ISSN 2220-3230 (online)

World Journal of *Transplantation*

Quarterly Volume 15 Number 4 December 18, 2025

Published by Baishideng Publishing Group Inc

World Journal of Transplantation

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ABOUT COVER

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INDEXING/ABSTRACTING

The *WJT* is now abstracted and indexed in PubMed, PubMed Central, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The *WJT*'s CiteScore for 2024 is 3.3 and Scopus CiteScore rank 2024: Transplantation is 24/55.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Transplantation

ISSN
ISSN 2220-3230 (online)

LAUNCH DATE
December 24, 2011

FREQUENCY
Quarterly

EDITORS-IN-CHIEF
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https://www.wjgnet.com/2220-3230/editorialboard.htm

PUBLICATION DATE
December 18, 2025

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World J Transplant 2025 December 18; 15(4): 104945

DOI: 10.5500/wjt.v15.i4.104945

ISSN 2220-3230 (online)

FIELD OF VISION

Current perspectives and guidelines on liver transplantation for metastatic colorectal cancer

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Specialty type: Transplantation

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B, Grade B, Grade B, Grade C

Novelty: Grade A, Grade A, Grade B, Grade B

Creativity or Innovation: Grade A, Grade A, Grade B, Grade B

Scientific Significance: Grade A, Grade A, Grade B, Grade B

P-Reviewer: Chen Z; Liu P

Received: January 7, 2025

Revised: March 3, 2025

Accepted: April 14, 2025

Published online: December 18, 2025

Processing time: 316 Days and 13.8 Hours

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Abstract

Colorectal cancer (CRC) is the third most common cancer globally, with 20%-25% of patients diagnosed at stage IV, significantly affecting overall survival (OS). Only 14% of stage IV patients survive for 5 years with palliative chemotherapy. However, the role of liver transplantation (LT) in the management of CRC liver metastasis (CRCLM) is an evolving area of interest. Recent advancements in oncologic outcomes and clinical understanding have prompted the re-evaluation of LT as a viable treatment option for CRCLM. A promising result from some prospective pilot studies reported a 5-year OS rate of 60% after LT for patients with CRCLM. Key factors influencing eligibility include tumor biology, absence of extrahepatic disease, and the patient's performance status. By synthesizing the latest research findings, we aim to provide a comprehensive overview that summarizes the most relevant data related to the clinical outcomes of patients who underwent LT for CRCLM. We aim to provide a comprehensive overview by synthesizing the latest research findings. This review discusses the inclusion criteria and eligibility for LT in CRCLM, which are of great importance to patient outcomes.

Key Words: Liver transplantation; Colorectal cancer; Colorectal liver metastasis; Transplant oncology

Core Tip: It is a well-established fact that more than 40% of patients with colorectal cancer (CRC) develop liver metastasis during the disease course despite all the surveys leading to more suitable systemic treatments, efficient chemotherapy, and surgical resections. liver transplantation (LT) could be a treatment option for patients with unresectable CRC liver metastasis without extrahepatic involvement. The initial assessment and proper selection of suitable patients is mandatory for better outcomes for these patients. It turns out that to be candidates for an LT, patients have to meet strict criteria described in the two prospective studies, SECA-I and SECA-II. Despite the proven benefits of LT for non-resectable colorectal liver metastases, this method is still not widely used worldwide due to a lack of policy and healthcare reforms in many countries.

Citation: Stoyanova M, Mircheva I, Chulkov I, Karamiteva M, Goranova Z, Simeonova V, Zashev M, Velikova T, Peruhova M. Current perspectives and guidelines on liver transplantation for metastatic colorectal cancer. *World J Transplant* 2025; 15(4): 104945
URL: https://www.wjgnet.com/2220-3230/full/v15/i4/104945.htm
DOI: https://dx.doi.org/10.5500/wjt.v15.i4.104945

INTRODUCTION

Liver transplantation (LT) has been established as a definitive treatment option for end-stage liver diseases such as decompensated cirrhosis, hepatocellular carcinoma, and certain primary hepatic malignancies such as neuroendocrine tumors and cholangiocellular carcinoma. However, the role of LT in the management of colorectal cancer liver metastasis (CRCLM) is an evolving area of interest[1,2].

Annually, the American Cancer Society evaluates and represents data related to the number of new cancer cases and deaths in the United States. It was estimated that in 2024, the number of patients diagnosed with cancer was 2001140, and the number of cancer-related deaths was 611720. Worrying statistics show that in the late 1990s, colorectal cancer (CRC) was the fourth-leading cause of cancer-related death in men and women younger than 50 years, unlike in the present, CRC is first in men and second in women. The data published by IARC's Global Cancer Observatory showed that 1.9 million people worldwide were diagnosed with CRC in 2022[3].

CRC is the third most prevalent malignancy worldwide[4]. Unfortunately, it is estimated that 20%-35% of patients are diagnosed with stage IV at the time of initial diagnosis, which has a substantial impact on overall survival (OS). According to the statistics, only 14% of the patients who are in the IV stage have a 5-year OS under palliative chemotherapy[5]. Liver metastases are the most common site of distant spread, accounting for approximately 40% of CRC patients[6].

Another essential fact is that 18%-25% of patients will develop distant metastases within 5 years from the first diagnosis, which significantly affects the outcomes of the patients with CRC[7].

Furthermore, several studies represent dada, that most often, patients with metastatic CRC die from liver metastasis. A study by Kemeny[8] represents data from autopsy patients with CRC. The results from the autopsy protocols demonstrate that patients who die from CRC had most often liver metastasis (one-third of the patients).

It is important to note that chemotherapy for CRC includes therapies that were introduced a long time ago. Through the years, the awareness of cancer biology and different oncogenic mutations in various oncogenes and tumor suppressor genes led to the development of new therapeutic strategies. Another huge progress in cancer treatment was achieved in the surgical aspect. Plenty of new surgical techniques have been developed, and the improvement of early cancer detection has promoted better outcomes after surgical procedures[9].

Traditional management strategies for CRCLM include surgical resection and loco-regional therapies (thermal ablation, intraarterial chemotherapy, chemo- or radioembolization) with or without systemic chemotherapy[10].

New chemotherapy regimens for the treatment of CRCLM include several active drugs, which may be given as a single-line therapy or in a combination. It has to be underlined that the choice of treatment protocol depends on many factors, such as the type and genetics of the tumor, mutations that it has, and toxicity of the drugs. During the chemotherapy treatment, patients often have a disease progression, which requires a change in the treatment strategy with second/third-line chemotherapy[10].

Contemporary chemotherapy protocols recommend the administration of 3 cytotoxic agents (*i.e.*, 5-FU/LV, oxaliplatin, irinotecan) in patients with advanced CRC as a first-line therapy.

In the past decades, a few new treatment strategies in MCRC have been developed, such as target therapy based on defined tumor gene status. Determinations of mutations in *KRAS*/*NRAS* and *BRAF* genes, microsatellite instability (MSI)/instability-high (MSI)/mismatch repair (MMR) status and HER 2 amplification are of great importance for customizing the chemotherapy regimen of the patients[11]. Surgical treatment of patients with liver metastasis can achieve 5-year survival rates of 42%, but in clinical practice, not all patients are eligible for liver resection[12].

Unfortunately, liver resection is not always feasible, and the definition of non-resectable liver metastases is still not universally well-established, further complicating this issue. Furthermore, relapse rates after liver resection are high; 3-year relapse rates are 60%-70%, with the liver being the most common site of recurrence. Nevertheless, these treatment options are not always curative and often come with significant limitations regarding patient eligibility and long-term efficacy[13].

Recent advancements and a deeper understanding of oncologic outcomes have prompted the re-evaluation of LT as a viable treatment option for CRCLM. Studies have highlighted that patients with unresectable colorectal liver metastasis

(CRLM) who do not respond to conventional chemotherapy may benefit significantly from LT, achieving 5-year survival rates comparable to those observed in primary liver malignancies[14].

A systematic review and pooled analysis published by Giannis *et al*[15] represent the post-LT follow-up in patients with CRCLM, including 110 patients from 8 studies. The results from the study showed that the mean follow-up period was 32.1 ± 22.2 months, and the 5-year OS rate was estimated at around 50.5%.

Key factors influencing eligibility include tumor biology, absence of extrahepatic disease, and the patient's performance status. Moreover, advances in imaging and molecular diagnostics have enhanced our ability to identify candidates most likely to benefit from this aggressive intervention[16].

This review aims to shed light on the criteria and clinical scenarios where LT can be considered for patients with CRCLM. We summarized the results from the clinical trials, enhanced the therapeutic landscape, and offered hope for an improved survival rate in this challenging patient population.

ELIGIBILITY CRITERIA FOR LT IN PATIENTS WITH METASTATIC CRC

Historically, LT for CRCLM was contraindicated because patients had poor outcomes. With the improving surgical techniques and immunosuppressive therapies, the management of these patients has improved.

There is increasing interest in the feasibility of LT in treating patients with non-resectable colorectal liver metastases (N-RCRCLM). Promising results in carefully chosen patients have been reported in several studies. The SECA-I study is the first prospective trial assessing LT for CRCLM, enrolled a heterogeneous study group, and showed an estimated 5-year survival of 60%[17].

Nevertheless, a study on patients with nonresectable CRC and liver-only metastases found that LT achieved a 5-year OS rate of up to 83%, compared to just 10% with palliative chemotherapy. The study evaluated various scoring systems, including the Fong Clinical Risk Score (FCRS), metabolic tumor volume, and Oslo Score, and demonstrated that these criteria could predict long-term survival outcomes, with 5-year survival rates of 100%, 78%, and 67% for patients meeting specific criteria[18].

The study by Sasaki developed and validated a prognostic model for patients undergoing hepatic resection of CRLM based on the "Metro-ticket" paradigm. The tumor burden score (TBS), combining maximum tumor size and number of lesions, outperformed traditional tumor morphology in predicting OS, with increasing TBS correlating with worse survival. The model demonstrated excellent discriminatory power and was externally validated in cohorts from Asia and Europe, suggesting TBS as a promising tool for predicting long-term survival in CRLM patients[19]. In 1999 Fong introduced a clinical risk score for predicting the long-term outcomes of operated patients for hepatic metastases from CRC. This clinical risk score involved two imaging factors (numbers and size of hepatic lesions) and three oncological criteria [level of carcinoembryonic antigen (CEA), node-positive primary tumor, and disease-free interval]. According to the aforementioned score, only patients with up to two criteria have a positive prognosis and good outcome after liver resection[20]. The data is presented in Table 1[13,18-20].

Fong's clinical risk score and Oslo score find clinical applications in the process of patient selections that are suitable for LT for MCRC.

A study by Dueland *et al*[21] represents data related to the ability of different scoring systems to predict long-term survival, disease-free survival, and survival after relapse after liver transplant for MCRC. The authors compared Fong's clinical risk score and Oslo score.

Results showed that patients with FCRS and Oslo Risk Score from 0 to 2 have 67% OS at 5 years[21].

In the SECA-I study, published in 2013[17], the inclusion criteria were broad, and the studied population was heterogeneous regarding the extent of disease and previous lines of cancer treatment. Patients were selected based on ECOG performance status of 0 or 1, having liver-only disease, undergone excision of the primary tumor, and received at least 6 weeks of chemotherapy. At the time of LT, a staging computed tomography (CT) scan was performed on each patient. Only patients with negative extrahepatic malignancy underwent a staging laparotomy where hilar lymph nodes and adjacent tissue were sent for frozen section pathological analysis. Only the patients with negative results were eligible for LT. Induction of immunosuppression in patients was initiated with basiliximab and methylprednisolone, followed by maintenance immunosuppression with sirolimus, mycophenolate, and prednisone[17].

All the patients included in the study were assessed using the so-called Oslo score, which ranged from 0 to 4. The score criteria include largest lesion diameter > 5.5 cm, pre-transplant CEA level > 80 μg/mL, progression on chemotherapy, and time from resection of the primary tumor to transplantation < 24 months with a score value of 1 point for each. For patients with an Oslo score of 0 or 1, the 5- and 10-year actual OS rates were 75% and 50%, respectively[19]. The data is presented in Tables 2 and 3.

The SECA-II trial was published in 2020. The selection criteria were more stringent, including only patients who had no tumor greater than 10 cm and those with multiple tumors, each with a size less than 5 cm. They required that LT be deferred until the patient was at least 1 year from the initial diagnosis and a 10% or more significant response to systemic chemotherapy. If this condition was not available, inclusion was allowed for patients who had at least a 20% response to transarterial chemotherapy embolization or transarterial yttrium-90 administration. The OS at 1, 3, and 5 years was 100%, 83%, and 83%, respectively[13].

Factors associated with worse survival were consistent with the results from the SECA I trial. They observed a significant decline in OS for patients with a FCRS (0-5) of > 2. FCRS includes the following criteria: Maximal lesion diameter > 5.0 cm, pre-resection CEA level > 200 μg/mL, > 1 liver metastasis, node-positive primary, and interval from diagnosis of primary to liver metastasis < 12 months. Each of them has a score value of 1[18].

Table 1 Criteria for patients with colorectal metastatic cancer based on SECA I trial: Oslo score and Fong clinical risk score

Oslo score	Fong clinical risk score
Largest lesion diameter > 5.5 cm	Maximal lesion diameter > 5.0 cm
Pre-transplant CEA level > 80 μg/mL	Pre-resection CEA level > 200 μg/mL
Progression on chemotherapy	> 1 liver metastasis
Time from resection of the primary tumor to transplant < 24 months	Node-positive primary interval from diagnosis of primary to liver metastasis < 12 months

CEA: Carcinoembryonic antigen.

Exclusion criteria in the SECA-I study were standard contraindications for LT, other malignancies, or weight loss for patients greater than 10%. In addition, patients with a body mass index > 30 were also excluded in the SECA-II trial.

We can summarize that the difference between inclusion criteria has a huge impact on the 5-year OS after LT for MCRC.

Since SECA-I was a pilot exploratory trial, it covered a diverse population concerning prognostic criteria such as lesion size and quantity, CEA level, chemotherapy use and response, and time from cancer diagnosis to LT. The SECA-II showed better results because it gathered a more selective group of patients who matched more stringent inclusion criteria, which included a minimum 10% response to chemotherapy and a minimum one-year period of time between diagnosis and LT.

Given the increasing interest and need for clear recommendations on LT for CRCLM in 2021, the International Hepato-Pancreato-Biliary Association published consensus guidelines[22]. This study aimed to standardize the nomenclature and define management principles in patient selection, evaluation of biological behavior, graft selection, recipient considerations, and outcomes. Patient selection includes clinical-path-radiological and molecular criteria.

Patients with N-RCRCLM considered for LT should undergo standard oncological resection of the primary tumor with clear resection margins[23]. Those with primary tumor histology of undifferentiated adenocarcinoma or signet ring cell carcinoma should be excluded from LT[24]. Extensive lymph node involvement of the primary tumor is associated with poorer survival in patients who have had a resection[25,26]. For those with late metachronous N-RCRCLM in the absence of nodal recurrence, it is less likely that the nodal stage of primary colon tumor might be of prognostic relevance. The absence of local recurrence should be confirmed using colonoscopy within 3 months of LT.

Patients who present with N-RCRCLM or who develop such in the setting of recurrence after resection might be considered for LT. MRI fine-cut triphasic liver CT, or both, are recommended for assessing the initial resectability of N-RCRCLM in patients before LT[27]. There is no clear evidence to exclude patients from LT for N-RCRCLM based on the initial number and size of lesions present before the initiation of systemic therapy. Caution should be taken in patients with multifocal disease or lesions that are large in size, or both, because these are associated with poorer outcomes.

The development of extrahepatic metastases is a sign of disseminated disease and a poor prognostic marker in metastatic CRC[28]. A fluorine-18-fluorodeoxyglucose PET-CT scan enables the detection of extrahepatic disease and should be used to exclude such patients[29]. Where an 18F-FDG PET-CT scan is available, metabolic tumor volume and total lesion glycolysis could be evaluated to assess tumor metabolic activity[30]. Patients with a metabolic tumor volume of > 70 cm^3 and total lesion glycolysis of > 260 g should be excluded.

There is no evidence to support LT in patients with N-RCRCLM who initially present with or subsequently develop extracolonic or extrahepatic metastases. High-resolution CT thorax and 18F-FDG PET-CT are recommended to rule out extrahepatic metastatic disease and are essential for follow-up during bridging chemotherapy to transplantation for the evaluation of response in metastases treatment. An initial scan before the commencement of chemotherapy would allow an evolution assessment. Systematic intraoperative nodal sampling before LT should be considered when clinical suspicion is high and preoperative PET imaging is inconclusive[31].

Molecular criteria for selecting patients with N-RCRCLM considered for LT include analysis of the primary tumor or hepatic metastases, or both, for *BRAF* and *RAS* mutations, as well as MSI and MMR status, which is mandatory.

Plenty of studies demonstrated that *RAS* and *BRAF* mutation status have independent prognostic value for patients suffering from CRC. These molecular tests could be very useful noninvasive decision-making tools, allowing precise decisions on which patients are feasible for LT[32].

Patients with *BRAF* V600E mutation should be excluded. RAS mutation is not a contraindication but a negative prognostic factor to LT for N-RCRCLM. Patients with RAS mutations can be considered if other favorable biological factors are present. Because of the favorable results with immunotherapy for patients with positive MSI status or MMR deficient metastatic CRC, at present, such patients should not be considered for LT[33].

In 2021, an international consensus guideline was published regarding treating LT patients with N-RCRCLM. To enhance patient selection and achieve optimal therapy outcomes, the guideline excludes patients with high-risk features of oncological relapse[22]. The guidelines state that the original tumor must be removed with defined resection margins under clinicopathological and radiological criteria[34].

It is important to point out that these patients have preserved liver function and are unlikely to be given priority over patients with end-stage liver disease. It may be necessary to implement a similar procedure to prioritize and include individuals with transplantable colorectal liver metastases on national waiting lists[35].

Table 2 Trials covering liver transplantation outcomes in patients with metastatic colorectal cancer

Trial	Country	Type of study	Oncological criteria/design	Primary outcomes	Secondary outcomes
Transmet	France	Multicentric phase III RCT randomized, controlled	Primary tumour resection according to oncological principles; *BRAF* non-mutated; CRLM definitively unresectable according to multidisciplinary panel expert; ≤ 3 chemotherapy lines for metastatic disease; Stable disease (RECIST criteria) on chemotherapy > 3 months; CEA level < 80 μg/L or at least 50% decrease of maximal level; No extrahepatic disease confirmed by CT and PET/CT	OS at 5 years	OS at 3 years, DFS, PFS, recurrence, QOL
SECA III	Norway	Randomized, controlled	LT *vs* other treatment options including chemotherapy, TACE, or SIRT	OS at 2 years	None listed
Soulmate	Sweden	Randomized, controlled	LT from extended criteria donors + best-established treatment (BET) *vs* BET alone	OS at 5 years	OS at 2 years, median OS, PFS, recurrence-free survival, QOL, QALY
Excalibur 1	Norway	Randomized, controlled	LT + chemotherapy *vs* HAI/FUDR + chemotherapy *vs* chemotherapy alone	OS at 2 years	QOL, 30-/90-day morbidity/mortality
Colt	Italy	Nonrandomized, prospective	LT *vs* triplet chemotherapy + anti-EGFR	OS at 5 years	PFS, complications
Melodic	Italy	Nonrandomized, prospective	LT *vs* chemotherapy	OS at 3 years, OS at 5 years	PFS, dropouts, complications
Livermore	Italy	Single group, open label	LDLT *vs* historical cohort of potentially transplantable patients who received chemotherapy only	OS at 5 years, DFS at 5 years	Graft survival, donor QOL
Litorale 2020	Italy	Single group, open label	LT	OS at 5 years	DFS
NCT04874259	Korea	Single group, open label	LDLT	OS at 1 year	DFS, OS at 3 years, recurrence
Livert(w) o heal	Germany	Single group, open label	LDLT with two-staged hepatectomy *vs* historic cohort of patients who received gold-standard chemotherapy	OS at 3 years	DFS, morbidity of recipient, morbidity of donor
RAPID-Padova	Italy	Single group, open label	LT with staged hepatectomy	Percent of patients receiving hepatectomy within 4 weeks of transplant	OS, PFS, dropouts, mortality, complications
Trasmetir	Spain	Cohort, prospective	LT	OS at 5 years	DFS, QOL
NCT02864485	Canada	Single group, open label	Primary CRC tumour stage ≤ T4a; *BRAF* non-mutated; Bilateral and non-resectable CRLM without major vascular invasion by LM; Time from primary CRC resection to transplant is ≥ 6 months; No extra hepatic disease; Preoperative systemic chemotherapy for ≥ 3 months; Stable disease on chemotherapy > 3 months; CEA values are stable or decreasing at all timepoints; LDLT *vs* patients who drop out prior to transplantation	OS at 5 years, DFS at 5 years	Recurrence, types of cancer recurrence treatments, dropouts, QOL, OS/DFS at 1 and 3 years
Metliver	Spain	Single group, open label	LT	OS at 5 years	OS at 1 and 3 years, recurrence-free survival, dropouts, recurrence, QOL
NCT06069960	China	Single group, open label	Hemihepatectomy with concurrent left lateral lobe LT followed by delayed residual liver resection	OS at 3 years post second liver resection	DFS
RAPID 2014	Norway	Single group, open label	Unresectable liver metastases technically; Maximal size of CRLM < 10 cm and total number < 20; CEA < 100 ng/mL at time of diagnosis; Standard surgical procedure with adequate resection; pN0 primary tumour as pN0; No extra hepatic disease confirmed by CT and PET/CT, except patients may have 1-3 resectable lung lesions all < 15 mm; At least 8 weeks of chemotherapy; Liver segmentectomy with concurrent left lateral lobe LT followed by delayed residual liver resection	Percent receiving second-stage hepatectomy within 4 weeks	OS

LT: Liver transplantation; OS: Overall survival; DFS: Disease-free survival; PFS: Progression-free survival; QOL: Quality of life; TACE: Transarterial

chemoembolization; SIRT: Selective internal radiation therapy; QALY: Quality-adjusted life years; HAI/FUDR: Hepatic arterial infusion with floxuridine; CT: Computed tomography; CRLM: Colorectal liver metastasis; CEA: Carcinoembryonic antigen; LDLT: Living donor liver transplant.

Table 3 Details on the study design, inclusion criteria, transplant type and additional therapy in the studies discussed

Study	Study design	Inclusion criteria	Transplant type	Additional therapy	Key findings
Transmet	Randomized controlled trial	Patients with resected primary tumors, stable disease post-chemotherapy	Deceased donor	Neoadjuvant chemotherapy	Study terminated due to low survival in the transplant group
SECA-III	Randomized controlled trial	Patients with limited liver metastases, controlled with chemotherapy	Deceased donor	Neoadjuvant chemotherapy	Ongoing; results pending
Soulmate	Randomized controlled multicenter	Patients with isolated colorectal liver metastases unsuitable for resection or ablation	Deceased donor (extended criteria)	Neoadjuvant and adjuvant therapy	Ongoing; aims to compare liver transplantation with best established treatment
Excalibur-1	Randomized controlled trial	Patients under 70 with inoperable colorectal liver metastases, insufficient response to current chemotherapy	Deceased donor	Hepatic Arterial infusion (HAI)/FUDR, systemic chemotherapy	Ongoing; compares liver transplantation, HAI/FUDR, and systemic chemotherapy. excaliburstudy.com
Colt	Prospective multicenter	Patients with limited liver metastases, resected primary tumors	Living donor	Neoadjuvant chemotherapy	5-year overall survival: 68%
Melodic	Randomized controlled trial	Patients with metastatic colorectal cancer meeting specific criteria	Deceased donor	Neoadjuvant and adjuvant therapy	Ongoing; results pending
Livermore	Prospective single-center	Patients with limited liver metastases	Deceased donor	Neoadjuvant chemotherapy	Ongoing; results pending
Litoral 2020	Randomized controlled trial	Patients with metastatic colorectal cancer meeting specific criteria	Deceased donor	Neoadjuvant and adjuvant therapy	Ongoing; results pending
NCT04874259	Randomized controlled trial	Patients with metastatic colorectal cancer meeting specific criteria	Deceased donor	Neoadjuvant and Adjuvant Therapy	Ongoing; results pending
Liver(t)wo heal	Prospective multicenter	Patients with limited liver metastases	Living donor	Neoadjuvant chemotherapy	Ongoing; results pending
RAPID-Padova	Prospective single-center	Patients with limited liver metastases	Deceased donor	Neoadjuvant chemotherapy	Ongoing; results pending
Transmetir	Randomized controlled trial	Patients with metastatic colorectal cancer meeting specific criteria	Deceased donor	Neoadjuvant and adjuvant therapy	Ongoing; results pending
NCT02864485	Randomized controlled trial	Patients with metastatic colorectal cancer meeting specific criteria	Deceased donor	Neoadjuvant and adjuvant therapy	Ongoing; results pending
Metliver	Randomized controlled trial	Patients with metastatic colorectal cancer meeting specific criteria	Deceased donor	Neoadjuvant and adjuvant therapy	Ongoing; results pending
NCT06069960	Randomized controlled trial	Patients with metastatic colorectal cancer meeting specific criteria	Deceased donor	Neoadjuvant and adjuvant therapy	Ongoing; results pending
RAPID 2014	Prospective single-center	Patients with limited liver metastases	Deceased donor	Neoadjuvant chemotherapy	Ongoing; results pending

Patients with N-RCRLM are more likely to tolerate a graft from an extended-criteria donor due to their preserved liver function and lack of portal hypertension. The utilization of formerly non-transplantable livers has grown due to normothermic machine perfusion (NMP) technologies, as evidenced by the VITTAL study's results, which showed that 70% of perfused discarded livers had sufficient survival rates after transplant. NMP technologies have shown significant promise in improving graft utilization rates in LT. NMP allows for the preservation of donor livers at physiological temperatures, which helps maintain cellular metabolism and function, thereby reducing ischemia-reperfusion injury and allowing for a better assessment of organ viability before transplantation.

A study by MacConmara *et al*[36] demonstrated that NMP significantly reduces the discard rate of donor livers. Even though the NMP group had greater donor risk factors, the discard rate for livers preserved with NMP was 3.5%, while the discard rate for livers preserved with normal cold-static preservation was 13.3%.

This suggests that more livers, including those from donors who meet extended criteria and those who donate after circulatory death, may become available for transplantation as a result of NMP. Furthermore, NMP offers a strong basis for possible treatment measures to enhance graft quality even more. Lascaris *et al*[37] discussed how NMP could develop into a dynamic platform for regenerative medicine. This includes the utilization of stem cell treatment, RNA interference, and defatting cocktails to repair and regenerate injured donor livers.

Furthermore, Hann *et al*[38] highlighted that NMP can improve the supply of transplantable livers for high-risk recipients by allowing for objective assessment of both hepatocyte and cholangiocyte function, thus facilitating the use of grafts with suboptimal features.

In summary, NMP technologies improve graft utilization rates by reducing discard rates, enabling the use of higher-risk donor livers, and providing a platform for therapeutic interventions to enhance graft quality[38].

The delayed total hepatectomy (RAPID) approach for partial LT (2-3 liver segments) has been used with grafts from both deceased and living donors[39]. The basic idea behind the RAPID procedure is initially to ligate the right portal vein and transplant a tiny auxiliary left liver graft. Later, after the enlargement of the graft sufficiently, a residual hepatectomy is performed[40].

Using a heterotopic transplant of a left lateral liver graft into the splenic fossa (RAVAS technique) following splenectomy is another technique to expand the donor pool. The outcomes of these treatments have only been documented in case reports, and it is impossible to extrapolate long-term survival statistics[41].

Initially, due to the small volume of transplanted liver, the recipient must have a working remnant liver until the transplanted graft has grown to a size and functional capacity that allows it to take over full liver function. Secondly, the small-for-size condition is more likely to affect a small graft. High portal venous pressures (> 15 mmHg) and portal hyperperfusion, which harm the liver sinusoids' microvascular systems, are the hallmarks of this pathologic entity. It is usually completely linked to arterial vasoconstriction, failed regeneration, dysfunction, or liver failure. Monitoring arterial flow is essential due to vasoconstriction and the risk of artery thrombosis following increased portal flow[42].

DISCUSSION

It is a well-established fact that more than 40% of patients with CRC develop liver metastasis during the disease course despite all the surveys leading to more suitable systemic treatments, efficient chemotherapy, and surgical resections. Recently published data showed that LT can improve 5-year OS in highly selected patients, reaching 80%[4,43].

In the past, LT for patients with unresectable CRLM showed insufficient results regarding long-term patient survival. This dogma was changed in 2013 when the group from Oslo University reported results from the Secondary Cancer (SECA I) pilot study, representing 60% 5-year OS after LT for N-RCRCLM. After these promising results, more trials were released with better patient outcomes[44].

For example, the SECA-II trial showed even better results, but the inclusion criteria were stricter than those of the SECA-II. The Oslo score, invented during SECA-I, is crucial in determining the group of eligible patients for LT. The results from the study represent the OS of the patients, showing up at 50% and 34% for Oslo I and II and 0% for Oslo III and IV[45].

The average time for disease recurring after LT for N-RCRCLM was estimated to be approximately 8 months. The results from studies represent data that none of the patients died of surgical complications. Most often, the lungs are affected, followed by a liver graft. Otherwise, clinical trials show a better resecting chance for lung metastases after LT, and it is also a well-established fact that immunosuppression after LT did not affect the growth of metastases in the lung [46].

The therapeutic strategy for patients with recurrence after LT includes surgery or radiofrequency ablation[47].

It has to be underlined that listing the patients for LT with N-RCRCLM depends on regulations in different countries worldwide. In most of them, oncological patients join the same list as non-oncological ones, but some centers prioritize the living donor-LT.

Regardless of the above facts, only carefully selected patients have been accepted for LT in published studies[48].

The distribution of donor organs is a crucial topic of discussion, particularly in nations with a shortage of available organs. The North American perspective is very different from Norway's, as 2000 to 3000 patients every year pass away while waiting for LT[49]. Accessing grafts for poorly defined purposes of LT for end-stage liver disease has become more difficult due to competing interests for well-established applications. Furthermore, there are ethical questions about organ distribution and patient prioritizing due to the limited supply of donor livers. Patients with possibly curable diseases may be at a disadvantage if patients with CRLM are added to the transplant pool, which could put further demand on the already scarce supply of organs[49].

National and worldwide registries are necessary to establish and make accessible for researchers and data analysts. These initiatives could be led by organizations like the international LT society and the IHPBA. This will make it possible to conduct a thorough and sound analysis of the results, which will not only produce research ideas but also enable the evaluation of centers, procedures, and methods.

An intriguing study by Liu and Tang[50] demonstrates some novel programmed cell death pathways that might be very useful soon in prognosis and tailoring oncological treatment of patients. The study explores the processes of dsulfidptosis, a unique programmed cell death process based on disulfide proteins, which has been discovered by a

recent study. This finding sheds fresh light on the processes underlying cell death and could affect treatment approaches that target these pathways. Disulfidptosis and disulfidptosis-related cell death genes, such as *SLC7A11*, *INF2*, *CD2AP*, *PDLIM1*, *ACTN4*, *MYH9*, *MYH10*, *IQGAP1*, *FLNA*, *FLNB*, *TLN1*, *MYL6*, *ACTB*, *DSTN*, and *CAPZB*, were evaluated in this work to assess their pan-cancer genomics and clinical associations. Disulfidptosis cell death genes may be implicated in a variety of cancer types and may be used as possible biomarkers for cancer diagnosis, prognosis, and treatment, particularly in patients with MCRC who are candidates for LT.

In LT for CRLM, preventing recurrence is one of the main objectives. Immunosuppressive regimens and selection criteria can be optimized to achieve this. The selection of patients and immunosuppressive regimens is of great importance in achieving the best results after LT. The stricter the criteria, the better results are achieved. As we discussed above, the criteria were much stricter in the SECA-II study, and the results were better.

It is a well-established fact that immunosuppressive therapy used to prevent allograft rejection may accelerate the progression and relapse of oncological disease. However, recent studies show that the rejection rate is not higher than that of other transplanted patients[51].

Mammalian target-of-rapamycin (mTOR) inhibitors were used as maintenance immunosuppression in all reported reports on LT for CRLM. For the SECA trials, the immunosuppressive regimen included induction with basiliximab, tacrolimus for 4-6 weeks, and conversion to sirolimus after that. Likewise, about six months after LT, the North American cohort had induction with tacrolimus, steroids, and basiliximab before switching to mTOR inhibitors (either sirolimus or everolimus). Although there was no apparent difference in OS or recurrence-free survival between the two immunosuppression groups, the Compagnons Hépato-Biliaires cohort is the only one that includes patients (4/12, 33%) who were not transferred to maintenance with mTOR[33].

Another interesting fact is that immunosuppressive therapy after LT could interact without serious toxicity with chemotherapy. These data are demonstrated in a study by Brandi *et al*[52], where 23 patients underwent LT for N-RCRCLM followed by treatment with chemotherapy. The authors demonstrate that chemotherapy has a safe profile, with more common development of diarrhea and mucositis[53].

Limitations

In view of the differences in medical levels and resources in different regions of the world, some of the recommended guidelines are difficult to implement in some regions with poor medical resources.

CONCLUSION

CRC is a "silent killer" worldwide. Unfortunately, in a large percentage of patients, when the disease is detected in the advanced stage development of unresectable liver metastases. The reviewed studies prove that thanks to LT, 5-year survival is achieved in 83% of those transplanted. It turns out that to be a candidate for a liver transplant, the patient has to meet the strict criteria described in the two prospective studies, SECA-I and SECA-II. The goal of applying the patient selection criteria is to achieve the most significant survival benefit from LT.

It should be remembered that these results are from studies that included a small number of heterogeneous populations. On the positive side, these results sound promising and give rise to a more extensive collaboration between surgeons, medical oncologists, and all medical professionals who may be involved in the fight against this severe complication of colorectal carcinoma.

Additionally, a team effort involving surgeons, medical oncologists, and translational researchers is required to achieve significant effect. Despite the proven benefits of LT for N-RCRCLM, this method is still not widely used worldwide due to a lack of policy and healthcare reforms in many countries. There are still many unanswered questions about the best preoperative imaging staging techniques, pre-LT chemotherapy regiments, and locoregional therapeutic alternatives, such as immune therapy indications, postoperative immunosuppressive protocols, and the use of the HAI pump. A unified database will facilitate multicenter and multi-society collaboration and make these concerns easier to examine.

FOOTNOTES

Author contributions: Stoyanova M, Peruhova M, and Velikova T wrote the majority of the manuscript; Chulkov I, Goranova Z, Mircheva I and Stoyanova prepared the tables; Zashev M wrote the part related to the surgical techniques. Karamiteva M and Simeonova V provided critical revision, designed the manuscript outline, and coordinated the writing of the paper.

Supported by the European Union-NextGenerationEU, through the National Recovery and Resilience Plan of the Republic of Bulgaria, No. BG-RRP-2.004-0008.

Conflict-of-interest statement: The authors declare no conflict of interest.

Country of origin: Bulgaria

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S-Editor: Qu XL
L-Editor: A
P-Editor: Zhang L

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