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REVIEW ARTICLE

Liver Transplantation in Patients with Colorectal Liver Metastases: a Literature Review

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ABSTRACT

Colorectal cancer (CRC) is on the rise and is already the second most common cancer in both men and women. Approximately 50% of CRC patients develop liver metastases (LM), and in about 35% of these, the lesions are confined to the liver. Unfortunately, only 20 to 40% of patients with CRC with LM (CRLM) have resectable disease, leaving the remainder with a poor prognosis, with 5-year survival rates of around 10%, despite advanced multimodal, systemic, and locoregional treatments. Since the 1980s, liver transplants have been performed to treat patients with unresectable CRLM. Poor survival rates, only slightly higher than with systemic chemotherapy, were observed at that time. With the publications from the Oslo group starting in 2013 and the establishment of selection criteria and immunosuppression strategies, significant life gains in survival have been achieved, leading to multicenter studies that are confirming the Norwegian findings and consolidating liver transplantation as a treatment alternative for selected patients with unresectable CRLM. This study presents a systematic review of published articles involving TF in CRLM, including case reports, case series, multicenter studies, and reviews on the subject, aiming to show the development, initial cases in various centers, and the current state of this important treatment alternative.

Descriptors: Liver Transplantation; Metastasis; Colorectal Cancer.

Transplante Hepático em Pacientes com Metástases Hepáticas Colorretais: Revisão da Literatura

RESUMO

O câncer colorretal (CCR) encontra-se em crescimento e já é o segundo em incidência, tanto em homens quanto em mulheres. Cerca de 50% dos pacientes com CCR desenvolvem metástases hepáticas (MH), e em cerca de 35% desses as lesões permanecem restritas ao fígado. Infelizmente, apenas 20 a 40% dos pacientes com MHCCR apresentam doença ressecável, ficando os demais com prognóstico sombrio, com sobrevida em 5 anos de cerca de 10%, apesar de tratamentos avançados multimodais, sistêmicos e locorregionais. Desde a década de 1980, transplantes de fígado (TF) foram realizados para tratamento de pacientes com MHCCR irressecáveis. Sobrevidas pobres pouco superiores à quimioterapia sistêmica foram observadas na época. Com as publicações do grupo de Oslo a partir de 2013 e o estabelecimento de critérios de seleção e estratégias de imunossupressão, alcançaram-se sobrevidas satisfatórias que impulsionaram estudos multicêntricos que estão confirmando os achados noruegueses e consolidando o TF como alternativa de tratamento para pacientes selecionados com MHCCR irressecáveis. Este estudo faz uma revisão sistemática dos artigos publicados envolvendo o tema TF em MHCCR, incluindo relatos de caso, séries de casos, estudos multicêntricos e

revisões sobre o tema, com o objetivo de mostrar o desenvolvimento, os casos iniciais em diversos centros e o estado atual dessa importante alternativa de tratamento.

Descritores: Transplante de Fígado; Metástase; Câncer Colorretal.

INTRODUCTION

According to data from the World Health Organization, colorectal cancer (CRC) is the third most prevalent type of cancer among men and the second most frequent among women, registering more than 1.8 million new cases and approximately 850,000 deaths annually worldwide[1].

Approximately 50% of patients with colorectal cancer (CRC) develop liver metastases (LM) at some point in their disease progression, and this situation can complicate the prognosis[2,3].

However, about 35% of LM cases develop metastases only in the liver, the progression of which can compromise the patient's life[4].

Despite advances in oncology, only 30-40% of patients with CRLM achieve survival beyond 5 years with multimodal treatment[5].

When CRLMs are unresectable, several therapeutic strategies have been employed, including thermal ablation, intra-arterial hepatic chemotherapy (CT), chemoembolization, radioembolization, and stereotactic radiotherapy, with or without palliative CT; however, 5-year survival rates are less than 10%[6-9].

Attempts to treat unresectable colorectal cancer through liver transplantation (LT) are not a new subject. In the 1980s, several attempts were made, without long-term success. In a 1991 publication by the Vienna group, Mühlbacher et al.[7] reported a 5-year survival rate of 12% in 17 transplanted patients, with a disease recurrence rate exceeding 60%.

Recently, LT has presented its re-evaluated role in the treatment of CRLM. With new patient selection and postoperative immunosuppression strategies, the SECA I and SECA II studies from the Oslo group demonstrated long-term survival rates never before seen, and paved the way for new protocols and a new era of transplantation for unresectable CRLM.

In this study, we reviewed publications from the last 34 years on LT in CRLM, including review articles and/or case reports or case series, to demonstrate the outcomes achieved.

METHODS

The present is a systematic literature review of publications from 1991 to 2025, based on a search of the PubMed, LILACS, and SciELO databases. The search was conducted using the keywords: liver metastases, colorectal cancer, and liver transplantation.

Next, the abstracts were reviewed to identify studies that met the previously established criteria; those that did not fit the defined parameters were excluded.

The inclusion criteria for study selection were articles that addressed one of the following topics on LT in CRCLM: review articles, case series, case reports, analysis of pre- and post-transplant multimodal therapies, median overall survival at 1, 3, and 5 years, identification of tests and biomarkers associated with recurrence and long-term mortality, and prognostic criteria.

The exclusion criteria adopted included the unavailability of the full text, incomplete articles, thematic deviations from the research scope, and duplicate publications. Studies that, although related to the oncological or hepatic context, deviated from the defined scope were also excluded. Among the main reasons for exclusion, the following stand out: investigations focused on chemotherapy, isolated hepatic resection, radioembolization, immunotherapies and immunobiologics, antiangiogenic or neoadjuvant therapies, studies on biomarkers for metastasis inhibition, xenograft, gene inactivation, approaches such as hepatectomy, laparoscopic surgery or radiological medications, as well as research on tumor mutations, splenic metastases, therapeutic diets and liver diseases unrelated to colorectal metastases.

RESULTS

The initial search resulted in 1,615 publications.

The careful selection resulted in 64 studies that met the inclusion and exclusion criteria, ensuring timeliness, clinical relevance, and achievement of the study's objectives.

The 64 selected articles were organized according to methodological type: 40 case reports, prospective and retrospective case series and meta-analyses, and 24 reviews.

The selected studies were organized into tables according to their specific themes: Table 1 – case reports, prospective and retrospective series, and meta-analyses on LT for colorectal LM; Table 2 – publications on hepatic resections of colorectal metastases used in comparative studies with transplantation outcomes; Table 3 – retrospective and prospective studies comparing LT outcomes in colorectal metastases versus CT; and Table 4 – review articles on LT for the treatment of colorectal LM.

Table 1. LT in the treatment of colorectal LM – case reports, prospective and retrospective case series, and meta-analysis.

Year	Authors	Journal	Methodology	Article	Number of cases	Living donor/ deceased donor	Follow-up time	Recurrence (%)	Overall Survival	Disease-free survival
2011	Uskudar et al.[33]	Transplantation Proceedings	Case report	Liver transplantation is possible in some patients with liver metastasis of colon cancer	2	Deceased donor	-	50	-	-
2013	Hagness et al.[29]	Annals of Surgery	Meta-analysis	Liver transplantation for nonresectable liver metastases from colorectal cancer.	21	Deceased donor	5 Years	90	60%	-
2016	Wang et al.[34]	Chirurgia (Bucureşti)	Case report	Clinical analysis of liver transplantation in the treatment of liver metastatic cancer	4	Deceased donor	5 years	90	25% in 5 years	-
2017	Yang et al.[65]	Nowotwory Journal of Oncology	Case report	Liver transplantation for progressive unresectable colorectal liver metastases: case report and review of the literature	1	Deceased donor	13 years	0	100%	13-year follow-up
2017	Toso et al.[35]	Liver Transplantation	Multicenter retrospective	Liver transplantation for colorectal liver metastasis: survival without recurrence can be achieved	12	Deceased donor	108 months	50	1 year: 83%; 3 years: 62%; 5 years: 50%	1 year: 56%; 3 years: 38%; 5 years: 38%
2018	Dueland et al.[17]	British Journal of Surgery	Retrospective comparative study	Survival following liver transplantation for liver-only colorectal metastases compared with hepatocellular carcinoma	44	Deceased donor	SECA I- 27 months; SECA II- 36 months	SECA I – 65-100% SECA II- 78.6	SECA I – 95%, 68%, and 60% at 1, 3, and 5 years; SECA II – 100% (1 year), 83% (3 years), and 83% (5 years)	SECA I – 35% (1 year), 0% (3 years); SECA II – 53% (1 year), 44% (2 years), 35% (3 years)
2019	Dueland et al.[31]	Annals of Surgery	Prospective study.	Survival following liver transplantation for patients with nonresectable liver-only colorectal metastases	15	Deceased donor	36 months	60 (9/15 patients)	1 year: 100% 3 years: 83% 5 years: 83%	1 year: 53% 2 years: 44% 3 years: 35%
2019	Fernandes et al.[38]	Arquivos Brasieiros de Cirurgia Digestiva	Case report	First case of living donor liver transplantation for unresectable colorectal liver metastasis in Latin America	1	Living donor	-	-	-	
2020	Choi et al.[41]	Annals of Hepato-Biliary-Pancreatic Surgery	Case report	Living donor liver transplantation for unresectable colorectal liver metastasis: report of a case with 13-year follow-up without recurrence	1	Living donor	156 months(13 years)	0	13 years: 100%	100% in 13 years
2021	Botha et al.[40]	Experimental and Clinical Transplantation	Prospective case series	Liver transplant for nonresectable colorectal cancer liver metastases in South Africa: a single-center case series	2	Deceased donor	40 months (case 1)/24 months (case 2)	0	100%	100% (in 40 and 24 months)

Continue...

Table 1. Continuation.

Year	Authors	Journal	Methodology	Article	Number of cases	Living donor/ deceased donor	Follow-up time	Recurrence (%)	Overall Survival	Disease-free survival
2021	Lanari et al.[36]	Transplant International	Multicenter retrospective	Liver transplantation versus liver resection for colorectal liver metastasis: a survival benefit analysis in patients stratified according to tumor burden score	61	Deceased donor	Median 26 months (range, 1–98 months)	70	56% in 5 years	25% in 5 years
2021	Tabbal et al.[3]	BMC Gastroenterology	Case report	Salvage liver transplantation after resection of colorectal cancer liver metastasis with favorable outcomes: a case report and review of the literature	1	Deceased donor	40 months	Recurrence-free (0)	Patient alive (100%)	40 months of follow-up (100%)
2022	Grut et al.[45]	Annals of Nuclear Medicine	Retrospective cohort study	Metabolic tumor volume predicts long-term survival after transplantation for unresectable colorectal liver metastases: 15 years of experience from the SECA study	61	Deceased donors	Median: 86 months (12-178 months)	72	41% in 10 years	24% in 5 years
2023	Rajendran et al.[42]	Journal of the American College of Surgeons	Prospective case series	Toronto management of initially unresectable liver metastasis from colorectal cancer in a living donor liver transplant program	10	Living donor	37.6 months	80	3 years: 83.3%	13.1 months
2023	Hagness et al.[29]	Annals of Surgery	Prospective pilot study	Liver transplantation for nonresectable liver metastases from colorectal cancer	23	Deceased donor	168 months	100	5 years: 43.5% 10 years: 26.1%	4 patients over 102 months
2023	Fernandes et al.[39]	ABCD – Arquivos Brasileiros de Cirurgia Digestiva	Retrospective	An experience on living donor liver transplantation for colorectal liver metastasis in South America: a new era in transplant oncology	4	Living donor	3 years	75	-	-
2023	Solheim et al.[32]	Annals of Surgery	Prospective trial	Transplantation for nonresectable colorectal liver metastases: long-term follow-up of the first prospective pilot study	23	Deceased donor	10 years	-	5 years: 43.5%; 10 years: 26.1%	4 patients alive with no evidence of disease (median DFS: 102 months); 1 died with no evidence of disease (DFS: 31 months)
2024	Adam et al.[43]	Lancet	Prospective, multicenter, open-label, randomized clinical trial	Liver transplantation plus chemotherapy versus chemotherapy alone in patients with permanently unresectable colorectal liver metastases (TransMet): results from a multicentre, open-label, prospective, randomized controlled trial	47	Deceased donors	41 months	79	5 years: 56%	13 months
2025	Byrne et al.[44]	American Journal of Transplantation	Retrospective	The Rochester protocol for living donor liver transplantation of unresectable colorectal liver metastasis: a 5-year report on selection, approval, and outcomes	23	-	21 months	60	91%	40%

Source: Elaborated by the authors.

Table 2. Publications on hepatic resections for colorectal metastases used in comparative studies with liver transplant outcomes.

Year	Authors	Journal	Methodology	Article	Number of cases	Number of resections	Follow-up time	Recurrence (%)	Overall survival	Disease-free survival
1996	Nordlinger et al.[8]	Cancer	Retrospective multicenter study	Surgical resection of colorectal carcinoma metastases to the liver: A prognostic scoring system to improve case selection	1,568	1,568	2 to 5 years	66	2 years 64%, 5 years 28%	-
1999	Fong et al.[19]	Annals of Surgery	Retrospective study with multivariate analysis	Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer	1,001	237 trisegmentectomies, 394 lobectomies, 370 minor resections	10 years	-	5 years 37%; 10 years 22%	-
1999	Iwatsuki et al.[48]	Journal of the American College of Surgeons	Retrospective cohort study	Hepatic resection for metastatic colorectal adenocarcinoma: a proposal of a prognostic scoring system	204	204	10 years	-	1 year 91%; 3 years 43%; 5 years 32%	-
2018	Sasaki et al.[37]	Annals of Surgery	Retrospective multicenter study	The tumor burden score: a new "metro-ticket" prognostic tool for colorectal liver metastases based on tumor size and number of tumors.	604	604	30.3 months	-	61,7 months: 93.9%; 68.9%; 49.9%	-
2021	Isoniem et al.[16]	British Journal of Surgery	Prospective	Centralized repeated resectability assessment of patients with colorectal liver metastases during first-line treatment: prospective study	1,086	511	58 months	-	5 years: R0-R1 resection: 68%; R2 resection: 37%	LM: 20 months; LM + extrahepatic: 7 months
2022	Milana[9]	Cancers	Retrospective cohort study	Multidisciplinary tumor board in the management of patients with colorectal liver metastases: a single-center review of 847 patients	521	404	36 months	70	-	-

Source: Elaborated by the authors.

Table 3. Retrospective and prospective studies comparing outcomes of LT versus CT in the treatment of unresectable colorectal LM.

Year	Authors	Journal	Methodology	Article	Number of patients	Living donor transplantation	Deceased donor transplantation	Adjuvant CT	Neoadjuvant CT	Number of CT cases	Follow-up time	Recurrence (%)	Overall survival	Disease-free survival
2015	Dueland et al.[66]	Annals of Surgery	Retrospective study	Chemotherapy or liver transplantation for nonresectable liver metastases from colorectal cancer	68	-	-	-	-	-	5 years	56% (LT) vs. 9% (CT)	LT: 6% at 5 years and CT: 9% at 5 years	8-10 months

Continue...

Table 3. Continuation.

Year	Authors	Journal	Methodology	Article	Number of patients	Living donor transplantation	Deceased donor transplantation	Adjuvant CT	Neoadjuvant CT	Number of CT cases	Follow-up time	Recurrence (%)	Overall survival	Disease-free survival
2017	Toso et al.[35]	Liver Transplantation	Retrospective multicenter study	Liver transplantation for colorectal liver metastasis: Survival without recurrence can be achieved	12	-	12	11	4		108 months	56 in 1 year	38–60% at 5 years	5 patients without recurrence at the end of follow-up
2018	Mazzaferro et al.[28]	Liver Transplantation	Prospective study	Extended oncologic indications in liver transplantation	36	-	36	0	36	36	27 to 36 months	90% at 24 months – SECA-I, and 53% during follow-up	1 year = 95%; 3 years = 68%; 5 years = 60% - SECA I and 1 year = 100%; 3 years = 83%; 5 years = 83%- SECA II	1 year = 35%; 2 years = 0% and 53% (1 year), 44% (2 years), 35% (3 years)
2023	Janesh et al.[26]	Journal of Clinical and Experimental Hepatology	Retrospective observational study	Outcomes of patients with colorectal liver metastasis in the developing world: Is liver transplantation for unresectable liver metastasis the next logical step?	13	-	-	12	0	12	36 months	100	3 years: 25%	Disease progression in all patients.

Source: Elaborated by the authors.

Table 4. Review articles on LT for the treatment of unresectable colorectal LM.

Year	Authors	Journal	Methodology	Article	Number of cases	Living donor/ deceased donor	Follow-up time	Recurrence (%)	Overall survival	Disease-free survival
2008	Hoti et al.[10]	Transplant International	Review	Liver transplantation for primary and metastatic liver cancers	58	Deceased donor	5 years	59	1 year: 62% 5 years: 18%	-
2014	Eghtesad[55]	J Gastrointest Cancer.	Review	Liver transplantation for malignancies	-	-	-	50	53% at 5 years	13% at 5 years
2017	Reyhan[49]	Liver Transplantation	Review	Liver transplant for nonhepatocellular carcinoma malignancy	403	-	3 to 5 years	High recurrence, though the percentage is not reported	1 year: 96%, 3 years: 77%, 5 years: 53%	1 year: 58%, 3 years: 33%, 5 years: 13%
2018	Gorgen et al.[56]	Canadian Journal of Gastroenterology and Hepatology	Review	The new era of transplant oncology: liver transplantation for nonresectable colorectal cancer liver metastases	36	Deceased donor	5 years	-	50% at 5 years	-
2018	Fehérvári[57]	Magyar Onkológia	Review	Liver transplantation in the treatment of hepatic tumors	48	Deceased donor	4 years	8	85% aos 4 years	92% aos 4 years

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Table 4. Continuation...

Year	Authors	Journal	Methodology	Article	Number of cases	Living donor/ deceased donor	Follow-up time	Recurrence (%)	Overall survival	Disease-free survival
2018	Andres[5]	Translational Gastroenterology and Hepatology	Review	Transplantation for colorectal metastases: on the edge of a revolution	SECA I: 21	-	5 years	-	5 years: 60%	-
2019	Kow[58]	Journal of Gastrointestinal Oncology	Review	Hepatic metastasis from colorectal cancer	-		-	49.8 mean	1 year 96%; 3 years 77%; 5 years 53% (IC 45-61%)	1 year 58%/3 years 33%/5 years 13%
2020	Line, Dueland[50]	Journal of Hepatology	Review	Liver transplantation for secondary liver tumors: The difficult balance between survival and recurrence	100	Deceased donor	2 to 5 years	40 and 60 in 3 to 5 years	50% to 70% in 5 years	30% to 50% in 3 to 5 years
2020	Nadalin et al.[27]	Digestive Medicine Research	Review	Living donor liver transplantation for colorectal liver metastasis: a narrative review	10	Living donor	10	0	3 years	30%
2020	Glinka et al.[4]	Langenbeck's Archives of Surgery	Review	Liver transplantation for non-resectable colorectal liver metastasis: where we are and where we are going	36	Deceased donor	27 to 36 months	53 to 90	1 year 53%; 2 years 44%; 3 years 35%	1 year = 35% to 53% and 2 years= 44% to 53%
2020	Giannis et al.[59]	Transplantation Reviews	Review	The role of liver transplantation for colorectal liver metastases: A systematic review and pooled analysis	110	-	22.2 months	1 year = 40	6 months 95.7%; 1year 88.1%; 2year 74.6%; 3years 58.4%; 5 years 50.5%	6 months 77.2%/1year 59.9%/2 years 42.4%/3 years 30.7%/5 years 25.6%
2020	de'Angelis et al.[53]	Plos One	Review	Surgical and regional treatments for colorectal cancer metastases in older patients: A systematic review and meta-analysis	29 studies		19 years	-	95%	-
2021	Abdelrahim et al.[60]	Cancers	Review	Transplant oncology: an evolving field in cancer care	SECA I: 21 SECA II 15	-	SECA I 36 months SECA II 60 months	SECA I 70-80/ SECA II 50-60	5 years: 83%	1 year: 53%; 2 years 44%; 3 years: 35%
2021	Chu et al.[18]	Gut and Liver	Review	Expanding indications for liver transplant: tumor and patient factors	110	Deceased donor	5 years	50	20-30%	33%
2021	Biller et al.[14]	JAMA	Review	Diagnosis and treatment of metastatic colorectal cancer: a review	-		5 years	50-80	5 years: 20-30%	70-75% in 1 year, 30-35% in 3 years, and < 20% in 5 years
2021	Cui et al.[51]	World Journal of Gastrointestinal Surgery	Review	Advances in liver transplantation for unresectable colon cancer liver metastasis	141	Mostly deceased donors; 26 living donors	1.5 to 15 years	50-100	26% to 88.9% at 5-10 years	4 months and 3 years,
2022	Ernani et al.[47]	ABCD – Arquivos Brasileiros de Cirurgia Digestiva	Review	Protocol for liver transplantation in unresectable colorectal metastasis	36	Deceased donor	SECA I- 27 months; SECA II- 36 months	50 to 60 at 5 years	30% a 40% em 3 years	-
2022	Reyhan[49]	American Journal of Roentgenology	Review	Liver transplant for nonhepatocellular carcinoma malignancy	403	-	3 to 5 years	High recurrence rate, but no percentage	1 year: 96%, 3 years: 77%, 5 years: 53%	1 year: 58%, 3 years: 33%, 5 years: 13%

Continue...

Table 4. Continuation.

Year	Authors	Journal	Methodology	Article	Number of cases	Living donor/ deceased donor	Follow-up time	Recurrence (%)	Overall survival	Disease-free survival
2022	Ahmed et al.[61]	Experimental and Clinical Transplantation	Review	Liver transplantation as a curative approach for patients with nonresectable colorectal liver metastases	46	Living and deceased donors	27 to 36 months	90 to 53	1 year 89%; 3 years 60.4%	1 year 75.1%; years 53.7%
2022	García et al.[62]	Revista Medica de Chile	Review	Liver transplantation for non-resectable colorectal liver metastases: A review	-	-	-	-	5 years: 60-80%	-
2024	Wehrle et al.[52]	Annals of Surgical Oncology	Review	Update to 'A Contemporary systematic review on liver transplantation for unresectable liver metastasis of colorectal cancer.'	46	20 deceased and 26 living donors	10 years	High recurrence, though no percentage was reported	1 year-95%; 5 years 60%	-
2024	Chandra et al.[54]	Cancers	Review	Contemporary surgical management of colorectal liver metastases	SECA I: 21 SECA II 15	-	SECA I 36 months SECA II 60 months	SECA I 70-80/ SECA II 50-60	5 years: 83%	1 year: 53%; 2 years 44%; 3 years: 35%
2024	Battistella et al.[63]	Medicina (MDPI)	Review	Evolution of liver transplantation indications: expanding horizons	SECA I: 21 SECA II 15	-	3-5 years	50 a 90	~60% (SECA-I), ~83% (SECA-II); Meta-analysis: ~53% in 5 years	13-38% em 5 years
2024	Robinson et al.[64]	Current Oncology	Review	Liver transplantation for unresectable colorectal liver metastasis: perspective and review of current literature	46	Living and deceased donors	Up to 3 years	1 year = 85.7	1 year 89%; 2 years 60.4%; 3 years 60.4%	1 year 75.1%; 2 years 53.7%; 3 years 53.7%

Source: Elaborated by the authors.

DISCUSSION

CRC is the third most prevalent malignancy globally and the second leading cause of cancer-related death. The incidence and mortality of CRC vary across different countries, and the disease has been affecting an increasing number of young patients. CRC remains a major cause of cancer death worldwide: 25% of patients present with synchronous LM, and another 25% will develop LM over the following 3 to 5 years, eventually reaching approximately 50% of cases. This makes the liver the primary site of metastasis, a condition that poses a significant challenge in the treatment of the disease[1,2,10-15].

In patients not undergoing resection, treatment is based on CT alone or a combination of CT with other bridging therapies, aiming to convert to radiologically resectable disease. The average survival for unresected cases is approximately 2 years, and the average overall 5-year survival rate is between 10 and 20%[14-18].

Patients who achieve R0 resections, in single metachronous metastases < 5 cm, with a disease-free interval > 12 months, carcinoembryonic antigen (CEA) levels < 200 ng/mL, no lymph node involvement, and no extra-hepatic disease (i.e., lacking the poor prognostic criteria of Fong et al.[19], can achieve a 5-year disease-free survival rate of 60%. In contrast, those with multiple metastases considered unresectable are treated with systemic CT, facing a dismal prognosis and a 5-year survival rate of approximately 10%.

Although surgical resection is the only approach with long-term curative intent, only 20 to 40% of these patients are eligible for resection. Indeed, technical limitations to surgical resection include the number of metastases, the volume of hepatic parenchyma occupied, the distribution of lesions, their relationship with vascular and biliary structures, the hepatic functional reserve, which is generally deteriorated after prolonged CT, and the patient's overall condition. In patients without prolonged chemotherapy and with preserved liver parenchyma, resection of up to 75% of the parenchyma is permitted. In contrast, after long periods of chemotherapy, resection is restricted to a maximum of 40 to 60% of the liver volume, depending on the degree of fibrosis, portal pressure, and impairment of liver function[8,14,15,19-21].

Studies from the beginning of this century have shown that 30%-40% of recurrences after resection occur exclusively in the liver. This indicates the existence of a subgroup of patients with liver-only disease who could potentially benefit from transplantation[22-24]. Unfortunately, this proportion is lower in patients considered unresectable and undergoing palliative CT, as reported by Dueland et al.[25] in 11% of cases (64 out of 571 patients).

Janesch et al.[26] evaluated 284 patients treated for CRLM over 2 years. The median overall survival of 73 unresectable patients treated exclusively with CT was 11 months. The authors applied the International Hepato-Pancreato-Biliary Association (IHPBA) criteria, the Oslo criteria, and the Fong clinical score for LT indication, identifying 13 potentially eligible patients. The median overall survival in this LT-eligible subgroup was 24 months, compared to 9 months in the ineligible subgroup. Similarly, the 3-year overall survival rate was 25% in the eligible group vs. 5% in the ineligible group. In the eligible group, 10/13 (76.9%) patients had exclusively hepatic progression, confirming that they could indeed have benefited from LT. These findings confirm that the criteria developed so far for transplantation indication in patients with unresectable MHCCR are indeed able to select patients with almost exclusively liver metastases who benefit from LT, with a lower risk of developing extra-hepatic disease progression[26].

Historically, LT for the treatment of CRLM was pioneered at the University of Vienna in the 1980s[27].

However, preliminary results from 50 patients with CRLM undergoing LT in Europe in the 1980s and 1990s showed a 5-year survival rate of only 18%, at a time when CT was based on 5-fluorouracil and response rates were <20%. The authors observed that 44% of deaths were not related to tumor recurrence[10].

Mühlbacher et al.[7] published in 1991 a series of 25 patients who underwent TF for CRLM, reporting a 5-year survival rate of 12%.

Liver transplantation for CRLM was abandoned in the 1980s and 1990s due to poor results, when many deaths still occurred as a result of perioperative complications and not due to disease recurrence. Furthermore, 5-year survival rates in patients who achieved late survival were less than 20% and were attributed to high recurrence rates, a lack of effective selection criteria, and the absence of effective adjuvant therapies. However, improvements in staging methods, therapeutic agents, and multimodal therapies, as well as improved perioperative outcomes, have enabled the establishment of rigorous selection criteria based on detailed morphological and biological analysis of the tumor, which have shown good results and more favorable survival rates[7,10,13].

In recent years, considerable advances in perioperative care, improvements in surgical techniques and the development of modern CT and more effective immunosuppression regimens have significantly changed the therapeutic landscape.

By definition, an inclusion criterion for transplant candidates is acceptable when a minimum 5-year survival rate of 60% can be achieved[28].

In 2013, Hagness et al.[29] published the SECA I study, with 21 patients with unresectable CRLM undergoing LT, who achieved a 5-year survival rate of 60% and a 1-year disease-free survival rate of 35% (mean follow-up of 27 months – 8 to 60 months), compared to a 10% survival rate in a control group treated with CT alone. The inclusion criteria for the study were resection of the primary R0, at least 6 weeks of CT, unresectable liver lesions, absence of extra-hepatic metastases, and a favorable performance status. The authors observed that patients with better survival outcomes did not present with tumors > 5.5 cm, a time interval between primary tumor resection and transplantation < 2 years, CEA levels > 80 ng/mL, or disease progression during CT. These promising results revitalized international interest in LT as a viable alternative for patients with unresectable LM.[5,12,13,27-29].

The SECA I study was a prospective pilot trial that established pre-transplant exclusion criteria for unresectable CRLM, including a tumor diameter greater than 5.5 cm, CEA levels greater than 80 µg/L, time since primary tumor treatment less than 2 years, and primary tumor location in the right colon[29]. This study was essential to evaluate the feasibility, safety, and efficacy of LT in patients with unresectable CRLM, showing, for the first time, good results in the 21 cases analyzed.[4-6,10,12,13,27,28]. Initially, strict inclusion criteria were adopted, but due to the small number of patients, these criteria were simplified, resulting in significant heterogeneity regarding tumor burden, tumor biology, and chemotherapy regimen used[30]. The SECA I study reported a 5-year survival rate of 60%, significantly higher than that with chemotherapy. However, there was a high recurrence rate, with 90% of patients experiencing a relapse, highlighting the need to refine selection criteria and adopt adjuvant treatments[5,12,13,27,29].

The SECA II study, conducted in 2011, expanded on this data through a clinical trial that led to the creation and standardization of the Oslo score, used to select patients with CRLM[31]. SECA II focused on evaluating the impact of stricter inclusion criteria, including 15 patients with isolated LM, a minimum response of 10% to chemotherapy according to RECIST (Response Evaluation Criteria in Solid Tumors) criteria, and an interval greater than 1 year between the diagnosis of the primary tumor and inclusion on the transplant list.

In SECA II, we noted some differences in patient selection compared to SECA I: i) the median age of patients was 59 years; ii) most presented with primary tumors on the left side of the colon; iii) the median Oslo score was 1; iv) the median time from primary resection to transplantation was 22 months; v) tumors showed a significant reduction in both size and number; vi) the median Fong clinical risk score decreased from 3 to 2; and vii) tumor metabolic volume (TMV) [calculated using fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT)] was added to the pre-transplant evaluation, showing that when < 70 mL, there was greater disease-free survival.

The SECA II trial involved 15 patients and achieved overall survival rates of 100%, 83%, and 83% at 1, 3, and 5 years, respectively. At a median follow-up of 36 months, disease-free survival rates at 1, 2, and 3 years were 53%, 44%, and 35%, respectively. Eight patients experienced recurrence, with six developing pulmonary metastases, five of which were treated with resections[31].

Overall survival at 5 and 10 years in transplant patients with none or one Oslo criterion has been reported as 75% and 50%[32].

The European Liver Transplant Registry showed frustrating results in initial experiences with patients undergoing LT for CRLM, with a 5-year survival rate of 18% in a series of 58 patients. However, in these early series, more than 40% of deaths resulted from perioperative complications rather than metastasis recurrence. Nonetheless, CRLM remained a contraindication for transplantation[7,10].

Uskudar et al.[33] reported 2 successful LTs in patients with CRLM whose indication was sclerosing cholangitis caused by intra-arterial infusion of chemotherapeutic agents that led to liver failure.

Dueland et al.[17], from the Oslo group, published a comparative study in 2015 involving patients with unresectable CRLM who underwent LT (21 patients included in the SECA-I trial)and submitted to CT (47 included in the NORDIC VII study), observing overall survival at 5 years of 56% vs. 9%, respectively. The same author observed that four patients with metachronous metastases and without lymph node involvement in the primary tumor were alive 6 to 10 years after transplantation[17].

Lianjiang et al.[34], from Tianjin, China, published a report in 2016 on deceased donor LT in four patients with unresectable LM, one of whom presented with CRLM. However, at the 3rd postoperative month, this patient developed bilateral lung metastases that were treated with systemic CT; nevertheless, the patient passed away 18 months after transplantation[34].

The Compagnons Hepato-Biliaires group published results from 12 patients transplanted for CRLM in a multicenter study that included patients with attempts at extreme resections, observing better survival rates in those transplanted, with survival rates of 83%, 62%, and 50% at 1-, 3-, and 5-year follow-ups, and disease-free survival at 1- and 5-year follow-ups of 56% and 38%, respectively[35].

In a comparative study of transplantation versus resection in CRLM, Lanari et al.[36] compared 128 patients who underwent CRLM resection at the University of Padua, Italy, with 56 LTs performed in Oslo, Norway. The 128 resected patients were selected from the 362 patients operated on during the same period in which the LTs were performed, using the same preoperative selection criteria. The mean follow-up was 30.7 months (16.8 to 57.5), being 27.1 months (15.2 to 45) in the resection group and 43.3 months (25.8 to 76.4) in the transplant group. The number of lesions was much higher in the transplant group (3 vs. 10), as was the size of the largest lesion (3 vs. 3.8 cm), with the mean tumor burden score (TBS) being 5.3 in the resection group and 11.9 in the transplant group. Overall survival rates at 1, 3, 5, and 7 years were 91.9%, 63.9%, 40.5%, and 31.9% in resections versus 92.9%, 71.2%, 54.7%, and 42.3% in transplants. Disease-free survival rates were 37.6%, 10.3%, 7.8%, and 7.8% in resections versus 41.8%, 20.6%, 14.1%, and 14.1% in transplants. In patients with high tumor burden, as proposed by Sasaki et al.[37], with TBS ≥ 9, 5-year survival rates were 22.7% in resections and 52.2% in transplants. Recurrences were similar, but more frequent in the liver in the resection group and in the lung in the transplant group. 5-year disease-free survival was zero in resections and 22.9% in transplants. All differences in favor of transplants become more pronounced when comparing the subgroup with an Oslo scale of 0 to 2 (77 resected and 42 transplanted), where survival rates at 1, 3, 5, and 7 years were 94.6%, 66.6%, 42.2%, and 35.1%, respectively, versus 95.1%, 87.6%, 65.3%, and 58.5%. This study suggests that transplantation should be considered even in resectable patients with a large volume of disease[36,37].

In our setting, Fernandes et al.[38] reported the first LT for CRLM in Latin America, performed in 2019 using a living donor. Both donor and recipient achieved good postoperative recovery. In 2023, the same group published their experience with four cases performed between 2019 and 2022. Exclusion criteria included right-sided colon primary tumors, Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations, Eastern Cooperative Oncology Group (ECOG) performance status > 1, lack of response to CT, and extra-hepatic disease. In accordance with the Brazilian reality of organ shortage and current legislation, all transplants were performed with living donors. In the group's four-case experience, with a short postoperative follow-up ranging from 4 months to 3 years, recurrence occurred in 50% of patients, and the survival rate was 75%[39].

Botha et al.[40] published a series of 5 cases of LT for CRLM following the Oslo criteria: SECA I, 2 with prior liver resection, at least 2 lines of CT, response in 4 and transplants performed with deceased donors. In a mean follow-up of 38 months (10 to 54 months), four patients (80%) were alive. The patient who died was the one who did not respond to pre-transplant CT and

presented disease progression that led to death 10 months later. All had recurrence between 3 and 6 months later, three in the lung, of which two underwent resection and remain disease-free, and the other two are on CT[40].

Choi et al.[41], from the ASAN Medical Center in South Korea, published a case report of a 49-year-old patient with synchronous LM from sigmoid cancer. The metastases were treated with intra-arterial CT, resulting in a partial response but subsequent liver cirrhosis. The patient had a Model for End-Stage Liver Disease (MELD) score of 8 and a CEA level of 220 ng/mL when she underwent living donor LT in 2007. This was the only case of transplantation with a living donor for the treatment of CRLM in more than 5,000 living donor transplants performed at that institution. With 13 years of follow-up and no postoperative adjuvant treatment, the patient is alive and disease-free[41].

Tabbal et al.[3], from Saudi Arabia, published a case of rescue transplantation performed in a 37-year-old patient who had undergone left colectomy, adjuvant CT, and subsequent resection of LM, following which he developed signs of liver failure. The patient received a deceased donor LT and was immunosuppressed with corticosteroids, mycophenolate, and tacrolimus. Mycophenolate was replaced by sirolimus 2 months later. At a 40-month follow-up, the patient was doing well, with a CEA level of 1.6 ng/mL and an abdominal computed tomography scan showing no evidence of disease[3].

Rajendran et al.[42], from Toronto, Canada, published an analysis of 81 patients evaluated for LT due to CRLM. Of these, seven underwent transplantation, 22 underwent resection, and 48 remained under conservative treatment. The interval between the start of evaluation and transplantation was 15 months. The mean follow-up times after transplantation and resection were 14.8 and 21.4 months, respectively. The 48 patients under conservative treatment showed the poorest survival. Comparing LT vs. resection, the 1-year overall survival was similar (100% vs. 93.8%), whereas, at 3 years, it was superior in the LT group (100% vs. 43.3%). Likewise, disease-free survival was higher in the LT group at both 1 year (85.7% vs. 11.4%) and 3 years (68.6% vs. 11.4%)[42].

Adam et al.[43] compared, in a randomized study, the outcomes of patients with unresectable CRLM meeting transplant indication criteria, who underwent systemic chemotherapy (CT) followed by transplantation versus systemic CT alone. This study involved 20 European centers and included patients aged 18 to 65 years, ECOG 0 or 1, with colon adenocarcinoma, wild-type B-type RAF kinase (BRAF), unresectable CRLM with an objective response for at least 3 months after the last line of CT, CEA < 80 ng/mL or a 50% decrease from its peak value, no extra-hepatic disease on CT and PET-CT, and oncological resection of the primary tumor. Ninety-four patients were randomized 1:1, with 47 assigned to CT and 47 to CT and LT. The 5-year survival rate was 56.6% in the CT + LT group and 12.6% in the systemic CT group. The median survival was 43.9 and 31.3 months, respectively, with a 12.6-month gain in the transplant group. In the intention-to-treat analysis, the 3-year survival was 65.5% in the LT + CT group and 38.9% in the CT group, while the 5-year survival from protocol inclusion was 73.2%. The median time without disease progression was 17.4 vs. 6.4 months in favor of the LT group[43].

Byrne et al.[44] recently published their 5-year experience, which began in 2019, following the University of Rochester protocol (New York, USA). Patients were enrolled in the LT evaluation after removal of the primary tumor and at least 9 months of stable CRLM control. They became eligible for LT at least 12 months after the CRLM diagnosis, with primary tumor resection occurring at least 6 months prior. Patients with right-sided colon tumors, BRAF V600E mutations, or microsatellite instability required an observation period of at least 18 months. The Rochester protocol was an adaptation of the Oslo protocol and the IHPBA guidelines. As in other services, all patients were deemed unresectable following a multidisciplinary team meeting at a center experienced in extensive resections, parenchyma-sparing resections, two-stage resections, and the technique of associating portal vein ligation and liver division for staged hepatectomy, also known as ALPPS (Associating Liver Partition and Portal vein ligation for Staged hepatectomy). Patients with disease progression and/or elevated CEA levels were contraindicated, and those with positive lymph nodes at the time of transplantation were excluded. A total of 225 patients were referred, and 206 completed the evaluation, of whom 135 became candidates for LT. CRLM were synchronous in 86% and bilobar in 90% of cases. Twenty-three patients, with a mean age of 43 years, underwent living donor LT (LDLT); 96% had synchronous metastases, and 91% had primary tumors in the left colon or rectum. The 1-year and 3-year overall survival rates were 100% and 91%, respectively, while recurrence-free survival rates were 100% and 40% for the same periods[44].

More recent studies have sought to refine selection criteria to improve long-term outcomes. The combination of advanced imaging, such as PET/CT scans, with the Oslo score and the Fong clinical risk score has been used to evaluate prognosis and patient eligibility for LT[19,30-32]. This approach allows for more selective treatment and a higher probability of success, with 5-year survival rates reaching up to 75% for those meeting the ideal criteria[31,32].

Different indication protocols are being practiced across various centers. Table 5, published in the work by Byrne et al.[44], compares three protocols from three high-volume studies.

Table 5. Comparison of inclusion and exclusion criteria for the SECA-II, TransMet, and University of Rochester protocols for LT in unresectable colorectal LM.

Criteria	SECA-II	TransMet	University of Rochester
Age (years)	18-65	18-65	N/A
Diagnosis	Histologically confirmed colorectal adenocarcinoma with unresectable CRLM	Histologically confirmed colorectal adenocarcinoma with unresectable LM	No signs of primary tumor recurrence nor extra-hepatic metastases in CT scan or MRI, negative PET before transplant
Extra-hepatic disease	No extra-hepatic disease	No extra-hepatic disease on CT scan and PET-CT scan	No extra-hepatic disease
Local recurrence of the primary tumor.	No local recurrence of the primary tumor	Absence of local recurrence of the primary tumor on colonoscopy performed up to 3 months before the committee meeting	No signs of local recurrence of the primary tumor
Time	1 year or more since CRC diagnosis	Stable or partial response on the last imaging assessment before the committee meeting	1 year or more since CRC diagnosis
ECOG	≤ 1	≤ 1	≤ 1
Child score	≤ 6	≤ 6	≤ 6
CEA	≤ 80 ng/mL	≤ 80 ng/mL and a 50% reduction from baseline	No increase in CEA > 80 ng/mL at the time of listing
Disease progression	Patients should be on CT with no disease progression	No disease progression under CT	No disease progression under medical treatment in the 6 months before transplantation
Nodal sampling	N/A	N/A	Negative lymph node count confirmed by diagnostic laparotomy
Tumor burden	Before CT, no lesion should be >10 cm; if>10 lesions are present, at least 30% should respond	Stable or partial response according to imaging criteria	Stable or partial response in the 6 months before transplantation
Tumor response	At least 10% response rate based on imaging criteria under CT, or patients with a response rate of ≥ 9 months	Stable or partial response according to the CT protocol	Stable or partial response under standard clinical treatment
Previous local therapies	Response after TACE or iodine spheres	Imaging criteria with no progression ≥ 6 months after CT	High-risk primary tumors treated with surgery and controlled LM for ≥ 6 months
Special considerations	N/A	Absence of BRAF mutation	Patients with KRAS mutation and sustained response for ≥ 6 months may be considered
Exclusion	Weight loss > 10% in the last 6 months, muscle mass index > 30 kg/m², additional neoplasms, medical or surgical contraindications, pregnancy or lactation	No health insurance, active alcoholism, chemical dependency, BRAF mutation or medical or surgical contraindications	Hemodynamic instability, BRAF mutation, serious medical contraindications, occult extra-hepatic disease

Source: Extracted from Byrne et al.[44]. N/A = Not evaluated.

Despite progress, the recurrence rate is still a significant challenge, with many patients presenting relapses, especially in the liver.

Several authors have published overall survival rates at 1, 3, and 5 years of 95, 68, and 60%, respectively[29,31,32,44]. Although these survival results are promising, the majority of patients presented disease recurrence after 2 years of LT. Among the risk factors associated with low survival, the largest tumor diameter, elevated CEA levels, the time elapsed since the primary surgery, lack of response to CT, and MTV assessed by FDG PET-CT stand out[30-32].

Grut et al.[45] evaluated 40 patients undergoing LT for CRLM (SECA I = 23; SECA II = 17) regarding the metabolic expression of metastases, as assessed preoperatively with FDG PET-CT. The metabolic volume was calculated manually for each nodule and summed at the end. MTV > 70 mL was associated with worse overall and disease-free survival, thereby introducing another criterion for patient selection[45]. However, even in recent studies utilizing all patient selection methods, relapses remain high (> 30% after 3 years), despite superior results when compared to resection[42].

In the TransMet Trial, Adam et al.[43] showed recurrence in 74% of transplanted patients at a median follow-up of 59 months[43].

Although the high recurrence rate remains a significant challenge, advances in patient selection and adjuvant therapies have considerably increased long-term survival rates, a fact that places LT for CRLM in a similar position to other indications and bolsters arguments for including these patients on waiting lists to receive grafts from deceased donors. Indeed, the continuous

refinement of selection criteria and the combination with innovative treatments may make LT an increasingly viable and effective option for this select group of patients[5,12,13,27].

Impacts on waiting lists

Each time new indications are added, pressure is placed on waiting lists, resulting in increased mortality due to a lack of sufficient donors to meet the growing demand for organs.

In Norway, Sjule et al.[46] published an impact study on the inclusion of patients with unresectable CRLM, within the Oslo criteria, on the waiting list for deceased donor transplantation, concluding that there is scientific support for the benefits of this type of transplantation in Norway. However, in several other countries, including Brazil, living donor transplantation may be the primary source of grafts for this type of transplant. A protocol for LT in CRLM was published by two Brazilian groups in 2021, recommending a MELD score of 30 for patients meeting the proposed criteria. Still, this regulation has not yet been instituted by the National Transplant System. The possibility of this type of transplantation with a deceased donor does not yet exist in Brazil, where an impact study of the inclusion of these patients on the waiting list also does not yet exist[47].

A recently published Indian study retrospectively analyzed 284 patients with CRLM treated at a single center to evaluate how many would be eligible for LT. Exclusively hepatic metastases were present in 173 (60.9%), and 138 were considered unresectable (48.6%). Following the IHPBA consensus criteria, 14 patients would be eligible for transplantation, and if up to two exclusion criteria from Oslo and Fong were considered—representing patients with the best prognoses—13 would be included on the waiting list, which represents 4.5% of all those treated at the service and 9.4% of those considered unresectable. These data show that the impact of including these patients on the waiting list would not be large, given the small number of patients with CRLM who are truly eligible for transplantation[26].

These data are corroborated by the Toronto group, which evaluated 81 patients referred for LT for CRLM, of whom 11 (13.5%) were selected and only 7 (8.6%) transplanted, over a period of 15.4 months after the initial evaluation. In this study, all patients underwent living donor LT, with 1 and 3-year overall and disease-free survival rates of 100, 100 and 85.7, 68.6% respectively[42], and also in the study by Byrne et al.[44], in which, among 225 patients with CRLM referred for LT evaluation, 135 became candidates for LT, but only 37 remained on the list, in an interval of 8 to 12 months, with only 23 (10.2%) transplanted during the 5-year study period.

It should also be considered that CRLM patients who are candidates for LT present good hepatic functional reserve and may perhaps tolerate marginal grafts that are not accepted for patients with hepatic failure and worse clinical conditions[36,37].

Subsequent studies, such as SECA III, COLT, SOULMATE, MELODIC, and EXCALIBUR1, were developed to refine patient selection criteria, comparing LT with standard CT or other alternative therapies[12,13,27].

LT has become an alternative for the treatment of selected patients with CRLM. The careful selection of patients, evaluation of tumor biology and implementation of personalized therapeutic strategies are fundamental to optimizing long-term outcomes. Despite this, the issue of organ allocation and selection criteria remains a subject of debate in the transplant community[10,12,13,27].

CONCLUSION

LT has become a well-established therapeutic option for patients with unresectable CRLM, demonstrating superior outcomes compared to conventional options such as systemic CT. Comparative studies of patients with similar staging undergoing LT, resection, or CT show that LT has advantages in both recurrence and overall survival. Selecting patients with a better prognosis—following the Oslo, Fong, and TMV criteria—provides the best overall and disease-free survival rates, which can exceed 50% at 5 years. The use of living donor livers offers a solution to organ shortage; furthermore, waitlist analyses for deceased donors show that only 5% to 10% of evaluated patients actually reach transplantation, representing a minimal impact on other candidates. However, the high recurrence rate remains a significant challenge. Small series and case reports from various parts of the world encourage continued research so that LT can definitively enter the therapeutic arsenal for this population of patients with unresectable CRLM, whose prognosis remains dismal.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Genzini T; **Conception and design:** Genzini T, Barbosa BT, Luca VP, Coelho AIC; **Data analysis and interpretation:** Genzini T, Lerner FK, Genzini MC; **Article writing:** Genzini T, Grochoski KCV; **Critical revision:** Genzini T, Chiavegatto MA, Perosa M; **Final approval:** Genzini T.

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All dataset were generated or analyzed in the current study.

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DECLARATION OF USE OF ARTIFICIAL INTELLIGENCE TOOLS

The authors declare that no artificial intelligence tools were used in the preparation, writing, data analysis, or review of this manuscript.

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