry** (USA) provides long-term comparative survival data between transplanted patients and those who declined or were ineligible for LT.

8.7. Expansion of Transplant Strategies

In Italy, the **Modena clinic** utilizes real-world protocols involving RAPID, split-liver grafts, and LDLT to increase access for patients with stable, liver-limited CRLM. The University of Oslo is refining two-stage auxiliary LT for patients with minimal extrahepatic involvement, including those with resectable pulmonary metastases.

In Germany, **Jena University** is investigating a two-stage LDLT protocol with right portal vein ligation, aiming to achieve favorable three-year overall survival outcomes. In China, **Renji Hospital** (Shanghai) is testing a modified auxiliary transplant strategy (LTLR-LC) for end-stage liver cancers, including CRLM. These hypertrophy-driven protocols aim to expand donor utility while preserving recipient outcomes.

8.8. Perioperative Optimization and Adjuvant Therapies

Adjunctive interventions to improve post-transplant outcomes are also under investigation. A U.S. multicenter **phase II trial** is studying neoadjuvant duralumin and tremelimumab in patients with hepatocellular carcinoma awaiting LT. Although not focused on CRLM, the trial's outcomes regarding safety and graft rejection may be applicable to transplant oncology.

The **HOPE trial** (Italy) evaluates hypothermic oxygenated perfusion (HOPE) in donor livers to minimize ischemia–reperfusion injury and reduce recurrence rates. The **ImmunoXXL project** monitors long-term outcomes in previously unresectable patients who underwent downstage with atezolizumab–bevacizumab and subsequently underwent transplantation.

These perioperative strategies highlight the growing integration of systemic therapy, immunotherapy, and surgical innovation in the evolving field of oncologic liver transplantation.

9. Conclusions

The treatment of unresectable colorectal liver metastases (CRLM) has evolved from palliative care to aiming for long-term survival. European studies like SECA showed over 80% 5-year survival in carefully selected patients, shifting perceptions of transplant candidacy. The TRANSMET trial confirmed these findings, showing 57–73% survival with transplantation plus chemotherapy versus under 15% with chemotherapy alone. North American data supports similar outcomes, especially with living-donor grafts. Despite promising results, questions remain about optimal patient selection, organ allocation, and post-transplant management. Ongoing studies like SECA-III and SOULMATE aim to refine criteria and strategies.

We conclude that liver transplantation for incurable CRLM can be provided safely, prudently, and in a way that optimizes benefit for each person by working closely with surgical oncologists, transplant surgeons, hepatologists, and medical oncologists and by continuing to establish registries, improve guidelines, and exchange data internationally. Our guiding philosophy must not change in light of new information: careful patient selection combined with interdisciplinary teamwork so that patients who previously had no other options for treatment can now view transplantation as a real means of achieving long-term survival.

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