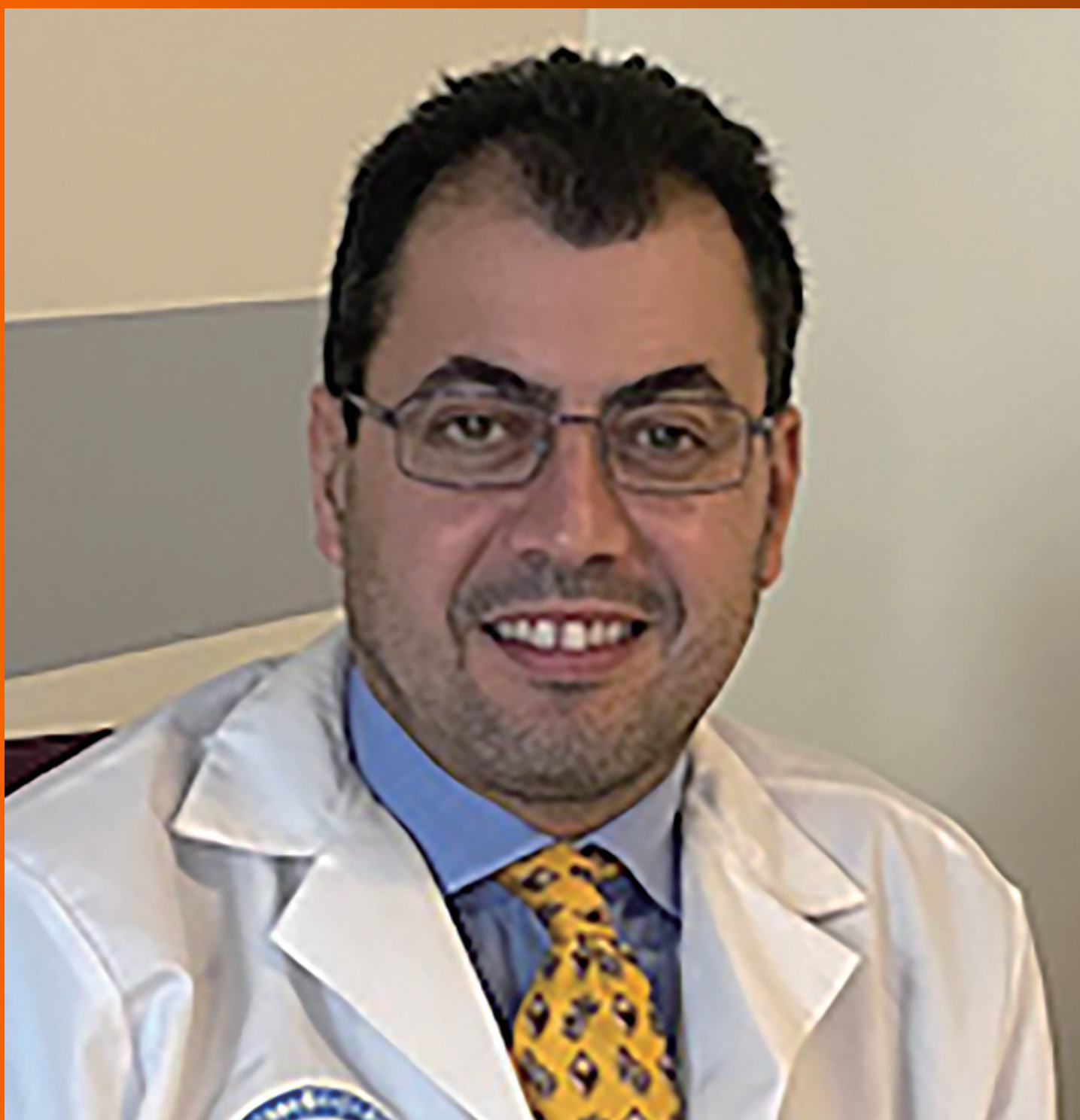


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Editorial Board Member of *World Journal of Gastrointestinal Surgery*, Marcello Donati, FACS, MD, PhD, Professor, Department of Surgery and Medical-Surgical specialties, University of Catania, Catania 95125, Italy. mdonati@unict.it

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Advances in liver transplantation for unresectable colon cancer liver metastasis

Xiao Cui, Xiao-Ping Geng, Da-Chen Zhou, Ming-Hao Yang, Hui Hou

ORCID number: Xiao Cui 0000-0002-2456-5634; Xiao-Ping Geng 0000-0002-6543-6492; Da-Chen Zhou 0000-0003-3228-0206; Ming-Hao Yang 0000-0001-5631-7056; Hui Hou 0000-0003-0463-4783.

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Xiao Cui, Xiao-Ping Geng, Da-Chen Zhou, Ming-Hao Yang, Hui Hou, Department of General Surgery, The Second Hospital of Anhui Medical University, Hefei 230601, Anhui Province, China

Corresponding author: Hui Hou, MD, Professor, Department of General Surgery, The Second Hospital of Anhui Medical University, No. 678 Furong Road, Hefei 230601, Anhui Province, China. hui0402@hotmail.com

Abstract

It is estimated that 50% of patients with colorectal cancer will develop liver metastasis. Surgical resection significantly improves survival and provides a chance of cure for patients with colorectal cancer liver metastasis (CRLM). Increasing the resectability of primary unresectable liver metastasis provides more survival benefit for those patients. Considerable surgical innovations have been made to increase the resection rate and decrease the potential risk of hepatic failure postoperation. Liver transplantation (LT) has been explored as a potential curative treatment for unresectable CRLM. However, candidate selection criteria, chemotherapy strategies, refined immunity regimens and resolution for the shortage of grafts are lacking. This manuscript discusses views on surgical indication, peritransplantation anti-tumor and anti-immunity therapy and updated advances in LT for unresectable CRLM. A literature review of published articles and registered clinical trials in PubMed, Google Scholar, and Clinicaltrials.gov was performed to identify studies related to LT for CRLM. Some research topics were identified, including indications for LT for CRLM, oncological risk, antitumor regimens, graft loss, administration of anti-immunity drugs and solutions for graft deficiency. The main candidate selection criteria are good patient performance, good tumor biological behavior and chemosensitivity. Chemotherapy should be administered before transplantation but is not commonly administered posttransplantation for preventive purposes. Mammalian target of rapamycin regimens are recommended for their potential oncological benefit, although there are limited cases. In addition to extended criterion grafts, living donor grafts and small grafts combined with two-stage hepatectomy are efficient means to resolve organ deficiency. LT has been proven to be an effective treatment for selected patients with liver-only CRLM. Due to limited donor grafts, high cost and poorly clarified oncological risks, LT for unresectable CRLM should be strictly performed under a well-organized study plan in selected patients. Some vital factors, like LT indication and anti-tumor and anti-immune treatment, remain to be confirmed. Ongoing clinical trials are

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expected to delineate these topics.

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Core Tip: Liver transplantation (LT) for colorectal cancer liver metastasis (CRLM) has been explorably performed in the early stage of LT, but it was abandoned for its poorly oncological prognosis. Several newly released clinical studies showed the promising prospect of LT for CRLM. This review summarizes the history of LT for CRLM and lists the updated advancement in candidate selected criterion, potential immunosuppression and oncological safety balance strategies, surgical technique improvement and ongoing clinical trials.

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INTRODUCTION

In 2020, over 1.8 million new colorectal cancer (CRC) patients were diagnosed, while approximately 915880 deaths were caused by CRC worldwide[1]. Twenty percent of CRC patients are estimated to have developed metastatic disease at the time of diagnosis[2]. The liver is the second most common metastatic site for CRC following the lung[3]. The management of metastatic colon and rectal cancer has significantly progressed over the last few decades. Owing to advancements in surgery, modern chemotherapy and perioperative care, the 5-year overall survival (OS) rate of patients with CRC liver metastasis (CRLM) has approached 35%–40%. In well-selected patients, the 5-year OS has reached over 50%[4–6].

Although early recurrence is mostly unavoidable, patients who are treated with curative-intent liver resection for CRLM have favorable survival outcomes[7]. However, despite advances in preoperative portal vein embolization, two-stage liver resection and systemic treatment, more than 70% of CRLM patients are not suitable for liver resection[8]. Complete removal of the tumor mass by liver transplantation (LT) has been explored, but this approach has received little attention in recent decades.

In the first cohort study of LT for CRLM conducted in Austria between the 1980s and 1990s, the 5-year survival rate was less than 20%[9]. No clear enrollment criteria were defined in this study. The early attempt was soon abandoned after the data were published in the 1990s. Due to advances in the understanding of oncology mechanisms, surgical techniques, immunosuppression therapy and refined systemic treatment regimens, exploratory studies have been reinitiated in the last decade. Secondary cancer (SECA) serial studies showed that the 5-year OS of patients with unresectable CRLM treated with LT was up to 60%–83%[10,11]. The selection criteria for LT for unresectable CRLM, neoadjuvant therapy and postoperative immunity suppression regimens have not been clearly delineated. Here, we have reviewed this field.

THE SELECTION CRITERIA FOR LT IN CANDIDATES WITH UNRESECTABLE CRLM

There are no widely accepted criteria for an ideal candidate to date due to the limited number of study. The first LT for patients with CRLM was performed in Boston, 1963[12]. The patients soon died of pneumonitis and hepatic failure 11 d postoperation (Table 1). As an experimental procedure, CRLM used to be an indication for LT in the early exploration stage of LT surgery. Fifty cases were recorded between 1968 and

Table 1 Published data on liver transplantation for colorectal cancer liver metastasis

Ref.	Year	Center	Period	Patients number	Survival time
Moore <i>et al</i> [12]	1964	Peter Bent Brigham Hospital, United States	September, 1963	1	11 d
Demirleau <i>et al</i> [58]	1964	Hospital St. Antonie, France	January, 1964	1	0 d (died of bleeding)
Andersen <i>et al</i> [59]	2012	Oslo University Hospital, Norway	1970	1	24 d (died of fulminating sepsis)
Penn [13]	1991	Cincinnati Medical Center, United States	September 1968-March 1991	8	Mortality 11% recurrence rate 70%
Pichlmayr <i>et al</i> [60]	1997	Hannover Medical School, German	1972-1995	4	11 mo, 8 d, 33 mo
Honoré <i>et al</i> [61]	2003	University of Liege, Belgium	1992	1	10 yr
Kappel <i>et al</i> [9]	2006	Medical University of Vienna, Austria	1983-1994	24	5-yr OS rate 12%-18%
Hoti <i>et al</i> [14]	2008	European Liver Transplant Registry	1968-1995	50 (including 24 above)	1- and 5-yr OS rate were 62% and 18%
Uskudar <i>et al</i> [62]	2011	The Mount Sinai Hospital, United States	2005, 2008	2	5 yr (no recurrence); 2 yr (no recurrence)
Kocman <i>et al</i> [63]	2011	University Hospital Mekur (Croatia)	2006	1	5 yr (no recurrence)
Hrehoreț <i>et al</i> [64]	2013	University of Medicine and Pharmacy Carol Davila, Romania	January, 2012	1	20 mo post-operation (lung recurrence)
Line <i>et al</i> [46]	2015	Oslo University Hospital, Norway	2014-2017	3	40 d (died of complications); 5.5 yr (no recurrence); 2 yr (recurrent at 12 mo)
Caicedo <i>et al</i> [65]	2016	ICESI University, Colombia	November, 2014	1	19 mo (no recurrence)
Toso <i>et al</i> [66]	2017	Portugal, Paris, Geneva	1995-2015	12	5-yr OS 50% ± 16%, 5-yr PFS 38% ± 15%
Dueland <i>et al</i> [10]	2020	Oslo University Hospital, Norway	2006-2012	23	5-yr OS 60%
Yang <i>et al</i> [67]	2019	Zhongnan Hospital of Wuhan University, China	2016	1	34 mo (recurrent at 4 mo)
Lerut <i>et al</i> [68]	2019	University Hospital Saint-Luc, Belgium	1985-2016	4	17 mo (recurrent at 6 mo), 64 mo (recurrent at 47 mo), 32 mo (no), 28 mo (recurrent at 4 mo)
Fernandes <i>et al</i> [69]	2019	Rio de Janeiro Federal University, Brazil	December, 2018	1	No prognosis information
Dueland <i>et al</i> [10]	2019	Oslo University Hospital, Norway	2012-2016	15	5-yr OS 83%
Smedman <i>et al</i> [25]	2019	Oslo University Hospital, Norway	2014-2018	10	Median OS 18 mo. Median DFS 4 mo
Coubeau <i>et al</i> [52]	2020	Cliniques Universitaires Saint-Luc	2019	1	180 d (no recurrence)

OS: Overall survival; DFS: Disease-free survival; PFS: Progression-free survival.

1995 in the European Liver Transplant Registry (ELTR), and their 1- and 5-year survival rates were 62% and 18%, respectively, which is in accordance with the data from 8 cases in a North American cohort reported in 1991 [13,14]. Due to this unsurprisingly poor survival compared to that achieved by R0 liver resection and the deficiency of organs for transplantation, the initial exploration was abandoned. Risk factors predicting a survival benefit were identified *via* a retrospective analysis of a 25-case cohorts from Vienna [9]. Three patients in this cohort with lymph node negativity and no p53 or K-RAS mutations showed a significantly longer OS than patients with positive lymph nodes and p53 or K-RAS mutations.

Hagness *et al*[11] performed the first prospective pilot study, SECA-I, to evaluate the possibility of LT for CRLM in Oslo University Hospital[11]. The work of Hagness showed a potential curative effect of LT for CRLM. The 1- and 5-year OS rates were 95% and 60%, respectively, although the patients enrolled in this study were diverse. This study identified independent risk factors for OS: CEA > 80 µg/L, tumor size > 5.5 cm, interval time between primary resection and LT less than 2 years, and failure to respond to chemotherapy[11]. These risk factors had also been identified previously for hepatectomy and are defined as the Oslo score here.

In the SECA II trial, clearer characteristic selection criteria that showed a better benefit on prognosis [lower number of metastatic masses, smaller size of the largest lesion, lower CEA levels, Oslo score < 2, and Fong Clinical Risk Score (FCRS) < 2] were summarized based on data from the SECA I trial, which included the following factors: Primary tumor with positive nodes, disease-free survival less than 12 mo, more than 1 metastasis, CEA levels greater than 200 ng/mL, and diameter of the largest metastasis greater than 5 cm. The 5-year OS rate was surprisingly 83% among the 15 patients selected according to the criteria[10]. The SECA I and SECA II trials explored stringent criteria for LT, suggesting that patients with good tumor performance could be candidates.

Although transplantation is a successful treatment, recurrence is mostly unavoidable. The 2-year recurrence was 100% for SECA I, while the 3-year recurrence was 75% in SECA II. In addition to these completed studies, there are several ongoing prospective clinical studies led by different groups exploring stricter inclusion criteria to optimize oncological outcomes and delineate the benefits of LT in CRLM. These inclusion criteria are summarized in Table 2.

The common inclusion criteria are as follows: Good performance status as indicated by Eastern Cooperative Oncology Group (ECOG) score 0–1, confirmed primary tumor R0 resection, completion of at least 2 mo or several cycles of chemotherapy with a stable or partial response based on Response Evaluation Criteria in Solid Tumors (RECIST) at 8 wk or beyond, and no recurrence at the primary tumor location or at extrahepatic sites as confirmed by colonoscopy and positron emission tomography/computed tomography (PET/CT).

The role of PET/CT in precisely evaluating disease progression and stage was strongly emphasized in the inclusion criteria. The metabolic tumor volume and total lesion glycolysis value before transplant are both correlated with OS[15]. With the increasing number of trials whose outcomes are awaited, clearer selection criteria based on larger cohorts of patients will become available.

PERITRANSPLANTATION CHEMOTHERAPY FOR UNRESECTABLE CRLM

Chemotherapy is commonly used as the first choice in treating patients with unresectable CRLM. It is expected to inhibit tumor progression and convert unresectable CRLM into potentially resectable disease. If conversion therapy is not successful, maintaining disease stability is acceptable (Table 3).

The efficacy of LT and chemotherapy in treating unresectable CRLM was compared between the cohorts from the SECA I and NORDIC VII trials[16]. Three different first-line regimens based on fluorouracil/folinic acid and oxaliplatin (FLOX), FLOX combined with cetuximab, and intermittent FLOX with cetuximab were included in NORDIC VII trials[17]. The 5-year survival rate in the SECA I trial was 56%, while it was 19% in the chemotherapy groups. Similar disease-free survival (DFS) times were observed in the transplantation group and chemotherapy group (8 mo *vs* 10 mo). The postrecurrence 5-year OS rate in the SECA I group was significantly superior to that in the chemotherapy group (53% *vs* 6%). It is also notable that current first-line regimens were not available at that time: FOLFIRINOX or mFOLFOX-6 combined with bevacizumab promoted conversion, with resection rates of 61% and 49%, and the tumor response rates were 81% and 62%, respectively[18–20]. In the SECA I trial, no chemotherapy response was a required inclusion criterion, and progression occurred under treatment with 1st- and 2nd-line chemotherapy[11].

Given the early experience of transplantation in the CRLM and SECA serial trials, recurrence is considered inevitable. Although tumor progression could not be preoperatively inhibited under 1st-, 2nd-, or even 3rd-line chemotherapy, transplantation showed a survival benefit over standard chemotherapy. In SECA II, a response to chemotherapy of at least 10% according to the standard RECIST was required as a major inclusion criterion and was a good biological behavior predictor. Due to advances in chemotherapeutic regimens and the hepatic artery infusion technique, a

Table 2 Inclusion criteria in some prospective studies on liver transplantation for colorectal cancer liver metastasis

Study	SECA I	SECA II	LIVERTWOHEAL	TRANSMET	Toronto NCT02864485
Inclusion criteria	Primary tumor R0 resected; ECOG 0-1; More than 6 wk chemotherapy; No extrahepatic metastasis or recurrence confirmed by PET/CT, bone scan	Addition standard: No signs of extra hepatic metastatic disease (except resectable lung metastasis) or local recurrence according to colonoscopy, CT or MRI within 12 mo; Chemotherapy response > 10%; If not, TACE or Y-90 response > 20%; More than 12 mo from diagnosis or adjuvant therapy	Unresectable CRLM without extrahepatic tumor burden, except resectable pulmonary metastases; Disease regresses or keeps stable after more than 8 wk chemotherapy	ECOG 0-1; BRAF wild type; Primary tumor R0 resected; No primary recurrence within 12 mo confirmed by colonoscopy. Disease stable or regress more than 3 mo with chemotherapy; CEA < 80 ng/mL or decrease ≥ 50%; No extrahepatic metastasis confirmed by CT or PET-CT	ECOG 0-1; Primary tumor stage is ≤ T4a; More than 6 mo since liver resection; No major vascular invasion; More than 3 mo chemotherapy; Disease regression or stable more than 3 mo; Stable CEA value or decrease at all time prior to LT
Outcome	OS	OS 10 yr	OS 3 yr	OS 5 yr	OS 5 yr; PFS 5 yr

TACE: Transcatheter arterial chemoembolization; Y-90: Yttrium; PET/CT: Positron emission tomography/computed tomography; MRI: Magnetic resonance imaging.

promising oncological benefit could be expected for candidates who undergo LT for unresectable CRLM.

Adjuvant chemotherapy is not commonly employed posttransplantation and is instead only used when recurrence is confirmed (Table 4). There are some differing views on this issue: (1) Complete resection of a liver metastasis with a margin-negative edge offers great benefit for long-term survival. No high-level evidence of a survival benefit of adjuvant therapy for CRLM postoperation exists[21,22]; (2) Adjuvant chemotherapy combined with immune checkpoint inhibitors or without combination might cause graft loss or an increase in the failure rate[23,24]; and (3) After tumor progression posttransplantation, chemotherapy can be administered safely, and it improved survival relative to nonchemotherapytreatment[25].

POSTTRANSPLANTATION IMMUNOSUPPRESSION AND ONCOLOGICAL SAFETY

Long-term immunosuppression promotes secondary malignancy, primary tumor recurrence and subclinical micrometastasis progression posttransplantation. Chronic immunosuppression directly related to malignancy is expected to be the leading cause of death in transplant recipients[26-28]. From the data reported, the estimated standardized incidence ratio of de novo malignancies after LT in CRC ranges from 1.2-12.5-fold to 3.3-fold for anal cancer[26,28,29]. Among United States transplant societies, the guidelines suggest that the common malignancy-free period before transplantation for patients with CRC should be more than 2 years (0-5 years, depending on the TNM stage). In European guidelines, this delay period has been extended to more than 5 years[30].

Immunosuppression increases *de novo* malignancy occurrence and cancer recurrence *via* several mechanisms: (1) Negative modulation of immune surveillance that increases the risk of oncovirus-driven malignancy and tumor cell escape from immunity[31]; and (2) A nonspecific mode of action induced by immunosuppressive drugs that promotes insulin resistance, inhibits DNA damage repair and enhances tumor angiogenesis and invasiveness[32]. Calcineurin inhibitors (CNIs), such as tacrolimus and cyclosporine, are the most commonly used immunosuppressive drugs, and they work by inhibiting calcineurin and downregulating nuclear factor of activated T cells, which is related to the gene expression of IL-2, IFN- γ , and GM-CSF [33,34]. CNIs promote the activation of oncogenes and tumor progression, and they are positively correlated with the incidence of malignancy in a dose-dependent manner [35]. Compared to continuation of CNIs, a change to mycophenolate mofetil significantly reduced the occurrence of de novo malignancies[36]. Mammalian target of rapamycin (mTOR) inhibitors exert antitumor effects in experimental studies and protective effects in reducing malignancy posttransplantation, especially within the first year[37]. Although all immunosuppressive drugs, including mTOR inhibitors and mycophenolate mofetil, increase the risk of malignancy based on SRTR data analysis, it is highly recommended to switch from CNIs to mTOR inhibitors when there is a risk of malignancy or a malignancy diagnosis has been made posttransplantation[38].

Table 3 Treatment for unresectable colorectal cancer liver metastasis prior to transplantation

Ref.	Year	Treatment prior to liver transplantation		
		Liver resection	Local therapy	Systemic therapy
Moore <i>et al</i> [12]	1964	NR	NR	NR
Demirleau <i>et al</i> [58]	1964	NR	NR	NR
Andersen <i>et al</i> [59]	2012	NR	NR	NR
Penn[13]	1991	NR	NR	NR
Pichlmayr <i>et al</i> [60]	1997	NR	NR	NR
Honoré <i>et al</i> [61]	2003	Yes	No	No
Kappel <i>et al</i> [9]; Hoti <i>et al</i> [14]	2006; 2008	NR	NR	NR
Uskudar <i>et al</i> [62]	2011	Yes	Yes, TACE, HAI. Yes, HAI (causing liver failure)	Yes
Kocman <i>et al</i> [63]	2011	Yes (Two times)	No	Yes, 1/1
Hrehoreţ <i>et al</i> [64]	2013	Yes (ALPPS one stage)	Yes, radio therapy	Yes, FOLFOX AND bevacizumab
Line <i>et al</i> [46]	2015	No; NR	No; NR	Yes, 3/3, FLIRI/cetuximab
Caicedo <i>et al</i> [65]	2016	No	Yes, 1/1 RFA	Yes, 1/1, FOFIRI + cetuximab
Toso <i>et al</i> [66]	2017	Yes, 10/12	1/12 RFA	11/12, irinotecan, oxaliplatin, cetuximab, bevacizumab
Dueland <i>et al</i> [10]	2020	Yes, 4/23	2/23	Yes, 23 (1 st line, 10 patients; 2 nd line, 9 patients; 3 rd line, 4 patients)
Yang <i>et al</i> [67]	2019	No	Yes, 1/1; TACE + RFA	Yes, 1/1, mFOLFOX6 + bevacizumab
Lerut <i>et al</i> [68]	2019	No	No	Yes, 4/4, 5-FU, Oxaliplatin irinotecan, bevacizumab,
Fernandes <i>et al</i> [69]	2019	Yes	Yes	FOLFOX/FOLFIRI
Dueland <i>et al</i> [10]	2020	4/15	NR	Yes, 15/15
Smedman <i>et al</i> [25]	2019	2/10	2/10 RFA	Yes, 10 patients (1 st line), 10 (2 nd line), 3 (3 rd line)
Coubeau <i>et al</i> [52]	2020	NAR	NAR	Yes, 1/1

NR: Not report; RFA: Radiofrequency ablation; mFOLFOX-6: Modified 5-fluorouracil/folinic acid and oxaliplatin; FOLFIRI: Fluorouracil, folinic acid, and irinotecan.

The data on the administration of immunosuppressive drugs to patients with CRLM posttransplantation come from a few case reports and only limited clinical trials. The patients with pulmonary metastasis posttransplantation in the SECA I study were compared to the nontransplantation patients with pulmonary metastasis. Neither a worse oncological prognosis nor a correlation between sirolimus concentration and DFS was observed in the transplantation group[39]. No other published data are available.

Experience from patients with HCC who underwent LT might provide some evidence: (1) Elevated CNI levels in the early posttransplantation period were correlated with an increased rate of recurrence of HCC[40]; (2) mTOR inhibitor-based regimens showed significantly lower recurrence of HCC after LT and 5-year survival advantages relative to CNI-based regimens[41,42]; and (3) A multicenter randomized clinical trial (RCT) showed that incorporating mTOR inhibitor regimens after six weeks of non-mTOR regimens could benefit 1- and 3-year disease-free survival in patients with HCC in contrast to continuation of non-mTOR regimens[43].

In the limited case series, the most commonly used regimens are mTOR inhibitors, including everolimus or sirolimus, prednisolone, mycophenolate mofetil, and basiliximab. The use of relatively low CNI levels in the early posttransplantation period keeps the balance between antiproliferative and rejection effects, and transitioning to mTOR inhibitors at a reasonably early stage might be a safe strategy, but more evidence is needed.

Table 4 Adjuvant therapy for recurrence after liver transplantation for unresectable colorectal cancer liver metastasis

Ref.	Overall survival (months)	Die/alive	Recurrence	Adjuvant therapy post recurrence after LT
Yang <i>et al</i> [67]	34	0/1	Yes	Chemotherapy
Lerut <i>et al</i> [68]	28	3/1	Yes, 4, 6, 47 mo	Chemotherapy
Toso <i>et al</i> [66]		6/6	Median DFS 6 mo	5 chemotherapy; 1 radiotherapy
Hagness[39]	27	6/15	Median DFS 19 mo	11 Chemotherapy; 1 TACE; 7 Radiation therapy; 11 Re-resection
Smedman <i>et al</i> [25]	18	5/5	Median DFS 8 mo	3 Chemotherapy combined radiation therapy; 2 Chemotherapy; 1 Radiation; 1 Surgery
Dueland <i>et al</i> [10]	36	2/13	Median DFS 8 mo	6 Surgery; 2 Surgery combined Radiation therapy; 2 Chemotherapy
Hrehoreț <i>et al</i> [64]	20	0/1	Yes, 6 wk	Chemotherapy

LT: Liver transplantation.

ADVANCES IN LT SURGERY FOR CRLM

The scarcity of liver grafts is the most common reality worldwide, in contrast to the relatively plentiful liver graft pool in Norway. The challenge of obtaining liver grafts for those with end-stage liver disease is inevitably brought to mind when allocating the limited livers to those patients with CRLM, who fall beyond the existing indications. Living liver donors and extended criteria donors might be a potential resolution. In SECA II arm D, the authors utilized extended criteria livers for 10 patients who had exceeded the inclusion criteria. Their outcome was inferior to that of patients from the other arms, which was mainly due to oncological progression. No dysfunction of the grafts occurred[44]. Three prospective trials using partial livers from living or deceased donors for CRLM were initiated. One is from Toronto University (NCT02864485), and the other two are from Europe, Oslo University (NCT02215889) and Tübingen and Jena University (NCT03488953); these trials introduced a new surgical technique and concept, the RAPID technique (resection and partial liver segment 2–3 transplantation with delayed total hepatectomy)[45]. This technique is derived from the associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) technique, which efficiently increases the volume of future liver remnants and improves surgery safety and curability in patients with potentially resectable CRLM[46].

In traditional deceased donor split LT, donor grafts are divided into two sections according to the clinical needs of the recipients. Donor livers that are suitable for splitting are not plentiful. Functional liver remnants are also not sufficient for some recipients. The basic principle of RAPID is as follows: In the first stage, left hemihepatectomy is performed in the recipients, and transplantation with segmental grafts (segments 2 and 3) and ligation of the right portal vein are performed. During the waiting time, the remnant hemiliver is supposed to support body requirements while the transplant graft becomes established. In the second stage, the right hemiliver is removed when the transplant graft has grown to a sufficient size. The remaining donor extended right liver graft can then safely be transplanted to another recipient, which does not carry a significantly increased risk compared to using a whole liver graft[47].

The physical background for this surgical procedure is based on two points. (1) RAPID is considered an advanced variant of ALPPS. The ALPPS technique enhances future remnant liver (FRL) regeneration by diverting portal vein inflow into the FRL. In RAPID, ligation of the right portal vein and removal of the left hemiliver totally divert the main portal vein inflow into the transplant graft, which induces fast regeneration of liver volume and functional capacity[48]; and (2) Immunosuppressive regimens posttransplantation do not increase CRLM recurrence in comparison with no immunosuppressive regimens[16,49]. Relatively good tumor biological behavior is required for candidates according to the inclusion criteria. A sufficient length of the interval stage could be expected for liver graft regeneration before second-stage surgery.

As a common risk for all small transplant grafts, the RAPID technique also needs to resolve PV hyperperfusion, which causes arterial vascular structure damage, inhibits

liver regeneration and causes graft dysfunction[50]. Based on ALPPS and hepatectomy experience, higher portal vein inflow pressure is associated with an increased incidence of morbidity and mortality. High portal vein pressure is not very common in CRLM. The suggested resolution for PV hyperperfusion is to monitor the PV; if PV pressure > 15 mmHg, an inflow shunt should be considered[51].

Eleven patients with unresectable CRLM, specifically eight patients with LD-RAPID (five in Germany, two in Italy, and one in Belgium), had undergone RAPID surgery using deceased donor (DD) grafts and living donor (LD) grafts by the end of 2019[52]. Of the German patients, three patients were alive without tumor recurrence within 6 to 18 mo of follow-up; one patient died of pulmonary embolism at 24 mo post transplantation, with tumor recurrence in the thoracic vertebral body, skull and bilateral lung but not the liver at the fifth month[53]. No recurrence or death occurred at 180 d according to published data[52]. In the Oslo group, 3 patients underwent DD-RAPID transplantation, and one died of hepatic artery thrombosis and sepsis 40 d post operation. The first patient survived for 5.5 years without recurrence, and the other patient survived for 2 years but experienced recurrence in the 12th month.

CONCLUSION

When treating unresectable CRLM with standard chemotherapy, the 2- and 5-year OS have been found to be 10% [54,55]. If unresectable CRLM patients cannot tolerate second- and third-line chemotherapy after disease progression, the median survival period is only 5 to 7 mo[56,57]. Based on the present clinical outcome and previous data, LT has promise for treating unresectable CRLM, with a 5-year survival rate of over 50%. However, the scarcity of grafts worldwide and lack of clear indications challenge the implementation of LT for unresectable CRLM.

Resolution of these challenges requires two approaches: (1) Developing stringent selection criteria that can identify the candidates who can most benefit from LT; and (2) Increasing the suitable graft pool or extending donor graft criteria for unresectable CRLM. Good biological tumor behavior identifications have been explored to establish better criteria. Most patients experience recurrence after LT, but the median survival time from relapse of such patients is better than that of a cohort of patients with HCC. Recurrence does not shorten their survival time. DFS and its related factors are not considered an appropriate indicator for LT for CRLM.

The prognostic biological factors associated with survival were extrahepatic metastasis status confirmed by 18-FDG/PET scans, CEA level, the period between diagnosis confirmation and LT, chemotherapy response, and clinical risk scores (FCRS and Oslo scores). In well-selected patients with the above good behavior characteristics, the 5-year survival rate was 100%[10]. There are also some common risk factors for chemotherapy and liver resection in CRLM that have been found to be closely correlated with a poor survival rate. The location of the primary tumor significantly affects the survival prognosis. A K-RAS mutation in the tumor could be a powerful prognostic factor based on early studies of LT for unresectable CRLM. With more data from ongoing trials, the definite pathological characteristics of the group of patients who can benefit the most from LT will become clearer (Table 5).

Another strategy to overcome the lack of organs is to extend the present transplantation indications. This solution includes two parts: Showing superiority in survival of patients under stringent criteria or using small grafts with the RAPID technique or extended-criteria grafts to expand the donor pool. The fear of wasting valuable grafts can be re-evaluated and overcome by a better understanding of the biological outcomes based on up-to-date data on LT for CRLM. The RAPID concept provides a better resolution for the shortage of organ grafts. Segment transplantation, especially through LDLT, could balance the risks of living donors and the needs of recipients. The difficulty of the RAPID surgical technique will be more challenging for surgeons than standard split LT.

There are also some other techniques and oncological questions that need to be further explored: (1) Defining suitable second surgical indications that both ensure sufficient graft function and lower the risk of tumor dissemination; and (2) Determining the suitable graft-to-recipient weight ratio for the recipients when a standard or extended left hemihepatectomy is performed to ensure the patient is tumor-free.

The current ongoing trials will further advance the insights into the oncological behavior of CRLM post-LT and better define the transplantation indications. Due to the need for solid evidence, this promising treatment option should be carefully

Table 5 Ongoing clinical trials on liver transplantation for colorectal cancer liver metastasis

NCT number	Study name	Year	Type	Patients	Unit, country	Study aims
03494946	SECA III	2016-2027	RCT	25	Oslo University hospital, Norway	LT <i>vs</i> chemotherapy
02215889	No	2014-2028	Intervention	20	Oslo University hospital, Norway	Single arm (segment 2, 3 partial LT)
03488953	LIVERTWOHEAL	2018-2023	Intervention	40	Jena University Hospital, German	Single arm (Living donor liver transplantation with two-staged hepatectomy)
02597348	TRASMET	2015-2027	RCT	90	Hôpitaux de Paris, France	LT plus chemotherapy <i>vs</i> chemotherapy
03231722	COLT	2019-2024	Multi-center non-RCT		Fondazione IRCCS Istituto Nazionale dei Tumori, Italy	LT <i>vs</i> chemotherapy (parallel arm in TRIPLETE trial)
04161092	SOULMATE	2020-2030	Multi-center RCT	45	Vastra Gotaland Region, Sweden	LT (extended criteria graft) <i>vs</i> best alternative therapy

RCT: Randomized clinical trial; LT: Liver transplantation.

implemented.

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